TESIS DOCTORAL

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EVALUACIÓN DEL EFECTO DE LAS ALTERACIONES DEL SUEÑO EN EL DOLOR, LA FATIGA Y LA DEPRESIÓN EXPERIMENTADA POR LOS PACIENTES CON FIBROMIALGIA

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Memoria presentada por

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Memoria de tesis esponsorizada por Grupo Lo Monaco

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La Tesis Doctoral titulada Evaluación del efecto de las alteraciones del sueño en el dolor, la fatiga y la depresión experimentada por los pacientes con fibromialgia ha sido realizada por Dña. Carolina Díaz Piedra reúne las condiciones de calidad, originalidad y rigor científico necesarias para su defensa pública según establece la legislación vigente para aspirar al grado de Doctor en Psicología según la modalidad de agrupación de publicaciones.

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Granada, a 7 de Octubre de 2013

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Esta Tesis Doctoral se ha realizado según las Normas Reguladoras de las Enseñanzas Oficiales de Doctorado y del Título de Doctor por la Universidad de Granada aprobada por el Consejo de Gobierno el 2 de Mayo de 2012 (artículo número 18) referida a la modalidad de Tesis Doctoral compuesta por el reagrupamiento de trabajos de investigación publicados por el doctorando.

A Rocío.

Es ella quien me recuerda por qué estamos aquí.

Me permite experimentar, discutir, soñar y,

sin más remedio, crecer.

TABLA DE CONTENIDOS

Sé que he despertado y que todavía duermo.

Mi cuerpo antiguo, molido de que yo viva, me dice que todavía es muy pronto...

Me siento febril de lejanía. Me peso no sé por qué...

En un torpor lúcido, pesadamente incorpóreo, me estanco, entre el sueño y la vigilia, en un sueño que es la sombra de soñar.

Mi atención flota entre dos mundos y ve ciegamente la profundidad de un mar y la profundidad de un sueño; y estas profundidades se interpenetran, mezclándose, y yo no sé dónde estoy ni lo que sueño.

Fernando Pessoa

El libro del desasosiego

RESUMEN

La fibromialgia es una condición reumática muy frecuente, sobre todo entre las mujeres, que presenta una elevada complejidad de cara al diagnóstico y tratamiento. Esto se relaciona con que su etiología es aún desconocida, no habiendo ninguna prueba diagnóstica o alteración fisiológica que permitan un claro diagnóstico. Además, no existen evidencias claras acerca de las estrategias terapéuticas más efectivas. Por todo ello, muchos investigadores están centrados en comprender mejor en qué consiste el síndrome, lo que incluye la identificación de los factores precipitantes del dolor y de aquellas variables que incrementan la gravedad de los síntomas, así como las consecuencias de sufrir dolor crónico. Así, aunque el dolor es el síntoma cardinal en la fibromialgia, otros síntomas típicos del síndrome, como por ejemplo, los problemas de sueño, son también altamente incapacitantes. Los problemas de sueño son una de las quejas más frecuentes en los pacientes que sufren fibromialgia. La investigación acerca del sueño en pacientes con fibromialgia ha crecido de forma exponencial en los últimos cuarenta años, ya que el reconocimiento y manejo de los problemas de sueño podría mejorar la morbilidad en estos pacientes. Para ampliar el conocimiento acerca del sueño en fibromialgia se ha llevado a cabo esta Tesis Doctoral, cuyos objetivos principales están relacionados con, por una parte, (1) caracterizar los problemas de sueño en esta población y conocer el papel de estos problemas en la clínica y patofisiología del síndrome y, por otra, (2) valorar la efectividad de un tratamiento para los problemas de sueño en diferentes variables.

Para alcanzar el primer objetivo, en primer lugar, se realizó una revisón sistemática de estudios empíricos acerca de las características de sueño en mujeres con fibromialgia. En esta revisón se evidenció como, aunque las pacietnes tienen una peor calidad de sueño subjetiva, la evidencia acerca de trastornos en la fisiología del sueño es inconsistente. Aún así, los resultados polisomnográficos más frecuentes tienen que ver con altos índices de fragmentación del sueño (en medidas de arquitectura y microestructura del sueño) y una tendencia a presentar un sueño más ligero (mayor porcentaje de sueño en fases 1 y 2 del sueño no REM). Dadas las limitaciones metodológicas en la mayoría de los estudios revisados, se planteó un estudio empírico para intentar superar algunas de ellas. Así, los estudios empíricos correspondientes al primer objetivo son tres estudios transversales que intentaban clarificar 1A) si existen

alteraciones polisomnográficas en las pacientes con fibromialgia y no sólo quejas de sueño no reparador; 1B) cuál es el papel de estas alteraciones del sueño en la clínica del trastorno; y 1C) el papel de la calidad de sueño en las alteraciones cerebrales estructurales que ocurren en pacientes con fibromialgia. Así, en el primero de ellos, se pretendía comparar variables subjetivas y objetivas de sueño entre mujeres con fibromialgia y mujeres sanas, controlando el efecto de la edad. Para ello, se evaluó la calidad subjetiva de sueño y la somnolencia diurna mediante el Índice de Calidad de Sueño de Pittsburgh y la Escala de Somnolencia de Epworth y se llevó a cabo una polisomnografía ambulatoria a 40 pacientes y 35 controles. Los resultados mostraron que las pacientes presentaban una menor calidad subjetiva de sueño y una mayor somnolencia diurna que las participantes control y, además, presentaban alteraciones en la organización de los ciclos de sueño y una mayor fragmentación del sueño. Algunas de estas medidas subjetivas y objetivas del sueño correlacionaban entre sí. Estos hallazgos sugieren que los síntomas de problemas de sueño serían el resultado de alteraciones en la fisiología del sueño entre las pacientes con fibromialgia y no una mera exageración por parte de las pacientes. Una vez establecida la existencia de alteraciones subjetivas y objetivas en fibromialgia, en el segundo estudio se pretendía conocer si, no sólo la calidad subjetiva de sueño, sino también las variables polisomnográficas mediaban la relación entre el dolor y variables afectivas en la fibromialgia. Aunque tradicionalmente se ha asumido que el dolor es la causa de los problemas de sueño en estas personas, las evidencias al respecto muestran que la relación entre estas variables es más compleja y las estrategias analíticas más simples probablemente no logren capturar esa complejidad. De ahí, nuestra propuesta de análisis de mediación. En este estudio, se evaluó la calidad subjetiva de sueño y los niveles de ansiedad y depresión mediante el Índice de Calidad de Sueño de Pittsburgh y la Escala Hospitalaria de Ansiedad y Depresión y se llevó a cabo una polisomnografía ambulatoria a 55 mujeres con fibromialgia. En los análisis de mediación se muestra como la calidad subjetiva de sueño y la eficiencia objetiva de sueño mediaban, junto con la autoeficacia, el impacto del dolor sobre la ansiedad y la depresión en fibromialgia. Estos hallazgos enfatizan el rol del sueño (y, en especial, de las alteraciones objetivas) como recurso personal capaz de mediar las respuestas afectivas a la experiencia de vivir con dolor crónico. Por otra parte, se sabe que existen estructuras cerebrales que son comunes tanto a los mecanismos asociados a la modulación del dolor como a los mecanismos relacionados

con el funcionamiento del ciclo sueño-vigilia. Esto sugiere la existencia de alteraciones estructurales y funcionales en dichas estructuras del sistema nervioso central de los pacientes con fibromialgia. En el tercer estudio, se pretendía comparar los volúmenes de materia cerebral entre pacientes con fibromialgia y controles, controlando por los efectos del sexo y el estatus menopáusico. Para ello, se evaluó la intensidad del dolor, la calidad subjetiva de sueño y los niveles de ansiedad y depresión mediante una escala visual analógica de dolor, el Índice de Calidad de Sueño de Pittsburgh y la Escala Hospitalaria de Ansiedad y Depresión, respectivamente, y se llevó a cabo una resonancia magnética a 23 mujeres con fibromialgia y 24 participantes sanas, todas premenopáusicas. En los resultados se encontró un menor volumen total de materia gris, que es predicha por los niveles de dolor, ansiedad y depresión en las pacientes con fibromialgia. En este caso, la calidad subjetiva de sueño no se relacionaba con los volúmenes de materia cerebral. Se ha sugerido que las alteraciones estructurales responderían a la plasticidad cerebral ante la experiencia crónica de dolor, estos hallazgos sugieren que las alteraciones estructurales en fibromialgia, dado que están relacionadas con diversos síntomas, podrían ser revertidas tras la aplicación de un tratamiento exitoso de la fibromialgia.

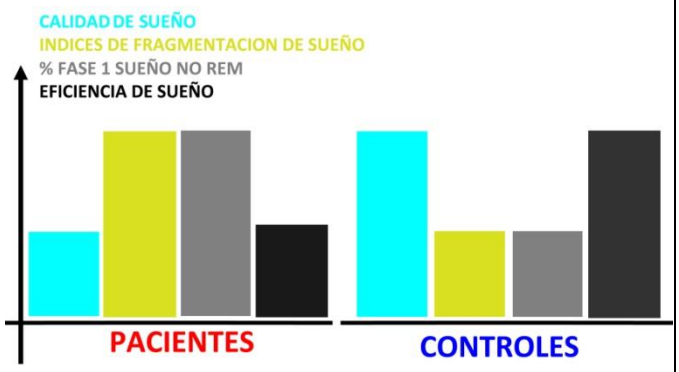
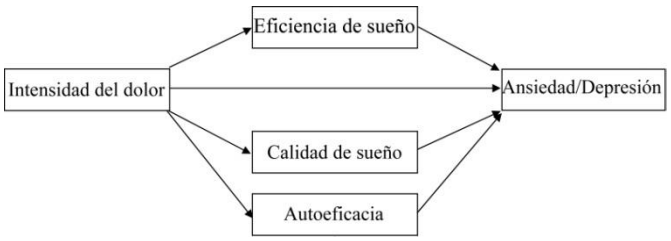
Dado que se ha propuesto que un sueño reparador sería un recurso fundamental en el funcionamiento óptimo de las personas que tienen que vivir diariamente con las demandas impuestas por el dolor crónico, el tratamiento de los problemas de sueño podría ser un objetivo terapéutico crucial en los pacientes con fibromialgia, ya que los potenciales beneficios irían más allá de la mejora de la calidad sueño. Dichos efectos beneficiosos se relacionarían con cambios positivos en otros síntomas. En el segundo bloque de estudios de esta Tesis Doctoral se pretendía valorar la efectividad de un tratamiento para los problemas de sueño en la mejora de varios de estos síntomas, a través de un ensayo clínico aleatorizado. Para ello, se llevaron a cabo tres estudios experimentales para conocer la efectividad del tratamiento cognitivo conductual para el insomnio (CCT-I) en comparación con un grupo que recibe únicamente educación en higiene de sueño para mejorar 2A) la calidad de sueño y otras manifestaciones clínicas (afectivas, cognitivas y de funcionamiento) de la fibromialgia; 2B) la función atencional y 2C) variables polisomnográficas. El programa de TCC-I se desarrolló en seis sesiones que incluían educación acerca de la relación entre sueño y dolor, nociones básicas sobre el sueño y pautas de higiene de sueño; restricción del tiempo en cama junto con

instrucciones de control de estímulos; entrenamiento en relajación; terapia cognitiva para las creencias disfuncionales sobre el sueño y una última sesión de mantenimiento de ganancias y prevención de recaídas. El programa de educación en higiene de sueño se desarrolló también en seis sesiones que incluían educación acerca de la relación entre sueño y dolor, nociones básicas sobre el sueño y pautas de higiene de sueño; reglas de higiene de sueño sobre los factores ambientales; factores del estilo de vida (consumo de estimulantes y otras sustancias) que influyen en el sueño; información sobre la dieta y el ejercicio físico y una última sesión de mantenimiento de ganancias y prevención de recaídas. En el primer estudio, sesenta y cuatro pacientes fueron asignadas, de forma aleatoria, a la condición TCC-I o la condición de higiene de sueño. Estas mujeres fueron evaluadas en el pretratamiento, postratamiento y en seguimientos a los tres y seis meses. Se obtuvieron medidas de dolor, calidad de sueño, fatiga, funcionamiento diario, autoeficacia, catastrofización del dolor y niveles de ansiedad y depresión mediante el Cuestionario de Dolor de McGill, el Índice de Calidad de Sueño de Pittsburgh, el Inventario Multidimensional de Fatiga, el Cuestionario de Impacto de la Fibromialgia, la Escala de Autoeficacia para el Dolor Crónico, la Escala de Catastrofización del Dolor y el Cuestionario de 90 síntomas, respectivamente. Treinta pacientes del grupo TCC-I y 29 del grupo de higiene de sueño finalizaron el tratamiento. En los resultados se muestran mejoras en el postratamiento el grupo TCC-I en todas las variables de calidad subjetiva de sueño, en los niveles de fatiga, de funcionamiento diario, catastrofización del dolor y ansiedad y depresión. Estas mejoras se mantuvieron en el primer seguimiento en calidad de sueño, niveles de funcionamiento diario y depresión. En el segundo estudio, cuarenta y cuatro mujeres fueron asignadas, de forma aleatoria, a la condición TCC-I o la condición de higiene de sueño. Dieciseis pacientes del grupo TCC-I y quince del grupo de higiene de sueño finalizaron el tratamiento. Se evaluaron, en el pretratamiento y postratamiento, las redes atencionales (alerta, función ejecutiva y orientación), los niveles de dolor, la calidad de sueño y el funcionamiento diario mediante la tarea neuropsicológica ANT-I (Attentional Network Test-Interactions), el Cuestionario de Dolor de McGill, el Índice de Calidad de Sueño de Pittsburgh y el Cuestionario de Impacto de la Fibromialgia, respectivamente. En los resultados se muestra que, tras el tratamiento, aumentaron los niveles de alerta y hubo un menor efecto de interferencia únicamente en el grupo TCC-I. Los índices atencionales de Alerta y Función Ejecutiva mejoraron tras el tratamiento en el grupo TCC-I, cambios

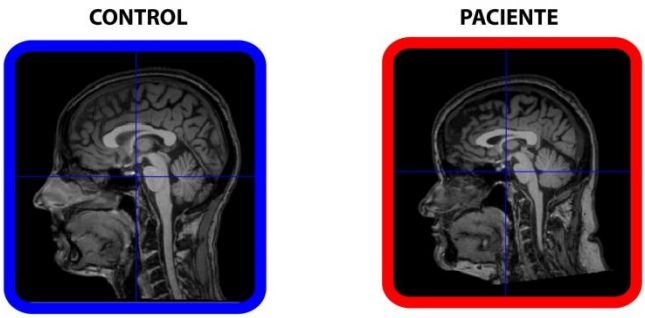
relacionados con la mejora en la calidad de sueño. En el tercer estudio, veintiseis mujeres fueron asignadas, de forma aleatoria, a la condición TCC-I o la condición de higiene de sueño. Estas pacientes fueron evaluadas, en el pretratamiento y postratamiento, mediante una polisomnografía ambulatoria para conocer diferentes parámetros de la arquitectura de sueño. Únicamente las mujeres que recibieron TCC-I mejoraron en variables objetivas de sueño: disminuyó el tiempo en cama, el porcentaje de vigilia y el porcentaje de tiempo en fase 1 del sueño no-REM, aumentó la eficiencia y el porcentaje de sueño profundo (fases 3 y 4 del sueño no-REM). En conjunto, los resultados de estos tres estudios proporcionan sólidas evidencias a favor de la inclusión del TCC-I en los tratamientos multicomponente para la fibromialgia. No sólo se mejora la percepción de los pacientes acerca de su sueño, sino que también mejoran índices objetivos de sueño muy relevantes, como son la eficiencia de sueño y la cantidad de sueño profundo. Además, los beneficios se extienden al área afectiva (mejoras en los niveles de ansiedad y depresión), al área cognitiva (disminución de la catastrofización del dolor) y al rendimiento diurno (fatiga, funcionamiento diario, nivel de alerta y función ejecutiva).

En conclusión, los resultados presentados en esta Tesis Doctoral aclaran la importancia del sueño en la fibromialgia no sólo porque los pacientes presenten alteraciones subjetivas y objetivas, sino porque el sueño tendría un papel fundamental en relación con otros síntomas principales del síndrome y su tratamiento proporcionaría beneficios más allá de las variables de sueño.

Resumen esquemático de los estudios empíricos del proyecto de tesis

<table>
<tr><th colspan="2">ESTUDIO 1
¿Qué alteraciones de sueño caracterizan la fibromialgia?</th></tr>
<tr><td> 
</td><td>Participantes
- 40 mujeres con fibromialgia
- 35 mujeres sanas
Variables e Instrumentos
- Calidad subjetiva de sueño
Índice de calidad de sueño de Pittsburgh [PSQI]
- Somnolencia diurna
Escala de Somnolencia de Epworth
- Parámetros polisomnográficos
Polisomnografía ambulatoria
Principales resultados
Las pacientes presentan:
- Peor calidad subjetiva de sueño
- Mayor somnolencia diurna
- Mayores índices de fragmentación del sueño
- Alteraciones en la organización de los ciclos de sueño</td></tr>
<tr><th colspan="2">ESTUDIO 2
¿Qué papel juegan las características de sueño en la clínica del trastorno?</th></tr>
<tr><td> 
</td><td>Participantes
- 55 mujeres con fibromialgia
Variables e Instrumentos
- Calidad subjetiva de sueño
PSQI
- Intensidad del dolor
Cuestionario de Dolor de McGill [MGPQ]
- Niveles de ansiedad y depresión
Escala Hospitalaria de Ansiedad y Depresión [HADS]
- Parámetros polisomnográficos
Polisomnografía ambulatoria
Principales resultados
- La calidad subjetiva de sueño, la eficiencia objetiva de sueño y la autoeficacia median el impacto del dolor sobre la ansiedad y la depresión en fibromialgia</td></tr>
</table>

ESTUDIO 3
¿Qué alteraciones cerebrales estructurales están presentes en la fibromialgia? ¿Con qué síntomas se relacionan?



Participantes

- 23 mujeres con fibromialgia premenopáusicas
- 24 mujeres sanas premenopáusicas

Variables e Instrumentos

- **Calidad subjetiva de sueño**
  PSQI
- **Intensidad del dolor**
  MGPQ
- **Niveles de ansiedad y depresión**
  HADS
- **Volúmenes de materia cerebral**
  Resonancia magnética estructural

Principales resultados

Las pacientes presentan:

- Menor volumen total de materia gris
- Las alteraciones estructurales en fibromialgia son predichas por los niveles de dolor, ansiedad y depresión.

ESTUDIO 4
¿Es el tratamiento cognitivo-conductual para el insomnio efectivo para mejorar la calidad de sueño, el dolor y otros síntomas?

Participantes

- 64 mujeres con fibromialgia
  - 32 TCC/I
  - 32 Higiene sueño

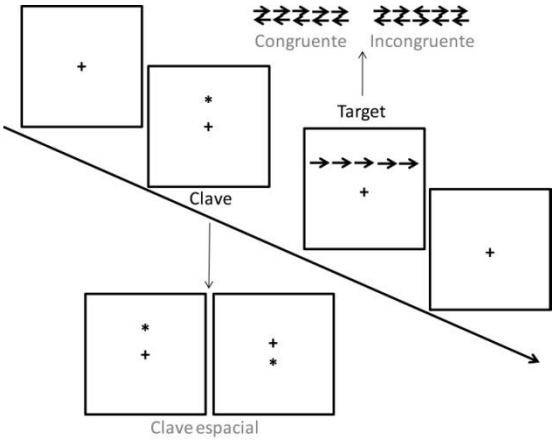
Variables e Instrumentos

- **Calidad subjetiva de sueño**
  PSQI
- **Intensidad del dolor**
  MGPQ
- **Niveles de fatiga**
  Inventario Multidimensional de Fatiga
- **Funcionamiento Diario**
  Cuestionario de Impacto de la Fibromialgia [FIQ]
- **Autoeficacia**
  Escala de Autoeficacia para el Dolor Crónico
- **Catastrofización del dolor**
  Escala de Catastrofización del Dolor
- **Niveles de ansiedad y depresión**
  Cuestionario 90 Síntomas

Principales resultados

El grupo de TCC-I mejoró la calidad de sueño, la fatiga, el funcionamiento diario, los niveles de Catastrofización y de ansiedad y depresión.

ESTUDIO 5
¿Es el tratamiento cognitivo-conductual para el insomnio efectivo para mejorar la función atencional?



Participantes

- 44 mujeres con fibromialgia
  - 22 TCC/I
  - 22 Higiene sueño

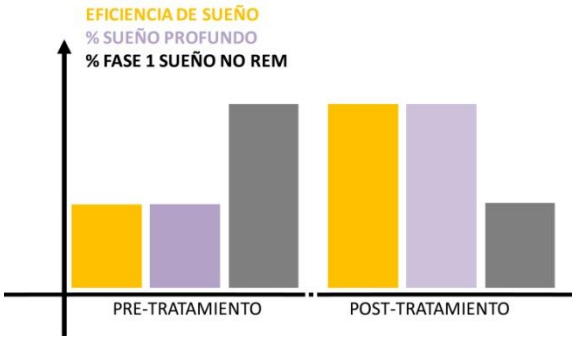
Variables e Instrumentos

- **Calidad subjetiva de sueño**
  PSQI
- **Intensidad del dolor**
  MGPQ
- **Funcionamiento Diario**
  FIQ
- **Niveles de ansiedad y depresión**
  HADS

Principales resultados

El grupo de TCC-I mejoraba los índices de alerta y función ejecutiva, una mejora que se relacionaba con la mejora de la calidad de sueño.

ESTUDIO 6
¿Es el tratamiento cognitivo-conductual para el insomnio efectivo para mejorar parámetros polisomnográficos?



Participantes

- 26 mujeres con fibromialgia
  - 13 TCC/I
  - 13 Higiene sueño

Variables e Instrumentos

- **Parámetros polisomnográficos**
  Polisomnografía ambulatoria

Principales resultados

El grupo de TCC-I disminuyó

- el tiempo en cama,
- el porcentaje de tiempo en vigilia
- el porcentaje de tiempo en fase 1 del sueño no-REM

y aumentó

- su eficiencia de sueño
- el tiempo de sueño profundo.

INTRODUCCIÓN

Dolor crónico

El dolor es uno de los síntomas más comunes de enfermedad o daño que lleva a las personas a buscar atención médica (Pearce y McDonald, 1998; Sauver et al., 2013). Aunque es un fenómeno muy frecuente, esta experiencia y su definición es, cuando menos, compleja y controvertida. La definición de dolor más aceptada es la propuesta por la *International Association for the Study of Pain*, que lo define como una "experiencia sensorial y emocional desagradable asociada a un daño tisular, potencial o actual, o que se describe en términos de dicho daño" (Merskey y Bogduk, 2011). Esta definición del dolor captura dos elementos que son fundamentales para comprender los desarrollos teóricos existentes acerca de la naturaleza del dolor. Por una parte, se entiende que el dolor es el resultado perceptivo de la aplicación de un estímulo nocivo.[1] Por otra, queda claro que la relevancia del dolor viene de la experiencia subjetiva, es decir, de la evaluación que realiza la persona que sufre acerca de la experiencia de dolor, incluyendo cuál es su origen y si puede o no controlarlo, entre otros. El dolor puede ser clasificado atendiendo a varias dimensiones, cada una de las cuales incluye diferentes tipos de dolor. Por ejemplo, existen clasificaciones según su etiología, según su localización o regiones afectadas, o en base al patrón de ocurrencia de los episodios de dolor.

Entre esas dimensiones, también se encuentra la cronicidad. En contraposición al dolor agudo, el dolor crónico se ha definido como "aquel dolor que persiste más allá del periodo habitual de curación (usualmente, tres meses) y cuyo valor biológico es discutible" (Ospina y Harstall, 2002). Esta definición no sólo incluye la evidente dimensión temporal (más o menos arbitraria), referida al tiempo transcurrido desde el comienzo del dolor, sino que tiene en cuenta la "adecuación" de la experiencia de dolor. Es decir, el dolor agudo, en general, posee un valor adaptativo, ya que señala la posible existencia de un daño. Sin embargo, el dolor crónico es un trastorno en sí mismo, en

[1] Esta definición, aunque ampliamente aceptada, obvia la existencia de lo que se ha llamado "dolor patológico" o de origen central (Møller, 2012). Existen diversas clases de dolor patológico, todas ellas causadas por cambios en la función del sistema nervioso central y que ocurren sin la existencia de estimulación de los nociceptores. El dolor patológico es muy relevante en los síndromes de dolor crónico.

donde el dolor debe ser interpretado como una experiencia multidimensional, sensorial y emocional que es diferente del proceso fisiológico puramente nociceptivo del dolor agudo (Flor, 2001). Los síndromes de dolor crónico son muy frecuentes en la población general (Croft, Rigby, Boswell, Schollum y Silman, 1993; Papageorgiou, Silman y Macfarlane, 2002). Dependiendo de la definición utilizada y de los grupos de población evaluados, la prevalencia del dolor crónico oscila entre un 10 y un 55% (Harstall y Ospina, 2003). Además, las consecuencias negativas de sufrir dolor crónico son muy acusadas a nivel psicológico y físico, lo cual disminuye la calidad de vida de estas personas (Kroenke et al., 2013). Esto, sumado a su elevada prevalencia, origina unos gastos sanitarios extremadamente elevados. Verhaak y colaboradores (1998) estimaron unos gastos a nivel mundial que rondarían los 40.000 millones de dólares anuales.

Fibromialgia

Un caso particular entre los síndromes de dolor crónico es la fibromialgia, un síndrome que ha recibido cada vez más atención por parte de clínicos e investigadores (Merayo Alonso, Cano García, Rodríguez Franco, Ariza Ariza y Navarro Sarabia, 2007), sobre todo a partir de los primeros criterios para su diagnóstico a mediados de los años setenta (Smith y Moldofsky, 1977). Descripciones acerca de dolores generalizados en el sistema músculo-esquelético pueden encontrarse en tratados médicos europeos a partir del siglo XVI utilizando diferentes términos como son "reumatismo muscular", "fibrositis" o "reumatismo psicogénico" (para una revisión ver Inanici y Yunus, 2004 o Marson y Pasero, 2008). Sin embargo, no fue hasta la década de los noventa cuando se consensuaron los criterios de clasificación de la fibromialgia, publicados por el *American College of Rheumatology* en 1990 y revisados en 2011 (Wolfe et al., 1990; 2011). En su versión inicial, estos criterios se basaron en aquellas características clínicas que mostraban mayor sensibilidad y especificidad en el diagnóstico de fibromialgia. Ello incluía la combinación de dolor generalizado y dolor en once o más puntos sensibles del cuerpo. En la práctica clínica habitual, este síndrome se diagnostica en aquellas personas con dolor crónico generalizado para el que es imposible identificar una causa alternativa (Sommer, 2010). De hecho, dado que el diagnóstico clínico frecuentemente presenta discordancias con respecto a los criterios establecidos (Katz, Wolfe y Michaud, 2006), en la última revisión, los criterios diagnósticos no otorgan tanto peso a la presencia de dolor en puntos sensibles y sí a toda una miríada de síntomas que ocurren de forma comórbida al dolor. Entre estos están la fatiga, los

problemas de sueño, las parestesias y otros síndromes asociados, como cefalea tensional o síndrome del intestino irritable. La fibromialgia es una condición clínica muy prevalente en la población adulta en general, aunque afecta sobre todo a las mujeres, y conlleva un gran impacto en el funcionamiento diario de las personas que lo sufren (Birtane, Uzunca, Tastekin y Tuna, 2007; Branco et al., 2010; Lindell, Bergman, Petersson, Jacobsson y Herrström, 2000; Wolfe et al., 1995). En España, se estima que un 2,4% de la población general mayor de 20 años padece fibromialgia (Rivera et al., 2006). Entre la variedad de síntomas que tienen repercusiones sobre las actividades de la vida diaria, los síntomas evaluados como más graves por los pacientes son la rigidez matutina, la fatiga, el dolor y los problemas de sueño (Bennett, Jones, Turk, Russell y Matallana, 2007; Rutledge, Mouttapa y Wood, 2009). En particular, la duración del sueño y la calidad del sueño jugarían un papel central en el funcionamiento diario de las personas con fibromialgia, por su relación directa con el estado de ánimo, las funciones neuropsicológicas e, incluso, el propio dolor. A su vez, estos problemas perjudican las relaciones sociales y la participación en actividades de promoción de la salud (Affleck et al., 1998; Hamilton et al., 2008).

La etiología del síndrome de fibromialgia es aún desconocida. Ello, junto con la dificultad de encontrar signos físicos comunes a los pacientes con fibromialgia, hace que, actualmente, el diagnóstico siga realizándose en base al juicio clínico de reumatólogos y otros especialistas. Este juicio clínico se basa, principalmente, en la existencia concomitante de dolor y otros síntomas habituales, como problemas de sueño, fatiga, rigidez o distrés emocional. Sin embargo, en los últimos años, están bajo estudio toda una serie de manifestaciones pato-fisiológicas que sugieren la existencia de alteraciones en la fisiología del Sistema Nervioso Central (SNC) en pacientes con fibromialgia. Estas alteraciones darían lugar a distintos procesos de sensibilización central, fundamentales en los síndromes de dolor crónico. De confirmarse, esto facilitaría el diagnóstico de fibromialgia.

Fibromialgia como síndrome de dolor central

Los síntomas de la fibromialgia también pueden estar presentes en toda una serie de síndromes de dolor crónico y de sensibilidad alterada. Diversos autores han señalado la existencia de solapamientos entre los síntomas de varios síndromes (ver Figura 1), lo que implica que los pacientes cumplirían los criterios diagnósticos de varios de ellos

(Aaron y Buchwald, 2001). El mayor solapamiento entre estos síndromes tiene que ver con alteraciones en el procesamiento sensorial y del dolor. Así, en numerosos estudios experimentales se ha mostrado como, aunque estos pacientes no detecten estímulos eléctricos, termales o mecánicos con menores niveles de intensidad, el umbral al que esos estímulos son desagradables o causan dolor sí es más bajo (Gracely, Petzke, Wolf y Clauw, 2002). Estas alteraciones tendrían un origen central, ya que, en particular en la fibromialgia, no se ha podido comprobar la existencia de alteraciones periféricas en estos pacientes (Dadabhoy y Clauw, 2006).

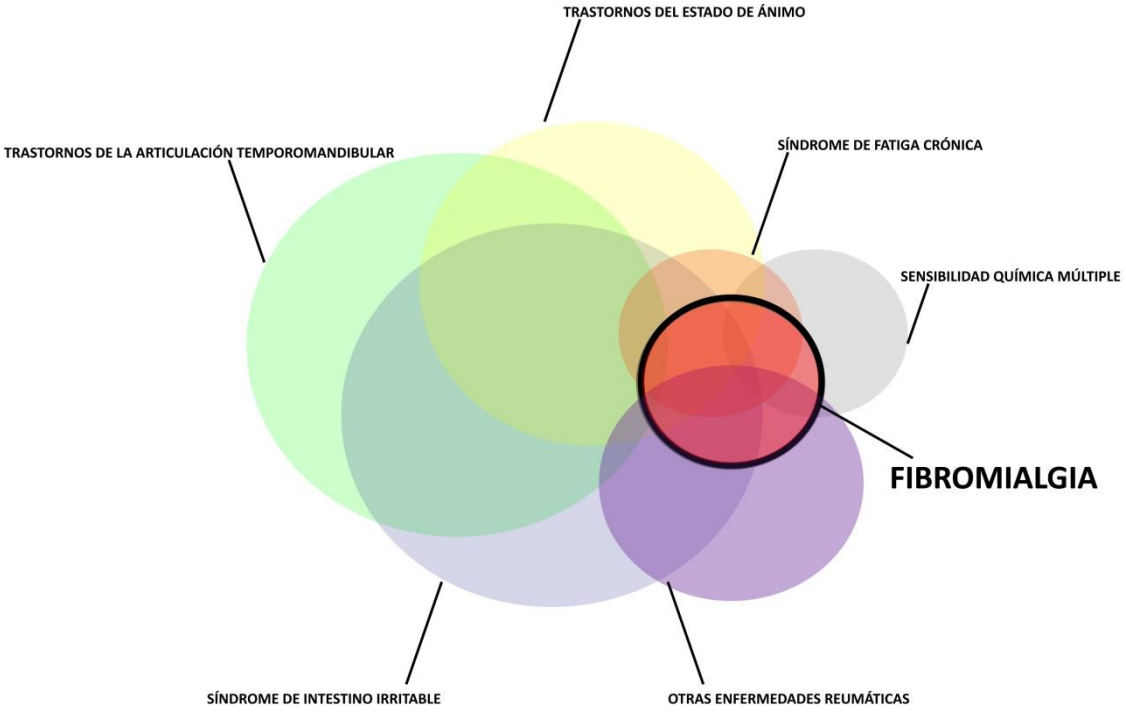


Figura 1- Ejemplos de condiciones clínicas que presentan solapamiento de síntomas con la fibromialgia, muchas de ellas caracterizadas por alteraciones a nivel central. El tamaño de cada círculo representa aproximadamente la prevalencia del trastorno correspondiente, siendo la prevalencia de la fibromialgia de alrededor del 4,7% en la población general (Branco et al., 2010) (adaptado de Dadabhoy y Clauw, 2006).

Patofisiología cerebral en pacientes con fibromialgia

Diversos estudios sugieren ciertas alteraciones en la fisiología del SNC como base de los síntomas de la fibromialgia (para una revisión ver Schweinhardt, Sauro y Bushnell, 2008). Por un lado, están los hallazgos psicofísicos que se basan en los informes subjetivos de intensidad de dolor. Los pacientes con fibromialgia sentirían mayor dolor ante la aplicación de diferentes estímulos nocivos (Petzke, Clauw, Khine y Gracely, 2000; Staud, Vierck, Cannon, Mauderli y Price, 2001) y presentarían alteraciones en ciertos fenómenos relacionados con la percepción del dolor, como la sumación temporal

o el control inhibitorio difuso (Staud, 2012). Por otro lado, se ha encontrado un aumento de la actividad cerebral en el procesamiento del dolor durante pruebas psicofísicas (Maestu et al., 2013), así como alteraciones cerebrales específicas del síndrome que podrían contribuir a mantener y magnificar la experiencia de dolor en los pacientes con fibromialgia. Entre estas alteraciones están la hipoperfusión e hiperperfusión en ciertas regiones del cerebro (Usui et al., 2010), las disfunciones en los sistemas de neurotransmisores (Becker y Schweinhardt, 2011) y ciertos cambios estructurales en el cerebro (ver más abajo). Especialmente interesantes son los hallazgos sobre cambios cerebrales de tipo estructural en pacientes con dolor crónico, ya que estos sugieren cierta neuroplasticidad en áreas relacionadas con la nocicepción.

Neuroplasticidad en el contexto del dolor crónico

El dolor crónico puede ser considerado el resultado de una neuroplasticidad desadaptativa (May, 2008). Cualquier reto suficientemente significativo, que requiera una función específica, tiene el potencial de alterar la estructura cerebral (Draganski y May, 2008). Así, si la cronificación del dolor es entendida como la consecuencia del procesamiento de los estímulos nociceptivos, además de la respuesta conductual hacia dichos estímulos, es de esperar que ocurran cambios estructurales y funcionales en áreas de la red cerebral del dolor.

Técnicas de neuroimagen estructural

Hasta hace unas décadas, el estudio de la estructura cerebral se venía realizando *post mortem* a través de la conducción de autopsias. El reciente desarrollo técnológico en las técnicas de neuroimagen, especialmente en la imaginería por resonancia magnética, ha permitido la caracterización de la neuroanatomía *in vivo*. Estas técnicas permiten conocer tanto las diferencias macroscópicas en la estructura cerebral, como la composición más localizada del tejido cerebral, una vez que esas diferencias macroscópicas se han eliminado. Estas últimas técnicas incluyen la morfometría basada en voxels (VBM, por sus siglas en inglés). Dicha técnica consiste en la comparación de cerebros voxel por voxel. Esto proporciona una mayor sensibilidad para localizar pequeñas diferencias tanto de materia cerebral gris como blanca, en ciertas regiones cerebrales.

Cambios cerebrales estructurales en fibromialgia

Las evidencias actuales sugieren la existencia de cambios en la anatomía cerebral en pacientes con fibromialgia, principalmente relacionados con la disminución del volumen de materia gris. Dicho decremento aumenta con el número de años de padecimiento de la enfermedad, y parece ser siempre mayor que en personas sanas de cualquier edad (Kuchinad et al., 2007). Además, las reducciones de materia gris ocurren en regiones ostensiblemente involucradas bien en la percepción del dolor, en ciertas disfunciones neuropsicológicas o en las respuestas de estrés (Burgmer et al., 2009; Schmidt-Wilcke et al., 2007; Wood, Glabus, Simpson y Patterson, 2009).

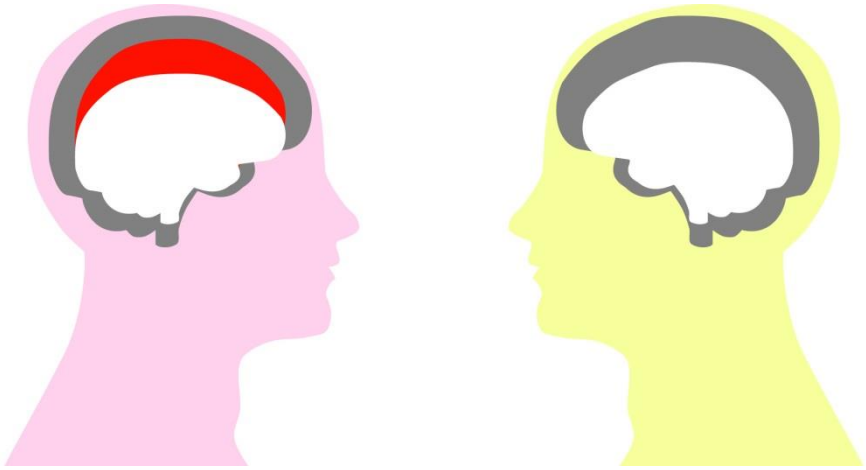


Figura 2- Representación de los cambios de volumen cerebral en pacientes con fibromialgia. En pacientes con fibromialgia (representados en la imagen de la izquierda) se han observado incrementos y decrementos, tanto globales como localizados, de materia gris cerebral como consecuencia de la plasticidad cerebral en respuesta al dolor crónico y otros síntomas.

Relaciones entre sueño y dolor

Las alteraciones del sueño son frecuentes en los pacientes con algún síndrome de dolor crónico. Se estima que entre el cincuenta y el noventa por ciento de estos pacientes se quejan de mala calidad de sueño (Smith, Perlis, Smith, Giles y Carmody, 2000). En el caso concreto de la fibromialgia, este porcentaje es aún mayor. En los estudios epidemiológicos se muestra que el sueño no reparador es un componente fundamental del síndrome, ya que el noventa y nueve por ciento de estos pacientes informan de una mala calidad de sueño (Hamilton et al., 2008; Theadom, Cropley y Humphrey, 2007). Cuando dolor crónico y problemas de sueño ocurren de forma comórbida, el impacto sobre la salud y el sufrimiento de estas personas se magnifica. Las alteraciones de la fisiología del sueño en personas con dolor crónico no sólo dan lugar a quejas de mala calidad de sueño, sino que contribuyen a un círculo vicioso de sueño no reparador,

dolor, rigidez y fatiga durante el día (Affleck, Urrows, Tennen, Higgins y Abeles, 1996; Moldofsky, 2008).

La interrelación entre sueño y dolor se ha analizado desde diferentes perspectivas. En general, se puede afirmar que los estudios experimentales han confirmado que la disrupción del sueño tiene un impacto directo sobre los procesos nociceptivos (Chhangani et al., 2009; Lautenbacher, Kundermann y Krieg, 2006; Onen, Alloui, Gross, Eschallier y Dubray, 2001; Roehrs, Hyde, Blaisdell, Greenwald y Roth, 2006), mientras que una mayor duración del sueño se relaciona con una menor sensibilidad para el dolor (Roehrs, Harris, Randall, y Roth, 2012). Por su parte, la estimulación dolorosa durante el sueño provoca cambios en la microestructura del sueño (Drewes, Nielsen, Arendt-Nielsen, Birket-Smith y Hansen, 1997; Lavigne et al., 2000). En investigación clínica, gran parte de ésta realizada en personas diagnosticadas con fibromialgia, se han hallado asociaciones entre los problemas de sueño y un aumento de la intensidad del dolor (Roizenblatt, Moldofsky, Benedito-Silva y Tufik, 2001; Smith et al., 2000). Estos estudios concluyen que el dolor impacta de manera negativa sobre el sueño tanto a corto (Affleck et al., 1996) como a largo plazo (Drewes et al., 2000). Además, se ha propuesto que las relaciones que se establecen en el caso del dolor crónico serían de tipo bidireccional (Edwards, Almeida, Klick, Haythornthwaite y Smith, 2008) y estarían mediadas por diversos factores psicológicos (O'Brien et al., 2010). Una aproximación interesante sugiere que el sueño podría funcionar como un recurso fisiológico y conductual para un funcionamiento óptimo de las personas con dolor crónico, así como un moderador de las respuestas cognitivas y emocionales al estrés y al dolor. Los problemas de sueño no sólo serían el resultado del estrés provocado por sufrir dolor crónico, sino que podrían tener un papel determinante en la salud de estas personas, ya que limitarían los recursos personales para gestionar el dolor y el estrés asociado al sufrimiento de esta condición crónica (Hamilton, Catley, & Karlson, 2007; Hamilton et al., 2008).

La evaluación de los problemas de sueño

Resulta evidente, por tanto, que la relación entre el dolor crónico y el sueño es de elevada relevancia clínica, especialmente en personas que sufren de fibromialgia, ya que los problemas de sueño contribuirían tanto al origen como al mantenimiento de la sintomatología fibromiálgica (Affleck et al., 1996; Nicassio, Moxham, Schuman y

Gervirtz, 2002). La polisomnografía, considerada como el *gold standard* en la evaluación del sueño, es una herramienta muy útil para conocer la fisiología del ciclo sueño-vigilia de manera objetiva en las pacientes con fibromialgia. Sin embargo, en la actualidad muy pocos estudios sobre fibromialgia incorporan esta herramienta, sino que se centran en medidas de autoinforme. Esto ha condicionado, sin duda, el tipo de conclusiones que pueden extraerse al respecto, ya que las medidas objetivas y subjetivas evalúan aspectos diferentes de la experiencia de sueño. Las medidas subjetivas reflejan la vivencia personal y no indican los síntomas de forma tan precisa como las medidas objetivas (Krystal y Edinger, 2008).

El tratamiento de los problemas de sueño en fibromialgia

El tratamiento de los problemas de sueño podría romper el círculo vicioso de sueño no reparador, dolor, rigidez y fatiga antes comentado (Edinger, Wohlgemuth, Krystal y Rice, 2005). No obstante, el número de estudios centrados en el cambio de los patrones de sueño para mejorar éstos y otros síntomas en pacientes con fibromialgia es muy reducido. Ciertas investigaciones sobre la efectividad de la terapia cognitivo-conductual para el insomnio presentan hallazgos muy prometedores al respecto, aunque su interpretación requiere tener en cuenta que la evaluación de dicha efectividad se ha limitado al análisis de autoinformes de los pacientes únicamente (Currie, Wilson, Pontefract y deLaplante, 2000; Edinger et al., 2005; Jungquist et al., 2010, 2012).

OBJETIVOS

La presente tesis se ha planteado para intentar dar respuesta a varios de los interrogantes actuales acerca de las interrelaciones que se dan entre el sueño y el dolor en pacientes con fibromialgia, intentando superar ciertas limitaciones habituales en este tipo de estudios (asociadas principalmente a una evaluación inadecuada del sueño).

En primer lugar, ¿qué evidencias hay de que existan alteraciones específicas del sueño en fibromialgia? ¿Qué papel tienen estas alteraciones del sueño en la clínica del síndrome? Para ello, se realizó una investigación sistemática de estudios empíricos sobre sueño en mujeres con fibromialgia y se planteó una investigación clínica transversal con dos estudios. Por un lado, se comparó a una muestra clínica con una muestra control en calidad de sueño subjetiva y parámetros polisomnográficos. Por otro lado, se evaluaron las relaciones entre el dolor, el sueño y los niveles de ansiedad y depresión.

En segundo lugar, dado que las características de la fibromialgia podrían ser explicadas por ciertas alteraciones del sistema nervioso central, ¿qué evidencias hay de que existen cambios estructurales en el cerebro de personas con fibromialgia? ¿Con qué síntomas se relacionan estos cambios cerebrales? Para ello, se planteó una investigación clínica transversal con un estudio en el que se comparó el volumen de materia gris en una muestra clínica de mujeres con fibromialgia y un grupo de mujeres control.

En tercer lugar, si los problemas de sueño son uno de los factores que mantienen y agravan los síntomas en las personas con fibromialgia, estos problemas de sueño tendrían que ser uno de los principales objetivos terapéuticos. Por lo tanto, ¿qué evidencias hay de que una intervención cognitivo-conductual para el insomnio (TCC-I) mejore, no sólo la calidad de sueño, sino también disminuya la intensidad de dolor, el distrés emocional, otras variables psicopatológicas y ciertas funciones neuropsicológicas? Para ello, se planteó un ensayo clínico aleatorizado en el que se aplicó TCC-I y un programa de higiene de sueño a sendos grupo de mujeres con fibromialgia y se evaluó su efectividad diferencial para mejorar los parámetros subjetivos y objetivos de sueño, su impacto sobre el dolor y otras variables psicológicas.

REVISIÓN TEÓRICA

Sleep disturbances of adult women suffering from fibromyalgia: a systematic review of observational studies[1]

Abstract

Fibromyalgia syndrome (FMS) is a rheumatologic disorder characterized by chronic widespread pain and multiple tender points, often accompanied by non-specific symptoms that include sleep difficulties. Even though sleep complaints are often reported, there is no conclusive evidence that these complaints represent symptomatic disorders of sleep physiology. Thus, the question of the role of sleep disturbances as an etiological or maintenance factor in FMS remains open. Here we wanted to identify the characteristics of sleep disturbances in adult women diagnosed with FMS; and to outline the relationships between subjective and objective measures of sleep as well as between these sleep outcomes and other clinical variables in FMS. Methods: We carried out a systematic review of English and non-English publications –since 1990. Bibliographic and grey literature electronic databases were used as literature's source. We selected empirical studies concerning sleep characteristics of adult women diagnosed with FMS, compared with healthy women or female patients diagnosed with other rheumatic disease. Results: Thirty-nine articles were identified: 21 articles had as main objective to compare sleep behavior between FMS and comparison groups. Most these articles (15) lacked methodological rigor, however. Patients with FMS exhibited more often sleep symptoms. The evidence on objective measures of sleep is mixed and inconsistent, however. Discussion: Current evidence cannot confirm the role plays by sleep physiology in the pathogenesis or maintenance of FMS symptoms; however, it is clear that sleep disturbances are present in this syndrome.

Keywords: Actigraphy; Chronic pain; Fibromyalgia; Polysomnography; Sleep

[1] **Diaz-Piedra, C.**, Buela-Casal, G., & Catena, A. (under review). Sleep disturbances of adult women suffering from fibromyalgia: a systematic review of observational studies. *Sleep Medicine Reviews* (manuscript under review). (Invited review).

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Introduction

Fibromyalgia syndrome (FMS) is characterized by chronic widespread musculoskeletal pain and multiple tender points (Wolfe et al., 1990, 2011). The prevalence rate of FMS in general population ranges between 1.3-4.7%, being higher common among middle-age and elder women (Branco et al., 2010; Lindell, Bergman, Petersson, Jacobsson, & Herrström, 2000; Wolfe et al., 1995). The syndrome has a severe impact on health systems due to the frequent use of healthcare providers and its elevated treatments' costs (Lachaine, Beauchemin, & Landry, 2010): recent simulations estimated that the costs for managing care of patients with FMS have a combined value up to $10 K per patient per year (Wagner, Chandran, DiBonaventura, & Cappelleri, 2012). Further, approximately one quarter of all patients receives disability payments (Wolfe et al., 1997). Fibromyalgia also has a great impact on patients' and their relatives' quality of life (Birtane, Uzunca, Tastekin, &Tuna, 2007), being a significant source of suffering (Turk, 2002).

The experience of diffuse pain is associated with a large number of symptoms and comorbidities (Wolfe et al., 2010), e.g. sleep disturbances, fatigue, headache and migraine, neuropathic disorders, anxiety and/or depression disorders (Lachaine et al., 2010; Rutledge, Mouttapa, & Wood, 2009). Sleep disturbance is one of the most common and relevant symptom in FMS (Rutledge, Jones, & Jones, 2007). Experimental and clinical studies have shown the complex relationship existing between sleep and pain, where pain can disrupt sleep and, as the same time, sleep deprivation enhances pain sensibility (Smith & Haythornwaite, 2004). The so called *vicious cycle* clearly explain this incapacitating condition: a day with intense pain is followed by a night of poor sleep quality and a poor night's sleep is followed by a reduction of pain perception threshold -i.e. an increment in pain intensity (Affleck, Urrows, Tennen, Higgins, & Abeles, 1996). It is also known that the above-mentioned symptoms (psychological distress, fatigue, etc.) are, *per se*, related to sleep disturbances (e.g. Nicassio, Moxham, Schuman, & Gevirtz, 2002). Thus, the early recognition and management of sleep disturbances in FMS patients might help to ameliorate morbidity in this syndrome (Korszun et al., 2002). Moreover, the study of sleep physiology and sleep behavior in these specific patients might improve the explanatory power of models that try to relate the etiology of FMS to sleep disturbance (Bennett, 1989; Hamilton, Atchley, Karlson,

Taylor, & McCurdy, 2012; Moldofsky, Scarisbrick, England, & Smythe, 1975, Moldofsky, 2008).

Since the pioneering polysomnographic investigations -in patients with *fibrositis*- (e.g., Moldofsky et al., 1975), several physiological studies have tried to define FMS in terms of the electroencephalographic (EEG) sleep activity. Unfortunately, current findings are inconsistent yet. Population-based studies found that subjective poor sleep quality was reported by 99% of patients with FMS (Hamilton et al., 2008; Theadom, Cropley, & Humphrey, 2007). Regardless subjective-based findings, the presence of specific FMS-EEG sleep patterns is not clear. Several studies have found sleep architecture and microstructure abnormalities in FMS, as well as higher prevalence of different sleep disorders (e.g. sleep apnea, restless leg syndrome, or periodic limb movement syndrome) (see Moldofsky, 2001, 2008). However, to date, polysomnographic results are inconsistent (e.g., Besteiro et al., 2011; Roizenblatt, Moldofsky, Benedito-Silva, & Tufik, 2001; but see Roehrs et al., 2013). Thus, despite the efforts, subjective-based findings have not been yet objectively validated.

Here -by reviewing the literature on FMS and sleep of the last two decades- we wanted to determine the characteristics of sleep disturbances in adult women diagnosed with FMS and to define the relationship between subjective and objective measurements of sleep as well as between these sleep outcomes and other clinical variables (e.g., pain, depression, anxiety,…).

Methods

Study eligibility criteria

We followed specific inclusion criteria to select the articles analyzed in this review: (1) participants: adult women primary diagnosed with FMS, according the American College of Rheumatology (ACR) fibromyalgia classification criteria (Wolfe et al., 1990) (see Figure 3); (2) study design: observational designs (i.e. case-control studies); (3) comparisons: healthy women or female patients with other chronic rheumatic diseases; (4) reported measured outcomes: a) subjective and objective sleep parameters (considered as main outcome measurements); b) pain intensity, anxiety, and depression levels (considered as secondary outcome measurements).

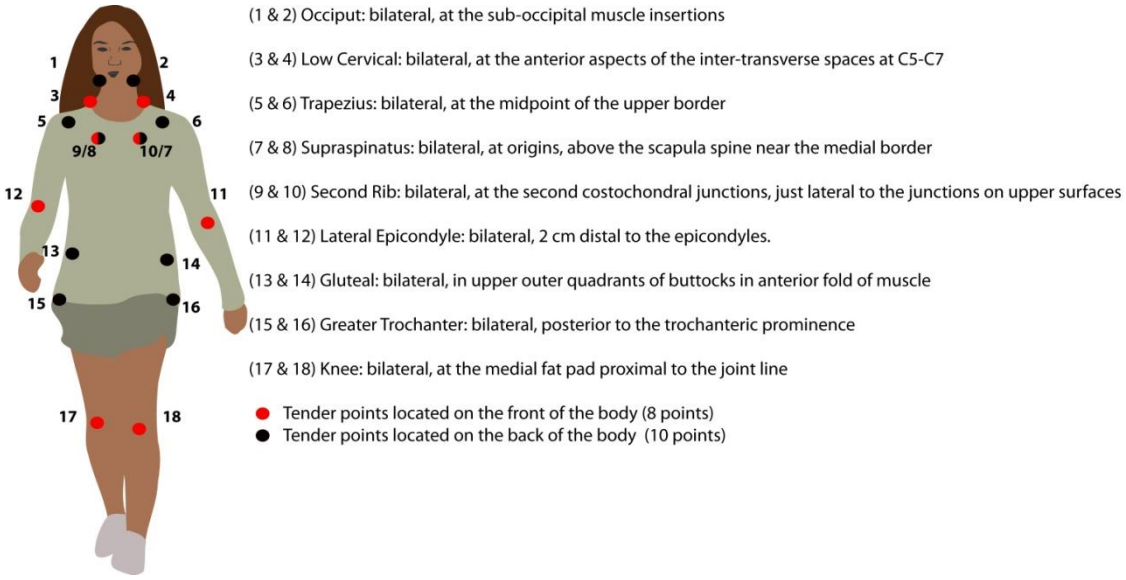


Figure 3- Usual tender point locations in fibromyalgia syndrome (FMS). The American College of Rheumatology (ACR) classification criteria (Wolfe et al., 1990) are the most widely used guidelines for making a diagnosis of FMS. These criteria required the presence of widespread pain in, at least, three out four body quadrants, in combination with eleven (or more) out of eighteen specific tender point. Although these criteria have helped the recognition of the FMS, since their development, the research about the underlying pathology of the syndrome has progressed significantly and the need for new criteria has been raised. Recently, the 2010 ACR criteria for FMS (Wolfe et al., 2010, 2011) have been introduced. They recognize the role of other non-specific symptoms in the severity of the FMS. Furthermore they simplify the diagnosis, making the criteria suitable for primary care practice use (i.e. without requiring a tender point examination).

Search methods

We conducted a deeply search of the relevant peer reviewed articles by using four electronic bibliographic databases: SCOPUS, PsycINFO, Medline, and Lilacs/Ibecs. We included English and non-English (Spanish, Portuguese, and Italian) scientific literature since 1990 (publication year of the ACR Criteria for the Classification of FMS [Wolfe et al., 1990]) to September, 2013. Search terms were: "fibromyalgia", "sleep*", "polysomnography", "PSG", "actigraphy", "AKT". The complete search algorithm with the keywords for each database is displayed in Appendix 1. To identify additional studies -not found in the electronic search- we also conducted a manual search of the bibliographies of each retrieved article. Additionally, we examined relevant grey literature (thesis and reports) by using two online databases: OpenGrey and OAIster.

Data collection and analysis

Selection of studies

Initially, two independent reviewers (MGG, MIM -both expert sleep researchers) initially screened title and abstract of the retrieved articles for relevance. Articles included by either reviewer were considered potentially relevant and eligible for full text screening. Then, a discussion about the inclusion criteria - for each article- follows. This process continued until both reviewers reached a consensus. Finally, a third sleep researcher (CDP) examined all the articles included from each database to ensure that the selected works fulfilled the study and report eligibility criteria. For those citations fulfilling the inclusion criteria or for which inclusion or exclusion could not be ascertained, two researchers (CDP, MIM) independently reviewed the full texts. Figure 4 shows a detailed outline of the study selection process.

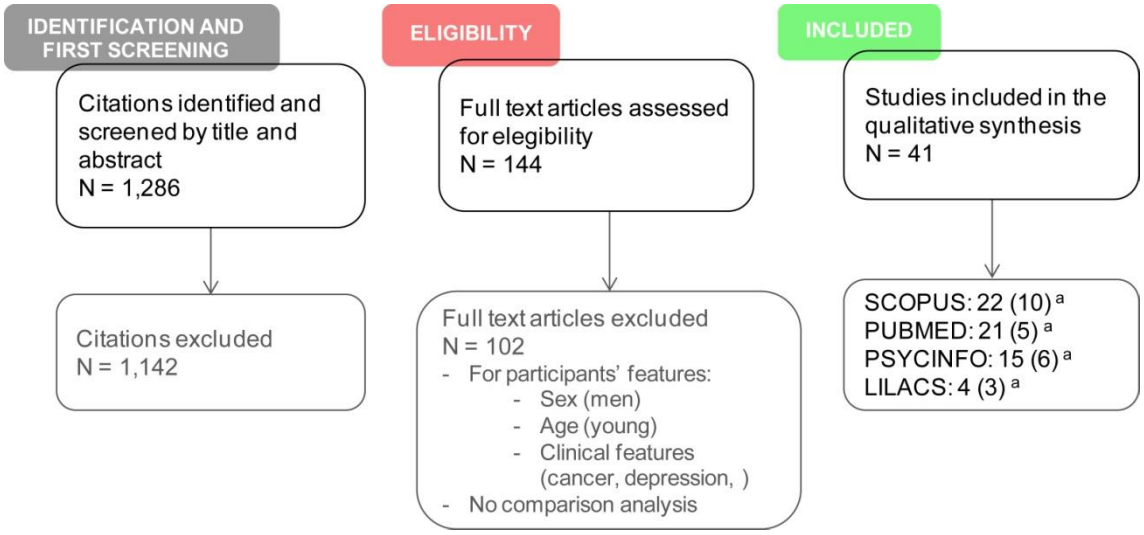


Figure 4- Systematic review flowchart.

[a] Numbers in brackets are number of articles that appear only in the respective database.

Data extraction and management

We assessed the selected articles using a standardized form which included: data regarding to authors, date of publication, objective, research design, participants, measurement instruments, outcomes, and results. Then, we grouped the selected articles according their main aim: a) to compare sleep variables (henceforth, *Objective 1*) or b) to compare another health outcome -being sleep variables included in the assessment

only to characterize participants' status or symptoms- (henceforth, *Objective 2*). Please, see Appendices 2 and 3 with *Data extraction results for included studies* with *Objective 1* and *Objective 2*, respectively.

Quality assessment and strength of evidence

We assessed the methodological quality of the studies whose principal objective was to compare sleep variables between patients with FMS and comparison group (i.e. *Objective 1*), by using an adaptation of the Effective Public Health Practice Project's (EPHPP) tool (Deeks et al., 2003). This tool is based on guidelines set out by Mulrow, Cook, and Davidoff (1997) and Jadad and colleagues (1996) and includes the following items: selection of participants and allocation bias, blinding, confounders, data collection methods, and withdrawals and dropouts. The adaptations consisted in minor changes regarding several item descriptions in confounders, so that we could assess observational studies. Each item was rated as strong, moderate, or weak, depending of the reported characteristics of every study. A global rating for each study was obtained (see Appendix 4 with *Quality assessment tool for included studies*).

Results

From a total of 1,286 retrieved articles, 144 titles and abstracts were identified as potentially relevant. After excluding duplicate records and the full text screening, 41 articles fulfilled the inclusion criteria to be included in the review. Finally, 39 articles were reviewed -2 articles were translations from Portuguese to English.

Research designs

Twenty-one articles (53.8%) were grouped under the aims of *Objective 1*; the others 18 articles (46.1%) were grouped under the aims of *Objective 2* (see Table 1).

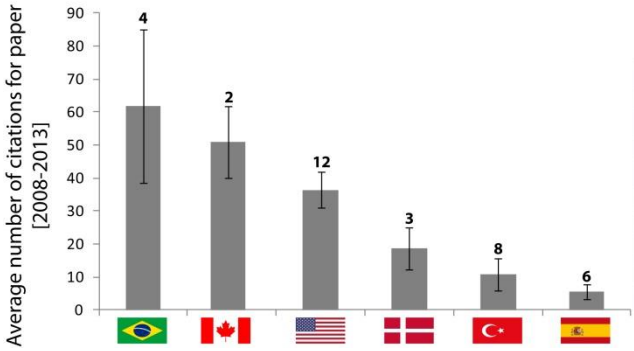
Table 1- Summary of reviewed articles.

OBJECTIVE 1 (N = 21)			
Authors, year	Article title	Country	Assessment tool
Besteiro et al., 2011	Sleep architecture in patients with fibromyalgia. *(Cit.= 2)*	Spain	PSG
Burns, Crofford, & Chervin, 2008	Sleep stage dynamics in fibromyalgia patients and controls. *(Cit.= 36)*	US	PSG
Chervin et al., 2009	Objective measures of disordered sleep in fibromyalgia. *(Cit.= 33)*	US	PSG
Côté & Moldofsky, 1997	Sleep, daytime symptoms, and cognitive performance in patients with fibromyalgia. *(Cit.= 122)*	Canada	PSG
Drewes et al., 1995a	Clustering of sleep electroencephalographic patterns in patients with the fibromyalgia syndrome. *(Cit.= 80)*	Denmark	PSG
Drewes et al., 1995b	Sleep intensity in fibromyalgia: focus on the microstructure of the sleep process. *(Cit.= 85)*	Denmark	PSG
Drewes, Svendsen, Nielsen, Taagholt, & Bjerregård, 1994	Quantification of alpha-EEG activity during sleep in fibromyalgia: a study based on ambulatory sleep monitoring. *(Cit.= 18)*	Denmark	PSG
Korszun et al., 2002	Use of actigraphy for monitoring sleep and activity levels in patients with fibromyalgia and depression. *(Cit.= 73)*	US	AKT
Landis et al., 2003	Self-reported sleep quality and fatigue correlates with actigraphy in midlife women with fibromyalgia. *(Cit.= 53)*	US	AKT
Landis, Lentz, Rothermel, Buchwald, & Shaver, 2004	Decreased sleep spindles and spindle activity in midlife women with fibromyalgia and pain. *(Cit.= 72)*	US	PSG
Landis et al., 2001	Decreased nocturnal levels of prolactin and growth hormone in women with fibromyalgia. *(Cit.= 62)*	US	PSG
Landis, Lentz, Tsuji, Buchwald, & Shaver, 2004	Pain, psychological variables, sleep quality, and natural killer cell activity in midlife women with and without fibromyalgia. *(Cit.= 53)*	US	PSG
Lario et al., 1996	Fibromyalgia syndrome: overnight falls in arterial oxygen saturation. *(Cit.= 46)*	Spain	Self-reports/PSG
Miró, Martínez, Sánchez, Prados, & Diener, 2012	[The role of dysfunctional beliefs in self-reported poor sleep quality in fibromyalgia patients]. *(Cit.= 0)*	Spain	Self-reports
Miró, Martínez, Sánchez, Prados, & Medina, 2011	When is pain related to emotional distress and daily functioning in fibromyalgia syndrome? The mediating roles of self-efficacy and sleep quality. *(Cit.= 14)*	Spain	Self-reports
Munguía-Izquierdo & Legaz-Arrese, 2012	Determinants of sleep quality in middle-aged women with fibromyalgia syndrome. *(Cit.= 4)*	Spain	Self-reports
Osorio, Gallinaro, Lorenzi-Filho, & Lage, 2006	Sleep quality in patients with fibromyalgia using the Pittsburgh Sleep Quality Index. *(Cit.= 55)*	Brazil	Self-reports
Roehrs et al., 2013	Nocturnal sleep, daytime sleepiness and fatigue in fibromyalgia patients compared to rheumatoid arthritis patients and healthy controls: a preliminary study. *(Cit.= 1)*	US	PSG/Self-reports
Roizenblatt, Moldofsky, Benedito-Silva, & Tufik, 2001,2002	Alpha sleep characteristics in fibromyalgia. *(Cit.= 212)*	Brazil	PSG/Self-reports
Shaver et al., 1997	Sleep, psychological distress, and stress arousal in women with fibromyalgia. *(Cit.= 77)*	US	PSG/Self-reports
Ulus et al., 2011	Sleep quality in fibromyalgia and rheumatoid arthritis: associations with pain, fatigue, depression, and disease activity. *(Cit.= 6)*	Turkey	Self-reports

OBJECTIVE 2 (N = 18)			
Authors, year	Article title	Country	Assessment
Akdoğan, Ayhan, Yıldırım, & Borman, 2013	Impact of fatigue on cognitive functioning among premenopausal women with fibromyalgia syndrome and rheumatoid arthritis: the controlled study. *(Cit.= 1)*	Turkey	Self-reports
Akkaya et al., 2013	Assessment of the relationship between postural stability and sleep quality in patients with fibromyalgia. *(Cit.= 0)*	Turkey	Self-reports
Bagge, Bengtsson, Carlsson, & Carlsson, 1998	Low growth hormone secretion in patients with fibromyalgia- A preliminary report on 10 patients and 10 controls. *(Cit.= 73)*	Sweden	Self-reports
Borman & Çeliker, 1999	A comparative analysis of quality of life in rheumatoid arthritis and fibromyalgia. *(Cit.= 25)*	Turkey	Self-reports
Can & Can, 2012	Assessment of cognitive function in patients with fibromyalgia using the clock drawing test. *(Cit.= 1)*	Turkey	Self-reports
Dick, Verrier, Harker, & Rashiq, 2008	Disruption of cognitive function in fibromyalgia syndrome. *(Cit.= 65)*	Canada	Self-reports
Gur et al., 2002	Regional cerebral blood flow and cytokines in young females with fibromyalgia. *(Cit.= 66)*	Turkey	Self-reports
Lario, Valdivieso, López, Bañuelos, & Cabello, 1996	[Fibromyalgia syndrome: clinical characteristics of Spanish patients]. *(Cit.= 13)*	Spain	Self-reports
Lerma, Martinez, Ruiz, Vargas, Infante, & Martinez-Lavin, 2011	Nocturnal heart rate variability parameters as potential fibromyalgia biomarker: correlation with symptoms severity. *(Cit.= 11)*	Mexico	Self-reports
Malin & Littlejohn, 2012	Neuroticism in young women with fibromyalgia links to key clinical features. *(Cit.= 4)*	Australia	Self-reports
Martinez, Ferraz, Sato, & Atra, 1994, 1995	Fibromyalgia versus rheumatoid arthritis: a longitudinal comparison of the quality of life. *(Cit.= 180)*	Brazil	Self-reports
Martinez et al., 1998	[Clinical and functional comparison of patients with fibromyalgia and myofascial pain]. *(Cit.= 5)*	Brazil	Self-reports
Parrish, Zautra, & Davis, 2008	The role of positive and negative interpersonal events on daily fatigue in women with fibromyalgia, rheumatoid arthritis, and osteoarthritis. *(Cit.= 35)*	US	Self-reports
Riva, Mork, Westgaard, Rø, & Lundberg, 2010	Fibromyalgia syndrome is associated with hypocortisolism. *(Cit.= 39)*	Norway	Self-reports/PSG
Shaver, Wilbur, Robinson, Wang, & Buntin, 2006	Women's health issues with fibromyalgia syndrome. *(Cit.= 55)*	US	Self-reports
Tander, Atmaca, Aliyazicioglu, & Canturk, 2007	Serum ghrelin levels but not GH, IGF-1 and IGFBP-3 levels are altered in patients with fibromyalgia syndrome. *(Cit.= 6)*	Turkey	Self-reports
Tüzün, Albayrak, Eker, Sözay, & Daşkapan, 2004	A comparison study of quality of life in women with fibromyalgia and myofascial pain syndrome. *(Cit.= 41)*	Turkey	Self-reports
Zautra, Fasman, Parish, & Davis, 2007	Daily fatigue in women with osteoarthritis, rheumatoid arthritis, and fibromyalgia. *(Cit.= 80)*	US	Self-reports

Note. PSG = Polysomnography; Cit. = Number of citations in GoogleScholar ®; AKT = Actigraphy. Article titles in brackets were translated to English.

American women were the most numerous samples (12 articles were carried out in US institutions). Studies were also conducted in Turkey (8 articles), Spain (6 articles), Brazil (4 articles), Denmark (3 articles), Canada (2 articles), and Sweden, Norway, Mexico, and Australia (1 article each), however (see Figure 5).



	NUMBER OF CITATIONS			
	Total	Average	Total [08-13]	Average [08-13]
Brazil	452	113	247	62
Canada	187	94	102	51
US	631	53	437	36
Denmark	183	61	56	19
Turkey	146	18	86	11
Spain	79	13	34	6
Norway	39	-	38	-
Sweden	73	-	19	-
Mexico	11	-	11	-
Australia	4	-	4	-

Figure 5- Distribution of scientific production on sleep disturbances in women with fibromyalgia syndrome across countries. The chart on the left shows the overall impact of these articles on the research field (i.e. average number of citations received) within the last five years, organized by countries. The number on the stripe represents the number of papers included in this review according the country. Error bars indicate the S.E.M. across papers. The table on the right summarizes all the citations that papers have received since the publication date and in the last five years, organized by countries. [GoogleScholar ®, 11th of October 2013].

The comparative group generally was composed by healthy control women (32 articles), or patients, suffering from rheumatoid arthritis (6 articles), osteoarthritis (2 articles), or myofascial pain (2 articles). Some articles included a combination of three groups (generally, FMS, healthy controls and a rheumatologic patients group). The sample's characteristics of reviewed studies are displayed at Table 2.

Table 2- Sample's characteristics of reviewed studies.

Authors, years	Patients sample size	Setting	Method of recruitment	Comparison group	Comparison group sample size	Setting	Method of recruitment
Articles with sleep assessment as a main objective (*Objective 1*) (N = 21)							
Besteiro et al., 2011	32	PHC	Selected consecutively	HC	20	Unclear	Volunteers
Burns et al., 2008/ Chervin et al., 2009[a]	15	PHC	From referrals/ advertisements	HC	15	Community	Volunteers
Côté & Moldofsky, 1997	10	PHC	From referrals/ patients' files	HC	9	Community	Volunteers
Drewes et al., 1994, 1995a, 1995b [b]	14	PHC	Selected consecutively	HC	12	N/A	N/A
Korszun et al., 2002	16	PHC	Selected consecutively	HC	28	N/A	Volunteers
Landis et al., 2003	23	PHC	Volunteers from referrals	HC	22	Community	Volunteers
Landis et al., 2001	25	PHC	Volunteers from referrals	HC	21	Community	Volunteers
Landis, Lentz, Rothermel et al., 2004	37	PHC	Volunteers from referrals	HC	30	Community	Volunteers
Landis, Lentz, Tsuji et al., 2004	33	PHC	Volunteers from referrals	HC	37	Community	Volunteers
Lario et al., 1996	28	PHC	Selected consecutively	Rheumatologic patients	15	N/A	N/A
Miró et al., 2012	90	PHC/ ECF	From referrals	HC	70	Community	Volunteers
Miró et al., 2011	104	PHC/ ECF	From referrals	HC	86	Community	Volunteers
Munguía & Legaz, 2012	66	ECF	Volunteers	HC	48	N/A	N/A
Osorio et al., 2006	30	PHC	Selected consecutively	HC	30	Patients' companions	N/A
Roehrs et al., 2013	18	PHC/ Community	From referrals/ volunteers	HC/ RA	16/16	Community	Volunteers
Roizenblatt et al., 2001, 2002	40	PHC	Randomly selected from a list	HC	43	Community	Volunteers
Shaver et al., 1997	11	Community	Volunteers	HC	11	Community	Volunteers
Ulus et al., 2011	40	PHC	N/A	HC/ RA	40/40	PHC/N/A	N/A
Articles with sleep assessment as a secondary objective (*Objective 2*) (N = 18)							
Akdoğan et al., 2013	40	N/A	N/A	HC/ RA	30/28	N/A	N/A
Akkaya et al., 2013	48	PHC	Volunteers from medical records	HC	32	Hospital staff's relatives	Volunteers
Bagge et al., 1998	10	N/A	N/A	HC	10	N/A	N/A
Borman & Çeliker, 1999	22	N/A	N/A	HC	25	University staff	Volunteers
Can & Can, 2012	63	N/A	N/A	HC	62	N/A	N/A
Dick et al., 2008	30	PHC/ Community	Volunteers	HC	30	PHC/ Community	Volunteers
Gur et al., 2002	19	PHC	N/A	HC	20	Community	Volunteers

Lario et al. 1996	60	PHC	Selected consecutively	Rheumatologic patients	60	PHC	Selected consecutively
Lerma et al., 2011	22	PHC	From referrals	HC	22	Medical staff	Volunteers
Malin & Littlejohn, 2012	25	PHC/ ECF/ Community	Volunteers	HC	27	Community	Volunteers
Martinez et al., 1994, 1995	44	PHC	Selected consecutively	RA	41	PHC	Selected consecutively
Martinez et al., 1998	26	PHC	Selected consecutively	MPS	18	PHC	Selected consecutively
Parrish et al., 2008/ Zautra et al., 2007 [c]	90	PHC/ ECF/ Community	Volunteers	RA/OA	89/76	PHC/ECF/ Community	Volunteers
Riva et al., 2010	29	ECF	Volunteers	HC	29	Blood donors	Volunteers
Shaver et al., 2006	442	PHC/ECF/ Community	Volunteers	HC	205	Patients' relatives/ Community	Volunteers
Tander et al., 2007	47	N/A	N/A	HC	28	N/A	N/A
Tüzün et al., 2004	33	PHC	Selected consecutively	RA/MPS	33/33	PHC	Selected consecutively

Note. PHC = Primary health center; ECF = Extended care facility; RA = Rheumatoid arthritis; N/A = Without information or not applicable; MPS = Myofascial pain syndrome; OA = Osteoarthritis.

[a,b,c] Articles' samples come from the same study .

Sleep assessment

Whereas objective assessment of sleep is the methodology more used in studies pursuing *Objective 1*, subjective assessment of sleep is almost the unique methodology in studies pursuing the *Objective 2*. Self-reports were used in 28 articles (10 of them pursed *Objective 1*, and 18 studies pursed *Objective 2*). Polysomnographic assessment has been reported in 15 articles (10 studies, 9 of them pursued *Objective 1*-although polysomnographic outcomes were secondary in one of them (Lario et al., 1996)- and 1 study pursued *Objective 2*). Actigraphic assessment was carried out in two articles (*Objective 1*).

Subjective sleep measures

In most cases, subjective sleep outcomes were assessed by questionnaires (including sleep subscales), and visual analogue scales, Likert scales, and questions created *ad hoc* (see Table 3). The most common tool to assess sleep quality was the PSQI. It was used in nine articles (out of 29). Scores at the Pittsburgh Sleep Quality Index (PSQI) -in FMS patients- ranged from 9.70 to 15.15, always higher than the established cut-off to classify people as having sleep disturbances (Buysse et al. 1989; Carpenter & Andrykowski, 1998). It is important to note, that none of these sleep measures has been validated in chronic pain populations, however.

Table 3- Summary of self-report instruments to assess sleep outcomes used in the reviewed articles.

Authors, year & Country	Sleep self-report instrument/s	Validation
Articles with sleep assessment as a main objective (*Objective 1*) (N = 10)		
Landis et al., 2003 US	Sleep items from the Washington Women's Health Diary (3 days)	Yes (for the whole diary): Mitchell et al., 1991 Reliability assessed for this study
Lario et al., 1996 Spain	Epworth sleepiness scale	Not for this population
Miró et al., 2012 Spain	Pittsburgh sleep quality index Dysfunctional beliefs about sleep scale	Yes: Royuela & Macias, 1997; Sierra et al., 2006
Miró et al., 2011 Spain	Pittsburgh sleep quality index	Yes: Royuela & Macias, 1997
Munguía-Izquierdo & Legaz-Arrese, 2012 Spain	Pittsburgh sleep quality index	Yes: Royuela & Macias, 1997
Osorio et al., 2006 Brazil	Pittsburgh sleep quality index	Yes Ceolim et al., 2001
Roehrs et al., 2013 US	Epworth sleepiness scale	Yes: Johns,1992
Roizenblatt et al., 2001, 2002 Brazil	Questionário dos distúrbios do sono	Yes: Braz et al., 1987
Shaver et al., 1997 US	Items from the Specific Health Symptom Questionnaire	No Reliability assessed for this study
Ulus et al., 2011 Turkey	Pittsburgh sleep quality index	Yes: Agargun et al., 1996
Articles with sleep assessment as a secondary objective (*Objective 2*) (N = 18)		
Akdoğan et al., 2013 Turkey	Pittsburgh sleep quality index	Not for this population
Akkaya et al., 2013 Turkey	Pittsburgh sleep quality index	Not for this population
Bagge et al., 1998 Sweden	VAS in mm (0-100): Sleep quality during last month/ last week	No
Borman & Çeliker, 1999 Turkey	Sleep Subscale of the Nottingham Health Profile	Yes: Küçükdeveci et al., 2000
Can & Can, 2012 Turkey	VAS in mm (0-100): Sleep disturbance during last week	No
Dick et al., 2008 Canada	Average total hours of sleep Average number of awakenings per night Time period not specified	No
Gur et al., 2002 Turkey	Likert scale: Sleep disturbances Time period not specified	Not for this population
Lario et al. 1996 Spain	Campbell's questionnaire	Not for this population
Lerma et al., 2011 Mexico	Medical Outcome Sleep Scale	Yes: Without reference
Malin & Littlejohn, 2012 Australia	Sleep Subscale of the Fibromyalgia Impact Questionnaire	Yes: Burckhardt et al., 1991
Martinez et al., 1994, 1995 Brazil	Modified Post-Sleep Inventory	Not for this population
Martinez et al., 1998 Brazil	Modified Post-Sleep Inventory	Not for this population
Parrish et al. 2008 US	Pittsburgh sleep quality index	Yes: Buysse et al., 1989
Riva et al., 2010	One question (Sleep problems) of the Subjective	Yes (for the whole inventory):

Norway	Health Complaints inventory	Eriksen et al. 1999
Shaver et al., 2006 US	Questions about sleep-related diagnoses and lifestyle behaviors related to sleep pattern	No
Tander et al., 2007 Turkey	VAS in mm (0-100): Sleep disturbance Time period not specified	No
Tüzün et al., 2004 Turkey	One question about sleep	No
Zautra et al., 2007 US	Pittsburgh sleep quality index	Yes: Buysse et al., 1989

Note. VAS = Visual analogue scale.

Studies, primarily aimed to asses sleep behavior -i.e. *Objective 1*-, generally used validated sleep questionnaires to evaluate sleep quality (Miró et al. 2011, 2012; Munguía-Izquierdo & Legaz-Arrese, 2012; Osorio et al., 2006; Roizenblatt et al., 2001, 2002; Ulus et al. 2011), daytime sleepiness (Lario et al., 1996; Roehrs et al., 2013), and dysfunctional beliefs about sleep (Miró et al., 2012). In addition, two studies have used several sleep items -from more comprehensive health questionnaires- to assess sleep outcomes (Landis et al., 2003; Shaver et al. 1997). On the other hand, among those studies that were not primarily aimed to asses sleep outcomes -i.e. *Objective 2*-, six used validated sleep questionnaires (Borman & Çeliker, 1999; Lerma et al., 2011; Malin & Littlejohn, 2012; Parrish et al., 2008; Riva et al., 2010; Zautra et al., 2007), five used not validated questionnaires (Akdoğan et al., 2013; Akkaya et al., 2013; Lario et al., 1996; Martinez et al., 1994, 1995, 1998). Visual analogue or Likert scales were applied by four studies (Bagge et al., 1998; Can & Can, 2012; Gur et al., 2002; Tander et al., 2007), and four used items about sleep (Dick et al., 2008; Henriksson et al., 1996; Shaver et al., 2006; Tüzün et al., 2004).

Regardless of the specific self-report tool -when compared to healthy controls- women with fibromyalgia reported poorer sleep quality, less hours of sleep, more number of awakenings, or not refreshed sleep. When compared to other clinical populations -rheumatoid arthritis, osteoarthritis or myofascial pain- women with FMS reported poorer sleep quality (but see Martinez et al., 1994, 1995).

Objective sleep measures

Actigraphy (AKT). Only two studies have used actigraphic assessment to study the characteristics of sleep disturbances in women with FMS (Korszun et al., 2002; Landis et al., 2003). The number of days assessed were 5-7 days (Korszun et al., 2002) and 3 days (Landis et al., 2003). Participants -16 FMS patients vs. 28 healthy control

(Korszun et al., 2002) and 23 patients vs. 23 healthy control (Landis et al., 2003)- wore a wrist actigraphy and scored their activity data and sleep-wake times in written diaries. Controls related to participants' physiological status prior assessment were reported only by Landis and colleagues (2003). Korszun and colleagues (2002) reported differences in nighttime activity levels, whereas Landis and colleagues (2003) did not found differences.

Polysomnography (PSG). When a polysomnographic assessment was used, almost all reviewed studies (8 out of 9 studies) used the Rechtschaffen and Kales scoring criteria (Rechtschaffen & Kales, 1968). The rules set out by Iber and colleagues (2007) were followed only by one study (i.e. Riva et al., 2010). All Studies - except for Burns et al., 2008/ Chervin et al., 2009; and Roehrs et al., 2013- did not report number of sleep scorers, their blinding conditions, and/or the established minimum level of agreement between scorers. Most of the studies were conducted in a sleep laboratory or hospital hotel during two nights. Only one study collected ambulatory data (Drewes et al., 1994, 1995a, 1995b). The time of PSG recording varies from a laboratory fixed schedules (e.g. 8 hours: Besteiro et al., 2011) to participants' usual schedules (e.g. Shaver et al., 1997) and a mixture of both options (e.g. Landis et al., 2001, Landis, Lentz, Rothermel et al., 2004; Landis, Lentz, Tsuji et al., 2004). The montage always included EEG channels (central derivations are present in all studies), bilateral electrooculography, and chin electromyography. The inclusion of different polygraphic and electrocardiographic channels varies among studies. Regarding participants, patient's sample sizes range from 10 to 40 patients (mean = 23.5), healthy participants' samples sizes range from 9 to 43 (mean = 21.6). Patients with rheumatoid arthritis were the control group only in one study (N = 18).

Sociodemographic and clinical variables can account for differences in sleep behavior (Fernandez-Mendoza et al., 2012; Grandner et al., 2013). Thus, studies have tried to match participants from clinical and control groups for several of these variables. Although all samples were matched for age, only one article included age as covariate in its analysis (i.e Landis, Lentz, Rothermel et al., 2004). Several studies have matched their samples for body mass index (Burns et al., 2008; Chervin et al., 2009; Landis et al., 2001, Landis, Lentz, Rothermel et al., 2004; Landis, Lentz, Tsuji et al., 2004; Roizenblatt et al., 2001, 2002, Shaver et al., 1997), race (Landis et al., 2001, Landis, Lentz, Rothermel et al., 2004), and/or educational level (Besteiro et al., 2011;

Roizenblatt et al., 2001, 2002; Shaver et al., 1997). Studies generally do not report information regarding menopausal status. When it is reported, only two articles selected homogenous samples (premenopausal, Côté & Moldofsky, 1997; postmenopausal, Roizenblatt et al., 2001,2002) and the rest of articles used heterogeneous samples, with (Landis et al., 2001) or without (Burns et al., 2008; Chervin et al., 2009; Landis, Lentz, Rothermel et al., 2004; Shaver et al., 1997) significant differences in this variable. Controls related to participants' physiological status -at the time of the polysomnographic assessment- are taken into account in almost all studies. Nearly all studies controlled the medication intake (which was suppressed from 2 days to 3 months prior assessment, or only recruiting patients who do not take medications). Most of the studies have controlled for the consumption of psychotropic substances -like tobacco, alcohol, or caffeine-.previous the PSG; however, mostly no studies have instructed participants for not taking naps or controlled menstrual cycle in pre-menopausal women. Table 4 shows the main protocol's characteristics used in the reviewed polysomnographic assessment studies. Specific details about the assessment of sleep microstructure are shown at Table 5.

Table 4- Summary of protocols' features of the polysomnographic assessment (8 studies with *Objective 1* and 1 study with *Objective 2*).

Authors & Country	Scoring criteria	Number of sleep scorers/ Agreement	Blinding	Automatic scoring	Setting	Number of nights	Time of recording	PSG equipment/ montage	Physiological status controls
Besteiro et al., 2011 Spain	R&K	N/A	N/A	No	Sleep laboratory at hospital	1	8 hours Fixed: 11pm-7am	32-channel *Discovery* EEG (Medelec Vickers Medical, Inc.) Cz/A1-O1/A1 EOG/ EMG EKG Polygraphic channels	- Without medication that could affect sleep 3 months prior PSG
Burns et al., 2008/ Chervin et al., 2009 US	R&K	1*/ N/A *Borderline PSG features were discussed with an investigator	Yes	No	Sleep laboratory at clinical research center	3	N/A	Telefactor DEEG/TWIN F3/A2-F4/A1-C3/A2- C4/A1-O1/A2- O2/A1 EOG/ EMG EKG Polygraphic channels	- Without psychotropic medications, hypnotics, analgesics, and herbal or over-the-counter supplements 2 weeks prior PSG - Without acetaminophen and diphenhydramine 3 days prior PSG - Without caffeine, nicotine, or alcohol 3 days prior study
Côté & Moldofsky, 1997 Canada	R&K	N/A (1, for alpha scoring)	N/A (Yes, for alpha scoring)	No	Sleep laboratory	2	Fixed: 10.30pm-7.00am	Oxford Medilog 9000 recorder C3/A2- C4/A1-O1/A2-O2/A1 EOG EMG Polygraphic channels	- Without medication - Nonsmokers
Drewes et al., 1994, 1995a, 1995b Denmark	R&K	N/A	Yes	No	In-home	2	7.30 hours Participants' usual sleep schedule	Judex Datasystems A/S, Denmark F3/A2- C4/A1 EOG/ EMG Polygraphic channels	- Without psychotropic medications 2 weeks prior PSG - Caffeine, nicotine, or alcohol allowed until 6pm

Landis et al., 2003, Landis, Lentz, Rothermel et al., 2004; Landis, Lentz, Tsuji et al., 2004 US	R&K	1 >90% interrater agreement	N/A	Yes, Oxford Sleep Adquisition Computer system (Clearwater, FL)	Sleep laboratory at research center	3	Participants' usual bedtime-7.00am	Grass model 7 polygraph C3/A2- Fz/A1-A2 - Cz/A1-A2 EOG/ EMG Polygraphic channels	- Without psychotropic, hypnotic, or sedative medications 2 weeks prior PSG - Caffeine, nicotine, or alcohol allowed until 1pm. - Naps not allowed - PSG 5-10 days following menses
Roehrs et al., 2013 US	R&K	2 90%	Yes	No	Sleep laboratory at hospital	2	8 hours Participants' usual sleep schedule	N/A C3/A2- O2/A1 EOG/ EMG	- Without medication that could affect sleep, including antidepressants - Without pain medications (NSAIDS, opioids, other analgesics) 1week prior PSG
Roizenblatt et al., 2001, 2002 Brazil	R&K	N/A	Yes	No	Sleep laboratory	2	N/A	9.2 Medilog Sleep Analyzer Computer C3/A2- C4/A1-Oz/Fz EOG/ EMG EKG Polygraphic channels	- Without medication that could affect sleep 1 month prior PSG. - Without caffeine, nicotine, or alcohol 1 day prior study
Shaver et al., 1997 US	R&K	N/A 92%	Yes	Yes, Oxford Sleep Adquisition Computer system	Sleep laboratory	2	Typical hours for duration of sleep length	Oxford Sleep Adquisition Computer system C3/A2- C4/A1 EOG/ EMG Polygraphic channels	- PSG 4-10 days following menses
Riva et al., 2010* Norway *Objective 2	Iber et al. 2007	N/A	N/A	N/A	Hospital hotel	1	Interval since 10.15pm-1.00am to 5.45am-7.30am	N/A 2 EEG channels EOG/ EMG EKG Polygraphic channels	- Without medication that interact with neural, vascular, or muscular function or psychophysiological measures - Without analgesics and/or sleep medicines 2 days prior PSG

Note. R&A = Rechtschaffen and Kales; N/A = Without information or not applicable; PSG = Polysomnography; EEG = Electroencephalography; EOG = Electrooculography; EMG = Electromyography; EKG = Electrocardiography.

Table 5- Features of the assessment of sleep microstructure (*Objective 1*).

Authors & Country	Number of channels	Brain lobe analyzed	Reference electrodes	Filters	Sampling frequency	Artifact rejection	Signal segmentation	Signal analysis
Besteiro et al., 2011 Spain	N/A	N/A	Bipolar reference (A1)	N/A	N/A	N/A	N/A	Visual alpha scoring
Chervin et al., 2009	1	Central Left hemisphere: C3	Bipolar reference (A2)	N/A	200Hz	N/A	1 second	Fourier power analysis
Côté & Moldofsky, 1997 Canada	4	Central Both hemispheres: C3/C4 Occipital: Both hemispheres: O1/O2	Bipolar reference (A1/A2)	N/A	N/A	N/A	N/A	Visual alpha scoring
Drewes et al., 1994, 1995a, 1995b Denmark	1	Frontal Left hemisphere: F1	Bipolar reference (A2)	Highpass: 0.5Hz Lowpass: 25Hz Notch filter 50Hz	100Hz	EEG samples without artifacts, but procedure is not explained	2 seconds	Power spectral analysis by autoregressive modeling
Landis, Lentz, Rothermel et al., 2004 US	3	Central Left hemisphere and vertex: C3/ Cz Frontal Midline: Fz	Bipolar reference (A2) Linked-mastoids: A1-A2	N/A	250Hz	Data with temporary spikes, sweating and/or body movements were removed	2 seconds	Fourier power analysis
Roizenblatt et al., 2001, 2002 Brazil	2	Central Both hemispheres: C3/C4	Bipolar reference (A1/A2)	Highpass: 0.3Hz Lowpass: 90Hz	500Hz		2 seconds	Waveform analysis Fourier power analysis Visual alpha scoring
Shaver et al., 1997 US	2	Central Both hemispheres: C3/C4	Bipolar reference (A1/A2)	N/A	N/A	N/A	N/A	Visual alpha scoring

Note. N/A = Without information or not applicable.

From the thirteen polysomnographic articles (*Objective 1*), three reported sleep microstructure measures, four, sleep architecture measures, and six articles, a combination of both. Results are summarized in Figure 6.

Sleep microstructure differences were found in five (out nine) articles (e.g., α-EEG sleep: Drewes et al., 1994, 1995a, 1995b; Roizenblatt et al., 2001, 2002; spindle activity: Landis, Lentz, Rothermel et al., 2004). Regarding sleep architecture measures, six articles found slightly differences in the organization of sleep cycles- particularly, an increment in the percentage of S1NREM sleep- (Côté & Moldofsky, 1997; Roizenblatt et al. 2001, 2002; Shaver et al., 1997) or in fragmentation measures (Burns et al., 2008; Chervin et al., 2009; Roehrs et al., 2013); whereas four studies found solid differences between groups (Besteiro et al., 2011; Drewes et al., 1994; Landis et al., 2001, Landis, Lentz, Tsuji et al., 2004).

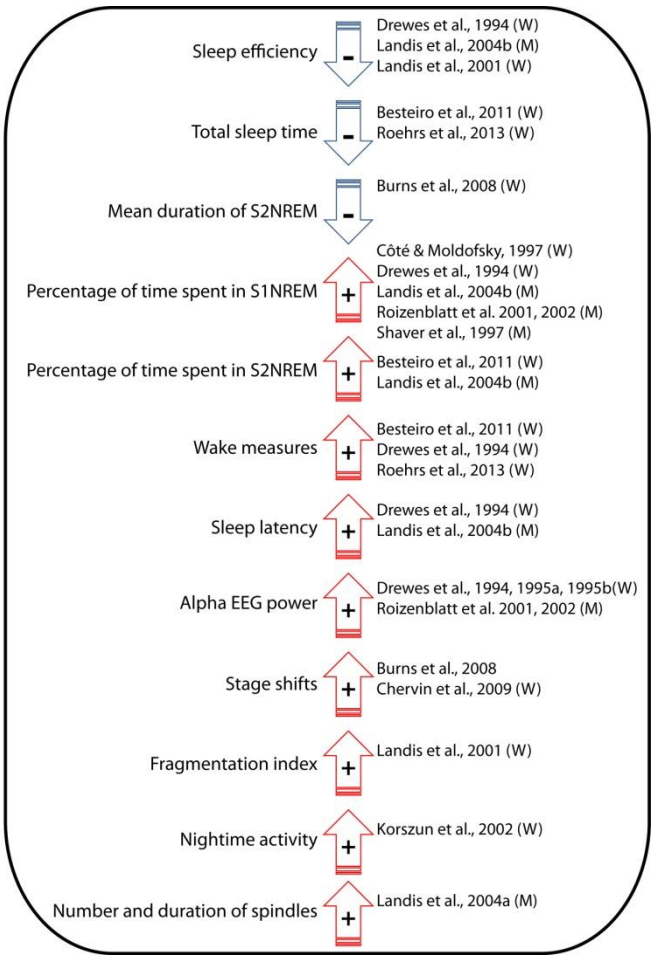


Figure 6- Alterations in objective sleep measures in patients whit fibromyalgia, when compared to healthy controls, in terms of increased or decreased findings.

Note. W = Study rated as "weak quality"; M = Study rated as "moderate quality"; NREM = Non REM sleep; EEG = Electroencephalography.

Correlational analyses

Studies often reported correlational analyses between sleep measurements and other outcomes; principally, pain intensity, daytime impairment, and mood measures. Objective measures of sleep, as mean S2NREM sleep duration, number of stage changes, number and duration of spindles, and alpha activity have been found to be related to pain intensity (Burns et al., 2008; Landis, Lentz, Rothermel et al., 2004; Roizenblatt et al., 2001, 2002). In addition, time in oxygen saturation less than 92% and number of desaturations were also related to the number of tender points (Lario et al., 1996). Poor sleep quality, measured by PSQI, was related to pain intensity (Miró et al., 2011, 2012; Munguía-Izquierdo & Legaz-Arrese, 2012). Côté and Moldofsky (1997) found a relationship between S1NREM sleep percentage and daytime performance measured by a neuropsychological task. Regarding self-reports, poor sleep quality, measured by PSQI, was also related to daytime impairment (Miró et al., 2011, 2012; Munguía-Izquierdo & Legaz-Arrese, 2012; Ulus et al., 2011). Scores from questionnaires about anxiety and depression (principally, Beck Depression Inventory, Hospital Anxiety and Depression Scale, State-Trait Anxiety Inventory) were related to both objective- S1NREM sleep percentage- (Côté & Moldofsky, 1997) and subjective sleep measures- sleep quality and dysfunctional beliefs about sleep- (Miró et al., 2011, 2012; Munguía-Izquierdo & Legaz-Arrese, 2012).

Finally, Roizenblatt and colleagues (2001, 2002) was the only study that analyzed - as an external validation of the polysomnographic measurements in chronic pain patients- the relationship between PSG (total sleep time, sleep efficiency, and slow wave sleep percentage) and subjective (poor) sleep quality. Strong associations between architecture measures and poor sleep quality were found.

Limitations of the reviewed studies

Risk of bias in included studies

All articles pursuing *Objective 1* were assessed for the quality of research. [Here, we did not asses for the quality of research of those articles included in the *Objective 2* group, because sleep variables were only used for the assessment of the participants' status as reported symptoms]. Among polysomnographic studies, 5 studies (38.46%) were categorized as moderate quality, whereas the remainder 8 studies displayed weak quality. The majority of studies which carried out a subjective assessment of sleep were

categorized as weak quality (4 studies, 80%). Their weakness derives from the inadequate control of confounders and insufficient information regarding withdrawals and drop-outs, and blinding of assessors and participants. However, participants' selection bias, study design, and data collection methods were usually rated as moderate or strong. The rates of each item of the quality assessment tool for these studies are detailed at Appendix 4.

Methodological quality

Since bias in our reviewed studies might cause bias in our conclusions, a more qualitative assessment of common research limitations and methodological concerns seems useful to fully understand the results of the review and their implications. Moreover, discrepancies in polysomnographic results might be due to these methodological limitations and inconsistencies in recording techniques.

a) *Methodological quality*. The presence of basic methodological weaknesses among studies was frequent -only 6 studies have moderate quality (according to the EPHPP criterion). Therefore, our results should be interpreted with caution. It has to be noted, however, that several studies have been carried out before the publication of the guidelines to assess the quality of reports (or risk of bias) (e.g., Moher et al., 1999; Mulrow et al., 1996).

b) *Sample size*. Due to the small number of participants, many of the reviewed studies lack the power to reject a false null hypothesis. Even though patients' recruitment is a challenge, too many "pilot" studies are still carrying out.

c) *Confounding factors: Individual differences and technical factors*. Common sociodemographic and clinical factors account for differences in sleep (Fernandez-Mendoza et al., 2012; Grandner et al., 2013). Thus, age, gender, ethnic group, educational level, and marital status are important contributor factors to understand sleep health. Body mass index, menopausal status, and medications also alter sleep. These variables have been often neglected in the reviewed studies. Moreover, the relationships between sleep and FMS are quite complex, and it is well established that pain, psychological distress, and other somatic and psychological factors -that have a key role in FMS- can modify sleep patterns (Nicassio et al., 2002). These comorbidities did not always were addressed in the reviewed studies. Particularly, in polysomnographic studies, extraneous and uncontrolled variables are especially

undesirable because PSG *per se*, as other biomedical signals, exhibits a low signal to noise ratio (Sameni, 2004). Regarding technical factors in the reviewed studies, PSG devices were always digital, but recording parameters and recording digital specifications varied across studies. Many of them (12 out 13 articles) did not follow the American Academy of Sleep Medicine guidelines (Iber et al., 2007) (i.e. a minimum of three EEG derivations- frontal, central, and occipital- with a minimum sample rate of 200Hz are recommended).

d) *Assessment setting (ecological validity)*. Polysomnography is often considered as non ecological measurement because recordings have to be done in sleep laboratories. This is one of the reasons why PSG measurements have failed to gain traction in clinical practice. All studies, except Drewes and colleagues (1994, 1995a, 1995b), conducted in-lab PSG. Although researchers and sleep technicians take precautions to help prevent uncomfortable rest and, specially, the *first night effect*, sleep laboratories are still too artificial when compared with home settings. In recent years, however, user-friendly commercial and portable PSG devices have overcome some drawbacks of classical PSG (i.e. technical and methodological difficulties of measuring these signals out of controlled settings, and the intrusiveness and bulkiness of the equipments). Many of these devices, have been validated for clinical uses and can obtain high quality data, in spite of possible limitations (above all, more likelihood of artifacts and loss of data) (e.g., Shambroom, Fábregas, & Johnstone, 2012; Tonetti et al., 2013). Notwithstanding the above, ambulatory PSG has still the potential to *provide information about the typical sleep/wake patterns that subjects display in their day-to-day environment* (McCall, Erwin, Edinger, Krystal, & Marsh, 1992).

e) *Multidimensional assessment*. Even though PSG is considered the *gold standard* to measure sleep objectively, almost all studies have included several self-reports to investigated the subjective experience of sleep. However, the analysis of convergences or divergences between objective and subjective measures is exceptionally scarce. Among the revised investigations, only one study has correlated sleep outcomes from PSG and questionnaires (Roizenblatt et al., 2001, 2002). To understand the possible discrepancies between the physiological assessment of sleep and the subjective experience of resting in patients with FMS is of great interest, particularly for theories proposing sleep as an etiological and maintenance factor for FMS symptoms (e.g., Bennett, 1989; Hamilton et al., 2012; Moldofsky et al., 1975; Moldofsky, 2008).

Discussion

In this systematic review we wanted to identify the characteristics of sleep disturbances in women diagnosed with FMS and to outline the relationships between subjective and objective measures of sleep as well as between these sleep outcomes and other clinical variables (e.g., pain, depression, and anxiety). To summarize, we found that women with FMS exhibited more often sleep symptoms (poorer sleep quality, more complaints of insufficient sleep, a great number of awakenings, and/or the experience of unrefreshing sleep) when compared to healthy controls (or other rheumatologic patients). Evidence on objective measures of sleep in patients with FMS was mixed and inconsistent, however. As we stated before, discrepancies in these results might be due to methodological inconsistencies among studies, but also to the intrinsic heterogeneity that might characterize FMS population. Since the clinical profile of these patients is quite variable, FMS would not constitute a single clinical entity (Müller, Schneider, & Stratz, 2007). Several authors have tried to construct FMS patients clusters according to their variations in symptoms and symptoms severity (Calandre et al., 2010; De Souza et al., 2009; Rehm et al., 2010; Turk, 2002). All these studies agree that sleep disturbances are key symptoms to differentiate patients subgroups. Accordingly, sleep architecture and sleep microstructure have been found to vary in FMS population.

In the reviewed works, sleep architecture and sleep microstructure outcomes vary among studies. All studies found, at least, one difference among the objective measurements of overall sleep quality, sleep depth, sleep continuity, or arousal activity, but the relevance of these measurements to explain sleep health is variable (Kushida et al., 2005). Higher proportion of lighter sleep and more fragmented sleep were the most common polysomnographic characteristics among women with FMS. Alteration of the cyclic organization of sleep in favor of lighting sleep and the occurrence of signs of fragmented sleep are often present in several sleep disorders (Hening, 2004; Kimoff, 1996; Littner et al., 2003). Furthermore, lighter and fragmented sleep is also present in other rheumatic conditions (Taylor-Gjevre, Gjevre, Skomro, & Nair, 2011), psychopathological disorders (Chellappa & Araújo, 2007; Riemann, 2007), and even characterize sleep age-related changes (Ohayon, 2004). Thus, it could be the case that differences in sleep architecture measures among disorders is more quantitative than qualitative, being sleep-related disorders arrayed along a simple progression of increasing sleep disturbances (Hudson et al., 1992). Thus, sleep architectures could be

disturbed in a limited number of ways and it might not be possible to detail more than good or bad sleep quality. Consistent with this idea, recent theoretical proposals (Hamilton et al., 2012) do not define anymore specific types of sleep disturbance in FMS, instead indicate poor sleep quality as the important issue for FMS development. It is possible that Hamilton's hypothesis results from the impossibility, until now, to find a valid explanatory theory for sleep disorders physiology in FMS. Several attempts (Bennett, 1989; Moldofsky et al., 1975; Moldofsky, 2008) have tried to identify the missed link between sleep physiology and chronic pain in FMS looking into brain's sleep-waking systems and, especially, in arousal systems.

Plausible physiological explanations for sleep disturbances in FMS

Theories about disorders of sleep physiology in FMS have focused, specially, on two polysomnographic parameters: slow wave sleep (SWS) deprivation and fragmented sleep.

Bennett (1989) proposed that SWS deprivation -which would come from patients' inactivity- initiates a cascade of symptoms in FMS. Since SWS would be related to restorative functions of sleep, this is an attractive hypothesis to explain somatic symptoms and, especially, a negative effect on skeletal muscle. However, despite a higher proportion of light sleep in patients with FMS, none of the reviewed studies found a lower percentage of SWS (see Figure 6). Moreover, as Mahowald and Mahowald (2000) stated, *there is no evidence that any organ of the body other than the brain benefits from or is restored by sleep*. In consequence, Bennett's hypothesis, formulated in this way, would not be valid to explain FMS symptoms. However, considering all recent hypothesis about central sensitization in FMS (e.g., Meeus & Nijs, 2007), restorative functions of sleep on brain functions might have a significant role.

Moldofsky and colleagues (1975) were the first to propose an etiological role of sleep disturbances in FMS. Since this work, over the past three decades, research community has dedicated a lot of efforts to understand the role played by fragmented sleep in FMS (see Figure 7). Pioneering studies proposed that α-EEG sleep represented fragmented sleep (Moldofsky & Scarisbrick, 1976), as it was similar to α-EEG activity that appeared in healthy people in response to depriving noise stimuli during sleep hours (Moldofsky et al., 1975). The transition from wake to sleep involves a *disconnection*

from the external world, which results in increased lower EEG rhythms and an attenuation of the α-EEG rhythm (McKinney, Dang-Vu, Buxton, Solet, & Ellenbogen, 2011). Thus, these authors proposed that α-EEG sleep in fronto-central derivations during NREM sleep might indicate a vigilant arousal state during sleep and a shift toward wakefulness in patients with FMS (Anch, Lue, MacLean, & Moldofsky, 1991; Moldofsky, 2008). It means that patients do not *disconnect* and rest appropriately, hence the complaints of unrefreshing sleep. However, other authors suggested that the fronto-central distribution of this type of α-EEG activity may not reflect the typical arousal-associated α-EEG activity which occurs in occipital areas (and which is associated with limb movements or cardio-respiratory events) (Pivik & Harman, 1995). It has been proposed that fronto-central α-EEG activity during sleep might represent a sleep maintaining rather a fragmentation process –as Moldofsky and colleagues (1975, 2008) stated- (for a review, see Mahowald & Mahowald, 2000). This counterintuitive argument leads to the hypothesis that NREM sleep in patients with FMS would be characterized by α-EEG sleep because of some bodily counter-reaction to pain symptoms. This latter hypothesis would not explain sleep fragmentation outcomes in sleep architecture, but would support the appearance of signs of restorative sleep in FMS population (i.e. an increment of total sleep time or in the percentage of SWS), something which does not occur in these patients, however (see Figure 6).

Another working hypothesis would be that α-EEG activity in FMS might be generated by the activity of the locus coeruleus due to insomnia. Neurotransmitters, as wake and sleep signals, are precisely regulated during the sleep-wake cycle, *switching on* /*switching off* the brain (e.g., Peplow, 2013). Catecholamines, including noradrenaline and dopamine, are one of the most relevant wake signals. The locus coeruleus is the preeminent noradrenergic nucleus involved in the regulation of arousal and alerting (Samuels & Szabadi, 2008). This nucleus releases noradrenaline and the cessation of this neurotransmitter is linked to muscle tone suppression during sleep (John, Wu, Boehmer, & Siegel, 2004) and cognitive deactivation (Di Stasi, Catena, Cañas, Macknik, & Martinez-Conde, 2013). Noradrenaline seems to modulate the response of *waking-active* neurons to other inputs (Osaka & Matsumura, 1993), which are not inhibited during sleep in insomnia (Schwartz & Roth, 2008). Several observations indicate that increased discharge activity of noradrenergic neurons of locus coeruleus are followed by high-frequency and low-amplitude EEG activity in frontal cortex -α-

EEG activity- (McCormick, Pape, & Williamson, 1991). The majority of the patients with FMS have insomnia complaints and, therefore, expend more time awake, with their eyes open. The light is an important external wake signal that *activates* the brain and disrupts the natural release of melatonin (Eisenstein, 2013). Thus, it is possible that a higher amount of α-EEG sleep in FMS is mediated by higher light exposure during night hours and, consequently, by the activation of the locus coeruleus (Vandewalle et al., 2007). State of hyperarousal during sleep in patients with FMS might be essentially the same as that in patients with insomnia.

In that case, the related dopamine system might be a common mechanism which regulates insomnia and chronic pain (Finan & Smith, 2013). Evidence is definitive to that dopaminergic system promotes and maintains arousal states, modulating sleep and wakefulness (Monti & Monti, 2007). Furthermore, several results suggest that endogenous dopamine in the mesolimbic dopamine system may produce analgesia (Sotres-Bayón, Torres-López, López-Ávila, del Ángel, & Pellicer, 2001) and that alterations in dopamine processing affect the efficacy of the opioid system in producing endogenous analgesia (Zubieta et al., 2003). Although more evidence is needed, the functional overlap provides an important role of dopamine in the pathophysiology of FMS. Future studies should identify the role played by fragmented sleep in FMS and if α-EEG activity pattern, related to arousal states, is a distinctive feature in FMS.

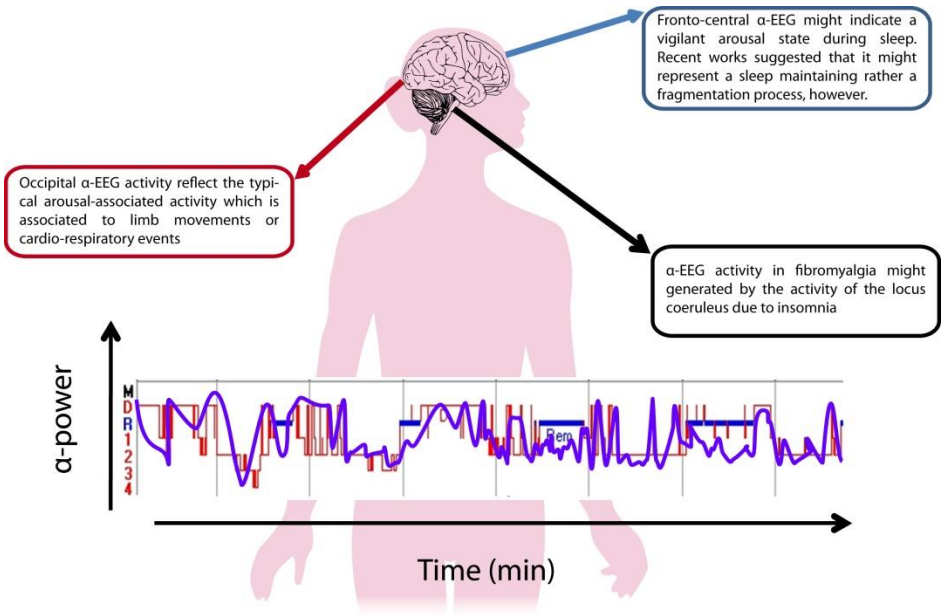


Figure 7- Schematic diagram of the variations of α-EEG sleep activity in tandem with sleep depth. A typical FMS sleep hypnogram and simultaneous alpha power fluctuations are shown from a hypothetical patient.

Concluding remarks

We conclude that sleep disturbances characterize FMS, regardless of the sleep assessment tool. Women with FMS complain of poor sleep, insufficient sleep, a great number of awakenings, and exhibit objective signs of light and fragmented sleep. Clinical features and physiological abnormalities of sleep in FMS are important source of information in the assessment and management of patients and in the pathophysiology of the syndrome. However, the role that sleep disturbances play in FMS is far from being settled. Current evidence could not confirm the importance of sleep physiology in the pathogenesis or maintenance of FMS symptoms. Several theoretical approaches have tried -without reaching a consensus- to explain the relationship between sleep physiology and FMS symptoms. Further studies must be performed, with higher methodological quality standards, in order to elucidate if sleep symptoms in patients with FMS reflect more than sleep misperception.

Practice points

1. Women with fibromyalgia exhibited more sleep symptoms. Evidence on objective measures of sleep in this population is mixed and inconsistent, however. Even so, sleep in FMS seems to be lighter and fragmented.
2. Given the lack of data regarding the convergences between subjective and objective measurements of sleep, conclusion about sleep misperception in FMS cannot be validly drawn.
3. Both subjective and objective sleep measurements are related to pain intensity, daytime impairment, and mood measures in patients with FMS.
4. General methodological weaknesses have been found in most of the published studies. These recommendations will improve research designs in order to obtain consistent results:
    a. Enlarge the sample size until the minimum number of participants required to ensure optimal statistical power.
    b. Achieve a representative sample through the selection of a random subset of patients and controls, when excluding patients means a loss of statistical power and loss of generalizability.
    c. Control potential confounders -if it is not possible to obtain a random sample -by matching, stratifying or selecting appropriate samples, and/or using statistical control for confounding.

d. Comply with standards of recording techniques and current recommendations.
e. Achieve more ecological validity by using home-setting recording.
f. Analyze convergences /divergences between objective and subjective measures to validate sleep measures in chronic pain populations.

Research agenda

Future research efforts should address:

1. If some disturbances in sleep physiology are intrinsic to fibromyalgia and their role in the pathogenesis of fibromyalgia symptoms.
2. If norepinephrine levels during sleep hours reflect a hyperarousal state.
3. If differences in patients' sleep physiology support the hypothesis of FMS heterogeneity.
4. How sleep disturbances influence daytime symptoms in FMS, including objective measures of sleepiness and arousal.

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ESTUDIOS EMPÍRICOS

Objective and subjective sleep assessment in patients with fibromyalgia[1]

Abstract

Background: Clinical research seems to support the presence of a close relationship between pain and sleep among patients with fibromyalgia syndrome (FMS). Sleep complaints are frequent among these patients. Several sleep disturbances have also been described in these patients, including sleep architecture abnormalities, α-EEG sleep, and sleep disorders. Despite the efforts to find a clear association between particular objective sleep disturbances and FMS, the few studies that have addressed the relationship between pain and sleep in FMS population have had inconsistent results, however. Several confounding variables, epidemiological and clinical, may modulate sleep outcomes in FMS, and, probably, may explain discrepancies among studies. Objective: To compare objective and subjective sleep parameters between women with FMS and healthy controls, considering age as a covariate. Methods: Forty female with FMS (M_{age} = 47.05 ± 5.48 years) were compared to thirty-five healthy controls (M_{age} = 44.54 ± 7.32 years) in sleep architecture (obtained through an ambulatory polysomnographic recording), and subjective sleep quality (using Pittsburgh Sleep Quality Index). Results: We found objective alterations in the cyclic organization of sleep and the occurrence of signs of sleep fragmentation, being the sleep lighter and less consolidated. Subjective poor sleep quality, in almost all patients, corroborated this result. Conclusions: Our findings support the idea that patients with FMS exhibit, not only sleep complaints, but also polysomnographic abnormalities that might magnify or maintain pain and other FMS symptoms.

Keywords: Chronic pain; Fibromyalgia; Sleep; Polysomnography.

Introduction

Pain is the cardinal feature in fibromyalgia syndrome (FMS) and the main reason that leads patients to look for medical care (Wolfe et al., 1997). However, diverse

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[1] **Diaz-Piedra, C.**, Catena, A., Sánchez, A. I., Miró, E., Martínez, M. P., & Buela-Casal, G. (under review). Objective and subjective sleep assessment in patients with fibromyalgia. *European Journal of Pain* (manuscript under review).

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experimental and clinical evidence claims that there is a close relationship between pain and sleep in patients with chronic pain (Smith & Haythornthwaite, 2004). Since the first polysomnographic study in patients with *fibrositis* (e.g., Moldofsky, Scarisbrick, England, & Smythe, 1975), where α-EEG sleep was described and, then, proposed to play an important role in the pathophysiology of FMS (Drewes, Nielsen, Arendt-Nielsen, Birket-Smith, & Hansen, 1997; Drewes, Svendsen, Nielsen, Taagholt, & Bjerregård, 1994; Moldofsky & Lue, 1980; Perlis, Giles, Mendelson, Bootzin, & Wyatt, 1997; Roizenblatt, Moldofsky, Benedito-Silva, & Tufik, 2001), sleep became an important outcome because it seems to be highly disturbed in this syndrome.

Although, after these pioneer studies, α-EEG sleep was not considered as a distinctive FMS symptom anymore, over the last forty years, a considerable amount of literature has been published on sleep assessment in patients with FMS. Subjective assessment of sleep consistently shows that patients with FMS use to complain of poor sleep quality, exhibiting insomnia symptoms, and feelings of unrefreshing sleep, daytime tiredness, and sleepiness (Moldofsky, 2008; Smith & Haythornthwaite, 2004). However, objective sleep data across studies is still inconclusive. Several studies have shown differences in sleep architecture and sleep microstructure between patients with FMS and healthy controls, as well as greater prevalence of sleep disorders, besides insomnia complaints (see Table 6). Despite the efforts to find an association between specific sleep abnormalities and FMS, the majority of the above mentioned studies did not find conclusive evidence to support this association and other studies, have shown no abnormalities at all, however (see, for example, Chervin et al., 2009; Rains & Penzien, 2003; Roehrs et al., 2013). One plausible explanation for these incongruent results could arise from several confounding variables (e.g. methodological aspects of the sleep assessment, sample selection criteria, or other clinical variables) that modulate sleep outcomes in FMS. Among these confounding variables, age plays an important role in explaining sleep disturbances. It has to be noticed that age-related variables have been often neglected in the above cited studies. Older age is associated with changes in the macrostructure of sleep (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004) and, although the aging process per se is not responsible for the increase of sleep symptoms, there are increased amount of sleep complaints (Ohayon, Zulley, Guilleminault, Smirne, & Priest, 2001). Indeed, fibromyalgia is more prevalent in median age/older women (Wolfe, Ross, Anderson, Russell, & Hebert, 1995), when menopause is present.

Troubled sleeping already seems to be worse in postmenopausal compared with premenopausal women (Eichling & Sahni, 2005). Moreover, menopausal women are more prone to depression and anxiety (Llaneza, García-Portilla, Llaneza-Suárez, Armott, & Pérez-López, 2012), disorders which are also highly prevalent in patients with FMS and related (for their-self) to sleep difficulties in these patients (Ashworth, Davidson, & Espie, 2010).

Therefore, the primary purpose of this study was to compare objective and subjective sleep parameters between women with FMS and healthy controls, taking into account that age and other clinical variables might explain part of the variance of sleep difficulties.

Table 6- Characterization of sleep alterations in patients with fibromyalgia.

Sleep architecture: Signs of sleep fragmentation	
Greater number of awakenings	Besteiro et al., 2011
Greater number of stage changes	Burns, Crofford, & Chervin, 2008; Landis et al., 2001
Sleep architecture: Alterations in the cyclic organization of sleep	
Decrease of total sleep time	Besteiro et al., 2011; Roehrs et al., 2013
Increase of light sleep to the detriment of deep sleep	Besteiro et al., 2011; Côté, & Moldofsky, 1997; Drewes, Svendsen, Nielsen, Taagholt, & Bjerregård, 1994; Landis, Lentz, Tsuji, Buchwald, & Shaver, 2004; Roizenblatt, Moldofsky, Benedito-Silva, & Tufik, 2001; Rizzi et al., 2004; Sergi et al., 1999
Prolonged sleep onset latencies	Drewes et al., 1994; Landis et al., 2004
Lower sleep efficiency	Drewes et al., 1994; Landis et al., 2001, 2004; Rizzi et al., 2004; Sergi et al., 1999
Sleep architecture: Sleep events	
Respiratory events (e.g., apnea-hypopnea index, flow-limited breaths, periodic breathing)	Gold, Dipalo, Gold, & Broderick, 2004; Sergi et al., 1999
Cardiac events (e.g., heart rate variability [HRT], ratio-based HRT, complexity of HRT)	Chervin et al., 2009
Oxygen desaturations	Lario et al., 1996; Rizzi et al., 2004
Limb movements	Besteiro et al., 2011; Rizzi et al., 2004
Sleep microstructure	
Greater number of arousals	Rizzi et al., 2004; Sergi et al., 1999
α-EEG sleep	Branco, Atalaia, & Paiva,1994; Drewes et al., 1994; Roizenblatt et al., 2001
Cyclic alternatic pattern	Rizzi et al., 2004
Primary sleep disorders	
Sleep apnea	Gold et al., 2004; May, West, Baker, & Everett, 1993
Periodic limb movement disorder	Shaver, Wilbur, Robinson, Wang, & Buntin, 2006; Tayag-Kier et al., 2000

Methods

Participants

An observational case-control study was carried out to compare objective and subjective sleep variables in 40 patients with FMS and 35 control participants. Patients were referred from the Rheumatology Unit of the Virgen de las Nieves University Hospital in Granada (Spain). Patients' selection criteria were: (1) being a women (pain responses differ between sexes [Alabas, Tashani, Tabasam, & Johnson, 2012]), (2) fulfill the American College of Rheumatology criteria for FMS diagnosis (Wolfe et al., 1990) as their primary pain condition screened by a rheumatologist, and (3) stability on a medical regimen under the care of a rheumatologist. Exclusion criteria were as follows: (1) being pregnant; (2) having a medical history of significant head injury or neurological disorder; (3) having major concomitant medical conditions, including other pain conditions; (4) having major depressive disorder with suicidal ideation or other major Axis I diagnoses (American Psychiatric Association, 2000); (5) having a primary sleep disorder, based on screening polysomnography (apnea-hypopnea index ≥ 5 or periodic limb movement-related arousal index ≥ 15); (6) having a severe hypnotic dependence, suggested by the use of a hypnotic in a higher than recommended dosage or repeated episodes of rebound insomnia on withdrawal (Edinger, Wohlgemuth, Krystal, & Rice, 2005); and (7) use of recreational drugs or alcohol consumption of more than 40 g per day. Controls fulfilled the FM patients' inclusion and exclusion criteria, except FMS or chronic pain diagnosis, medication intake (except birth control pills), or sleep complaints or disorder. Healthy controls were recruited from local community by advertisement and word-of-mouth.

Table 7 displays descriptive analysis of the socio-demographic variables of the participants of the study. No significant differences were observed in age, body mass index, educational level, marital status, and employment status between women from clinical and control groups (p values > .05).

Table 7- Descriptive statistics for demographic and clinical characteristics of the fibromyalgia patients and the healthy controls.

	Fibromyalgia patients N = 40	Controls N = 35
	Mean (SD), range	Mean (SD), range
Age (years)	47.05 (5.48), 37-50	44.54 (7.32), 30-58
Body mass index (Kg/m^2)	26.08 (4.09), 19.10-35.80	24.50 (3.64), 17.50-34.60
Length of time since diagnosis (months)	80.38 (66.02), 1-240	-
VAS Pain intensity	7.41 (1.83), 3-10	-
Total PRI	20.82 (9.37), 4-40	-
HADS: Psychological distress*	21.20 (6.94), 1-39	8.54 (6.31), 0-24
	N (%)	N (%)
Medication		
Antidepressants	52.5	-
Anxiolytics	50	-
Opioids	47.5	-
Aniline analgesics	30	-
Nonsteroidal anti-inflammatory analgesics	57.5	-
Anticonvulsants	12.5	-
Education		
Without formal education	6 (15)	4 (11.4)
Basic education	10 (25.0)	5 (14.3)
High school	6 (15.0)	4 (11.4)
Professional instruction	8 (20.0)	5 (14.3)
University studies	10 (25.0)	17 (48.6)
Marital status		
Single	3 (7.5)	4 (11.4)
Married	34 (85.0)	25 (71.4)
Divorced or widowed	3 (7.5)	6 (17.2)
Work status		
Currently employed	20 (50.0)	20 (57.1)
Unemployed	14 (35.0)	15 (42.9)
Retired	0 (0)	0 (0)
Disabled	6 (15.0)	0 (0)

Note. SD = Standard deviation; VAS = Visual analogue scale; PRI = Pain Rating Index; HADS = Hospital Anxiety and Depression Scale
* t (71) = 8.075, $p < .001$

Measures

Polysomnography (PSG). An ambulatory PSG recording (with a SomnoScreen PSG-Tele, Somno Medics GmbH, Randersacker, Germany) was used to assess sleep parameters. The recording included EEG in several regions (in the frontal, central, parietal, and occipital midline regions [F_Z/A_1, C_Z/A_1, P_Z/A_1, O_Z/A_1], bilateral

electrooculography, bilateral submental and anterior tibial electromyography, and respiratory variables (nasal/oral airflow, thoracic effort, snoring, and pulse oximetry). Sleep stages were visually scored according to the standard criteria (Silber et al., 2007) by two sleep technologists, one of them masked to subject group. The following parameters were derived from the PSG data: Total sleep time (TST, total amount of sleep received from onset of sleep to onset of awakening), Sleep efficiency (proportion of sleep in the period potentially filled by sleep: percentage of TST to time in bed), Percentage of REM sleep (REM%, total time spent in REM sleep as a percentage of TST), Percentage of stage 1, stage 2, stage 3 NREM sleep (S1%, S2%, S3%, respectively; total time spent in stage 1, stage 2, and stage 3 NREM sleep as a percentage of TST), Wake percentage (W%, percentage of Wake time scored from bedtime to the final wake-up), Sleep latency (SL, total amount of time between "lights out" and sleep onset, defined as the first epoch of stage 1, followed by six consecutive epochs of stage 1 or a deeper NREM sleep stage), Wake after sleep onset (WASO, total amount of Wake time scored after sleep has been initiated and before final awakening), Number of awakenings (Number of epochs scored as wakefulness), Number of awakenings greater than 3 minutes (Number of more than six consecutive epochs scored as wakefulness), and Index of stage shifts (Number of sleep stage changes to wakefulness or another sleep stage per hour of sleep).

Pittsburgh Sleep Quality Index, PSQI (Spanish version of Royuela & Macías, 1997). The PSQI includes 19 items which provide a global index of sleep quality over a 1-month time interval, with a range of 0-21, higher scores indicating worse sleep quality. Scores above 8 have been used to indicate a clinically significant level of sleep disturbance in populations with physical illnesses (Carpenter & Andrykowski, 1998). Scores higher than 5 indicate poor sleep quality in general population. The internal consistency of the Spanish version of the PSQI subscales ranged between .67 and .81.

Epworth Sleepiness Scale, ESS (Spanish version of Ferrer et al., 1999). The ESS is a unidimensional scale which presents the respondent with eight soporific situations requesting selection of a Likert response option for each situation from a scale ranging from never dozing (0) to high chance of dozing (3). The global ESS score has a range of 0-24, with higher scores indicating higher levels of sleepiness. At a cut-off score of 10, this measure has high sensitivity and specificity to distinguish excessive daytime sleepiness from normal daytime sleepiness.

Hospital Anxiety and Depression Scale, HADS (Spanish version of Herrero et al., 2003). The HADS assesses anxiety and depression symptoms in non-psychiatric hospital contexts. The HADS includes 14 items (grouped into Anxiety and Depression dimensions) that are scored from 0 to 3. The HADS score has a range of 0-21with higher scores indicating higher anxiety and depression, respectively. Psychological distress was computed adding the subscales scores. The Cronbach's alpha is .84 for the Depression subscale and .85 for the Anxiety subscale.

McGill Pain Questionnaire, MPQ (Spanish version of Lázaro et al., 2001). The MPQ assesses pain quality, using 15 verbal pain descriptors, yielding a total pain rating index (total PRI) with a scoring range from 0 to 45, with higher scores indicating higher pain levels, and pain intensity, using a visual analogue scale (VAS) to assess pain intensity in the last week (from 1 = no pain to 10 = extreme pain). The Cronbach's alpha of the Spanish MPQ Total score is .74.

Procedure

We conducted the study in conformity with the Code of Ethics of the World Medical Association (Declaration of Helsinki) (World Medical Association, 2008). The study protocol was approved by the University of Granada's Ethics Committee. All participants were screened at the Sleep Unit of the Faculty of Psychology, where they provided informed consent and completed screening procedures including socio-demographics (age, gender, educational level, marital status, and employment status), general and sleep health, and pain conditions. Participants who met the criteria underwent a semi-structured clinical interview to assess clinical features like length of FMS diagnosis, comorbid medical diseases or psychopathological disorders, medication intake, and pain intensity. The history of sleep problems was assessed by the Insomnia Interview Schedule (Morin, 1999). We used questionnaire measures to evaluate sleep quality, sleepiness, pain, and anxiety and depression. In-home polysomnographic studies were scheduled for one night. Ambulatory polysomnography reduces significantly the first night effect, allowing a representative sampling of sleep parameters with a single night of recording (McCall et al., 1992). Despite knowing the impact of drugs on sleep architecture (Plante & Winkelman, 2009), patients were allowed to continue with their routine medication during the study to ensure the generalization to the larger population of patients with FMS who take many

medications. Despite this, patients were grouped depending on medication intake to compare sleep features among them.

Statistical Analysis

Descriptive statistics were computed for socio-demographic and clinical variables in patients with FMS. Student's *t* tests were carried out to compare the socio-demographic and clinical variables between groups. To check the possible covariates, regression analyses were computed to determine if age or psychological distress predicted sleep variables. Psychological distress did not predict any sleep variable. Then, to compare the results obtained in the polysomnography for the two groups, we carried out multivariate analysis of covariance (MANCOVA)[1], entering age as a covariate factor. When Wilks' λ was significant, univariate analyses of covariance (ANCOVA) was used to determine the variables in which the groups differed. We used η^2 as an effect size index. Values of $\eta^2 > .15$ can be considered high, and when $\eta^2 > .06$, the effect size is moderate. Significance was set at $p < .05$. All the statistical analyses were conducted with Statistical Package for the Social Sciences (SPSS 20.0).

Results

Polysomnographic features during sleep and subjective sleep quality

Multivariate analyses showed significant differences between the groups on sleep variables (Wilks' λ value: 0.23; F (14, 59) = 14.13, $p < .001$; $\eta^2 = .77$). Size effect was high, since 77% of the variability between groups in sleep variables is attributable to the clinical condition, once age effect was controlled for.

Sleep variables, derived from PSG data and self-reports, are detailed in Table 8. Regarding polysomnographic assessment, there were differences in sleep efficiency, several wake measures, and S1% (p values < .05). Differences in sleep efficiency, WASO, W%, and number of awakenings were high ($\eta^2 = .15$, $\eta^2 = .17$, $\eta^2 = .16$, $\eta^2 = .26$, respectively).

[1] A MANOVA was carried out to ensure that sleep variables did not differ between patients depending on medication intake (patients were grouped as not on medication, antidepressants intake, benzodiazepines intake, opioids intake, combined drugs intake). Wilks' value: 0.25; F (56, 83.9) = 0.64, $p < 0.960$.

Regarding subjective assessment, women with FMS rated their overall sleep quality as poor compared to control women and exhibited a greater daytime sleepiness (p values < .05). Differences in poor sleep quality were high (η^2 = .70). Despite that all the control women reported "good sleep" during interview, ten had a PSQI total score greater than five. Thirty-nine patients suffer from subjective poor sleep quality (PSQI total score > 8). Eleven patients and three controls have an ESS score greater than ten.

Correlation of subjective sleep quality, daytime somnolence, and PSG parameters

For patients with FMS, subjective poor sleep quality was associated with measures of alterations in the cyclic organization of sleep, e.g., inversely correlated with sleep efficiency, $r_{(40)}$ = -0.33 (p = .037); and directly associated with S2%, $r_{(40)}$ = 0.35 (p = .026); SL, $r_{(40)}$ = 0.34 (p = .031); and W%, $r_{(40)}$ = 0.33 (p = .037). Daytime somnolence was correlated with the index of stage shifts, $r_{(40)}$ = 0.36 (p = .023); and inversely associated with WASO, $r_{(40)}$ = -0.37 (p = .019), both measures of sleep fragmentation.

Table 8- Self-report and polysomnographic sleep variables in fibromyalgia patients and healthy controls

	Fibromyalgia patients N = 40 Mean (SD), range	Controls N = 35 Mean (SD), range	F	*p*	η^2
Self-reports					
PSQI Total Score	14.08 (3.67), 6-21	3.97 (2.77), 0-11	165.17	<.001	.70
ESS	8.43 (5.21), 1-21	5.23 (3.65), 0-12	9.59	.003	.12
Polysomnography					
Total Sleep Time (minutes)	442.42 (63.06), 265.50-557.50	425.95 (44.01), 317.50-517.00	1.22	.270	.02
Sleep efficiency (%)	85.35 (8.28), 60.00-96.83	91.07 (4.54), 80.54-97.04	12.88	.001	.15
Sleep latency NREM stage1 (minutes)	23.45 (19.83), 4.00-71.00	16.01 (14.76), 2.50-59.00	3.15	.080	.04
Wake After Sleep Onset (minutes)	49.46 (29.01), 9.50-109.50	25.00 (22.40), 1.5-105.16	14.28	<.001	.17
Wake, % TIB	14.65 (8.28), 3.17-40.00	8.80 (4.66), 2.70-19.46	13.20	.001	.16
NREM stage 1, % TST	6.99 (3.22), 1.20-15.20	5.29 (2.50), 2.20-15.70	5.46	.022	.07
NREM stage 2, % TST	51.44 (9.72), 35.00-69.10	47.97 (7.58), 29.00-59.90	1.31	.257	.02
NREM stage 3, % TST	18.29 (7.81), 4.00-34.00	22.48 (8.31), 10.10-48.00	2.79	.099	.04
REM sleep, % TST	23.28 (6.47), 8.90-34.30	24.87 (4.15), 13.50-32.00	1.04	.312	.01
Index of Stage Shifts	12.63 (4.10), 6.89-25.60	11.66 (2.32), 6.80-18.70	3.63	.061	.05
Number of awakenings	23.68 (8.24), 11-49	15.00 (5.76), 3-27	25.30	<.001	.26
Number of awakenings greater than 3 minutes	2.59 (1.78), 0-6	1.23 (1.43), 0-5	9.71	.003	.12

Note. SD = Standard deviation; PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; TIB = Time in Bed; TST = Total Sleep Time

Discussion

Patients with FMS commonly report sleep complaints. Due to their relevance, earliest and current diagnostic criteria for FMS include sleep abnormalities to categorize this syndrome (Wolfe et al., 2010; Yunus et al., 1981). Several studies have investigated sleep physiology in FMS population reporting inconsistent results, however. Thus, the aim of this study was to assess FMS sleep complaints objectively by using polysomnographic parameters that provide additional and important information about the characterization of actual sleep difficulties. To achieve this aim, we compared objective and subjective sleep variables between patients and healthy controls, controlling for age as a potential confound that can alter sleep parameters. Moreover, to ensure the generalization to the larger population of patients with FMS -who are actually taking medications- we allowed the use of pain medications during assessments.

We found objective alterations in the cyclic organization of sleep and the occurrence of signs of sleep fragmentation. In particular, we found lower sleep efficiency, and a greater percentage of sleep spent in stage 1 of NREM sleep. Several wake measures (e.g., WASO, W%, number of awakenings) were longer or more frequent during sleep period in patients with FMS. Previous studies have shown that sleep is lighter and less consolidated in patients with FMS (Besteiro et al., 2011; Burns, Crofford, & Chervin, 2008; Côté, & Moldofsky, 1997; Drewes et al., 1994; Landis et al., 2001; Landis, Lentz, Tsuji, Buchwald, & Shaver,, 2004; Roizenblatt et al., 2001, Rizzi et al., 2004; Sergi et al., 1999). In line with these results, recently, the *Sleep and Pain Diatheses model* of FMS (Hamilton, Atchley, Karlson, Taylor, & McCurdy, 2012) has considered the disrupted sleep as an etiological factor of FMS. Furthermore, in their review analysis, Hamilton and colleagues (2012) found that almost all FMS patients suffered from sleep problems and stated that "*polysomnographic abnormalities ... are the most consistently found objective clinical symptom of fibromyalgia*" (cit. p.84, Hamilton et al., 2012). Despite the above, the use of polysomnographic abnormalities as an objective and symptomatic criteria in FMS is not worldwide accepted. Different are the reasons why clinical and translational science is unwilling to accept Hamilton's idea. Firstly, results based on everyday clinical practice are few, being polysomnography not routinely indicated for patients with FMS due to the highly costs and inconvenience of this methodology. Secondly, the complex clinical profile observed among patients with

FMS indicates that it is a heterogeneous disorder with various subgroups, not only related to different clinical settings (Häuser et al., 2011), but also based on several combinations of sensory symptoms and comorbidities (e.g., group with extreme tenderness without depressive and/or sleep symptoms; group with pain attacks and tenderness and moderate sleep problems; group without discrimination among pain qualities and severe depression and sleep problems, etc.) (Rehm et al., 2010). In this vein, the *Sleep and Pain Diatheses model* only defines a *sleep-subtype* of FMS patients (similar to the latter cluster proposed by Rehm and colleagues [2010]) and other groups of patients might not be characterized by polysomnographic abnormalities. Finally, some of the most important causes that do not allow to reach a clear conclusion about polysomnographic features in FMS arise from the insufficient sample size used in previous studies and from the confounding effects generated by several uncontrolled clinical variables (e.g. psychological distress age-related). Aware of these limitations, we have examined a larger group of patients and controlled for the confounding factor of the patients' age. In line with Hamilton and colleagues (2012) and contrary to previous studies (Chervin et al., 2009; Roehrs et al., 2013) we have found unambiguous differences between groups, showing powerful and clear polysomnographic results. Furthermore, in this study, the alterations in the cyclic organization and occurrence of signs of fragmented sleep were corroborated by the self-report assessment of sleep quality. Data shown that women with FMS exhibited higher rates of subjective poor sleep quality, as shown by the global PSQI score. This finding is consistent with previous results: population-based studies found that subjective poor sleep quality was reported by 99% of patients with FMS (Hamilton et al., 2008; Theadom, Cropley, & Humphrey, 2007). Clinical studies also found that, symptoms related to non-restorative sleep are described as severe by patients with FMS (Rutledge, Jones, & Jones, 2007). Moreover, patients with FMS tend to perceive their nightly sleep as light and unrefreshing regardless of its duration (Moldofsky, 2008) and they suffer from elevated daytime symptoms. In our study, subjective assessment of sleep quality, as well as daytime somnolence, have a significant association with PSG parameters, confirming the original results by Landis and collleagues (2003) in their actigraphic study of women with FMS. Even though the current findings provide strong evidence on disturbed nocturnal sleep in FMS, future research should involve other independent

psychophysiological/ clinical measures of fatigue and sleepiness to clarify the daily repercussions of sleep disturbances (e.g. Multiple Sleep Latency Test).

In addition to the clinical implications, this study has also revealed clinical and practical consequences. Sleep disturbances are related to nociceptive mechanisms, including pain perception and modulation (Campbell et al., 2011). Moreover, sleep disturbances in patients with FMS lead to repercussions in the level of diurnal activity and performance, compromising patient safety. In fact, excessive daytime somnolence and fatigue in chronic medical conditions have been related with a higher risk of occupational and automobile accidents (Di Stasi, Diaz-Piedra, Catena, & Buela-Casal, 2012; Smolensky, Di Milia, Ohayon, & Philip, 2011; Williamson et al., 2011). Our findings provide relevant information on management of patients with FMS, as well as on scientific-based recommendations for the development of health and safety programs. Patients should learn to recognize their arousal levels in order to avoid sleepiness-related mistakes and accidents. Moreover, since all the ubiquitous symptoms in FMS and safety concerns are related to sleep disturbances, the recognition and treatment of sleep difficulties in patients with FMS can help to diminish morbidity in the syndrome (Korszun et al., 2002). Future studies should underlie if the improvement of sleep quality, both subjective and objective, also ameliorates other FMS symptoms. Indeed, several studies have shown that cognitive-behavioral therapy for insomnia is an effective intervention for sleep problems and for the improvement of diverse outcomes in patients with FMS (Edinger et al., 2005; Martínez et al., 2013; Miró et al., 2011; Sánchez et al., 2012).

Summarizing, our findings support that there are physiologic abnormalities in sleep that characterize patients with FMS (also when results are controlled for age as a confounding factor), which justify sleep symptoms in these patients, as well as complaints of daytime sleepiness.

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The impact of pain on anxiety and depression is mediated by objective and subjective sleep characteristics in fibromyalgia patients[1]

Abstract

Objectives: Pain is the cardinal feature in fibromyalgia syndrome (FMS) and increases risk of anxiety and depression. Patients with FMS frequently complain of sleep disturbances as well. Sleep may intermediate the association between pain and emotional symptoms, an idea which has been scarce studied. The objective of this study is to uncover the role of subjective and objective sleep characteristics as mediators of the relationship between pain and anxiety and depression in FMS. Methods: Fifty-five female patients with FMS (mean age, 47.62 ± 7.64 years) were assessed to obtain self-reports measures of pain, sleep quality, anxiety and depression levels, as well as self-efficacy to cope with pain. An ambulatory polysomnographic recording was performed to assess sleep architecture. Results: Subjective poor sleep quality was found in all patients. Pain correlated with subjective and objective sleep parameters, self-efficacy, anxiety, and, marginally, with depression. The mediated regression analysis suggested that the best models to explain the impact of pain on anxiety and depression included, as mediators, subjective sleep quality, objective sleep efficiency and self-efficacy (these models explained 34% of the variance), objective sleep efficiency being the mediator with the highest influence (p<.05). Discussion: These findings show a high prevalence of sleep problems in patients with FMS and suggest that they play a role in the relationship between pain and anxiety and depression. In fact, the impact of chronic pain on the later emotional variables was mediated, not only by self-efficacy, but also by subjective sleep quality and, especially, by objective sleep efficiency.

Keywords: Anxiety; Chronic pain; Depression; Fibromyalgia; Mediation analysis; Sleep; Polysomnography.

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Introduction

Fibromyalgia syndrome (FMS) is characterized by chronic widespread musculoskeletal pain and multiple tender points (Wolfe et al., 1990; 2010). It is also associated with a large number of symptoms and comorbidities, including fatigue, headache and migraine, other body and joint pains, neuropathic disorders, anxiety and/or depression disorder, and sleep disturbances (Lachaine, Beauchemin, & Landry, 2010; Rutledge, Mouttapa, & Wood, 2009). While the prevalence of FMS in the Spanish general population is 2.4%, there are marked gender differences, the syndrome being more than 20 times more prevalent among women (4.2%) than among men (0.2%) (Carmona, Ballina, Gabriel, & Laffon, 2001). Fibromyalgia has a severe impact on health systems, due to the increase in healthcare utilization and costs (Lachaine et al., 2010)[3], as well as on patients' quality of life (Rivera et al., 2006). Such an impact, together with he absence of clear evidence on its etiology and on effective therapeutic strategies (Bennett, 2005), makes the identification of precipitating factors of pain and the factors that increase the FMS symptoms greatly necessary and relevant at this point in time.

Chronic pain is considered the main symptom that characterises FMS. Such chronic pain often leads to the great challenges which are related to the continuous stressful demands resulting from pain experiences, and usually has complex relationships with other symptoms. Among these symptoms are sleep disturbances. Restorative sleep is normally a beneficial resource for patients who need to deal with these demands of chronic pain (Hamilton, Catley, & Karlson, 2007). However, patients with FMS often suffer from sleep disturbances, among which are complaints of poor sleep quality, and disturbances of sleep architecture and microstructure (Hamilton et al., 2008; Kooh et al., 2003; Moldofsky, 2008; Rizzi et al., 2004; Roehrs et al., 2013; Roizenblatt, Moldofsky, Benedito-Silva, & Tufik, 2001; Rutledge et al., 2007; Theadom, Cropley, & Humphrey, 2007). In fact, experimental and clinical evidence about the effects of chronic pain suggest that pain has a negative impact on sleep quality, not only in the short term but also in the long term (Smith & Haythornthwaite, 2004). Moreover, pain has been found to be the most important determinant of subjective sleep quality (Hamilton et al., 2007).

Sleep disturbances have been reported to be highly pernicious in patients with FMS (Rutledge et al., 2007), due to their ability to magnify adverse pain-related outcomes such as anxiety and/or depression (Hamilton et al., 2008). In addition, sleep disturbances in FMS may diminish the patient's affective resources, as well as their

ability to deal with and to recover from psychosocial stress resulting from pain experiences (Hamilton et al., 2008). This point of view derives from the consideration of illness as a result of *allostatic load*. The *allostatic load* can be defined as the physiological effect of accumulated adaptational demands on an individual, which is closely linked to the role of stress hormones in maintaining the homeostasis in the human body, including the brain (McEwen, 2003). Based on these grounds, sleep may affect the *allostatic load* because of its positive or negative impact on the daily functioning, when it is either restorative or disturbed, respectively (Hamilton et al., 2007).

Nonetheless, such links between the experience of pain and disturbed sleep appear to be bidirectional. Several clinical studies with patients suffering from chronic pain, including longitudinal studies, have suggested that pain prior to sleep can lead to poor sleep quality, and poor sleep quality would be related to increased pain during the subsequent day, when they are measured along consecutive days (Edwards et al., 2008; Smith & Haythornthwaite, 2004). In addition, disrupted sleep has also been found to influence other variables, such as, the inability to shift the attention away from pain and towards more rewarding activities (Affleck, Urrows, Tennen, Higgins, & Abeles, 1996).

Finally, there is a relationship between the experience of pain and negative affective responses (Bigatti, Hernandez, Cronan, & Rand, 2008). However, this relationship varies both between individuals and within the same individual over time. Poor sleep quality may have a role explaining this variations. The affective state which results from the stressful demands of the experience of pain depends on sleep quality (Hamilton et al., 2007). Although poor sleep quality is also independently related to negative affect in these patients (Hamilton et al., 2007; Theadom et al., 2007), sleep quality can be an important mediator of the relationship between pain and emotional distress and functioning (Miró, Martínez, Sánchez, Prados, & Medina, 2012). Miró and colleagues (2012) pointed out that pain *per se* does not directly produce emotional distress. The model proposed by these authors also included self-efficacy because pain-related outcomes vary with the level of perception of control and helplessness (Keefe et al., 2002). Additionally, self-efficacy to cope with pain can predict psychological and physical well-being in people with FMS (Culos-Reed & Brawley, 2000), that one being negatively related with pain, anxiety, and depression (Sánchez, Martínez, Miró, & Medina, 2011). From this point of view, sleep is considered as a resource to cope with

stressful events that mediates the affective responses to pain in chronic pain patients. This attempt to know about processes underlying the association between pain and emotional variables and the role of sleep as possible mediator of these relationships was limited by assessment of subjectively reported sleep. Physiological sleep parameters can contribute to a better understanding of relationships among different symptoms in this syndrome since both animal and human studies have demonstrated the relationships between physiological sleep disturbances (e.g.,fragmented sleep, alpha-delta electroencephalography [EEG] sleep) and pain and psychological distress (for a review, see Moldofsky, 2008). Our main aim is to uncover the role of both subjective and objective sleep characteristics as mediators of the influence of pain on anxiety and depression in patients with FMS, including self-efficacy as mediator of these relationships as well.

Methods

Participants

The sample included 55 women affected with FMS (M_{age}=47.62 ± 7.64 years). Time since FMS diagnosis ranged from one month to 27 years. Table 9 displays descriptive analysis of the socio-demograhic and clinical variables of the participants of the study.

Patients' selection criteria were: (1) diagnosis of FMS according to the American College of Rheumatology diagnostic criteria (Wolfe et al., 1990), (2) stability on a medical regimen under the care of a rheumatologist, and (3) being a woman (pain sensitivity and response to analgesic drugs differ between sexes (Wiesenfeld-Hallin, 2005)). Exclusion criteria, designed to exclude patients whose sleep complaints was better explained by other comorbid conditions, were as follows: (1) being pregnant; (2) having a medical history of significant head injury or neurological disorder; (3) having major concomitant medical conditions; (4) having major depressive disorder with suicidal ideation or other major Axis I diagnoses (APA, 2000); (5) having an apnea-hypopnea index or periodic limb movement-related arousal index of 15 or more per hour of sleep; and (6) having a severe hypnotic dependence as defined by Edinger and colleagues (2005).

The University of Granada Ethics Committee approved the study protocol and a written informed consent form was obtained from all the participants.

Table 9- Demographic and clinical characteristics of the 55 patients with fibromyalgia

		M (SD)
Age (years)		47.62 (7.64)
Duration of fibromyalgia symptoms (years)		8.48 (6.99)
		N (%)
Education		
	Without formal education	6 (10.9)
	Basic education	14 (25.5)
	High school	10 (18.2)
	Professional instruction	12 (21.8)
	University studies	13 (23.6)
Marital status		
	Single	3 (5.5)
	Married	48 (87.3)
	Divorced or widowed	4 (7.3)
Work status		
	Currently employed	21 (38.2)
	Unemployed	12 (21.8)
	Retired	5 (9.1)
	Disabled	17 (30.9)
Medication		
	Antidepressants	29 (56.9)
	Anxiolytics	29 (56.9)
	Analgesics	
	Opioids	26 (47.3)
	Aniline analgesics	28 (54.9)
	Nonsteroidal anti-inflammatory analgesics	25 (55.6)
	Anticonvulsants	13 (25.5)

Note. M = Mean; SD = Standard deviation.

Materials and procedure

We performed a cross-sectional descriptive study on 57 female patients with FMS referred from the Rheumatology Service and the Pain Unit of the of Virgen de las Nieves University Hospital in Granada and from the FMS association in Almería to the University of Granada Sleep Unit. The assessment process took place during around two weeks for each patient. It consists of two clinical interviews, questionnaires, and a polysomnography. Between the two interviews, a polysomnographic assessment was scheduled. Questionnaires were collected at the second interview. All participants were interviewed at first time to obtain their socio-demographics characteristics (age, gender, educational level, marital status, and employment status) and FMS features (length of illness, current medication, and pain intensity) with a semi-structured clinical interview.

Participants completed an ambulatory polysomnography to assess sleep architecture up to two weeks after first interview. In-home polysomnographic studies were scheduled for one night. Ambulatory polysomnography reduces significantly the first night effect, allowing a representative sampling of sleep parameters with a single night of recording (McCall, Erwin, Edinger, Krystal, & Marsh, 1992) . After this evaluation, two women were excluded because of sleep apnea. Self-reports measures were used to evaluate sleep quality, anxiety and depression levels, and self-efficacy for coping with chronic pain. At the second interview, where patients were asked about sleep and psychiatric history, they brought completed questionnaires back. Participants were allowed to continue with their routine medication during the study. The potential effects of medication on sleep were taken into account and controlled for in the analysis. The study was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2012).

Polysomnography (PSG). An ambulatory PSG recording (with a SomnoScreen PSG-Tele, Somno Medics GmbH, Randersacker, Germany) was obtained to assess sleep architecture and was also used to exclude subjects with sleep-disruptive comorbidities. The recording included EEG in the frontal, central, parietal, and occipital midline regions (F_Z/A_1, C_Z/A_1, P_Z/A_1, O_Z/A_1) in the subgroup of 47 patients from Granada, and in the central region (C_3/A_2, C_4/A_1) in the subgroup of 10 Almería patients, bilateral electrooculography, bilateral submental and anterior tibial electromyography, and respiratory variables (nasal/oral airflow, thoracic effort, snoring, and pulse-oximetry). Sleep studies were programmed according to usual sleep schedules for each patient. Sleep stages were scored visually according to standard criteria (Iber et al., 2007). The following parameters were derived from the PSG data: Total sleep time (TST, total amount of sleep received from onset of sleep to onset of awakening), Sleep efficiency (proportion of sleep in the period potentially filled by sleep: percentage of TST to time in bed), Percentage of REM sleep (REM%, total time spent in REM sleep as a percentage of TST), Percentage of stage 1, stage 2, and stage 3 NREM sleep (S1%, S2%, S3%, respectively; total time spent in stage 1, stage 2, and stage 3 NREM sleep as a percentage of TST), Percentage of deep sleep (DS%, total time spent in Stage 3 as a percentage of TST), Percentage of light sleep (LS%, total time spent in Stage 1 and Stage 2 as a percentage of TST), Wake percentage (W%, percentage of Wake time scored from bedtime to the final wake-up), Sleep latency (SL, total amount of time

between "lights out" and sleep onset, defined as the first epoch of stage 1, followed by six consecutive epochs of stage 1 or a deeper NREM sleep stage) and Wake after sleep onset (WASO, total amount of Wake time scored after sleep has been initiated and before final awakening). To quantify alpha activity, EEG data was analyzed by power spectral analysis (fast Fourier transform) performed in every 2-secod segment of NREM sleep stages for the whole night.

Pittsburgh Sleep Quality Index, PSQI (Spanish version of Royuela & Macías (1997)). The Spanish version includes 19 items which provide a global index of sleep quality over a 1-month time interval. The global PSQI score has a range of 0-21, with higher scores indicating worse sleep quality. Scores above 8 have been used to indicate a clinically significant level of sleep disturbance in populations with physical illnesses (Carpenter, & Andrykowski, 1998). The internal consistency of the Spanish version of the PSQI subscales ranged between .67 and .81(Royuela & Macías, 1997).

McGill Pain Questionnaire, MPQ (Spanish version of Lázaro et al. (2001)[1]). The MPQ assesses pain using 15 verbal pain descriptors (yielding sensory, affective, and total pain rating indices with a scoring range from 0 to 33, 0 to 12, and 0 to 45, respectively, with higher scores indicating higher pain levels), and a visual analogue scale to assess pain intensity in the last week (from 1 = no pain to 10 = extreme pain). The present study used the total pain rating index. The Cronbach's alpha of the Spanish MPQ Total score is.74 (Lázaro et al. (2001)).

Hospital Anxiety and Depression Scale, HADS (Spanish version of Herrero et al., 2003). The HADS assesses anxiety and depression symptoms in non-psychiatric hospital contexts. It includes 14 items (grouped into Anxiety and Depression dimensions) that are scored from 0 to 3. The HADS score has a range of 0-21with higher scores indicating higher anxiety and depression, respectively. For each construct, a score above 10 indicates a probable disorder of the relevant mood. The Cronbach's alpha is .84 for the Depression subscale and .85 for the Anxiety subscale (Herrero et al., 2003).

Chronic Pain Self-Efficacy Scale, CPSS (Spanish version of Martín-Aragón et al., 1999). CPSS assesses chronic pain patients' perceived self-efficacy in coping with the consequences of chronic pain. It includes 19 items that are on a scale of 0-10 where the patient rates their perceived self-efficacy in each proposed situation. The CPSS score

has a range of 0-190 with higher scores indicating higher levels of self-efficacy. Factor analysis confirmed three factors: self-efficacy for pain management, self-efficacy for coping with symptoms, and self-efficacy for physical function. The internal consistency of the CPSS is .91 for the total scale (Martín-Aragón et al., 1999).

Statistical Analysis

Descriptive statistics were computed for socio-demographic and clinical variables in patients with FMS. Pearson correlation coefficients were used to quantify the relationships between variables. Two clusters of multiple mediation models were examined with different variables as mediators of the effect of pain, the independent variable, on anxiety and depression, the dependent variables. Although pain, sleep, and emotional variables are all interrelated, a mediation approach was chosen following previous works with a similar analysis scheme (Miró et al., 2011). These multiple mediation models resulted in a better fit to the data than an adaptation of the moderate mediation model (Hayes, 2012), which produced worse results. The effects of socio-demographical and clinical variables were controlled for when necessary in each analysis. The first cluster in the multiple mediation model included subjective sleep quality and self-efficacy as mediators. With this cluster of analysis, we wanted to know if the multiple mediation model already reported by Miró and colleagues (2011) was confirmed when modeling our data. The second cluster added polysomnographic parameters as mediator to check the contribution of objective measures to the first model. Objective sleep efficiency was chosen because it was the polysomnographic parameter with the highest correlation with all involved variables, including significant associations with anxiety (Spira, Stone, Beaudreau, Ancoli-Israel, & Yaffe, 2009) and depression levels (Nutt, Wilson, & Paterson, 2008). Direct effects, indirect effects (specific and total), and total effects were estimated. The direct path is the effect of a variable X on a variable Y. The specific indirect effect is the path linking X to Y via a specific mediator. The total indirect effect of X on Y is the sum of the specific indirect effects of all the mediators. The total effect of X on Y is the sum of the direct and indirect effects. When two or more variables are significant mediators of the relationships between X and Y, the indirect effects are significant in the mediation analyses. To test the statistical significance of the indirect effects, bias corrected and accelerated (BCa) bootstrap confidence intervals (CIs) were computed (Preacher & Hayes, 2004; Preacher & Hayes, 2008). The bootstrap estimates were based on 5,000

bootstrap samples and 95% CI were obtained for statistical decision-making. A comparison between the specific indirect effects was also conducted to determine the relative weight of each mediator in the relationship. Estimates of all paths were calculated using ordinary least squares regression. All analysis were conducted using the Statistical Package for the Social Sciences (SPSS 15.0). The Preacher-Hayes SPSS macro for multiple mediation (freely available at www.quantpsy.org) was used. Statistical significance was set at $p<.05$.

Results

Clinical measures

Table 10 shows results of objective sleep from polysomnography, subjective sleep quality, pain, anxiety, depression, and self-efficacy for chronic pain. Poor subjective sleep quality was found in all patients. Mean PSQI global score was 14.63 ± 3.44. The percentage of patients who scored above 10 in the HADS subscales was 45% for depression and 60% for anxiety. Large amount of alpha-activity were identified in 72% of patients during NREM sleep stages.

Table 10- Baseline evaluation of variables by diagnosis of the 55 patients with fibromyalgia

	Total M (SD)
Polysomnography	
Total sleep time (minutes)	425.69 (67.24)
Sleep efficiency (%)	83.76 (10.72)
Wake percentage (%)	16.22(10.69)
REM sleep (%)	22.12 (6.55)
S1 NREM sleep (%)	7.25 (3.91)
S2 NREM sleep (%)	54.01 (9.06)
S3 NREM sleep (%)	16.59 (7.42)
Sleep latency	28.63 (27.66)
Wake After Sleep Onset (minutes)	57.25 (43.02)
Questionnaires	
Subjective sleep quality: PSQI global index	14.63 (3.44)
Pain: Visual analogic scale	7.59 (1.76)
Pain: Total pain rating index	23.73 (9.53)
Anxiety: HADS	11.32 (3.96)
Depression: HADS	11.12 (4.01)
Self-efficacy in chronic pain: CPSS	77.51 (36.96)

Note. M = Mean; SD = Standard deviation; PSQI = Pittsburgh Sleep Quality Index; HADS = Hospital Anxiety and Depression Scale; CPSS = Chronic Pain Self-Efficacy Scale.

Correlational Analysis

Table 11 displays a summary of the relationships between subjective and objective sleep variables, pain, anxiety and depression.

Pain was correlated with subjective poor sleep quality(r=.35, p<.01), polysomnographic SL (r=.37, p<.01), objective sleep efficiency (r=-.40, p<.005), wake percentage (r=.41, p<.01) and TST (r =-.47, p<.005). It was also associated with self-efficacy (r=-.29, p<.05), anxiety(r=.33, p<.05) and, marginally, with depression (r=.23, p=.09).

Table 11- Correlations among sleep variables, pain, anxiety and depression of the 55 patients with fibromyalgia.

	PSG: TST	PSG: %W	PSG: WASO	PSG: SE	PSG: % LS	PSG: % DS	PSG: % REM	PSG: SL	PSQI: Global Index	MPQ: Total PRI	HADS: Anxiety	HADS: Depression
PSG: TST	-											
PSG: %W	-.62[b]	-										
PSG: WASO	-.51[c]	.81[c]	-									
PSG: SE	.62	-1.0[b]	-.81[c]	-								
PSG: % LS	.04	-.06	-.01	.07	-							
PSG: % DS	-.15	.09	-.00	-.09	-.73[c]	-						
PSG: % REM	.11	-.00	.03	.00	-.64	-.06	-					
PSG: SL	-.30[a]	.67[b]	.21	-.67[c]	-.11	.11	.03	-				
PSQI:Global Index	-.31[a]	.28[a]	.09	-.25	.04	-.02	-0.05	.29[a]	-			
MPQ: Total PRI	-.47[c]	.41[b]	.23	-.40[c]	-.17	.14	0.09	.37[b]	.35[b]	-		
HADS: Anxiety	.02	-.10	-.17	.20	.07	-.12	0.03	-.13	.44[c]	.33[a]	-	
HADS: Depression	-.13	-.20	-.13	.10	-.12	.03	0.13	.05	.26	.23	.54[c]	-

Note. PSG = polysomnography; TST = Total Sleep Time; W=Wakefulness; WASO = Wake after sleep onset; SE = Sleep Efficiency; LS= Light Sleep; DS = Deep Sleep; SL= Sleep Latency; PSQI = Pittsburgh Sleep Quality Index; MPQ = McGill Pain Questionnaire; PRI = Pain Rating Index; HADS = Hospital Anxiety and Depression Scale. [a]p<.05; [b]p<.01; [c]p<.005.

Multiple Mediation Analysis

Several socio-demographic and clinical variables explained part of the percentage of variance of pain (work status: R^2=.15, p<.05), subjective sleep quality (work status: R^2=.14, p<.05, medication intake: R^2=.09, p<.05), and objective sleep parameters (medication intake: R^2=.07, p<.05). These variables were controlled for in the mediation analysis.

Mediation Analysis on Anxiety

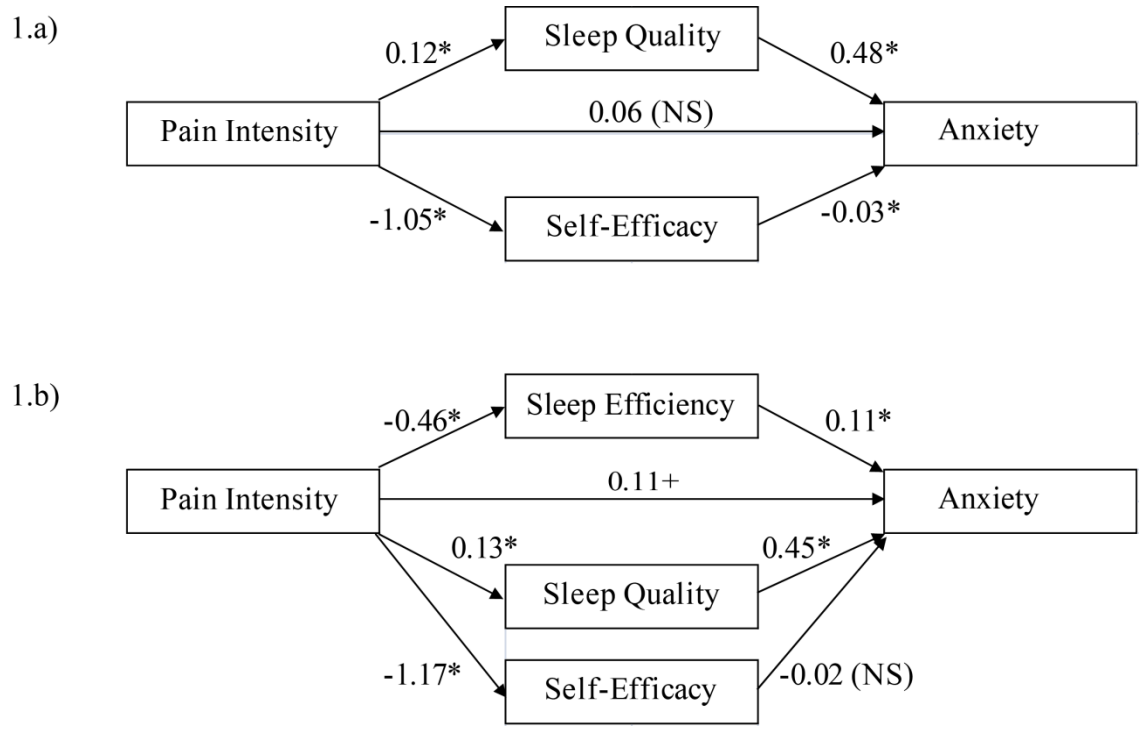
Figure 8 and Table 12 displays the multiple mediation models for the pain-anxiety relationship. In the first model (Figure 8a), the effect of pain on anxiety was mediated by subjective sleep quality and self-efficacy. The total effect (0.14, p<.02), but not the direct effect (0.06, p>.10) were significant. The effects of pain on these mediators were significant (0.12, p<.05 for subjective sleep quality; -1.05, p<.05 for self-efficacy), as well as the direct effects of the mediators on anxiety (0.48, p<.05 for subjective sleep quality; -0.03, p<.05 for self-efficacy). The contribution of mediators to this relationship was similar. The proposed model accounted for 32% of the variance of anxiety.

In the second model (Figure 8b), self-efficacy, subjective and objective sleep served as mediators of the pain-anxiety relationship. A significant total effect (0.14, p<.02), but marginally significant direct effect (0.11, p=.065) were observed. The contribution of pain to these mediators was significant (-0.46, p<.05, for sleep efficiency; 0.13, p<.05 for subjective sleep quality; -1.17, p<.05 for self-efficacy). The direct effects of sleep efficiency and subjective sleep quality on anxiety were significant (0.11, p<.05; 0.45, p<.05, respectively), whereas the direct effect of self-efficacy on anxiety was not (-0.02, p=NS).The indirect effect of sleep efficiency, when contrasted with the indirect effects of subjective sleep quality and self-efficacy, was higher (p<.05 in both contrasts). This model explained 34% of the variance in anxiety.

Table 12- Multiple mediation models of the effect of pain on anxiety through sleep and self-efficacy in the patients with fibromyalgia (controlling for work status and medication)

1.Subjective Measures mediating the Pain -Anxiety relationship			
		Bootstrapping	
		BCa 95% CI	
	Point Estimate	Lower	Upper
Total	0.090	0.041	0.179[a]
Sleep Quality	0.057	0.017	0.123[a]
Self-Efficacy	0.033	0.004	0.096[a]
Sleep Quality vs. Self-Efficacy	-0.024	-0.097	0.040[a]
2. Objective and Subjective Measures mediating the Pain -Anxiety relationship			
		Bootstrapping	
		BCa 95% CI	
	Point Estimate	Lower	Upper
Total	0.025	-0.043	0.108
Sleep Efficiency	-0.052	-0.111	-0.010[a]
Self-Efficacy	0.020	0.000	-0.971
Sleep Quality	0.057	-0.019	0.127[a]
Sleep Efficiency vs. Self-Efficacy	-0.073	-0.146	-0.018[a]
Sleep Efficiency vs. Sleep Quality	-0.108	-2031.00	-0.041[a]
Self-Efficacy vs. Sleep Quality	-0.036	-0.120	0.017

[a] $p<0.05$



*p<.05: +p=.065; NS: no-significant

Figure 8- Multiple mediation models examining 8.a) subjective sleep quality and self-efficacy; 8.b) subjective sleep quality, objective sleep efficiency, and self-efficacy as potential mediators of the relationship between pain and anxiety

Mediation analysis on Depression

Multiple mediation models for depression are displayed in Figure 9 and Table 13.

In the first mediation model (Figure 9a), involving the pain-depression relationship and subjective sleep quality and self-efficacy as mediators, only the contribution of pain to subjective sleep quality and self-efficacy was significant (0.12, p<.05; -0.05, p<.05, respectively). The direct effect of self-efficacy on depression was significant (-0.05, p<.05). The model accounted for 29% of the variance of depression.

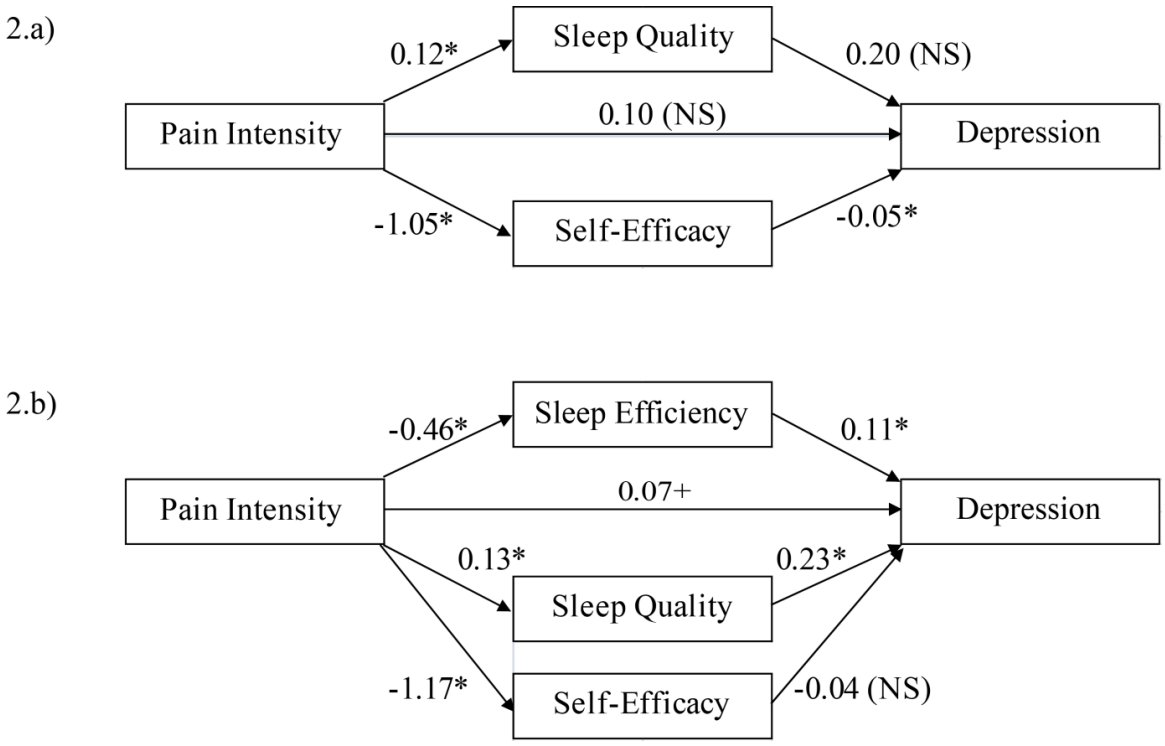
In the second model (Figure 9b), we observed significant total effect of pain on depression (0.14, p<.02). The contribution of pain to the mediators was significant (-0.46, p<.05, for sleep efficiency; 0.13, p<.05 for subjective sleep quality; -1.17, p<.05 for self-efficacy). The direct effects of sleep efficiency and subjective sleep quality on depression were significant (0.11, p<.05; 0.23, p<.05, respectively. The indirect effect of sleep efficiency was larger than the indirect effects of subjective sleep quality and

self-efficacy ($p<.05$ for both contrasts). This model accounted for 34% of the variance in depression.

Table 13- Multiple mediation models of the effect of pain on depression through sleep and self-efficacy in the patients with fibromyalgia (controlling for work status and medication)

1. Subjective Measures mediating the Pain - Depression relationship			
		Bootstrapping	
		BCa 95% CI	
	Point Estimate	Lower	Upper
Total	0.074	0.007	0.177 [a]
Sleep Quality	0.023	-0.012	0.076
Self-Efficacy	0.051	0.008	0.127 [a]
Sleep Quality vs. Self-Efficacy	0.028	-0.041	0.098
2. Objective and Subjective Measures mediating the Pain -Depression relationship			
		Bootstrapping	
		BCa 95% CI	
	Point Estimate	Lower	Upper
Total	0.023	-0.064	0.117
Sleep Efficiency	-0.053	-0.124	-0.010 [a]
Self-Efficacy	0.047	0.011	0.132 [a]
Sleep Quality	0.029	-0.009	0.084
Sleep Efficiency vs. Self-Efficacy	-0.102	-0.183	-0.038 [a]
Sleep Efficiency vs. Sleep Quality	-0.083	-0.182	-0.026 [a]
Self-Efficacy vs. Sleep Quality	0.019	-0.043	0.095

[a] $p<0.05$



*p<0.05. +p=.094. NS: non-significant

Figure 9- Multiple mediation models examining 9.a) subjective sleep quality and self-efficacy; 9.b) subjective sleep quality, objective sleep efficiency, and self-efficacy as potential mediators of the relationship between pain and depression

Discussion

Considerable research has focused on pain, as the main complaint, in FMS. The growing interest on sleep disturbances in these patients is based on the impact of sleep on FMS symptomatology (Smith & Haythornthwaite, 2004). In the present study, we aimed at uncovering the relationships among understudied variables in FMS, including sleep. Specifically, we asked whether the impact of pain on emotional variables is actually mediated by objective and subjective sleep parameters.

As expected, subjective poor sleep quality was found to occur commonly in these patients. This is a well-established result in previous research (Bigatti et al., 2008; Munguía-Izquierdo & Legaz-Arrese, 2012; Osorio, Gallinaro, Lorenzi-Filho, & Lage, 2006). Our results also agree that poor sleep quality is associated with anxiety levels (Miró et al., 2011; Munguía-Izquierdo, & Legaz-Arrese, 2012). However, we failed at observing a significant relationship between sleep quality and depression. In this vein, the literature shows mixed results. Munguía-Izquierdo and Legaz-Arrese (2012) also

failed to find an association between depressed mood and poor sleep quality in bivariate analysis, and found that only the state of anxiety, and not depression, contributed significantly to poor sleep quality. In stark contrast, Nicassio and colleagues (2002) found this association to be significant, and Ashworth, Davidson, and Espie (2009) observed a moderate association between depression and sleep quality, and depression was a significant predictor of sleep quality. Differences among depression measures can account for these discrepancies. For example, the HADS does not contain items referred to somatic symptoms (like sleep or fatigue).

Increased pain was associated with both objective and subjective sleep problems. Correlations among these subjective variables were also found in large samples of patients with FMS (Bigatti et al., 2008; Nicassio et al., 2002). Associations between pain and polysomnographic variables were described in chronic pain patients as well (Wilson, Watson, & Currie, 1998). However, there were no correlations between sleep PSG parameters and anxiety or depression. Stuifbergen and colleagues (2010) found that women with FMS with objective sleep deficits reported more depressive symptoms and a greater negative impact on functioning than those without objective deficits. These authors used an actigraphy, which does not measure the broad spectrum of sleep indices as PSG does. Kravitz and colleagues (2011), using PSG to assess sleep parameters in peri- and postmenopausal women from the general population, also failed to find associations between polysomnographic measures and depression or anxiety. Moreover, Edinger and colleagues (2000) suggested that depressed mood and anxiety, even at subclinical levels, are more predictive of subjective sleep complaints than of objective sleep disturbances, measured with PSG.

Pain complaints, anxiety, depression and psychological functioning are multidimensional constructs involving several biological, emotional, and behavioral components. The relationships among these factors in FMS may be confounded by other variables (Wong & Fielding, 2012), which can account for inconsistencies among studies. Multiple mediated models can be best suited to test complex relationships between pain and psychopathology than simple correlation analysis. Some authors (Miró et al., 2011) have observed mediational effects in the relationship between pain and anxiety, depression, and daily functioning. Their analysis was only performed with subjective sleep parameters.

Including subjective sleep quality, objective sleep efficiency and self-efficacy in the analysis, our mediation models accounted for more than 30% of the variance of these variables, being sleep efficiency the mediator with the highest influence in these relationships. Our results highlight, not only the importance of subjective assessment of sleep as compared to self-efficacy as noted by Miró, Martínez and colleagues (2011), but also the relevance of objective measures of sleep in understanding the impact of pain on emotional variables. Both subjective and objective sleep measures assess different aspects of an individual's sleep experience (Krystal & Edinger, 2008): Subjective sleep reflect mainly the patient's perception of sleep, but polysomnographyc measures can contribute several objective sleep indices derived from the architecture and microstructure of sleep. When both measures were contrasted, sleep efficiency, which has been usually considered less important in chronic pain populations than subjective sleep quality, had the largest weight.

Several studies reported no differences between FMS patients and controls in sleep efficiency when psychological distress was controlled for (Korszun et al., 2002; Roehrs et al., 2013). However, when emotional variables come into play, low objective sleep efficiency might explain greater fatigue, depression, and impairments in daily functioning (Korszun et al., 2002). Such physiological impairment in the sleep/wake cycle could account for problems in daily functioning and for affective responses as a consequence of chronic pain. The role of sleep as a maintenance, and probably etiological, factor of FMS symptoms was already proposed by Moldofsky (2008). Moreover, objective evidence of disrupted sleep is the key feature of the *Sleep and Pain Diatheses model* of FMS (Hamilton, Atchley, Karlson, Taylor, & McCurdy, 2012). FMS has traditionally been conceptualized as a pain disorder. This model states that sleep disturbances in people with high vulnerability to pain and sleep disruption initiates a cascade of symptoms which include pain, fatigue, cognitive impairment, somatic symptoms, and affective disruptions. Thus, interventions targeting sleep symptoms should improve sleep and other FMS symptoms, having long-term cost savings (Wagner, Chandren, DiBonaventura, & Cappelleri, 2013). Actually, several studies have shown improvements from cognitive-behavioral therapy for insomnia in diverse outcomes in FMS patient (Edinger et al., 2005; Martínez et al., 2013; Miró, Lupiáñez, Martínez, Sánchez, Diaz-Piedra, Guzmán, & Buela-Casal, 2011; Sánchez, Díaz-Piedra, Miró, Martínez, Gálvez, & Buela-Casal, 2012).

Our study has an important caveat. Although, like ours, most studies on the pain-sleep disturbances relationship have been cross-sectional, longitudinal designs will better disentangle the direction of relationships observed in this study.

Most patients with FMS reported poor sleep quality. Sleep disturbances are an important clinical concern in FMS, not only as a result of the general impact of sleep disorders on health (Buysse, Grunstein, Horne, & Lavie, 2010), but also because sleep disturbances may mediate and may perpetuate other symptoms associated with FMS (Abernethy, 2008). Accumulating evidence from clinical studies shows a complex relationship of disordered sleep to pain and affective disruptions. In fact, the impact of chronic pain on anxiety and depression was mediated not only by self-efficacy, but also by subjective sleep quality and, especially, by objective sleep efficiency.

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Changes in brain morphometry in women with fibromyalgia[1]

Abstract

Background: The pathophysiology of fibromyalgia syndrome (FMS) seems to be related to central nervous system alterations. Brain imaging data have provided with evidence suggesting that FMS is associated with structural cerebral changes which are related to clinical symptoms, especially psychological distress. The aim of this study is to compare brain matter volumes between patients with FMS and healthy controls and to determine whether these structural brain changes are related to depression, anxiety, pain intensity, and sleep quality. Methods: Brain matter volumes of twenty-three female patients with FMS were compared with twenty-four healthy women, using three Tesla magnetic resonance brain images. Self-reports of depression and anxiety levels, as well as of sleep quality, were also collected. Results: The group of patients presented a decrease in total gray matter volume. Pain intensity, depression, and anxiety levels predicted this brain structural alteration in patients with FMS. Although there were no statistically significant differences between patients and controls in total white matter volume, this tissue volume was determined by depression and anxiety levels in FMS patients. Conclusions: Brain structural alterations, specifically a reduction in total gray matter volume, are associated with FMS. The clinical significance of these alterations on the volume of gray matter is currently unknown. However, since neuroplasticity may determine these changes, and these are related to clinical symptoms, effective treatments of FMS symptoms could revert brain changes and improve patients' functionality in many areas.

Keywords: Anxiety; Chronic pain; Depression; Fibromyalgia; Magnetic Resonance Imaging; Sleep quality.

Introduction

In depth studies about the etiology of fibromyalgia syndrome (FMS) have yielded new insights into the pathophysiology of this syndrome, suggesting that FMS may be associated with central nervous system alterations (Schweinhardt, Sauro, & Bushnell, 2008). In particular, brain imaging data have provided with evidence about the

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associations between FMS and certain structural cerebral changes. Studies that have focused on gray matter alterations have found relevant differences in global and regional gray matter volumes between FMS patients and healthy controls. Kuchinad and colleagues (2007) found a decrease in total gray matter volume in patients, which was negatively associated, not only with age, but also with time since diagnosis. Reductions in regional gray matter density in regions associated with pain modulation or stress have also been described in other studies. These found significantly lower gray matter density in regions such as the cingulate, insular and medial frontal cortices, pahippocampal gyri, and thalamus (Kuchinad et al., 2007; Hsu et al., 2009; Lutz et al., 2008; Schmidt-Wilcke et al., 2007; Robinson, Craggs, Price, Perlstein, & Staud, 2011; Wood, Glabus, Simpson, & Patterson, 2009). Nonetheless, this finding was not always the case among those studies, occasionally there were not common regions of decrease in gray matter density. All these previously mentioned studies used a voxel-based morphometry (VBM) technique. This is a structural neuroimaging approach that uses differences in gray matter volume or density to study hypotheses regarding the central nervous system function, which probably reflects trait rather than state characteristics of the brain (Hsu et al., 2009). However, May (2008) stated that chronic pain is the result of a "maladaptive plasticity". In fact, central structural plasticity is important to understand that alterations in the cerebral pain network succeed the chronicity of pain and can be reversible, as found by Rodriguez-Raecke, Niemeier, Ihle, Ruether, and May (2009).

Since the structure of human brain may change because of environmental demands (Dragansky et al., 2004; May et al., 2007), it is important to known what factors are crucial in provoking these changes in patients with FMS. Fibromyalgia implies more than a chronic pain experience and other symptoms seem to be relevant to explain its pathophysiology (Wolfe et al., 2010). However, it is not clear whether changes in gray matter occur in relationship not only with pain, but also with other clinical symptoms frequently reported by patients with FMS, such as depression, anxiety, or sleep problems. Several studies have used depression, as the main potential confounding variable (Lorenzetti, Allen, Fornito, & Yücel, 2009), finding that there were no structural differences in the brain between patients and healthy controls after controlling for depression (Schmidt-Wilcke et al., 2007). This result was replicated by Robinson and colleagues (2011) for both depression and anxiety, because there were not associations between measures of negative effect and the gray matter volume. However,

studies carried out by Burgmer and colleagues (2009) and Hsu and colleagues (2009) found that the levels of psychological distress could explain part of the variance of regional gray matter density. In addition, several VBM studies have shown that insomnia patients also exhibit decrements in gray matter volume which correlate with the symptoms severity (Altena, Vrenken, Van der Werf, Van den Heuvel, & Van Someren, 2010; Riemann et al., 2007).

The aims of the present study were to compare brain matter volumes between patients with FMS and healthy controls and to determine whether these structural brain changes are related to the main FMS symptoms.

Methods

Subjects

Twenty-three female patients with FMS were referred from the Rheumatology Unit of the Virgen de las Nieves Hospital (Granada, Spain). Inclusion criteria were the diagnosis of FMS following the American College of Rheumatology criteria for FMS (Wolfe et al., 1990), and premenopausal status. Patients were not asked to alter or stop their medication prior to the study. Twenty-four healthy control women were recruited from local community by advertisements and word-of-mouth. They had no history of any chronic pain condition or sleep complaints or disorder, and did not intake central nervous system medications. The exclusion criteria for both groups included severe physical impairment; coexisting physical injury; comorbid medical illnesses (morbid obesity, autoinmune diseases, cardiopulmonary diseases, uncontrolled endocrine disorders – including diabetes -, uncontrolled allergic disorder/asthma, cancer, and/or medical history of significant head injury or neurological disorder); present psychopathological disorder (history of psychosis, current suicide risk- or attempt within 2 years of the study-, history of substance abuse, severe depression); pregnancy; use of recreational drugs; and alcohol consumption of more than 40 g per day. Written informed consent was obtained from all participants following the Declaration of Helsinki. No significant differences were observed in age, body mass index, marital status, and employment status between women from clinical and control groups (p values > .05). There were significant differences in their educational level (p = .009). All participants were Caucasian. Table 14 displays descriptive analysis of the socio-demographic variables of the participants of the study.

Table 14- Descriptive statistics for demographic and clinical characteristics of the fibromyalgia patients and the healthy controls

	Fibromyalgia patients N = 23	Controls N = 24
	Mean (SD), range	Mean (SD), range
Age (years)	41.57 (4.37), 27-47	39.75 (5.29), 30-47
Body mass index (Kg/m^2)	24.74 (4.15), 17.58-34.72	23.30 (3.44), 17.47-34.11
Length of time since diagnosis (months)	102.65 (75.91), 4-276	-
	N (%)	N (%)
Medication		
Antidepressants	13 (59.1)	-
Anxiolytics	9 (40.9)	-
Opioids	7 (31.8)	-
Aniline analgesics	9 (40.9)	-
Nonsteroidal anti-inflammatory analgesics	10 (45.4)	-
Anticonvulsants	4 (18.2)	-
Education		
Basic education	8 (34.8)	2 (8.3)
High school	2 (8.7)	5 (20.8)
Professional instruction	9 (39.1)	4 (16.7)
University studies	4 (17.4)	13 (54.2)
Marital status		
Single	4 (17.4)	6 (25.0)
Married	16 (69.6)	14 (58.3)
Divorced or widowed	3 (13.0)	4 (16.7)
Work status		
Housewife	8 (34.8)	3 (12.5)
Currently employed	6 (26.1)	12 (50.0)
Unemployed	5 (21.7)	9 (37.5)
Retired	2 (8.7)	-
Disabled	2 (8.7)	-

Note. SD = Standard deviation.

Assessment of pain

Patients exhibited a length of time since diagnosis with FMS ranged from four months to 23 years (102.6±75.9 months). The clinical pain experience was assessed using a numerical rating scale as a measure of pain intensity. Respondents were asked to choose a number between 0 and 10 to represent their pain experience during the last two weeks. In this scale, 0 meant no pain and 10 meant that pain was "as bad as it can be".

Assessment of psychological distress

The levels of depression and anxiety were assessed using the Hospital Anxiety and Depression Scale, HADS (Spanish version of Herrero et al., 2003). It includes 14 items,

grouped into Anxiety and Depression dimensions. The HADS score has a range of 0-21 with higher scores indicating higher anxiety and depression, respectively. For each construct separately, a score above 10 indicates a probable disorder of the relevant mood.

Assessment of sleep quality

Subjective sleep quality was assessed using the Pittsburgh Sleep Quality Index, PSQI (Spanish version of Royuela, & Macías, 1997). It includes 19 items which provides with a global index of sleep quality of over 1-month time interval. The global PSQI score has a range of 0-21, with higher scores indicating worse sleep quality. Scores above 8 have been used to indicate a clinically significant level of sleep disturbance in populations with physical illnesses (Carpenter, & Andrykowski, 1998). Scores higher than 5 indicate poor sleep quality in the general population.

Brain imaging: data acquisition and imaging protocol

Magnetic resonance imaging was performed on a 3T Phillips Achieva whole body MRI system (Philips Medical Systems, Best, The Netherlands) operating with eight channels phased-array head coil for reception. For each participant, a T1-weighted 3D volume was acquired using a MPRAGE sequence, in sagittal orientation with 0.94x0.94x1.0 mm resolution (160 slides, FOV=240x240 mm^2, matrix 256 x 256, 160 sagittal partitions) (repetition time, 8 ms; echo time, 4 ms; flip angle, 8º; fat saturation; band with 191 HZ/pixel). The voxels in all images before and after preprocessing were 1x1x1 mm. The sequence was designed to optimize the reduction of magnetic field inhomogeneities, motion sensitivity, and susceptibility artifacts.

Image analysis

Firstly, the T1 MRI-images were manually checked for morphological abnormalities or artifacts. Then, they were aligned to the anterior- posterior commissures line. We used the default parameters of SPM8 software (http://www.fil.ion.ucl.ac.uk/spm) and VBM8 (http://dbm.neuro.unijena.de/vbm.html) toolbox for SPM8 to process and analyze the data. Images were corrected for biasfield inhomogeneities, and registered using linear (twelve parameters affine) and non-linear transformations (warped), within a unified segmentation model (Ashburner, & Friston, 2005). Tissue was clustered into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Furthermore, we refined the segmentation procedure by using adaptive maximum a posteriori estimations

and by applying a hidden Markov random field model. In order to preserve local GM/WM values, we multiplied the segments by the Jacobian determinants of the deformation field to create modulated images. Finally, we smoothed segments using an isotropic Gaussian kernel (8 mm full-width at half-maximum). Afterwards, we conducted analysis on modulated GM and WM segments.

Statistical analysis

Comparison of clinical measures between patients and controls

Groups were compared in pain intensity, HADS anxiety and depression scores, and PSQI total score using two samples *t*-tests.

Comparison of whole-brain tissue volumes between patients and controls

To calculate total gray matter volume (TGMV), total white matter volume (TWMV), and total brain volume (TBV, the result of adding TGMV and TWMV), voxel values of GM/WM segments were added up. We performed two samples *t*-tests to assess differences in TGMV, TWMV and TBV between patients and controls.

Predictors of brain structural alterations

Multiple regression models were calculated using a backward procedure to determine the weight of clinical symptoms (pain intensity, depression, anxiety, and sleep quality), as well as time since diagnosis, explaining tissue brain volumes in FMS group.

Statistical significance was set on $p < .05$. All the statistical analyses were conducted with Statistical Package for the Social Sciences (SPSS 20.0).

Results

Clinical pain, psychological distress, and sleep symptoms

The pain intensity experienced by patients with FMS was higher than the pain experienced by participants of the control group (FMS group pain score = 6.8±3.6; control group pain score = 1.0±1.4; $p<.001$).

FMS patients also showed significantly higher scores in the HADS depression subscale (FMS group HADS depression score = 9.5±3.5; control group HADS depression score = 4.4±3.4; $p<.001$) and HADS anxiety subscale (FMS group HADS anxiety score = 10.8±4.3; control group HADS anxiety score = 5.7±3.1; $p<.001$). The majority of

patients had a score above 10 in the depression (61.9%) and anxiety (71.4%) HADS scales. Two control women obtained scores greater than 10 in these subscales.

Patients with FMS also reported poorer sleep quality (FMS group PSQI total score= 14.2±3.9; control group PSQI total score= 3.7±2.3; p<.001). Most patients (91.4%) showed a PSQI global score greater than eight, whereas four control women (16.6%) showed a PSQI global score greater than five, exhibiting poor sleep quality.

Global differences in brain morphometry

Patients had less TGMV than controls; t (45) = 2.21, p = .032, whereas there were no differences in TWMV; t (45) = 1.50, p = .139, and TBV; t (45) = 1.96, p = .057. Figure 10 shows cerebral resonance images from a patient with FMS compared to a healthy control.

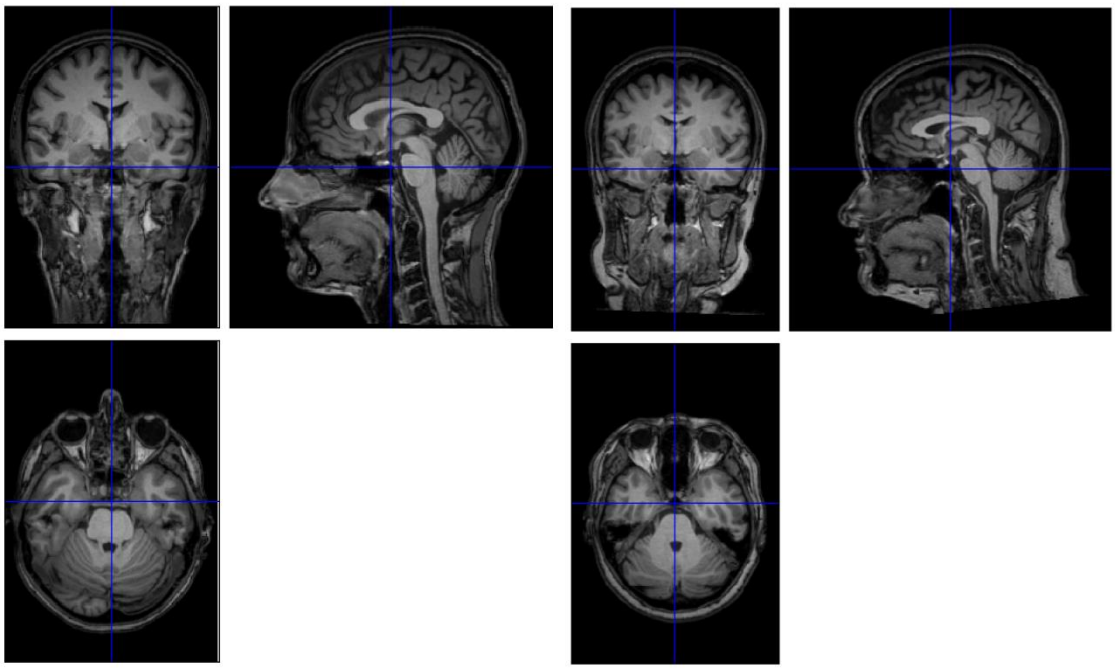

Figure 10- Cerebral resonance images from a patient with FMS (right) and a healthy control (left). Voxel-wise comparison of gray matter shows significantly less total gray matter volume in patients.

Multiple regression analysis

The multiple regression model with TGMV as dependent variable showed that depression levels (β = -.77; p = .026), anxiety levels (β = .88; p = .016), and pain intensity (β = -.44; p = .046) were the clinical variables that were independently and

significantly correlated with this brain tissue volume. The other tested variables (sleep quality and time since diagnosis) were removed from the model. This model accounted for 20.9% of the variance of TGMV (adjusted R^2).

The multiple regression model with TWMV as dependent variable showed that depression levels (β = -.86; p = .001) and anxiety levels (β = .96; p = .004) were the clinical variables that were independently and significantly correlated with this brain tissue volume. The other tested variables (pain intensity, sleep quality and time since diagnosis) were removed from the model. This model accounted for 29.0% of the variance of TGMV (adjusted R^2).

Discussion

The experience of chronic pain may lead to alterations in brain morphology in FMS. Therefore, we compared brain tissue volumes (TGMV, TWMV, TBV) between patients with FMS and healthy controls in order to determine whether structural brain changes are related to pain intensity, depression, anxiety, and sleep quality.

Our results show that patients with FMS exhibit reduced total gray matter volume, whereas there were no differences in total white matter volume or total brain volume when compared to age-matched controls. These findings are in agreement with the seminal results of Kuchinad and colleagues (2007), who first revealed a total gray matter decrement in patients with FMS. The authors explained this result by considering the normal age-related decrement of gray matter accelerated because of FMS. However, they assessed only small sample of pre- and post-menopausal women. Moreover, they could not determine the role of hormone replacement therapy (HRT) in this tissue loss because only two patients were on HRT. Importantly, there is evidence that HRT has an effect on gray matter morphology, slowing down the age-related gray matter loss in postmenopausal women (Boccardi et al., 2006). Contrarily, here, we have assessed a larger sample of pre-menopausal women and age-matched controls, and corroborated the hypothesis that gray matter loss in brain tissue are related to FMS. In fact, our results suggest that FMS symptoms influence brain morphology. Gray matter alterations were predicted by pain intensity, depression, and anxiety levels. This study also confirms previous documented observations, described by independent groups, on the relationship between various types of chronic pain and brain morphologic alterations (e.g., Smallwood et al., 2013). Several VBM studies have also found regional

decrements of gray matter density in pain-related brain areas (Kuchinad et al., 2007; Hsu et al., 2009; Lutz et al., 2008; Schmidt-Wilcke et al., 2007; Robinson et al., 2011; Wood et al., 2009), corroborating this global result. Furthermore, in our study, it is shown that clinical symptoms are influencing brain morphology. Pain intensity is independently related to gray matter decrement. Few studies have focused on the contribution of pain intensity, possible because it is the main symptom in FMS and they seem interchangeable. Several regional decrements in gray matter density have been related to pain experience. For example, the inferior frontal gyrus, insula, putamen, or anterior cingulate cortex are regions which exhibit gray matter decrements in chronic pain patients (Smallwood et al., 2013). They are involved in pain perception and related to the affective aspects of pain processing (Price, 2000; Wood, Glabus, Simpson, & Patterson, 2009). However, the pain experience is accompanied by other symptoms, including psychological distress or poor sleep quality (Wolfe et al., 2010). In fact, in our study, depression and anxiety levels predict brain structural changes, a similar result found by Burgmer and colleagues (2009) and Hsu and colleagues (2009). This result implies that altered brain morphology in FMS is related not only to altered pain processing but also to frequent symptoms. Although sleep disorders have been related to structural brain changes (Altena et al., 2010; Riemann et al., 2009), sleep quality did not predict brain alterations in FMS. Future studies should determine if objective sleep characteristics in FMS explain brain tissue decrements.

Although many resonance imaging studies have contributed to the understanding of the neurobiological aspects that are related to pain syndromes, the clinical significance of the gray matter volume alterations is currently unknown. The current findings support the idea that pain input on the brain and the underlying psychosocial mechanisms of pain are the cause of brain morphological changes in FMS. The concept of neuroplasticity, as described by May (2008), is essential to state that these morphological changes may be, at least in part, a consequence of suffering from constant pain rather the cause. From this point of view, an effective treatment may revert gray matter abnormalities; therefore these abnormalities would not reflect a brain damage. However, all brain imaging studies in FMS compared cohorts of patients and controls and, consequently, it is impossible to draw a clear conclusion on the cause or consequence of brain morphological changes. Future studies should address this question having in mind that there is evidence regarding a partly reversible gray matter

decrement after treatment in other chronic pain syndromes (Rodriguez-Raecke et al., 2009; Seminowicz et al., 2011).

Concluding remarks

The current study made a relevant contribution to the growing body of literature on FMS, suggesting that this syndrome is associated with changes in gray matter volumes. Our data argues against the idea that FMS is just an exaggerated report of pain of hypervigilant patients, providing evidence about the relationship between pain experience and changes in brain morphology, such as GM decrease. Whether it is not known the cause of these alterations, pain intensity, depression, and anxiety levels seem to play a critical role in FMS brain morphological changes**.**

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Cognitive-behavioral therapy for insomnia and sleep hygiene in fibromyalgia: a randomized controlled trial[1]

Abstract

Sleep disturbances play an important role in the exacerbation of pain and other troubling symptoms reported by patients with fibromyalgia syndrome (FMS). The objective of this trial was to analyze the efficacy of a cognitive behavioral therapy for insomnia (CBT-I) vs. a sleep hygiene (SH) education program at improving sleep and other clinical manifestations in FMS. Sixty-four FMS women with insomnia were randomly assigned to the CBT-I or the SH groups, and 59 completed the treatments (30 in the CBT-I group and 29 in the SH group). Participants completed several self-report questionnaires at pre-, post-treatment and follow-ups. The CBT-I group reported significant improvements at post-treatment in several sleep variables, fatigue, daily functioning, pain catastrophizing, anxiety and depression. The SH group only improved significantly in subjective sleep quality. Patients in the CBT-I group showed significantly greater changes than those in the SH group in most outcome measures. The findings underscore the usefulness of CBT-I in the multidisciplinary management of FMS.

Keywords: Cognitive-behavioral therapy; Fibromyalgia; Insomnia: Randomized controlled trial; Sleep hygiene.

Introduction

Fibromyalgia syndrome (FMS) is a chronic pain condition characterized by widespread pain for at least 3 months and 11 or more of 18 tender point sites on digital palpation, according to the American College of Rheumatology (ACR; Wolfe et al., 1990). FMS is the most common rheumatic disease after low back/neck pain and osteoarthritis (Lawrence et al., 2008) and affects mostly women (the female/ male ratio of FMS patients is as high as 21:1) (Mas et al., 2008). Annual medical costs per FMS patient ($4,065) are significantly higher than those of patients without FMS ($2,766) (Lachaine et al., 2010).

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[1] Martínez, M. P., Miró, E., Sánchez, A. I., **Díaz-Piedra, C.**, Cáliz, R., Vlaeyen, J. W. S., & Buela-Casal, G. (2013). Cognitive-behavioral therapy for insomnia and sleep hygiene in fibromyalgia: randomized controlled trial. *Journal of Behavioral Medicine*, 10.1007/s10865-013-9520-y.

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Disrupted sleep is a significant problem for many FMS patients. Recent studies have shown that 94.7-96% of such patients are bad sleepers (Bigatti et al., 2008). Yet, although 44% of FMS patients rate their sleep as bad or fairly bad, only 21% have objective sleep deficits (Stuifbergen et al., 2010). Non-restorative sleep is reported by FMS patients as the third symptom experienced with the highest intensity, after stiffness and fatigue (Rutledge et al., 2007), with FMS patients suffering more insomnia, less contentment with sleep and more lack of deep and restful sleep in comparison to rheumatoid arthritis patients and subjects of the general population (Belt et al., 2009). Although the physiological evidence for disordered sleep is not completely consistent across studies, several reports have described the anomalies in sleep continuity, architecture and microstructure of FMS patients. Many characteristics of sleep dysfunction in FMS patients include reduced total sleep time, greater number of awakenings and arousals, increased latency of sleep onset and of rapid eye movement (REM), more frequent changes of sleep stage, reduced percentage of slow-wave sleep, several manifestations of sleep instability such as alpha-delta activity, K-alpha periodic intrusions, and a cyclic alternating pattern of arousal (see reviews by Moldofsky, 2009, 2010; Prados & Miró, 2012; Spaeth et al., 2011). Consistent with this, unrefreshing sleep has been proposed by the ACR (Wolfe et al., 2010) as one of the most important diagnostic variables in FMS in addition to widespread pain, cognitive symptoms, fatigue and a number of somatic symptoms.

It has been suggested that genetic, neurophysiological, neuroendocrine and environmental factors contribute to the development/maintenance of FMS. From a psychological approach, the role of conditioning principles and cognitive processes has been considered in chronic pain conditions (see reviews by Gatzounis et al., 2012; Keefe et al., 2004; Leeuw et al., 2007; Meulders et al., 2011). However, the pathogenesis of FMS has not been definitely established yet.

Altered function of central pain-processing mechanisms, such as deficient descending analgesic activity and central pain augmentation or sensitization, has been proposed as playing an etiological role in FMS (Lee et al., 2011). In addition, several studies using functional magnetic resonance imaging (Cook et al., 2004; Gracely, Petzke, Wolf, & Clauw, 2002) have documented the relevance of central sensitization in FMS patients. In recent years, a promising approach emphasizing the influence of sleep on hyperalgesia in chronic pain syndromes has gradually gained importance. It has been

suggested that disordered sleep may contribute to a decrease in the sensory inhibitory function of the central nervous system to the perception of noxious stimuli (see reviews by Moldofsky, 2009, 2010). Along these lines, a recent prospective study has identified a strong association between sleep problems and risk of FMS among adult women (Mork, & Nilsen, 2012). Moreover, several clinical studies have evidenced the complex relationship between sleep disturbances and other clinical manifestations of FMS, showing that sleep quality may influence pain, fatigue, mood state, cognitive performance and daily functioning (Bigatti et al., 2008; Hamilton et al., 2008, 2012; Nicassio et al., 2002; Miró et al., 2011a, c; Theadom et al., 2007; for a review, see Prados, & Miró , 2012). For example, Nicassio and colleagues (2002) examined the relationship between pain, sleep, fatigue and depression in FMS patients, noting that in the cross-sectional assessment greater depression and lower sleep quality were associated with higher fatigue, and in the prospective daily assessment the previous day's pain and sleep quality predicted the next day's fatigue. Interestingly, the paths amongst various FMS symptoms are multidirectional. For example, it has been reported that the relationship between pain and emotional distress was mediated by sleep quality (and self-efficacy) (Miró et al., 2011c). In addition, the relationship between sleep and pain was mediated by cognitive processes and the relationship between sleep and disability was mediated by pain (Hamilton et al., 2012). In line with this, several models aimed at explaining FMS have considered the role of sleep. For example, the unifying model of central nervous system pathogenesis in FMS (Russell, & Larson, 2009) indicates that genetic predisposition to brain degeneration and a variety of factors (i.e., age, physical trauma, dysfunctional sleep) lead to neuroendocrine changes that seem to determine an abnormal processing of pain. Thus, the mechanisms of nerve repair of this cortical damage generate increased production of the nerve growth factor, which seems to be associated with a higher concentration of substance P, and this would cause hyperalgesia, insomnia, depression, low levels of biogenic amines and inhibition of the stress response system (Russell, & Larson, 2009).

If sleep disturbances play a significant role in the exacerbation of pain and other troubling symptoms associated with FMS, achieving restorative sleep is likely to lead to an improvement in all these symptoms. In a prospective study of people with chronic widespread pain, those who reported good-quality sleep were more likely to report the resolution of pain and return to musculoskeletal health (Davies et al., 2008). Recently,

some psychological treatments of chronic pain have started to include sleep management, among other components (e.g., Andersson et al., 2012). Yet, few treatment approaches focus on sleep problems of FMS patients. To the best of our knowledge, only seven randomized controlled trials have explored the efficacy of cognitive-behavioral therapy for insomnia (CBT-I) in chronic pain syndromes (Currie et al., 2000; Edinger et al., 2005; Jungquist et al., 2010; Miró et al., 2011b; Pigeon et al., 2012; Sánchez et al., 2012; Vitiello et al., 2009). Only three of such studies (Edinger et al., 2005; Miró et al., 2011b; Sánchez et al., 2012) were conducted with FMS patients. Edinger and colleagues (2005) compared CBT-I (n = 18), sleep hygiene (SH) (n = 18) and usual care (UC) (n = 11) in FMS patients at baseline, post-treatment and 6-month follow-up using sleep logs and actigraphy to assess various sleep parameters, and questionnaires on insomnia, pain, mood and quality of life. They found that 57% of participants in the CBT-I group met strict subjective sleep improvement criteria by the end of the intervention (vs. 17% in the SH group and 0% in the UC group). The other two studies were done by our research team, and we explored the efficacy of CBT-I in FMS using polysomnography (PSG) and neuropsychological tests. In the first study (Miró et al., 2011b), we compared CBT-I (n = 20) and SH (n = 20) at pre- and post-treatment with questionnaires and neuropsychological tests, and we evidenced the superiority of CBT-I to improve sleep and attentional functioning. In this study, 85% of patients in the CBT-I group showed clinically significant changes in sleep quality (vs. 55% in the SH group). In the second study (Sánchez et al., 2012), we compared the effect of CBT-I (n = 13) and SH (n = 13) at pre- and post-treatment on sleep parameters using PSG, and we identified improvements in the CBT-I group in time in bed, wake percentage, sleep efficiency, and changes in sleep architecture (an increase in deep sleep time and a decrease in light sleep time), which were not observed in the SH group.

Although the efficacy of CBT-I in FMS has been reported using objective measures, data provided by a self-reported measure are more informative than those obtained by an objective measure at identifying patients' perceived distress. It should be noted that complaints of poor sleep are more common than objective sleep deficits (Stuifbergen et al., 2010). Moreover, the usual sleep patterns obtained with subjective measures (e.g., Pittsburgh Sleep Quality Index, PSQI; Buysse et al., 1989) typically differ from those obtained with PSG; in fact, only weak correlations have been found between PSQI and PSG (Backhaus et al., 2002; Buysse et al., 1991). This relative lack of convergence

between measures may be explained considering that the PSQI assesses usual patterns of sleep and sleepiness, whereas PSG evaluates sleep and sleepiness on a specific occasion, and that the PSQI assesses aspects of sleep (such as sleep quality) that are not directly captured with PSG (Buysse et al., 2008). Hence, it is relevant to analyze whether the sleep improvements achieved with the CBT-I according to PSG in a small group of FMS patients in a previous study (Sánchez et al., 2012) are also observed using self-report measures of sleep quality in a larger sample; it is also interesting to explore whether these changes are also found in other clinical aspects and are maintained at follow-ups.

The evidence-based guidelines for the treatment of FMS of the American Pain Society (APS), the European League against Rheumatism (EULAR) and the Association of the Scientific Medical Societies in Germany (AWMF) propose a multidisciplinary approach. However, the EULAR mostly recommends pharmacological treatment, while the APS and AWMF mostly recommend exercise, CBT, amitriptyline, and multicomponent treatment (Hauser et al., 2010). Surprisingly, none of these guidelines includes specific recommendations for treating sleep problems, although CBT-I can improve the well-being of FMS patients. Moreover, although a recent meta-analysis of psychological treatment for FMS (Glombiewski et al., 2010) reported that CBT is better than other psychological interventions in reducing pain, studies about the efficacy of CBT focused on insomnia are scarce and the role of sleep in FMS symptoms needs further research.

The aim of this trial was to collect additional evidence of the efficacy of CBT-I to treat insomnia in FMS. To this end, we compared the effect of a CBT-I program versus an educational SH program on sleep quality and other troubling symptoms in FMS women. In order to explore the efficacy of this treatment, the statistical and clinical relevance of the changes was considered. The specific hypotheses proposed were: (1) CBT-I will produce significantly greater statistical and clinical improvements in sleep quality than SH; (2) CBT-I will produce significantly greater statistical and clinical improvements in pain intensity, fatigue and daily functioning than SH; and (3) CBT-I will produce significantly greater statistical and clinical improvements in self-efficacy and pain catastrophizing and emotional distress than SH.

The previous studies (Miró et al., 2011b; and Sánchez et al., 2012) and the present study are part of the same research. The present study, compared to the previous studies,

included a larger sample, PSQI subscales, self-report measures about fatigue, pain catastrophizing and self-efficacy for coping pain, and assessment at 3 and 6 month follow-up.

Methods

Design and participants

The guidelines of the CONSORT 2010 (Moher et al., 2010) were considered. An individually randomized, 2-group, parallel trial design was used. Fifty-nine adult women with FMS participated in the study. Patients were recruited from the Rheumatology Service and Pain Unit of Virgen de las Nieves University Hospital (Granada, Spain) and referred to the Clinical Psychology Unit of the University of Granada, where the psychological assessment and treatment sessions were conducted.

Inclusion criteria to participate in the study were: (1) being a woman aged between 25 and 60; (2) meeting the diagnostic criteria for FMS (ACR, Wolfe et al., 1990); (3) having had this disorder for more than 6 months so that adaptation to the impact of the diagnosis had already occurred; (4) being stable as regards the intake of analgesics, antidepressants or other drugs at least 1 month before the study; and (5) meeting the diagnostic criteria for insomnia (DSM-IV-TR, American Psychiatric Association, APA, 2000). Exclusion criteria were as follows: (1) being pregnant; (2) having a medical history of significant head injury or neurological disorder; (3) having major concomitant medical conditions; (4) having major depressive disorder with suicide ideation or other major Axis I diagnoses (APA, 2000); (5) having symptoms of sleep-disruptive comorbidities with insomnia; (6) having an apnea-hypopnea index or periodic limb movement-related arousal index of 15 or more per hour of sleep; (7) having a severe hypnotic dependence; and (8) being treated with another psychological or physical therapy at the time of the study.

One hundred and twelve eligible FMS women from 25 to 60 years old were screened using a brief interview administered by a psychologist via telephone. Of these patients, 77 women with FMS who fulfilled the inclusioncriteria were admitted for psychological assessment. The subjects completed a semi-structured interview in two sessions. Session 1 focused on the onset and course of FMS and insomnia, biographical history, lifestyle, work activity, family and social relations, and psychological state. After the interview the patients were given several self-report questionnaires and a sleep diary to

complete at home. Session 2 was devoted to completing additional data on insomnia, collecting questionnaires, and applying a neuropsychological test. Within 1 week after Session 2, a PSG recording was performed to exclude patients with sleep disorders other than insomnia. All patients completed the sleep diary for 2 weeks before treatment and during the time of intervention. A subgroup of patients was also assessed with PSG and a neuropsychological test at post-treatment (changes in these measures were reported in Miró et al., 2011b, and Sánchez et al., 2012).

After the initial assessment, 64 women with FMS were randomly assigned to either a cognitive-behavioral treatment for insomnia (CBT-I, n = 32) or a sleep hygiene educational program (SH, n = 32). For random allocation of the patients to the treatments (simple randomization, 1:1) a computerized number generator was applied by a researcher blinded to the implementation of the trial. Finally, 30 patients in the CBT-I group and 29 patients in the SH group completed the treatments and were included in the analyses (see Figure 11 for the flowchart of this study). Patients were instructed to strictly follow their treatment while participating in the study. All subjects received detailed information about the study and signed an informed consent form. The present research received ethical approval from the University of Granada Ethics Committee.

Measures

The questionnaires were applied at pre-, post-treatment and follow-up performed at 3 and 6 months after the intervention. The patients completed the questionnaires on these assessment moments, considering how they had felt in the previous week. The measures were assessed by a sleep expert (C.D.P.) who was blinded to group assignment. Sleep quality was considered as the primary outcome measure, and pain, fatigue, daily functioning, self-efficacy, catastrophizing, anxiety and depression were considered as secondary outcome measures.

Pittsburgh Sleep Quality Index (PSQI, Buysse et al., 1989): The PSQI includes 19 items that explore Subjective sleep quality, Sleep latency, Sleep duration, Habitual sleep efficiency, Sleep disturbances, Use of sleeping medication, and Daytime dysfunction. The subscale scores ranged from 0 to 3 and the Sleep quality-Total score ranged from 0 to 21, with high scores indicating disturbance. The Spanish version showed acceptable validity and internal consistency (Royuela, & Macías, 1997). The PSQI was selected as

a primary measure considering the following aspects: (a) it is a reliable and valid instrument to measure sleep quality in insomnia patients (Backhaus et al., 2002) and to characterize and quantify sleep disturbances in FMS patients (Osorio et al., 2006); (b) it is frequently used in clinical trials of pain treatment and is well suited to measure aspects of sleep that are of particular importance in the study of pain (Cole et al., 2007); and (c) the psychometric characteristics of the Spanish adaptation of PSQI are well established (Jiménez- Genchi et al., 2008; Royuela & Macías, 1997).

McGill Pain Questionnaire-Short Form (MPQ-SF, Melzack, 1987): This questionnaire assesses several dimensions of pain experience using 15 verbal pain descriptors, a current pain intensity index, and a visual analogue scale (VAS) to assess pain intensity in the last week (from 1 to 10). The present study used the VAS. Several studies have reported the reliability and validity of the Spanish version of the MPQ (e.g., Lázaro et al., 2001).

Multidimensional Fatigue Inventory (MFI, Smets et al., 1995; adaptation by Fillion et al., 2003): It consists of 20 items that assess several aspects of fatigue: General fatigue, Physical fatigue, Mental fatigue, Reduced motivation and Reduced activity. Items are assessed on a Likert scale ranging from 1 to 5. General fatigue subscale was selected for this study. The MFI showed adequate internal consistency, construct validity and convergent validity (Smets et al., 1995).

Fibromyalgia Impact Questionnaire (FIQ, Burckhardt et al., 1991): The FIQ includes 10 items that evaluate health status in FMS. Item 1 assesses functional capacity for daily living (ranging from 0 to 3). Items 2 and 3 ask patients to mark the number of days they felt well/ unable to work. Items 4 through 10 are scales that rate work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression from 0 to 10. The Spanish version was reliable, valid and responsive to changes (Rivera & Gonza ´lez, 2004).

Chronic Pain Self-efficacy Scale (CPSS, Anderson et al., 1995): The CPSS explores patients' self-efficacy expectations regarding pain management, coping with symptoms, and physical function. This instrument includes 19 items that are assessed on a Likert scale ranging from 0 to 10. The Spanish version showed good construct validity and internal consistency (Martín-Aragón et al., 1999).

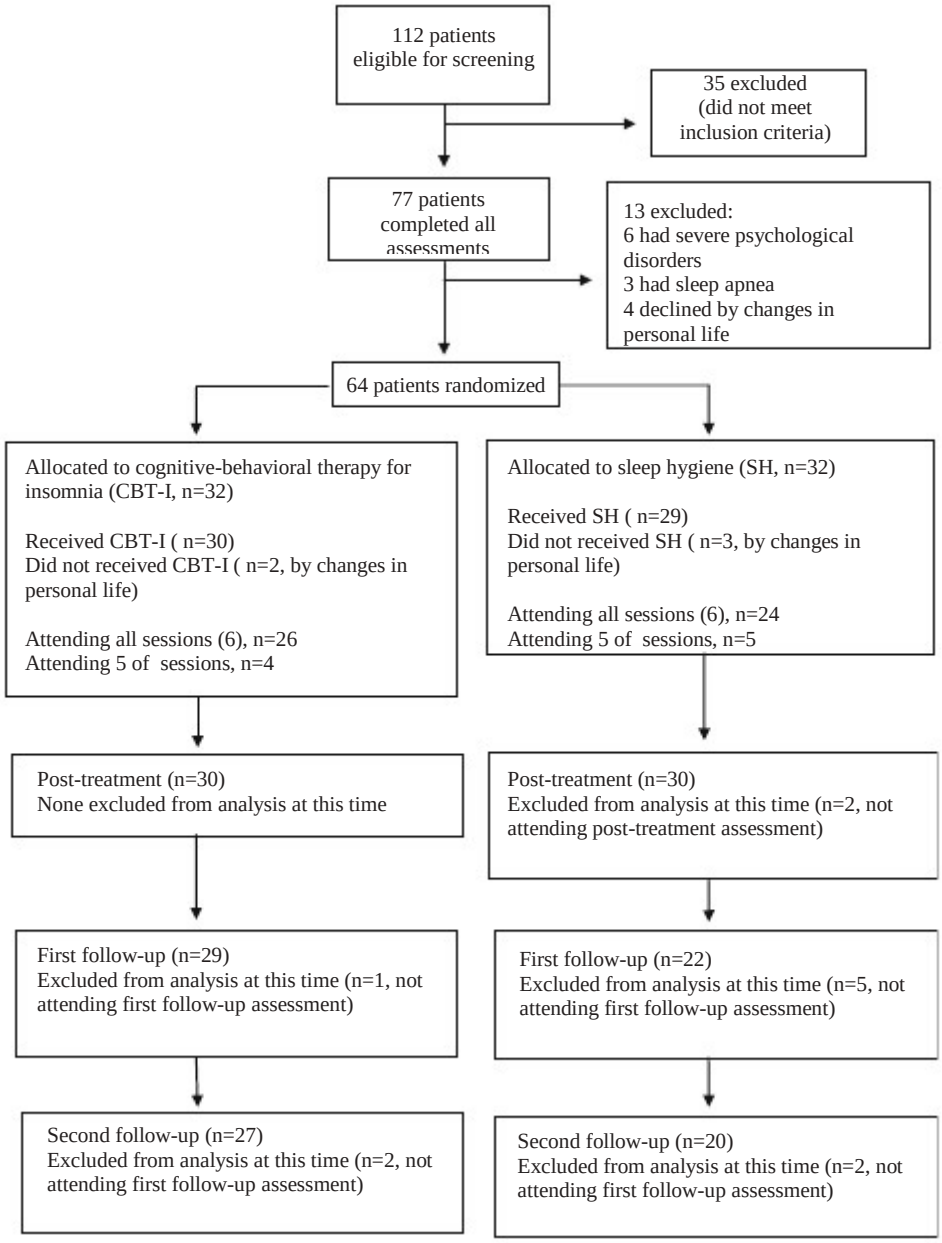

Figure 11- Flow diagram of participants through the phases of the trial

Pain Catastrophizing Scale (PCS, Sullivan et al., 1995): This instrument assesses rumination, magnification and helplessness associated to pain. It includes 13 items measured on a Likert scale ranging from 0 to 4. The Spanish version showed adequate internal consistency, test–retest reliability and sensitivity to change (García-Campayo et al., 2008).

Symptom Checklist-90-Revised (SCL-90-R, Derogatis, 2002): It contains 90 items grouped into 9 dimensions: Somatization, Obsessive–compulsive, Interpersonal sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation and Psychoticism. Each item is rated on a Likert scale ranging from 0 to 4. The Anxiety and Depression subscales were selected. The Spanish version showed good internal consistency and a factor structure that was similar to the original version.

Treatment protocols

The protocol-based psychological treatments (CBT-I and SH) were provided by three female therapists (M.P.M., E.M., and A.I.S.) with experience in the management of chronic pain and sleep disorders. All sessions were conducted in group format (5-6 participants) once a week for 6 weeks and lasted about an hour and a half. Patients in the CBT-I and SH groups continued with their usual medical care for FMS (on stable doses of medication) during the study. Patients also agreed not to participate in other interventions until the trial ended.

CBT-I program: This intervention was designed following the trial by Edinger and colleagues (2005) and met the recommendations of the American Academy of Sleep Medicine (Morgenthaler et al., 2006). Session 1 was focused on providing information about the relationship between sleep and FMS, basic notions about sleep, and sleep hygiene education. In Session 2, participants were given instructions for applying sleep restriction and stimulus control. Patients were asked to complete the sleep diary before applying sleep restriction. Sleep efficiency was calculated considering the sleep diary data, restriction of time in bed was established, bedtime and time to get up were set, and the sleep schedule was reviewed every 3-4 days by increasing bedtime as sleep efficiency was improving. Session 3 was aimed at training physiological deactivation procedures (slow breathing, passive relaxation and imagery training). Sessions 4 and 5 were focused on cognitive therapy to change negative thoughts about insomnia through

verbal discussion and behavioral experiments. Session 6 was devoted to maintaining achievements and preventing relapses.

SH program: The aim of this intervention was only to provide training about sleep hygiene rules. In Session 1, participants were given the same information about sleep as those in the CBT-I program. Session 2 was devoted to sleep hygiene rules related to environmental factors (e.g., noise, temperature, light). Session 3 was focused on learning about lifestyle factors that influence sleep (use of stimulants and other substances). Sessions 4 and 5 were aimed at providing information about diet and physical exercise, respectively. Session 6 was devoted to maintaining achievements and preventing relapses, as in the CBT-I program. Throughout the sessions, the educational content of sleep hygiene was illustrated and discussed in detail with active involvement of patients. After the follow-ups, patients in the SH group were given the possibility of receiving CBT-I.

The integrity of the interventions was ensured as follows: (a) the therapists had a high level of professional training and experience in the treatments applied; (b) a written therapy manual with detailed information about each session was used; and (c) the therapists had regular clinical meetings with the research group to monitor the implementation of the therapies and to follow the progress of patients.

Data analyses

Statistical analyses were performed using IBM SPSS Statistics 19 software. Probabilities less than or equal to .05 were used as the level of significance. Student's *t*, Mann–Whitney *U*, and χ^2 tests were used to compare baseline measures between the CBT-I and SH groups. After that, 2 (Group; CBT-I vs. SH) x 4 (Time; Pre-treatment vs. Post-treatment vs. First follow-up vs. Second follow-up) ANCOVAs were performed considering pre-treatment values as a covariate to verify whether both groups differed in the outcome measures. Mauchly's test of sphericity and the Greenhouse-Geiser correction were computed. Additionally, unpaired and paired two-samples Student's *t* tests were computed. The Bonferroni-Holm method for controlling Type I errors in multiple comparisons was applied in the PSQI analyses. In significant statistics, effect sizes were calculated via the partial η^2 and Cohen's d. According to Cohen's guidelines (1988), d .2 is a small effect, .5 is a medium effect and .8 is a large effect; in the η^2, .01 is a small effect, .06 is a medium effect and .14 is a large effect. Following the

recommendations made by Lambert and Ogles (2009) in psychotherapy outcome research, the estimate of clinical significance was based on the Jacobson-Truax method (Reliable Change Index, RCI; Jacobson & Truax, 1991). Patients were classified into different categories according to this index (Salaberría et al., 1996): *Same*, with no positive nor negative changes; *Deterioration*, negative change*; Improvement without complete recuperation*, positive change but < 1; *Somewhat positive change*, higher than 1 but < 1.96; and *Very positive change*, higher than 1.96. In the present study we considered the last three categories together. Considering the criteria used by Edinger and colleagues (2005), patients were classified as having improved sleep if at post-treatment they showed a mean total sleep time of 6.5 h or longer, a mean total wake time of < 60 min, or a mean sleep efficiency of 85% or greater. Patients who met the improvement criteria at pre-treatment were excluded from these analyses.

Results

Characteristics of the FMS sample

The CBT-I and SH groups were similar in the baseline measures (all *p*'s >.144; see Table 15). The mean age of the FMS sample was 47.58 years (SD = 6.82; range = 33-60). Most participants were married (84.7%) and had basic education (29.5%), high school (25%), professional instruction (22.7%), or university studies (22.7%). Almost half of the subjects had an inactive work situation. The mean duration of FMS diagnosis was 5.10 years (SD = 4.23), and the mean duration of the sleep problem was 9.17 years (SD = 7.82). Almost all subjects (91.52%) were receiving medication.

Table 15- Demographic and clinical characteristics of the patients with fibromyalgia who completed the treatments.

Variables	Total sample (n = 59)	CBT-I group (n = 30)	SH group (n = 29)	CBT-I vs. SH	
				t/U/ χ^2	*p*
Age, M (SD)	47.58 (6.82)	46.53 (6.31)	48.66 (7.27)	-1.19	.236
Education (%)					
Basic education	29.5	21.7	38.1	217.0	.552
High school	25.0	34.8	14.3		
Professional instruction	22.7	17.4	28.6		
University studies	22.7	26.1	19.0		
Marital status (%)				3.30	.347
Married	84.7	76.7	93.1		
Single	6.8	10.0	3.4		
Divorced	6.8	10.0	3.4		
Widowed	1.7	3.3	.0		
Work status (%)				3.39	.335
Currently employed	51.0	62.5	40.0		
Retired	6.1	4.2	8.0		
Unemployed	16.3	8.3	24.0		
Disabled	26.5	25.0	28.0		
Duration of FM diagnosis (years), M (SD)	5.10 (4.23)	4.25 (3.26)	5.92 (4.92)	-1.48	.144
Duration of FM symptoms (years), M (SD)	14.33 (9.17)	15.32 (10.13)	13.37 (8.22)	.76	.445
Duration of sleep problem (years), M (SD)	9.17 (7.82)	9.67 (8.76)	8.58 (6.77)	.41	.680
Sleep latency (h), M (SD)	1.12 (0.59)	1.12 (1.07)	1.11 (.47)	.06	.947
Number of awakenings per night, M (SD)	2.82 (1.30)	2.57 (1.19)	3.04 (1.37)	-1.28	.206
Sleeping hours per night, M (SD)	4.50 (1.25)	5.03 (1.30)	4.37 (1.18)	1.04	.300
Drug intake (%)					
Antidepressants	57.1	53.6	60.7	.29	.589
Anxiolytics	64.3	60.7	67.9	.31	.577
Anti-inflammatory drugs	64.3	60.7	67.9	.31	.577
Analgesics	60.7	64.3	57.1	.29	.584

Note. M = Mean; SD = Standard deviation; CBT-I = Cognitive-behavioral therapy for insomnia; SH = Sleep hygiene.

Changes in sleep quality

The ANCOVA for Sleep quality-Total revealed a significant effect of Group (see Table 16). Whereas the Sleep quality of the CBT-I group improved from pre- to post-treatment, the SH group showed no significant improvement. The CBT-I group reported better Sleep quality than the SH group at post-treatment and first follow-up.

In Sleep disturbances significant effects of Group, Time and Group x Time were found. Sleep disturbances improved from pre- to post-treatment in the CBT-I group but not in the SH group. The CBT-I group showed a greater reduction in Sleep disturbances than the SH group at post-treatment and first follow-up. In Subjective sleep quality, a significant effect of Time and an effect close to significance of Group x Time were

observed. Both groups improved in Subjective sleep quality from pre- to post-treatment. The CBT-I group showed better Subjective sleep quality than the SH group at all times except the second follow-up. In Habitual sleep efficiency a significant effect of Time was observed. The CBT-I group showed a significant improvement in Habitual sleep efficiency from pre- to post-treatment and the SH group showed an improvement close to significance. The CBT-I group showed better Habitual sleep efficiency than the SH group at post-treatment.

Daytime dysfunction showed a significant effect of Time and an effect close to significance of Group, but no specific between-subject or within-subject changes were identified. No significant effects were found in any factors regarding Sleep latency and Sleep duration. Both parameters improved from pre- to post-treatment in the CBT -I group but not in the SH group. Both the CBT-I and SH groups showed the same results over time in Sleep latency and Sleep duration. Neither significant effects nor specific changes were identified in Use of sleeping medication.

Applying the Bonferroni-Holm correction the Time factor in Habitual sleep efficiency, Sleep disturbances and Daytime dysfunction, the comparison pre vs. post-treatment in the CBT-I group in Sleep quality-Total, Subjective sleep quality, Sleep latency, Sleep duration, and Habitual sleep efficiency, and the comparison CBT-I vs. SH at post-treatment in Subjective sleep quality and at first follow-up in Sleep disturbances, were significant. According to the RCI, 87% of CBT-I patients and 45% of SH patients showed clinically significant changes in Sleep quality-Total. Considering sleep improvement criteria, 33.33% of the patients in the CBT-I group reported a mean total wake time of < 60 min (vs. 7.40% in the SH group), 33.33% reported a mean total sleep time of 6.5 h or longer (vs. 25.92% in SH), and 36.66% reported a mean sleep efficiency of 85% or greater (vs. 18.51% in SH).

Table 16- Changes in sleep quality (Pittsburgh Sleep Quality Index) in the treatment groups.

Variables Group	Pre- treatment M (SD)	Post-treatment M (SD)	First follow-up M (SD)	Second follow-up M (SD)	Group F (η^2)	Time F (η^2)	Group x Time F (η^2)	T1 vs. T2, t(d)	T2 vs. T3, t(d)	T3 vs. T4,t(d)
Sleep quality-total										
CBT-I	15.30 (3.03)	11.33 (4.03)	11.00 (3.88)	11.63 (4.63)	**5.64*(.11)**	1.87	2.11	**6.63*** (1.25)**	.55	-.55
SH	14.93 (3.35)	13.48 (2.88)	13.18 (3.73)	13.30 (4.15)						
CBT-I vs. SH, t (d)	.44	**-2.22*, (-.61)**	**-2.02*, (-.57)**	-1.27						
Subjective sleep quality										
CBT-I	2.07 (.52)	1.40 (.81)	1.44 (.68)	1.74 (.71)	1.48	**2.77* (.06)**	2.49, p=.06(.05)	**5.13**(1.0)**	-.23	-1.89
SH	2.45 (.63)	2.08 (.57)	1.95 (.78)	1.85 (1.04)				**2.09* (.43)**	1.56	.62
CBT-I vs. SH, t (d)	**-2.52* (-.69)**	**-3.62** (-.97)**	**-2.45* (-.69)**	-.42						
Sleep latency										
CBT-I	2.30 (.83)	1.70 (.79)	1.79 (.94)	1.93 (.91)	.01	1.21	1.03	**4.26***(.78)**	-.49	-.59
SH	1.97 (.94)	1.64 (1.15)	1.68 (1.04)	1.65 (1.18)				1.54	1.42	-.56
CBT-I vs. SH, t (d)	1.44	.22	.40	.86						
Sleep duration										
CBT-I	2.23 (.81)	1.46 (.86)	1.37 (.90)	1.63 (.96)	2.17	2.14	.85	**4.67*** (.85)**	.49	-1.41
SH	2.00 (1.00)	1.72 (.93)	1.68 (.89)	1.75 (.96)				.70	.32	-.56
CBT-I vs. SH, t (d)	.98	-1.04	-1.19	-.42						
Habitual sleep efficiency										
CBT-I	2.07 (1.01)	.96 (.99)	1.17 (1.13)	1.48 (1.08)	1.26	**4.86** (.10)**	1.65	**5.35***(.98)**	-1.02	-1.03
SH	2.14 (1.18)	1.60 (1.15)	1.54 (1.01)	1.65 (1.18)				1.83, p=.07 (.37)	.64	-.90
CBT-I vs. SH, t (d)	-.24	**-2.18*(-.59)**	-1.21	-.50						
Sleep disturbances										
CBT-I	2.20 (.48)	1.93 (.73)	1.89 (.55)	2.04 (.64)	**7.30** (.14)**	**5.09** (.10)**	**2.71* (.06)**	**1.97* (.38)**	.57	-1.14
SH	2.24 (.51)	2.40 (.57)	2.45 (.50)	2.30 (.47)				-1.44	.00	1.37
CBT-I vs. SH, t (d)	-.31	**-2.56* (-.71)**	**-3.67**(-1.06)**	-1.53						
Use of sleeping medication										
CBT-I	2.20 (1.12)	1.90 (1.32)	1.55 (1.29)	1.48 (1.25)	1.67	1.95	.57	1.43	1.43	-.15
SH	2.07 (1.36)	2.04 (1.27)	1.77 (1.23)	1.90 (1.33)				-.48	.58	-.89
CBT-I vs. SH, t (d)	.40	-.39	.61	-1.10						

Daytime dysfunction										
CBT-I	2.23 (.81)	1.96 (.99)	1.75 (.91)	1.81 (.92)	**3.02,p=.08(.06)**	**6.83***(.14)**	1.62	1.39	1.68	.27
SH	2.07 (.96)	2.00 (.95)	2.09 (.81)	2.20 (.83)				-.27	-.29	-.56
CBT-I vs. SH, t (d)	.70	-.12	-1.350	-1.47						

Note. M= Mean; SD = Standard deviation; CBT-I = cognitive-behavioral therapy for insomnia, SH = sleep hygiene, T1 = pre-treatment, T2 = post-treatment, T3 = first follow-up, T4 = second follow-up.

* p < .05; ** p < .01; *** p <.001

Changes in pain intensity, fatigue and daily functioning

As regards Pain intensity, the ANCOVA showed no significant effects on any factor. However, the CBT-I group showed significantly lower Pain intensity than the SH group at pre- and post-treatment, and only the CBT-I group showed a reduction in Pain intensity close to significance between both times (see Table 17). The ANCOVA for General fatigue revealed a significant effect of Group and Time. General fatigue decreased from pre- to post-treatment in the CBT-I group but not in the SH group. The CBT-I group showed lower General fatigue than the SH group at post-treatment. As regards Daily functioning, the ANCOVA showed a significant effect of Group, Time and Group x Time. Daily functioning improved from pre- to post-treatment in the CBT-I group but not in the SH group. The CBT-I reported better Daily functioning than the SH group at post-treatment and first and second follow-up. According to the RCI, 43% of the patients in the CBT-I group showed significant improvements in Pain intensity, 50% showed improvements in General fatigue and 63% showed improvements in Daily functioning, compared to 31, 41 and 21%of patients in the SH group, respectively.

Table 17- Changes in pain intensity, fatigue and daily functioning in the treatment groups

Variables	Group	Pre-treatment M (SD)	Post-treatment M (SD)	First follow-up M (SD)	Second follow-up M (SD)	Group F (g^2)	Time F (g^2)	Group x Time F (g^2)	T1 vs. T2 t (d)	T2 vs. T3 t (d)	T3 vs. T4 t (d)
Pain intensity (MPQ)											
	CBT-I	7.32 (1.94)	6.72 (2.08)	7.05 (1.70)	6.90 (2.12)	.02	1.99	.43	1.79, p = .08 (.31)	-.73	.26
	SH	8.46 (1.10)	8.23 (1.34)	7.84 (2.05)	7.60 (2.34)				.98	.70	.38
	CBT-I vs. SH, t (d)	**-2.73** (-.72)**	**-3.16** (-.86)**	-1.43	-.96						
General fatigue (MFI)											
	CBT-I	4.47 (.58)	4.05 (.79)	4.26 (.55)	4.16 (.68)	**3.87* (.08)**	**8.92*** (.18)**	2.34	**2.50* (.44)**	-1.30	1.05
	SH	4.65 (.53)	4.45 (.63)	4.51 (.64)	4.39 (.74)				1.07	.94	.66
	CBT-I vs. SH, t (d)	-1.21	**-2.04* (-.56)**	-1.43	-1.07						
Daily functioning (FIQ)											
	CBT-I	60.71 (11.83)	50.47 (18.43)	54.03 (15.76)	52.61 (15.65)	**8.71** (.17)**	**4.62** (.10)**	**3.65* (.08)**	**2.47* (.50)**	-.76	.51
	SH	64.09 (13.61)	64.46 (15.23)	63.52 (16.01)	62.39 (17.38)				-1.26	1.35	.33
	CBT-I vs. SH, t (d)	-1.02	**-2.98** (-.82)**	**-2.09* (-.59)**	**-2.02* (-.59)**						

Note. M = Mean; SD = Standard deviation; MPQ = McGill Pain Questionnaire; MFI = Multidimensional Fatigue Inventory; FIQ = Fibromyalgia Impact Questionnaire; CBT-I = cognitive-behavioral therapy for insomnia, SH = sleep hygiene, T1 = pre-treatment, T2 = post-treatment, T3 = first follow-up, T4 = second follow-up
* p < .05, ** p < .01, *** p < .001

Changes in self-efficacy, pain catastrophizing and emotional distress

The ANCOVA for Self-efficacy indicated significant effects of Group, Time and Group x Time (see Table 18). In the CBT-I group, Self-efficacy increased to a level close to significance from pre- to post-treatment. The CBT-I group showed higher Self-efficacy than the SH group at post-treatment, first- and second follow-up. In Pain catastrophizing, the ANCOVA showed an effect close to significance of Time. Pain catastrophizing significantly decreased from pre- to post-treatment in the CBT-I but not in the SH group. The CBT-I group showed significantly lower Pain catastrophizing than SH group at post-treatment.

As regards Anxiety, the ANCOVA revealed no significant effects on any factor. Anxiety decreased from pre- to post-treatment in the CBT-I group but not in the SH group. In Depression, the ANCOVA indicated an effect close to significance of Group. Depression decreased from pre- to post-treatment in the CBT-I group but not in the SH

group. The CBT-I group reported a higher improvement in Depression than the SH group at post-treatment and first follow-up.

According to the RCI, 63% of the CBT-I patients and 28% of the SH patients obtained significant clinical changes in Self-efficacy. The rate of patient improvement in the CBT-I group was 60% in Pain catastrophizing, 57% in Anxiety and 57% in Depression, and 48%, 55% and 41% of patients in the SH group, respectively.

Table 18- Changes in self-efficacy, pain catastrophizing, and emotional distress in the treatment groups.

Variables	Group	Pre-treatment M (SD)	Post-treatment M (SD)	First follow-up M (SD)	Second follow-up M (SD)	Group F (g^2)	Time F (g^2)	Group x Time F (g^2)	T1 vs. T2 t (d)	T2 vs. T3 t (d)	T3 vs. T4 t (d)
Self-efficacy (CPSS)	CBT-I	86.50 (36.63)	93.96 (33.60)	98.89 (33.81)	101.52 (31.51)	**4.63*** **(.09)**	**4.93**** **(.10)**	**2.82*** **(.06)**	-1.83, p = .07 (-.33)	-1.00	-1.52
	SH	71.59 (35.39)	70.48 (37.81)	74.77 (39.73)	71.95 (41.85)				.65	-.38	1.05
	CBT-I vs. SH, t (d)	1.59	**2.43*** **(.65)**	**2.34*** **(.65)**	**2.65*** **(.79)**						
Pain catastrophizing (PCS)	CBT	26.23 (13.91)	20.36 (11.50)	22.34 (14.85)	21.41 (13.65)	.59	2.51, p = .06 (.05)	.95	**2.87**** **(.53)**	-.93	1.64
	SH	31.00 (11.57)	27.28 (10.67)	26.77 (11.31)	25.85 (14.18)				1.41	.75	.40
	CBT-I vs. SH, t (d)	-1.42	**-2.29*** **(-.62)**	-1.20	-1.08						
Anxiety (SCL-90-R)	CBT-I	1.49 (.96)	1.23 (.79)	1.38 (1.07)	1.50 (1.02)	.19	1.06	1.20	**2.58*** **(.52)**	-1.28	-.81
	SH	1.75 (.86)	1.62 (.92)	1.53 (.80)	1.55 (.68)				1.64	.57	.26
	CBT-I vs. SH, t (d)	-1.09	-1.68	-.52	-.21						
Depression (SCL-90-R)	CBT-I	2.09 (.84)	1.63 (.84)	1.58 (.87)	1.78 (.88)	3.09, p = .08 (.07)	1.46	2.21	**3.44**** **(.75)**	1.12	-1.71
	SH	2.37 (.74)	2.29 (.77)	2.22 (.80)	2.11 (.88)				.68	.72	1.08
	CBT-I vs. SH, t (d)	-1.31	**-2.97**** **(-.82)**	**-2.63*** **(-.76)**	-1.24						

Note. M = Mean; SD = Standard deviation; CPSS = Chronic Pain Self-efficacy Scale; PCS = Pain Catastrophization Scale; SCL-90-R = Symptom Checklist-90-Revised; CBT-I = Cognitive-behavioral therapy for insomnia; SH = Sleep hygiene; T1 = Pre-treatment; T2 = Post-treatment; T3 = First follow-up; T4 = Second follow-up.
* p < .05; ** p < .01; *** p < .001

Discussion

This trial explored the efficacy of the CBT-I in comparison to the SH in FMS patients with comorbid insomnia and found that the former was better at improving sleep, daily functioning, and psychological well-being. Patients who received CBT-I reported significant and positive changes at post-treatment in subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency and sleep disturbances; these therapeutic gains were maintained at follow-ups. By contrast, patients in the SH group only reported a significant improvement in subjective sleep quality and a trend towards improvement in sleep efficiency. The CBT-I group obtained significantly higher changes than the SH group at post-treatment or follow-ups in several indices of sleep. The percentage of patients who showed clinical improvement in sleep quality according to the RCI was higher in the CBT-I group (87%) than in the SH group (45%). Considering sleep improvement criteria, in the CBT-I group 33.3% of patients reported a mean total wake time of <60 min (vs. 7.4% in the SH group), 33.3% showed a mean total sleep time of 6.5 h or longer (vs. 25.9% in the SH group), and 36.7% showed a mean sleep efficiency of 85% or greater (vs. 18.5% in SH). These results support the first hypothesis.

These findings are also in line with previous research in FMS patients. In the study by Edinger et al., (2005) the CBT-I and SH groups did not differ at post-treatment or follow-ups in sleep parameters (sleep logs and actigraphy); nevertheless, the CBT-I group showed lower total wake time and sleep latency and higher sleep efficiency than the UC group. As reflected in the sleep logs, 57% of CBT-I participants met strict subjective sleep improvement criteria (vs. 17% in the SH group and 0% in the UC group). The CBT-I and SH groups did not differ at post-treatment and follow-ups in insomnia (questionnaire); however, both groups showed a greater improvement than the UC group. In one of our studies (Miró et al., 2011b) the CBT-I group showed an improvement in sleep quality (questionnaire) from pre- to post-treatment, but the SH group did not show any changes between both moments. Additionally, 85% of the patients in the CBT-I group showed clinically significant changes in sleep quality (vs. 55% in the SH group). In another of our studies using PSG (Sánchez et al., 2012), the CBT-I group showed improvements in time in bed, wake percentage and sleep efficiency, as well as a decrease in light sleep and an increase in deep sleep that were not observed in the SH group.

The results of the present trial are also similar to those of studies that have explored the efficacy of CBT-I in non-fibromyalgia samples. The study by Currie and colleagues (2000) was conducted with 60 patients with chronic pain that were assigned to a CBT-I (n = 32) or a self-monitoring/waitinglist control condition (n = 28). The CBT-I group obtained higher improvements than the control group at post-treatment in sleep onset latency, sleep efficiency and wake time after sleep onset (sleep diary), and sleep quality (questionnaire), which were maintained at follow-ups. The control group only reported changes in sleep quality that were not maintained at follow-ups. In addition, 16% of the CBT-I patients fulfilled the criteria for good sleep (vs. 0% of controls). The study by Vitiello and colleagues (2009) included older adults with osteoarthritis that were assigned to CBT-I (n = 23) or an attention-control stress management and wellness intervention (n = 28). The CBT-I patients reported improvements in sleep latency, wake after sleep onset and sleep efficiency (sleep log) after the intervention that were maintained at follow-up, but patients in the control condition reported no changes. In the study by Jungquist and colleagues (2010), 28 subjects with chronic pain were assigned to CBT-I (n = 19) or a contact control condition (n = 9). The CBT-I group showed improvements in sleep latency, wake after sleep onset, number of awakenings and sleep efficiency (sleep diary), and in insomnia severity (questionnaire); however, the control condition did not exhibit changes in these aspects of sleep. Moreover, 42% of patients who received CBT-I achieved normal sleep (vs. 11% of controls).The study by Pigeon and colleagues (2012) included 21 chronic pain patients that were randomized to CBT for pain (CBT-P) (n = 5), CBT-I (n = 6), combined CBT-I/P (n = 6), or a waiting-list control condition (n = 4). The CBT-I and the CBT-I/P were better than CBT-P at decreasing insomnia severity (questionnaire). In the present study, pre vs. post-treatment size effects of CBT-I in sleep latency and efficiency were similar to those reported by previous studies (Currie et al., 2000; Edinger et al., 2005; Vitiello et al., 2009).

Patients receiving CBT-I in the present study showed significant improvement in fatigue and daily functioning at post-treatment and maintained the gains at follow-ups; however, only a trend towards relief of pain intensity was identified. These findings are in contrast with the failure of the SH to produce significant changes. The CBT-I group obtained significantly higher changes than the SH group at post-treatment or follow-ups in these measures. According to the RCI, 43% of the CBT-I subjects obtained clinically

significant improvements in pain intensity, 50% in fatigue and 63% in daily functioning (vs. 31, 41, and 21%, respectively, in the SH group). The second hypothesis of the study was only partially supported. Contrary to our prediction, the CBT-I did not change pain intensity significantly. It may be necessary for sleep to be normalized for a longer time before an effective change in pain can be observed.

Most studies on chronic pain have reported that CBT-I did not have a substantial impact on reducing pain, and data about adjustment are mixed. Edinger and colleagues (2005) observed that the CBT-I and SH groups did not differ at post-treatment and follow-ups in pain and quality of life; yet, the SH group reported less pain than the UC group, and the CBT-I and SH groups reported greater quality of life than the UC group. In a previous study (Miró et al., 2011b), we reported that the CBT-I group did not report any changes in pain intensity but showed a trend towards improvement in daily functioning after the intervention, whereas the SH group showed no changes in these measures. Currie and colleagues (2000) found that neither the CBT-I nor the control condition produced significant effects on pain severity at post-treatment and follow-up. Vitiello and colleagues (2009) showed that the CBT-I reduced pain at post-treatment, but this effect disappeared at follow-up. Jungquist and colleagues (2010) reported that the CBT-I led to a decrease of interference at post-treatment but not of pain severity and pain disability. The control group did not improve in these parameters. Pigeon and colleagues (2012) reported that the CBT-I and the CBT-I/P obtained better changes in fatigue than the CBT-P, the CBT-P showed a greater effect on pain than CBT-I, and all therapies led to improvements in pain disability.

Patients receiving CBT-I in the present trial reported significant and positive changes at post-treatment in anxiety, depression and pain catastrophizing, and a trend towards improvement in self-efficacy for coping pain. These gains were maintained at follow-ups. Patients receiving SH did not show any changes in the above mentioned parameters. The CBT-I group displayed significantly higher changes than the SH group at post-treatment or follow-ups in these measures, including a trend towards lower anxiety at post-treatment. According to the RCI, 63% of CBT-I patients obtained significant clinical changes in self-efficacy (vs. 28% in SH), 60% in pain catastrophizing (vs. 48% in SH), 57% in anxiety (vs. 55% in SH) and 57% in depression (vs. 41% in SH). The third hypothesis of the trial was partially supported.

Results about emotional distress differed from those of previous studies. Edinger and colleagues (2005) found that the CBT-I and SH groups did not differ at post-treatment and follow-ups in mood, but the CBT-I group showed more favorable changes than the UC group. In one of our studies (Miró et al., 2011b), we reported that the CBT-I and SH groups did not differ in the improvements obtained after the intervention in anxiety and depression. Currie and colleagues (2000) did not observe any differences between CBT-I and the control condition in depression at post-treatment and follow- up. Vitiello and colleagues (2009) and Jungquist and colleagues (2010) reported no changes in either the CBT-I or the control groups in depression from pre- to post-treatment. However, Pigeon and colleagues (2012) reported that CBT-I and CBT-I/P were better than CBT-P at reducing depression. Similarly to the present study, Jungquist and colleagues (2010) identified positive changes in self-efficacy in CBT-I (but not in the control condition) at post-treatment. None of these studies used measures about pain catastrophizing thoughts.

Note that some of the discrepancies between the findings of the present study and those of the previous ones may be due to differences in the methodology used. For example, unlike this study, Edinger and colleagues (2005), Jungquist and colleagues (2010) and Pigeon and colleagues (2012) used an individual therapy format, Vitiello and colleagues (2009) included a sample of older adults, and all studies (except our previous studies, Miró et al., 2011b, and Sánchez et al., 2012) included samples of men and women, considered different control conditions, and used partially different measures to assess sleep, pain, adjustment and mental well-being. Also, the estimated range for remission/improvement was defined differently among the trials. It is necessary to consider that sex differences can play a significant role. Women experience greater clinical pain, suffer greater pain-related distress, and show heightened sensitivity to experimentally induced pain compared to men (Paller et al., 2009); these differences may also be reflected in the differences in therapeutic gains between men and women in the CBT-I.

The results of the present trial should be considered with caution because of its limitations. Sleep quality (pre-, post-treatment, and follow-ups) was self-reported. Objective measures (PSG and actigraphy) applied at different stages of the clinical trial are needed to obtain a more complete assessment of sleep. However, it should be noted that a recent study has reported that FMS-related symptoms were related to participants'

subjective report (electronic diary) of how refreshed they were upon waking and the number of times they woke during the night but were not related to objective sleep (actigraphy) (Okifuji, & Hare, 2011). Therefore, self-report measures are particularly relevant to assess sleep complaints in FMS. It would also be desirable to include a sleep diary during the clinical trial allowing a more continuous evaluation of sleep characteristics and to compare these findings with those obtained with other subjective measures such as the PSQI. Since the PSQI only provides data on sleep quality, it would have been very valuable to include a self-report questionnaire focused on insomnia. Pain intensity was also self-reported. Although the MPQ has good psychometric properties, for future research it would be advisable to use a pressure algometer, which measures pain threshold and tolerance and may complete the information provided by self-reports. There is some overlap between FIQ, SLC-90-R and MFI, which might explain the correlations among outcome variables. Patients came from specialized medical settings and may have had different clinical characteristics from those observed in primary care patients and those in other community contexts (e.g., FMS associations). The integrity of the interventions was not verified using a procedure in which audiotapes were assessed by at least two independent raters. The data were analyzed considering only short-term changes. Despite the randomization, the SH group had higher pain scores at baseline that remained high at post-treatment compared to the CBT-I group, thus inflating post-treatment pain scores. Overall, the effect size was medium in both primary and secondary measures.

Future research has some important issues to address in this area. For example, whether there are any sex differences among FMS patients in the response to CBT-I, and whether CBT-I also improves the sleep of FMS patients with psychological and/or medical comorbid problems and patients from different care settings. Dismantling studies to identify which components of CBT-I contribute most to the efficacy of treatment is also necessary. Finally, it is of great interest to examine whether a treatment approach focused on disturbed sleep such as the CBT-I can increase the efficacy of multi-component therapeutic programs, and whether this combination contributes to a better quality of life in FMS patients than standard medical treatment.

The present study shows that CBT-I is useful to treat non-restorative sleep in FMS patients. Our findings extend those of previous research by suggesting the positive effect of the CBT-I not only on sleep, daily functioning and emotional distress, but also

on other symptoms such as fatigue and cognitive aspects such as catastrophic cognitions about pain. Nevertheless, these changes were not accompanied by significant reductions in pain severity, although changes in the expected direction were observed. Experimental and clinical reports show that non-restorative sleep worsens pain intensity. However, reversing this relationship in therapeutic contexts is difficult, and so far psychological interventions focused on insomnia have achieved limited improvements in reduction of pain. Moreover, several studies have reported that CBT improves pain and several adjustment variables in FMS patients (see reviews by Glombiewski et al., 2010; Hassett & Gevirtz, 2009) but has a limited positive impact on sleep in chronic pain syndromes including FMS (see review by Tang, 2009). Since CBT-I is effective at improving sleep but has limited effects on pain, and pain management programs based on CBT provide appropriate skills to cope with pain, it is suggested that a hybrid treatment is necessary to address both pain and sleep in patients with chronic pain (Tang, 2009). The pilot study by Pigeon and colleagues (2012) provides recent evidence of the usefulness of this hybrid approach. The typical components of CBT-I can be combined with other elements of CBT for chronic pain (pain education, balanced combination of activity and rest, emotions management, training of communication skills, training for problem solving, and cognitive therapy for negative thoughts about pain), providing potentially greater therapeutic benefits that each option separately. This is a promising issue that needs to be studied because of its potential to enhance the current multi-component programs for FMS.

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Cognitive-behavioral therapy for insomnia improves attentional function in fibromyalgia syndrome: A pilot, randomized controlled trial[1]

Abstract

This pilot, randomized controlled trial analyzed the effects of a cognitive behavioral therapy for insomnia (CBT-I, n = 20) vs. a sleep hygiene program (SH, n = 20) on the three attentional networks (alertness, orienting, and executive function) and other additional outcome measures (sleep, pain, depression, anxiety, and daily functioning) of fibromyalgia patients. The CBT group showed significant improvement in alertness ($F(1, 28) = 11.84$, $p = .0018$), executive functioning ($F(1, 28) = 15.76$, $p = .00059$), sleep quality ($F(1, 38) = 6.33$, $p = .016$), and a trend to improvement in daily functioning ($p > .06$), as compared with the SH group. The improvement in executive functioning was significantly related to the changes in sleep ($r = 0.40$, $p = .026$). A CBT-I represents a useful intervention in fibromyalgia patients not only regarding sleep disturbance but also attentional dysfunction and probably daily functioning.

Keywords: Attentional function; Cognitive behavioral therapy; Fibromyalgia; Insomnia; Randomized controlled trial.

Introduction

Fibromyalgia syndrome (FMS) is a chronic pain syndrome characterized by widespread musculoskeletal pain and multiple tender points (Wolfe et al., 1990). FMS is estimated to appear in 2-5% of the population (female/male ratio 9:1) and can severely affect the individual's quality of life, leading to substantial social and economic costs (Spaeth, & Briley, 2009).

Cognitive complaints may affect up to 70% of individuals with FMS and contribute to the global disability associated to the syndrome (Leavitt, & Katz, 2009). Patients often complain of forgetfulness, blurring of mental activity, and diminished ability to

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concentrate or follow conversations, which are sufficient to impair quality of life or occupational functioning.

Overall, FMS patients seem to have problems in working memory, episodic memory, and semantic memory access as compared to healthy controls (see Glass, 2009 for a review). Attention and concentration have also been analyzed in FMS patients, with contradictory results (Glass, 2009). A main limitation of existing studies is that attention has been broadly defined and the tasks used to measure it are not designed to cover all the main components of the attentional system.

Research on attention has identified three primary functions of attention, known as alerting, orienting, and executive functioning (Posner, & Rothbart, 2007). The alerting network is in charge of keeping the cognitive system properly activated. The orienting network selectively allocates attention to a potentially relevant area of the visual field and/or object to enhance its perceptual processing. The executive component of attention is active in situations that involve planning, maintaining goal-relevant priorities and avoiding interference, making a decision, detecting an error, or overcoming habitual actions (Fan et al., 2002). In a recent study designed to analyze the three attentional networks in FMS, observed impaired alertness (reduced vigilance) and executive control (greater interference) were observed in FMS patients as compared to healthy controls (Miró et al., 2010). The ability to control distraction is part of the executive component of attention. In fact, it has been recently suggested that FMS patients seem especially sensitive to distraction (Glass, 2009; Leavitt, & Katz, 2009) and have some impairment in executive processes (Verdejo-García et al., 2009).

Cognitive problems are a real and troubling symptom for FMS patients. However, very few studies have addressed whether cognitive dysfunction could be improved in FMS. From a pharmacological approach, it is not yet known whether any of the medications used in FMS are helpful to improve cognitive function. In a study with chronic pain patients, Dick and Rashiq (2007) found that cognitive function was not improved by short-term local analgesia in several tests of working memory and attention. Two recent studies have shown that exercise in a warm-water pool improves cognitive function in FMS patients. Munguía-Izquierdo and Legaz-Arrese (2007) performed a randomized controlled trial comparing an exercise training group vs. a control group. Their outcome measures included several memory tasks, attention and working memory assessed with the Paced Auditory Serial Addition Task (PASAT) and executive function in the Trail

Making Test (TMT). After training, exercise improved all neuropsychological tests, pain, and severity of FMS, while differences were not significant in the control group. In a later publication, Munguía-Izquierdo and Legaz-Arrese (2008) reported similar results, also finding that physical condition and subjective sleep quality improved in the exercise group, while anxiety remained unchanged during the trial.

However, to our knowledge, no study to date has analyzed the impact of a psychological therapy on cognitive function in FMS. Since the etiology of FMS is unknown, the relationship between its different symptoms is currently not well understood and there is no definitive treatment for the condition (Häuser et al., 2010). It is not clear whether cognitive deficits can be attributed to central nervous system dysfunction or may instead be due to the influence of psychological variables such as emotional distress or pain (see Glass, 2009 for a review).

The relationship between sleep and cognitive deficit has not been generally assessed. This is surprising, if we consider that fatigue and sleep disturbances may affect up to 99% of FMS patients and are particularly distressing to them (Hamilton et al., 2008). The inability to obtain restorative sleep produces an impairment in the cortical function (Lim, & Dinges, 2010), especially in the prefrontal cortex involved in alertness and executive functioning (Jones, & Harrison, 2001). In our previous research, sleep dysfunction was the measure that correlated the strongest with attention (Miró et al., 2010). Thus, a therapy focused on sleep may improve cognitive function. Accumulating evidence supports the idea that sleep disturbances have a reciprocal influence on pain, fatigue, mood, and cognitive functioning in FMS patients (see Moldofsky, 2010 for a review). A randomized clinical trial with FMS patients suffering from chronic insomnia showed that a cognitive-behavioral therapy (CBT) for insomnia significantly improves sleep quality (57% of improvement) as compared with sleep hygiene (SH) instructions (17%) and usual care (0%) (Edinger et al., 2005). In addition, the CBT group showed improvement in mood state as compared with the other groups. Non-pharmacological therapies currently recommended in the evidence-based guidelines for the management of FMS are aerobic exercise, cognitive-behavioral therapy, and multicomponent treatment (Häuser et al., 2010). However, in CBT, sleep disturbances in FMS are ignored or only deal with SH at the most.

In this trial we analyzed the effects of a CBT for insomnia on the cognitive function of FMS patients. The objectives of the study were the following: (1) to compare the effect

of a CBT- I vs. an SH education program on our primary outcomes (overall reaction time, alertness, orienting, and executive function) and other secondary outcomes (sleep, pain, depression, anxiety, and daily functioning) in FMS patients; and (2) to determine the relationships between possible changes observed over time as a result of the therapy in the different outcome measures.

Methods

Design and participants

The clinical sample was selected from the Rheumatology Service and Pain Unit of Virgen de las Nieves Hospital in Granada, Spain. Since FMS is infrequent in males and it is not clear whether FMS has differential characteristics depending on gender, only women were recruited. Women who fulfilled the inclusion criteria to participate in the pilot study were referred from the hospital to the Clinical Psychology Unit of the School of Psychology.

All patients met the diagnostic criteria for FMS (Wolfe et al., 1990) and the criteria for insomnia (APA, 2000). Exclusion criteria, designed to exclude patients whose insomnia and/or cognitive dysfunction were better explained by other comorbid conditions were as follows: (1) being pregnant; (2) having a medical history of significant head injury or neurological disorder; (3) having major concomitant medical conditions; (4) having major depressive disorder with suicide ideation or other major Axis I diagnoses (APA, 2000); (5) having symptoms of sleep-disruptive comorbidities with insomnia; (6) having an apnea-hypopnea index or periodic limb movement-related arousal index of 15 or more per hour of sleep; (7) having a severe hypnotic dependence, suggested by the use of a hypnotic in a higher than recommended dosage or repeated episodes of rebound insomnia on withdrawal (Edinger et al., 2005); and (8) being treated with another psychological or physical therapy at the moment of the study.

The study flow of participants is shown in Figure 12. Eighty-two eligible Spanish-speaking women from 25 to 60 years old with FMS were initially screened by a psychologist just before the medical examination. From these patients, 53 women with FMS who fulfilled the inclusion criteria were admitted for evaluation. The complete evaluation was carried out by CD and included, in this order, interviews (two sessions), questionnaires (to be completed at home after the first interview), a neuropsychological test (performed at the end of the second session), and a polysomnographic study. After

the evaluation, a final sample of 44 women with FMS was randomly assigned to either a cognitive-behavioral treatment (CBT, n = 22) for insomnia, or a sleep hygiene (SH, n = 22) group. Simple randomization (1:1) was implemented by a computerized number generator designed by a researcher with no clinical involvement in the trial. Finally, 16 patients in the CBT group and 15 patients in the SH group completed the whole trial and were included in the analysis of the ANT-I. All participants gave their informed consent prior to their inclusion in the study. The study received ethical approval from the University of Granada Ethics Committee.

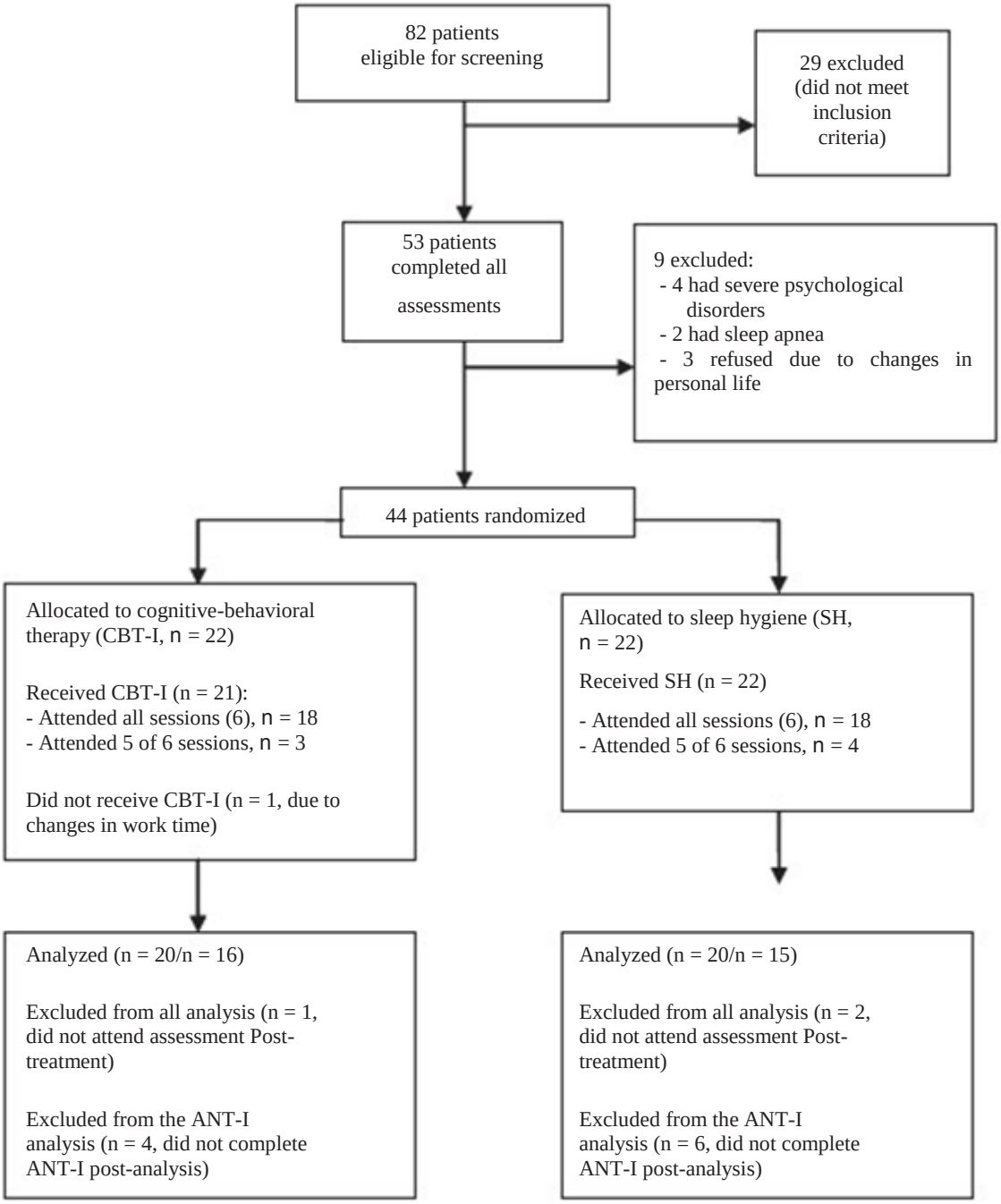

Figure12- Flow of participants throughout the study.

Treatments

Three female CBT experts with experience in FMS (EM, MPM, and AIS) provided the therapy guided by a treatment manual designed for the study. Each therapist applied both CBT-I and SH. All sessions were delivered in groups (five to six participants) once a week for six weeks, and lasted about 90 minutes. Patients in the CBT-I and SH therapy groups continued with their usual medical treatment for FMS. All participants were on stable doses of medication during the trial (see Table 19). The contents and format of the CBT-I program were designed according the work of Edinger and colleagues (2005) and met the recommendations of the American Academy of Sleep Medicine (Morgenthaler et al., 2006). In the first session, patients received information about the relationship between sleep and FMS, basic notions about sleep (sleep stages, sleep functions, circadian rhythms, sleep needs, effects of sleep deprivation on diurnal functioning, and explanation of insomnia) and sleep hygiene education. In the second session, the therapist provided sleep restriction and stimulus control instructions. The third session was devoted to relaxation training (a combination of passive relaxation and imagery training). The fourth and fifth sessions focused on cognitive therapy for the dysfunctional beliefs related to insomnia. Finally, the sixth session was devoted to maintaining achievements and preventing relapses. The SH group worked only with sleep hygiene rules. In the first session, participants were given the same information about sleep as the CBT group. The second session was devoted to sleep hygiene rules related to environmental factors. The third session focused on some lifestyle factors that influence sleep (consumption of stimulants and other substances). The fourth and fifth sessions were devoted to providing information about diet and physical exercise, respectively. The sixth session was similar in both groups.

At the beginning of the first session (CBT-I and SH groups), the therapist provided patients with a written manual with a summary of the information presented in every session and homework. Participants in the SH group were offered CBT-I after their post-treatment assessment.

Measures

The assessment of the outcome measures was performed within one week after the intervention by an examiner (CDP) who was blinded to group assignment.

Polysomnography (PSG). An ambulatory PSG recording (with a SomnoScreen PSG-

Tele, Somno Medics GmbH, Randersacker, Germany) was used to exclude subjects with sleep-disruptive comorbidities. The recording included electroencephalography in the frontal, central, parietal, and occipital regions (Fz/A1, Cz/A1, Pz/A1, Oz/A1), bilateral electrooculography, bilateral submental and anterior tibial electromyography, and respiratory variables (nasal/oral airflow, thoracic effort, snoring, and pulse oximetry). Sleep stages were scored visually according to Rechtschaffen and Kales' (1968) standard criteria.

Neuropsychological task. The ANT-I (Attentional Network Test-Interactions) task, developed by Callejas and colleagues (2004), explores the efficiency and interactions of the three attentional networks (alertness, orienting, and executive functioning). The ANT-I task was performed with a laptop computer with a 15" color screen monitor, with Windows Vista and E-Prime 2 software. Participants were instructed to respond to the direction of the target stimulus by pressing one of two possible keys on the keyboard. A fixation point was followed by the 50 ms alerting signal (a 2000 Hz sound), presented only in half of the trials. The orienting cue (an asterisk) was presented 400 ms later for 50 ms above or below the fixation point in two-thirds of the trials. After another 50 ms interstimulus interval, the target and flankers were shown at the same location of the previous orienting cue in 50% of the trials and at the opposite location in the remaining 50% of cue-present trials. Participants were to press the 'C' key on the keyboard if the central arrow pointed to the left and the 'M' key if it pointed to the right, while ignoring the flanking arrows. Target and flankers were congruent (i.e. showed the same direction) in 50% of the trials and incongruent (i.e. pointed in opposite directions) in the remaining 50%.

Participants performed two practice trials followed by four blocks of 48 experimental trials each, which amounted to 16 trials per experimental condition. The test session lasted for about 40 m. with similar test conditions for all subjects. All participants' self-reported chronotypes were estimated and participants were tested at their optimal time (e.g., evening types in the evening).

The task had a 2 (Alerting Signal) × 3 (Orienting Cue) × 2 (Congruency) design. The Alerting Signal, used as an index of Attention-Alerting, had two levels: presence vs. absence of the sound. The Orienting Cue, which measured Attention-Orienting, had three levels: no-cue trials (no orienting cue was presented, i.e. neutral trials), cued location trials (an orienting cue was presented at the same location as the subsequent

target, i.e. valid trials), and uncued location trials (the orienting cue was presented but at the opposite side to the target, i.e. invalid trials). Lastly, Congruency was used to measure Attention-Executive functioning and had two levels: congruent trials (the target was flanked by arrows pointing in the same direction as the target) and incongruent trials (the flanker arrows pointed in the direction opposite to that of the target).

Questionnaires

Pittsburgh Sleep Quality Index, PSQI (Spanish version of Royuela, & Macías, 1997). The PSQI includes 19 items that explore Sleep Quality, Sleep Latency, Sleep Duration, Habitual Sleep Efficiency, Sleep Disturbances, Use of Sleeping Medication, and Daytime Dysfunction. The present study used the total score (ranging from 0 = absence of perturbation to 21 = severe perturbation). The internal consistency of the PSQI ranged between .67 and .81 (Royuela, & Macías, 1997).

McGill Pain Questionnaire, MPQ (Spanish version of Lázaro et al., 2001). The MPQ assesses pain experience using 15 verbal pain descriptors (sensory and affective), a current pain index, and a visual analogue scale to assess pain intensity in the last week (from 1 = no pain to 10 = extreme pain). The present study used this last score. The Cronbach's alpha of the MPQ was .74 (Lázaro et al., 2001).

Hospital Anxiety and Depression Scale, HADS (Spanish version of Herrero et al., 2003). The HADS assesses anxiety and depression symptoms in non-psychiatric hospital contexts. The HADS includes 14 items (grouped into *Anxiety* and *Depression* dimensions) that are scored from 0 to 3. The Cronbach's alpha was .84 for the Depression subscale and .85 for the Anxiety scale (Herrero et al., 2003).

Fibromyalgia Impact Questionnaire, FIQ (Spanish version of Rivera, & González, 2004). The FIQ is composed of 10 items. The first item assesses functional capacity for daily living (ranging from 0 to 3). Items 2 and 3 ask the patients to mark the number of days they felt well/unable to work. Items 4 through 10 are scales marked in 10 levels which rate work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. The internal consistency of the FIQ showed an alpha coefficient of .82 (Rivera, & González, 2004).

Results

Table 19 shows the demographic and clinical characteristics of the FMS sample. The

Student's *t*-test, the Mann-Whitney *U*, and the χ^2 tests were used to compare baseline measures between the CBT-I and SH groups. The two groups completing the ANT-I task (CBT-I; n = 16 vs. SH; n = 15) differed significantly in terms of age; t (29) = -3.31, p = .002; but were similar in educational level, marital status, work status, and clinical variables such as years since the diagnosis of FMS, and insomnia, or type of insomnia problem; p > .2 for all effects. The CBT-I (n = 20) and SH (n = 20) groups completing self-reported measures were similar in all demographic and clinical variables (all ps > .37).

Attentional measures

Previous analyses showed that the main effects of each variable as well as the expected interactions were significant in the first session of the FMS sample. Thus, the same results obtained with the original task were perfectly replicated (Callejas et al., 2004).

Group and treatment effects

Mean and standard deviations of outcome measures are shown in Table 20 and Figure 13. A first analysis showed that attentional measures at baseline were no different between the CBT-I and SH groups (all p > .2). After that, a 2 (Alerting Signal) × 3 (Orienting Cue) × 2 (Congruency) × 2 (Time; Pre- vs. Post-treatment) × 2 (Group; CBT vs. SH) repeated measures ANCOVA was performed on the data from the two sessions to check whether the two groups differed across sessions in attentional functioning. Age was introduced in this analysis as a covariate to take into account age differences between the two groups. Age did not reach statistical significance in the ANCOVA; F(1, 28) = 2.31, p = .1401. The analysis showed a significant interaction between Alerting Signal, Time, and Group; F(1, 28) = 4.88, p = .0355. It revealed that, whereas the CBT-I group reduced the alertness effect from the Pre- (63 ms) to the Post-treatment (31 ms) Session; F(1, 28) = 11.84, p = .0018; the SH group showed similar alertness effects in both sessions; 47 and 46 ms, F < 1. Similarly, the interaction between Congruency, Group, and Time was significant; F(1, 28) = 5.27, p = .0294. Again, whereas the CBT-I group showed reduced interference from the Pre- (114 ms) to the Post-treatment (88 ms) session; F(1, 28) = 15.76, p = .0005, the SH group showed similar congruency effects in both sessions;114 ms and 104 ms, respectively, F < 1.

Table 19- Demographic and clinical characteristics of the FMS sample completing the ANT-I task.

Variable	Total sample (n = 31)	CBT-I group (n = 16)	SH group (n = 15)	p value
Age, mean (SD)	46.45 (7.03)	43.94 (6.06)	50.20 (6.12)	.002
Education (%)				.215
Basic education	35.5	32.5	30	
High school	19.4	21.3	16.7	
Professional instruction	16.1	14.5	18.0	
University studies	29	32.8	25.3	
Marital status (%)				.396
Married	90.3	87.5	93.3	
Single	3.2	6.3	0	
Divorced or widowed	6.4	6.3	6.7	
Work status (%)				.184
Currently employed	45.2	62.5	26.7	
Retired	3.2	0	6.7	
Unemployed	19.4	12.5	26.7	
Disabled	32.2	25.1	40	
Duration of FMS (years), mean (SD)	4.47 (3.83)	4.23 (3.44)	4.70 (4.30)	.744
Duration of sleep problem (years), mean (SD)	10.70 (8.62)	11.41 (9.24)	9.85 (8.23)	.682
Nature of sleep problem				
Onset (%)	74.3	75	73.3	.425
Maintenance (%)	90.3	87.6	93.4	.505
Early awakening (%)	71	62.5	80	.130
Sleep latency (hours), mean (SD)	1.16 (1.13)	1.12 (1.23)	1.23 (0.53)	.742
Number of awakenings per night, mean (SD)	2.93 (1.12)	2.71 (0.99)	3.14 (1.23)	.320
Sleeping hours per night, mean (SD)	4.42 (1.03)	4.48 (1.05)	4.36 (1.03)	.652
Drug intake (%)				
Antidepressants	64.4	64.2	64.3	.622
Anxiolytics	60.7	64.3	57.1	.699
Anti-inflammatory drugs	64.3	57.1	71.4	.430
Analgesics	64.3	64.2	64.3	.589

Note. FMS = Fibromyalgia, ANT-I = Attentional Network Test-Interactions, CBT-I = Cognitive-behavioral therapy for insomnia; SH = Sleep hygiene; SD = Standard deviation.

The CBT-I group reduced overall reaction time (RT) in the second session to a greater extent than the SH group, although the Time × Group interaction only approached significance; $F(1, 28) = 2.97$, $p = .0956$. Whereas the CBT-I group reduced overall RT significantly from the Pre- (717 ms) to the Post-treatment (617 ms) session; $F(1, 28) = 16.37$, $p = .0004$, the SH group showed rather similar overall RT in both sessions; 704 ms and 654 ms, respectively, $F(1, 28) = 1.74$, $p = .1984$. No other interaction involving the factor Group approached significance. In summary, the CBT-I group showed a significantly greater improvement than the SH group in Attention-Executive functioning (i.e. greater reduction in interference), Attention-Alerting (i.e. greater reduction in alertness), and a marginally significant larger reduction in overall RT.

Table 20- Mean and standard deviations of the clinical variables obtained by the therapy groups at Pre- and Post-treatment.

	CBT-I group (n = 20)				SH group (n = 20)			
	Pre-treatment		Post-treatment		Pre-treatment		Post-treatment	
	M (SD)		M (SD)		M (SD)		M (SD)	
MeanRT [(1)]	717.45	(124.82)	617.00	(78.39)	703.68	(111.73)	653.60	(88.57)
Control [(1)]	113.97	(33.74)	87.92	(29.13)	114.20	(49.81)	104.70	(33.84)
Orienting [(2)]	54.88	(43.25)	66.17	(24.26)	59.70	(20.34)	58.15	(38.16)
Alerting [(1)]	92.03	(74.17)	51.85	(31.33)	69.48	(47.39)	68.98	(44.81)
Sleep Quality (PSQI) [(1)]	15.05	(3.39)	11.55	(4.29)	14.15	(3.11)	13.20	(3.12)
Pain Intensity (MPQ) [(1)]	7.02	(1.92)	6.50	(2.46)	8.26	(1.70)	8.26	(1.48)
Anxiety (HADS) [(1)]	10.60	(4.13)	10.95	(4.26)	11.60	(4.12)	11.55	(3.84)
Depression (HADS) [(1)]	10.50	(3.69)	9.65	(4.39)	12.20	(3.73)	11.30	(4.61)
Daily Functioning (FIQ) [(1)]	59.66	(12.83)	49.25	(21.38)	62.19	(13.97)	63.67	(16.08)

Note. M = Mean; SD= Standard deviation; CBT-I = Cognitive-behavioral therapy for insomnia; SH = Sleep hygiene; PSQI= Pittsburgh Sleep Quality Index; MPQ = McGill Pain Questionnaire; HADS = Hospital Anxiety and Depression Index; FIQ = Fibromyalgia Impact Questionnaire.
(1) High scores indicate worse functioning
(2) High scores indicate better functioning

Attentional indexes

Indexes of the efficiency of each attentional network were computed as the following subtractions (Callejas et al., 2004): Attention-Alerting = NoTone-Tone conditions (restricted to the no-cue condition); Attention-Orienting = Uncued location-Cued location trials, and Attention-Executive functioning = Incongruent- Congruent. These indexes were computed for both the Pre- and Post-treatment sessions. Overall RT in each session was also taken as an index of overall performance. Furthermore, differences between the Pre- and Post-treatment sessions were computed as an index of improvement in each measure. Specific *t*-tests comparing each Pre-Post attentional index against 0 for each group were computed to test whether the functioning of each attentional network changed after treatment for each group.

In the SH group, there was no change after treatment in any of the attentional indexes (all *p*s > .45). In the CBT-I group, only the Alertness and Executive functioning attention indexes changed after treatment; $t(16) = 2.16$, $p = .0470$, $d = .70$ and $t(16) = 2.65$, $p < .0183$, $d = .82$, respectively; whereas no change was observed in the Attention-Orienting index; $t(16) = -.82$, $p = .4271$.

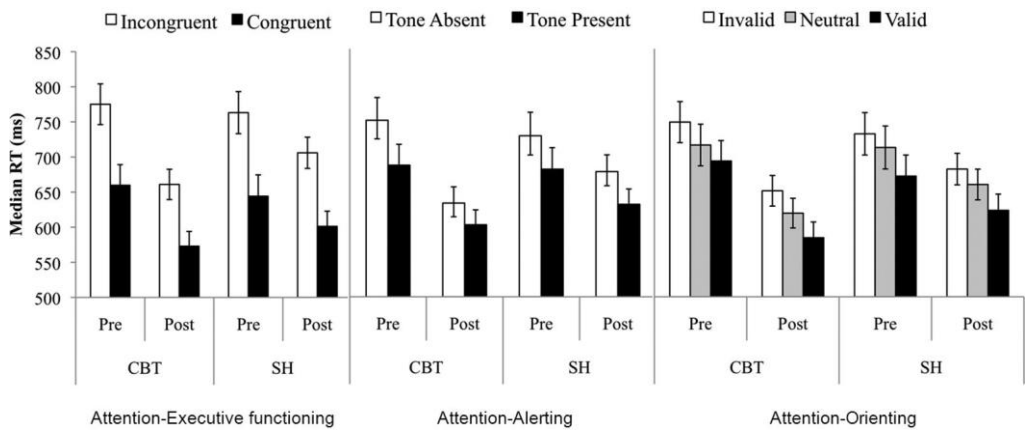

Figure 13- Attentional functioning of the CBT-I and SH groups in the Pre- and Post-Treatment sessions. Note that the CBT-I group showed a larger improvement in the Post-Treatment session, in Attention-Executive functioning (i.e. larger reduction in interference) and Attention-Alerting, as compared with the SH Group.

Self-report measures

Differences in self-reported measures between the CBT-I and SH therapy groups across sessions were compared using repeated-measures ANOVAs (Group; CBT-I vs. SH × Time; Pre vs. Post-treatment). Effect sizes were calculated via the partial η^2. For significant effects, Student's *t* test was computed for paired comparisons and Cohen *d* was used to examine the effect sizes (small .2, medium .5, and large .8) (Cohen, 1988). The statistical power of the analysis performed with the self-report measures was 70%.

Repeated-measures ANOVAs for Sleep Quality (PSQI) showed a significant effect for Time; $F(1, 38) = 19.29$, $p = .000$, $\eta^2 = .33$; and for Time × Group interaction; $F(1, 38) = 6.33$, $p = .016$, $\eta^2 = .14$; but no significant effect for Group. Whereas the CBT-I group reduced sleep dysfunction from the Pre- (15.05) to the Post-treatment (11.55) session; $t(19) = 5.01$, $p = .000$, $d = .90$, large effect size; the SH group showed no differences in sleep dysfunction between both sessions; 14.15 and 13.20, respectively, $t = 1.29$, $p = .211$.

The ANOVA for Daily Functioning (FIQ) showed a significant Time × Group interaction; $F(1, 38) = 4.09$, $p = .050$, $\eta^2 = .09$; whereas the effect of Group or Time factors was not significant. CBT-I group changed the Daily Functioning (FIQ) from the Pre- (59.66) to the Post-treatment (49.25) sessions at a level that approached significance; $t(19) = 1.94$, $p = .067$, $d = .59$, medium effect size; whereas the SH group did not change; 62.19 and 63.67, respectively. In short, 85% of the patients in the CBT-I

group and 55% in the SH group showed significant clinical changes in Sleep quality (PSQI). Similarly, 60% of the patients in the CBT-I group and 30% in the SH group improved Daily Functioning (FIQ) to a clinically significant level.

ANOVAs for Pain intensity (MPQ) and Anxiety and Depression (HADS) did not show any significant effects for Time, Group, and Time × Treatment interaction factors; between $F(1, 38) = .002$, $p = .961$ and $F(1, 38) = 2.93$, $p = .095$. Overall, these results show that the CBT-I group obtained greater improvement than the HS group in both Sleep Quality and Daily Functioning.

Relationships between outcome measures

For clinical variables that changed over time as a result of the therapy (CBT-I or SH), individual changes were calculated with the Reliable Change Index (RCI) (Jacobson, &Truax, 1991; Salaberría et al., 1996). Pearson's analysis was performed to examine relations between changes (Reliable Change Index) in Sleep Quality (PSQI) and Daily Functioning (FIQ) and changes (rate of change) in subtraction indexes of the ANT-I. Results revealed a significant correlation between the Attention-Executive functioning and the Reliable Change Index of Sleep quality (PSQI) ($r = .40$, $p = .026$). No significant correlations were observed between the Reliable Change Index of Sleep quality (PSQI) and Daily Functioning (FIQ) and the remaining indexes of the ANT-I (MeanRT, Alerting and Orienting) either at Pre-or Post-treatment (r between .29, $p = .104$, and -0.24, $p = .181$), nor subtraction indexes of the ANT-I (r between .19, $p = .300$ and -.25, $p = .162$). These results show that the change in sleep quality was related to the improvement in executive functioning.

Discussion

This is the first study to our knowledge that demonstrates the positive effect of a CBT for insomnia on cognitive function of patients with FMS. The CBT-I group showed significant improvement in alertness and executive functioning as compared with the SH group. In addition, the CBT-I group showed significant improvement in sleep quality and a trend to improvement in daily functioning, in contrast to the SH group. The analysis of relationships between changes in the ANT-I measures (alertness and control) and changes in psychological measures (sleep and daily functioning) showed that the improvement in executive functioning was significantly related to changes in sleep.

At Pre-treatment, participants with FMS showed the expected impairment in Attention-Alerting and Attention-Executive functioning reported in our previous study (Miró et al., 2010). The two FMS groups in the current study showed 115 and 119 ms Attention-Executive functioning, and 63 and 48 ms Attention-Alerting effects, while the control group in our previous study (Miró et al., 2010) showed 82 and 29 ms effects, respectively. The larger alerting effect is usually observed in populations with attentional deficits, and suggests that these subjects take greater advantage of the tone signal than healthy controls because they have difficulties in maintaining alertness without an external signal (Fan et al., 2002). After the treatment, the CBT-I group showed a significant reduction in the alertness effect as compared with the SH group. This seems to reflect an improvement in the capacity to endogenously maintain the level of activation that is necessary to perform the task, that is, an improvement in vigilance. This conclusion is somehow supported by the fact that, after treatment, the CBT-I also seems to decrease overall RT, a measure that is usually taken as an index of vigilance.

With regard to executive functioning, after the intervention, the CBT-I group showed a reduction in the interference effect as compared with the SH group. Sleep processes have strong relationships with executive functioning and attention (Lim, & Dinges, 2010), and there is evidence that sleep therapy can lead to an improvement in most of these cognitive domains, as happens in people with sleep apnea or with insomnia (Altena et al., 2008).

Previously, two studies have shown that exercise in a warm-water pool improved attentional function and executive control in FMS patients (Munguía-Izquierdo, & Legaz-Arrese, 2007, 2008). This training in a warm-water pool included three sessions a week and lasted for 16 weeks, while our CBT-I program is composed of six sessions, one every week for six weeks. However, before concluding that CBT-I is more efficient than exercise therapy a detailed cost- benefit analysis is mandatory. As regards the self-reported measures, after treatment FMS patients in the CBT-I group showed a significant improvement in sleep and showed a trend to improvement in daily functioning, as compared with subjects in the SH group. This finding is consistent with Edinger's work, which showed a significant improvement in sleep quality in a CBT-I group as compared with SH instructions and usual care (Edinger et al., 2005). Also, Munguía-Izquierdo and Legaz-Arrese (2008) reported an improvement in sleep quality in their exercise group vs. the control group. Sleep disturbances in FMS are usually

treated with tricyclic antidepressants or sleep medications which provide very limited effects and often have adverse consequences (Häuser et al., 2010). Again, our results suggest that a CBT-I that includes sleep education and cognitive-behavioral strategies for insomnia may be both effective and efficient to improve sleep quality as compared with medications or the longer duration exercise therapy. However, much more research is needed before reaching conclusions about the efficacy of these treatments.

Our data suggest that improvement in cognitive function seems to be related to a positive impact in daily functioning, although the effect was only marginally significant. No significant changes were found in anxiety, depression, or pain between both groups. In Edinger's work, the CBT-I group showed an improvement in mood state as compared with the remaining groups, but Edinger used the Profile of Mood States while we used the HADS. As in the present study, Munguía-Izquierdo and Legaz-Arrese (2008) did not find any differences in anxiety either after their treatment using the State Trait Anxiety Inventory. The difference seems to lie in testing state vs. trait. Improvements in trait rather than state may only appear after a longer period after treatment.

The absence of changes in pain may also be related to the instrument used to measure pain (MPQ). An objective measure of pain may be more sensitive to our intervention. Dick and Rashiq (2007) did not find any changes in the MPQ after procedures resulting in analgesia, while studies that have assessed pain with objective methods (dolorimeter) have found significant changes in the pain threshold after exercise training (Munguía-Izquierdo, & Legaz-Arrese, 2007, 2008).

In addition, most studies of CBT-I that have achieved major psychological improvements in emotional distress and pain have used longer programs and include a much greater intervention (Hassett, & Gevirtz, 2009). Moreover, it is important to consider that our results were obtained comparing a group of FMS patients who received CBT-I vs. a group of FMS patients who received SH. Note that psycho-education is a feature of both interventions. If we had compared our outcome results with a control group, the benefits would probably have been greater. It is known that education conditions such as SH lead to greater improvement than a waiting-list control group (Edinger et al., 2005; Yang et al., 2010).

Regarding the relationships between attentional deficits and psychological measures, we found that changes in executive functioning - but not in alertness - were correlated with the improvement in sleep quality. The improvement in alertness may relate better with

other sleep parameters that we have not considered in our study. Further research is needed to understand the relationships between sleep processes and cognitive functioning in FMS. Accumulating evidence suggests that FMS appears in response to chronic stressors (Oliveira, & Costa, 2009) and is associated with a disorder of the neuroendocrine stress response that may influence cognitive function through effects of hypocortisolism on the brain (Sephton et al., 2003). Also, for example, chronic stress produces alterations in prefrontal cortical morphology that may under-lie the observed deficits in executive control (Liston et al., 2006). In addition, chronic stress relates strongly to poor sleep quality (Hamilton et al., 2008; Moldofsky, 2010), and the inability to obtain a restorative sleep has been related with prefrontal cortex dysfunction (Jones, & Harrison, 2001; Lim, & Dinges, 2010).

Several methodological limitations of the present study should be taken into account in future research. First, our findings should be replicated with a larger sample recruited from other contexts. Although the diagnostic reliability of a sample collected from a hospital may be greater, these subjects may also have greater impairment than the participants recruited from FMS associations. Also, requiring participants to undergo many procedures and tests may have reduced the attendance to Post-treatment assessments (e.g. ANT-I). Follow-up assessments are necessary to clarify whether the observed benefits remain over time. In addition, it would be interesting for future trials to include objective measures of pain, a wide range of measures of emotional distress, and monitoring of therapy sessions to ensure fidelity of therapists to treatment protocols.

Furthermore, an added complication of the study of cognitive function in FMS is the frequent use in the sample of multiple drugs. Although this might be considered a limitation of the study, it makes our study more representative of a general clinical population. It is important to note that medication was kept constant through all the trial. Nevertheless, the results of the present study should be treated with caution, and replication is called for.

In short, the present study showed that a CBT-I for insomnia represents a promising intervention not only for sleep disturbance in FMS patients but also for attentional dysfunction, and probably for daily functioning. Our trial provides additional evidence for the relevance of sleep in FMS. The results of the present study should encourage the use of a more structured intervention for insomnia such as CBT. Similarly, further

research should address more specifically whether the combination of the usual CBT treatment with a CBT therapy for sleep may improve current management of FMS syndrome.

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Effects of cognitive-behavioral therapy for insomnia on polysomnographic parameters in fibromyalgia patients[1]

Abstract

This study aimed to evaluate the efficacy of cognitive-behavioral therapy for insomnia (CBT-I) on polysomnographic parameters in patients with fibromyalgia syndrome (FMS). Twenty-six women with FMS participated in the study and were randomly assigned to a CBT-I (n = 13) group or sleep hygiene (SH) condition (n = 13). The evaluation consisted in two interview sessions and an ambulatory polysomnography study before and after treatment. The results show that time-in-bed and wake percentage diminish after CBT-I. Improvements were also observed in sleep efficiency, which was close to normal levels. The percentage of NREM stage 1 sleep decreased and NREM stages 3 sleep and 4 increased. Similarly, light sleep (stages 1 and 2) diminished and deep sleep increased (stages 3 and 4) after CBT-I. No improvements were observed in any of these parameters in the individuals undergoing SH therapy. This randomized controlled trial provides new evidence that the use of CBT-I in FMS patients can significantly improve objective sleep parameters.

Keywords: Cognitive-behavioral therapy; Domiciliary polysomnography; Fibromyalgia; Insomnia; Randomized controlled trial.

Introduction

Fibromyalgia syndrome (FMS) is a disorder characterized by widespread musculoskeletal chronic pain and multiple tender points (11 of 18 tender points) (Wolfe et al., 1990). The symptoms of FMS are very heterogeneous. Besides pain, up to 96-99% of patients with FMS describe fatigue and sleep dysfunction (Lineberger, Means, & Edinger, 2007). They also complain of anxiety, depression, cognitive dysfunction, stiffness, cold sensitivity, irritable bowel syndrome and headaches (Gormsen, Rosenberg, Bach, & Jensen, 2010; Miró et al., 2011; Miró, Martínez, Sánchez, Prados, & Medina, 2011; Pérez-Pareja, Sesé, González-Ordi, & Palmer, 2010), with significant

[1] Sánchez, A. I., **Díaz-Piedra, C.**, Miró, E., Martínez, M. P., Gálvez, R., & Buela-Casal, G. (2012). Effects of cognitive-behavioral therapy for insomnia on polysomnographic parameters in fibromyalgia patients. *International Journal of Clinical and Health Psychology, 12*, 39-53.

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negative repercussions on the patient's quality of life (Lledó-Boyer et al., 2010; Sánchez, Martínez, Miró, & Medina, 2011).

The etiology of FMS is unknown. Thus, it is currently difficult to have an in-depth understanding of the role of, and relationships between, pain and other symptoms that may accompany this syndrome, and effective treatment is therefore lacking (Häuser, Thieme, & Turk, 2010). A number of hypotheses have been proposed regarding the pathophysiology of FMS, including central nervous system dysfunction affecting pain sensitivity, viral infections, immunological causes, neuroendocrine dysfunction, neuromuscular, metabolic or immune system issues, and it has even been suggested that FMS is associated with a history of trauma or other psychological disorders (Bradley, McKendree-Smith, Alarcón, & Cianfrini, 2002; Broderick, Junghaenel, & Schwartz, 2005; Gur & Oktayoglu, 2008).

Some authors suggest that sleep disturbances may have an important role in the maintenance of pain and other symptoms of FMS (for a review see Moldofsky, 2001, 2002, 2008, 2010). Moreover, Nicassio, Moxham, Schuman, and Gevirtz (2002) analyzed the influence of pain, depression and sleep disorders on fatigue in FMS using questionnaires and self-records, and observed multiple relationships between pain, sleep and fatigue, beyond the prevailing notion that pain is responsible for the other symptoms. Recently, Hamilton and colleagues (2008) reported that sleep duration and sleep quality are prospectively related to affect and fatigue. In addition, inadequate sleep has a cumulative effect on negative mood. In this line, recent clinical and experimental research shows that sleep disturbances have a reciprocal influence on musculoskeletal pain and fatigue (Moldofsky, 2008, 2010). In fact, the American College of Rheumatology has developed diagnostic criteria for FMS in which unrefreshing sleep is included as one of the most important diagnostic variables (Wolfe et al., 2010).

Although the presence of abnormal nocturnal sleep in FMS has been reported and recognized, its significance with respect to the pathophysiology of the syndrome is debated. Also, sleep recordings are rarely used for evaluation in these patients and sleep disturbance is often considered a consequence of pain (Spitzer & Broadman, 2010).

Most research studies that have used subjective measures of sleep (mainly self-reports) mention the poor subjective sleep quality in FMS patients. Thus, for example, 99% of FMS patients in the study by Theadom, Cropley, and Humphrey (2007) reported poor sleep quality measured using the Pittsburgh Sleep Quality Index (PSQI). Also, in this

study, sleep quality was significantly predictive of pain, fatigue, and social functioning in patients with FMS. Osorio, Gallinaro, Lorenzi-Filho, and Lage (2006), also using the PSQI, observed that patients with FMS achieved higher scores than healthy controls in all the PSQI components except *Use of sleep medications*.

Different alterations have been identified by polysomnography (PSG) in patients with FMS, although not all research results are consistent. Specifically, it has been described that these patients exhibited shorter total sleep time, greater sleep latency, more awakenings, less sleep efficiency, higher percentages of non-rapid eye movement (NREM) stage 1 sleep, greater fragmentation of sleep, lower percentages of REM (rapid eye movement) sleep and shorter NREM sleep stages 3 and 4 compared with healthy controls (Besteiro et al., 2011; Dauvilliers & Carlander, 2007; Moldofsky, 2001, 2008; Roizenblatt, Moldofsky, Benedito-Silva, & Tufik, 2001). A recent study used actigraphy, showed that female FMS patients with objective sleep deficits (less than 6 hours of sleep) presented significantly lower sleep efficiency, significantly longer sleep onset latency and significantly shorter nighttime sleep times than women without sleep deficits (Stuifbergen, Phillips, Carter, Morrison, & Todd, 2010).

In terms of the microstructure of sleep in FMS, observed alterations include alpha-delta intrusions, as well as regular K-alpha intrusions, decreased sleep spindles, larger number of oxygen desaturations per hour of sleep and twice as many arousals per hour of sleep than controls, with an alternating cyclic pattern associated with severity of pain and low sleep efficiency (Lineberger et al., 2007; Rizzi et al., 2004). Moldofsky in 1975 was the first to suggest, through polysomnography, that the presence of alpha intrusions in deep delta sleep could be related with the set of symptoms known as FMS. Other studies have also reported these alpha intrusions in slow-wave or NREM sleep, as well as different changes indicative of sleep fragmentation (Lineberger et al., 2007; Moldofsky, 2001; Roizenblatt et al., 2001). The alpha sleep pattern in FMS has been associated with longer duration of pain symptoms, a perception of generally non-restorative sleep and the presence of pain when getting up in the morning (Lineberger et al., 2007; Moldofsky, 2008).

As regards treatment, a recent review of the latest Clinical Practice Guidelines on the treatment of FMS of the American Pain Society (APS) (Burckhardt et al., 2005), the European League Against Rheumatism (EULAR) (Carville et al., 2008) and the Association of the Scientific Medical Societies in Germany (AWMF) (2008) (Häuser et

al., 2010), recommend that FMS should be treated using a multidisciplinary approach combining aerobic exercise, cognitive-behavioral therapy (CBT), amitriptyline and multicomponent treatments (Häuser et al., 2010). However, although it is accepted that sleep alteration is one key symptom of FMS, the treatment of sleep alterations is not covered in current clinical guidelines on this syndrome. In most cases, such guidelines only include sleep hygiene (SH) instructions and pharmacological therapies to treat such alterations, but other much more effective cognitive-behavioral therapy for insomnia techniques (CBT-I) are not applied (Edinger, Wohlgemuth, Krystal, & Rice, 2005; Miró, Sánchez, & Buela- Casal, 2003; Pigeon, 2010).

In existing literature, two pilot studies have shown that CBT-I may improve sleep (Edinger et al., 2005; Miró, Lupiañez et al., 2011). In this first study, Edinger and colleagues (2005) compared sleep and other symptom improvements in FMS patients who received CBT-I, sleep hygiene (SH) or only usual care: 57% of the CBT-I group reported significantly improved sleep quality and mood, compared with 20% of the SH group and 3.5% of the medication therapy group. However, Edinger and colleagues (2005) used different subjective scales and actigraphy, which are less reliable than PSG. Recently, Miró, Lupiañez and colleagues (2011) compared CBT-I with SH and observed greater improvements not only in sleep quality but also in attentional function and daily functioning in the CBT-I group. However, these studies did not use PSG records to evaluate changes in sleep quality.

In summary, sleep alterations are one of the most prevalent symptoms in FMS. Several studies have suggested that an improvement in sleep quality could be associated with a positive change in pain, fatigue and daily functioning. Therefore, determining whether CBT-I can improve not only subjective sleep quality but also objective sleep parameters is crucial to establish the clinical utility of this intervention. Thus, the aim of this study was to evaluate the efficacy of CBT-I on polysomnographic parameters in patients with FMS compared to a control group that received SH.

Methods

Participants

Twenty-six women with FMS (M = 46.79 years of age, SD = 5.15) participated in the study and were assigned to a CBT-I group (n = 13; M = 44.83 years, SD = 5.30) or a sleep hygiene (SH) condition (n = 13; M = 48.75 years, SD = 4.37). Simple

randomization (1:1) was implemented by a computerized number generator designed by an investigator with no clinical involvement in the trial. The clinical sample was selected from the Rheumatology Service and Pain Unit of the *Hospital Universitario Virgen de las Nieves* in Granada (Spain). The mean duration of the illness was 5.02 years (*SD* = 4.28), although the mean onset of symptoms was greater (*M* = 12.96 years; *SD* = 8.33). The women who were fulfilling the inclusion criteria to participate in the study (see Table 21) were referred from the hospital to the Clinical Psychology Unit of the Faculty of Psychology (University of Granada), where three psychologists conducted both assessment and treatment (CBT-I and SH). All participants were informed about the characteristics of the study and an informed consent was obtained. The study received ethical approval from the University of Granada Ethics Committee.

Table 21- Inclusion and exclusion criteria established for participation in the study.

Inclusion criteria
1. Age between 25 and 60 years old.
2. Met the diagnostic criteria for FM as defined by the American College of Rheumatology (ACR) (Wolfe *et al.*, 1990).
3. Have chronic insomnia according to the Diagnostic and Statistical Manual of Mental
Exclusion criteria
1. Currently pregnant.
2. Medical history of significant head injury or neurological disorder.
3. Concomitant major medical conditions (e.g., inflammatory rheumatic diseases, endocrine disturbances).
4. Major depressive disorder with severe symptoms or suicide ideation, or other major Axis I diagnoses of the DSM-IV-TR (American Psychiatric Association, 2000).
5. Severe hypnotic dependence.
6. Having symptoms of sleep-disruptive comorbidities with insomnia.
7. Having an apnea-hypopnea index or periodic limb movement (PLM) related arousal index of 15 or more per hour on a polisomnography recording.
8. To be receiving another psychological or physical therapy at the time of the study.

Measures

An ambulatory PSG recording (with a SomnoScreen PSG-Tele, Somno Medics GmbH, Randersacker, Germany) was used to collect information from key sleep parameters in patients with FMS. The PSG recordings included electroencephalography in the frontal, central, parietal, and occipital regions (Fz/A1, Cz/A1, Pz/A1, Oz/A1), bilateral electrooculography, bilateral submental and anterior tibial electromyography and respiratory variables (chest belt, respiratory thermistance and oximetry). Sleep stages were scored visually according to the criteria of Rechtschaffen and Kales (1968) using 30 seconds' epochs. Table 22 contains a brief description of the sleep variables analysis.

Table 22- Sleep variables analysis in the polysomnography.

Time in bed (TIB) (hours)	Time period between bedtime and awakening in the morning.
Total sleep time (TST) (hours)	Total sleep period less movement and awake time.
Wake percentage	Percentage of time awake scored from bedtime to the final wake-up.
% REM sleep	Total time spent in REM sleep as a percentage of TST.
% Stage 1, 2, 3, 4 NREM sleep	Total time spent in stage 1, stage 2, stage 3, and stage 4 NREM sleep as a percentage of TST.
Light sleep	% stage 1 + % stage 2
Deep sleep	% stage 3 + % stage 4
Sleep efficiency	Proportion of sleep in the period potentially filled by sleep: ratio of TST to TIB as a percentage.
NREM sleep latency	Time period from bedtime to the beginning of sleep.
REM latency	Time period from sleep onset to the first appearance of REM sleep.
REM density	Average rate of the whole REM phase with mini REM epochs (3 seconds).
Number of awakenings > 3 minutes (index)	Average number of wake periods longer than 3 minutes during SPT.
Wake after sleep onset	Time spent awake after sleep onset had occurred.
Arousals index	Average number of arousals per hour of sleep.

Procedure

The evaluation and therapeutic treatment of sleep disorders (CBT-I and SH) in patients with FMS was carried out at the Clinical Psychology Unit of the Faculty of Psychology. The whole evaluation consisted of two sessions of individual interviews focusing on the origin and evolution of the problem and an ambulatory PSG. Three female CBT experts with experience in FMS provided the therapy guided by a treatment manual designed for the study. Each therapist applied both treatments (CBT-I and SH). Therapists delivered CBT-I and SH treatment in 6 weekly groups sessions. Each session included 5-6 participants and lasted around 90 minutes. The CBT-I program was designed according the works of Edinger and colleagues (2005), and met the recommendations of the American Academy of Sleep Medicine (Morgenthaler et al., 2006). Subjects who participated in SH therapy just received sleep hygiene instructions and were offered CBT-I after their post-treatment assessment. The contents of the SH therapy can be seen in Table 23. Also, all patients continued with their usual medical treatment for FMS. All participants were on stable doses of medication during the trial (see Table 24). On the consumption of medicaments, 4 patients in the CBT-I group and 2 patients in the SH group consumed occasionally benzodiazepines (less than once a week). Moreover, most patients in both groups consumed regularly non-benzodiazepine anxiolytics (those patients with severe hypnotics dependence were excluded from the study), and

antidepressants. In relation to the latter category of medicaments, although they can affect sleep, we must specify that patients had taken these medicaments for months before the psychological interventions, so we think that the possible effect on sleep was controlled.

Table 23- Contents of the cognitive-behavioral therapy for insomnia and the sleep hygiene group.

	CBT-I sessions	SH sessions
Session 1	Information about the relationship between sleep and FMS, basic notions about sleep (e.g., sleep stages, sleep functions, effects of sleep deprivation on diurnal functioning, explanation of insomnia) and SH education.	Participants were given the same information about sleep as the CBT-I group.
Session 2	Sleep restriction therapy combined with stimulus control instructions.	Sleep hygiene rules related to environmental factors.
Session 3	Relaxation training (a combination of passive relaxation and imagery training).	Lifestyle factors that influence sleep (consumption of stimulants and other substances).
Session 4 and 5	Cognitive therapy for the dysfunctional beliefs related to insomnia.	Information about diet and physical exercise, respectively.
Session 6	Maintaining achievements and preventing relapses.	Similar as the CBT-I group.

Note. CBT-I = Cognitive-behavioral therapy for insomnia; SH= Sleep hygiene; FMS = Fibromyalgia.

Study desing and statistical analysis

This was a controlled randomized trial or "experimental design with an independent variable (IV) and random groups" in which the IV was the type of treatment to be received by the subjects (CBT-I and SH). Statistical analysis was performed using SPSS 15.0 for Windows. Non-parametric statistical tests were used because they are recommended when the sample size is less than 15 (Bryman & Cramer, 1990). To compare the groups on demographic and clinical variables at baseline the Mann-Whitney's *U* test for interval data and the Pearson chi-square (χ^2) test for nominal data were computed. In order to examine the therapeutic changes between-group in PSG parameters the Mann-Whitney's *U* test was used. Finally, the therapeutic changes intra-group in PSG parameters were analyzed via the Wilcoxon test.

Results

Table 24 shows the demographic and clinical characteristics of the FMS sample. The results of the non-parametric tests performed (Mann-Whitney's *U* and the Pearson chisquare test), showed that the two groups (CBT-I vs. SH) did not differ significantly

in terms of age, marital status and work, education, and clinical variables such as years since diagnosis of FMS, insomnia or type of insomnia problem and drug intake (all p >.05).

Table 24- Demographic and clinical characteristics of the fibromyalgia sample completing the ambulatory polisomnographic study.

Variables	*Total sample (n=26)*	*CBT-I group (n=13)*	*SH group (n=13)*	*p value*
Age, mean (SD)	46.79 (5.15)	44.83 (5.30)	48.75 (4.37)	.07
Education (%)				.08
Basic education	31.8	18.2	45.5	
High school	27.3	45.5	9.1	
Professional instruction	22.7	9.1	36.4	
University studies	18.2	27.3	9.1	
Marital status (%)				.386
Married	92.3	92.3	92.3	
Single	3.8	0	7.7	
Divorced or widowed	3.8	7.7	0	
Work status (%)				.094
Currently employed	50.0	69.2	30.8	
Unemployed	23.1	7.7	38.5	
Disabled	26.9	23.1	30.8	
Duration of FMS (years), mean (SD)	5.02 (4.28)	4.67 (3.66)	5.34 (4.91)	.913
Duration of sleep problem (years), mean (SD)	11.25 (9.08)	11.41 (9.24)	9.85 (8.23)	.682
Nature of sleep problem				
Onset (%)	69.3	69.3	69.5	.884
Maintenance (%)	84.6	84.7	84.6	.836
Early awakening (%)	76.9	69.3	84.6	.661
Drug intake (%)				
Antidepressants	50.0	45.5	53.8	.682
Anxiolytics	63.6	61.5	62.5	.916
Anti-inflammatory	63.6	69.2	66.7	.772
Analgesics	72.7	69.2	70.8	.851

Note. CBT-I = Cognitive-behavioral therapy for insomnia; SH= Sleep hygiene; SD = Standard deviation; FMS = Fibromyalgia.

Table 25 shows PSG variables before and after CBT-I or SH therapy. As can be seen, the results of the Mann-Whitney's *U* test indicate that prior to treatment there were no statistically significant differences in any of the PSG variables between the two groups (CBT-I and SH) (*U* values between 75.00 and 84.00, $p > .05$). Secondly, a Wilcoxon test was carried out to determine whether there were any differences in the PSG variables analyzed pre-post treatment in each treatment group (CBT-I and the SH). The results for the active treatment group receiving CBT-I showed a decrease in time-in-bed [$z = -2.62$, $p < .01$] and wake percentage [$z = -2.41$, $p < .05$] after treatment. Thus, sleep efficiency [$z = -2.41$, $p < .05$] improved, almost reaching normal levels. As regards sleep architecture, the results revealed a decrease in the percentage of non-rapid eye movement (NREM) stage 1 sleep [$z = -2.90$, $p < .01$] and an increase in the percentage

of NREM stage 3 sleep [z = -2.20, p < .05] and NREM stage 4 sleep [z = -2.19, p < .05]. No differences were observed between pre-post treatment in the percentage of REM sleep [z = -.17, p= .86] and NREM stage 2 sleep [z = -1.15, p=.24]. In addition, the results showed light sleep (NREM stages 1 and 2) decreased [z = -2.20, p < .05] and deep sleep (NREM stages 3 and 4) increased [z = -2.55, p < .01] after CBT-I. No differences were observed in sleep duration (hours) [z = -1.37, p= .12], NREM sleep latency [z = -1.49, p= .136], REM latency [z = -1.17,p= .23], % REM density [z = -.31, p= .75], wake after sleep onset [z = -.31, p= .75], number of awakenings greater than 3 minutes [z = -1.67, p = .09] and arousal index [z = -.80, p = .42]. Subjects participating in SH group therapy showed no significant improvements (z values between -1.50 and -.15, p > .05). Finally, we checked for significant differences in PSG sleep parameters post-treatment between the CBT-I group vs. HS group. The Mann-Whitney's U test revealed statistically significant differences in three of the PSG variables analyzed, namely % NREM stage 1 sleep [U = 44.50, p < .05], % stage 4 sleep [U = 48.00, p < .05] and deep sleep (NREM stages 3 and 4) [U = 44.50, p <.05]. As can be seen in the mean scores (Table 25), in the CBT-I group, a lower percentage of NREM stage 1, and a higher percentage of NREM stage 4 and deep sleep (stage 3 and 4) were observed, compared with the group that received only HS.

Table 25- Polysomnographic measures of the group assigned a cognitive-behavioral therapy for insomnia and the sleep hygiene group.

	CBT-I group			SH group			CBT-I vs. HS	CBT-I vs. HS
	Mean (SD)			Mean (SD)			Pre-treatment	Post-treatment
PSG variables	Pre-treatment	Post-treatment	Z	Pre-treatment	Post-treatment	Z	U	U
Total sleep time (hours)	7:03 (1:04)	6:53 (2:19)	-1.37	7:31 (0:54)	6:57 (0:55)	-1.21	84.00	77.00
Time in bed (hours)	8:54 (0:40)	8:21 (0:53)	-2.62**	8:31 (0:53)	7:45 (1:10)	-1.50	68.00	68.00
Wake percentage	15.51 (9.38)	12.51 (9.47)	-2.41*	11.56 (6.18)	10.06 (3.67)	-.52	64.00	77.00
% REM	23.88 (6.22)	23.83 (5.66)	-.17	22.02 (6.30)	25.43 (9.72)	-1.50	75.00	76.00
% Stage 1	6.89 (4.20)	4.55 (2.23)	-2.90**	6.50 (3.02)	7.00 (2.87)	-.80	80.00	44.50*
% Stage 2	54.05 (9.44)	50.74 (9.28)	-1.15	52.71 (7.50)	52.51 (7.78)	-.80	77.00	70.50
% Stage 3	10.20 (3.93)	13.17 (4.75)	-2.20*	11.24 (4.40)	11.36 (5.91)	-.21	77.00	72.00
% Stage 4	4.81 (3.67)	7.43 (5.56)	-2.19*	4.51 (4.55)	3.62 (3.82)	-.96	78.00	48.00*
Light sleep	60.95 (9.88)	55.26 (9.64)	-2.20*	62.20(7.78)	59.53 (8.24)	-.94	72.00	57.50
Deep sleep	15.03 (5.68)	20.58 (8.41)	-2.55**	15.76 (6.53)	14.97 (7.36)	-.31	81.00	44.50*
Sleep efficiency	84.48 (9.39)	87.48 (9.47)	-2.41*	88.43 (6.18)	89.29 (3.67)	-.52	64.00	77.00
NREM sleep latency	0:27 (0:24)	0:24 (0:45)	-1.49	0:19 (0:16)	0:15 (0:13)	-.80	58.00	74.00
REM latency	1:53 (0:55)	1:35 (0:56)	-1.17	2:05 (1:15)	1.55 (1.34)	-.15	64.00	83.00
% REM density	13.00 (8.57)	13.00 (6.32)	-.31	9.46 (9.78)	9.85 (6.40)	-.26	64.50	56.55
Nº of awakenings > 3 min.	3.33 (2.09)	2.15 (2.37)	-1.67	2.15 (1.62)	1.77 (1.92)	-.73	61.50	77.50
Wake after sleep onset	0:40 (0:18)	0:36 (0:23)	-.31	0.31 (0.22)	0.31 (0.20)	-.94	79.00	76.00
Arousals	10.55 (4.34)	13.18 (15.35)	-.80	13.86 (9.28)	13.56 (13.82)	-.94	74.00	80.00

Note. CBT-I = Cognitive-behavioral therapy for insomnia; SH= Sleep hygiene; SD = Standard deviation.
* p < .05; ** p < .01

Discussion

This clinical trial provides new evidence that the use of CBT-I in women with FMS can improve objective sleep disturbance parameters. The few studies identified in the literature that have used PSG to evaluate sleep in patients with FMS have reported relevant findings, including shorter total sleep time, greater sleep fragmentation, greater sleep latency, less sleep efficiency, an increase in NREM stage 1 sleep and a reduction of the quantity of NREM stage 3 and 4 sleep compared with healthy controls (Besteiro et al., 2011; Moldofsky, 2001, 2008; Roizenblatt et al., 2001). Moldofsky's studies in the seventies showed that patients with FMS did not reach NREM sleep stages 3 and 4, *i.e.* the deepest and most restful phases of sleep. Research comparing sleep problems in patients with FMS with those observed in other chronic pain diseases, including rheumatoid arthritis; have found that FMS patients reported more insomnia, less contentment with sleep and more lack of deep and restful sleep in comparison to rheumatoid arthritis patients (Belt, Kronholm, & Kauppi, 2009).

In the present study, patients with FMS showed at pre-treatment sleep onset insomnia, maintenance and early awakening (see Table 24). However, upon completion of treatment, the CBT-I group evidenced improvements in sleep efficiency to almost normal levels and a decrease in wake percentage and time-in-bed. Significant changes were also observed in sleep architecture; specifically, a decrease in the percentage of NREM stage 1 sleep and an increase in the percentage of NREM stages 3 and 4 sleep. Similarly, light sleep (NREM stages 1 and 2) decreased, accompanied by increased deep sleep (NREM stages 3 and 4). Despite the small size of the sample, the results showed objective evidence of a change in sleep features. Therefore, although no changes were observed in the total sleep time of patients with FMS, significant differences were observed in the percentages of deepest sleep, which increased after intervention, and a decrease in the percentage of wake that provided the most restful sleep. Although both sleep quality and sleep quantity parameters are relevant, the association with different health indicators is stronger in the case of the former (Miró, Cano Lozano, & Buela Casal, 2005; Pilcher & Ott, 1998). Deep sleep (stages 3 and 4) has been related with corporal and neurological restoration, and these stages are closely related to the correct immune system functioning (Buela-Casal & Miró, 2001). The improvement in these phases observed in this study could have a great positive impact on other symptoms of FMS and on the actual severity of the syndrome. However, further research is necessary

in order to determine how these changes in objective sleep parameters are related to the improvement of other FMS symptoms. Moreover, time-in-bed decreases and sleep efficiency increases, indicating an improvement in SH practices. These clinical parameters are normally used as evidence of improvements in sleep in insomnia treatment studies (Morin & Espie, 2003).

In this study, the patients in the SH therapy group showed no improvements in any parameter. These findings do not coincide with those reported elsewhere in the literature. For example, in a recent study, Miró, Lupiañez and colleagues (2011) reported that 55% of the subjects in their SH group displayd significant clinical changes in sleep quality compared with 85% in the CBT-I group. Edinger and colleagues (2005) also reported that the participants receiving SH therapy had reduced their nocturnal wake time by nearly 20% at the end of the study, compared with a 50% decrease in patients receiving CBT-I therapy. Patients receiving CBT-I also showed a higher rate of sleep improvement (57%) compared with patients in SH therapy (17%). A possible explanation for these results may be the evaluation instruments used. In our study, the pre- and post-treatment changes observed in sleep variables after the application of CBT-I and SH therapy were evaluated using polysomnographic measurements, whereas in the aforementioned studies measurements were taken using actigraphy and subjective measurements that provided different and complementary information to polysomnography. Many studies in the literature argue that therapy groups based on education (e.g., sleep hygiene) produce improvements, albeit more modest than those obtained with more structured therapy groups. Sleep hygiene may slightly improve the subjective sensation of sleeping better but it is not a sufficiently powerful treatment to change objective sleep parameters (for review about use of sleep hygiene in the treatment of insomnia see Stepanski & Wyatt, 2003).

Moreover, some studies have also examined CBT-I with chronic pain patients and obtained positive results, but basically using questionnaires. Previous studies have suggested that improving sleep quality (rapid sleep onset, absence of early awakening and restorative sleep) in chronic widespread pain subjects could decrease pain (Davies et al., 2008), as well as impact on daily life functioning and depression. In osteoarthritis patients, Vitiello, Rybarczyk, Von Korff, and Stepanski (2009) observed that patients receiving CBT-I reported significantly decreased sleep latency and wake after sleep onset and increased sleep efficiency after treatment, compared with before treatment.

They also reported significantly reduced pain. One-year follow-up found maintenance of improved sleep (in sleep latency and wake after sleep onset and increased sleep efficiency and total sleep time) and reduced pain in the CBT-I group. Finally, a recent study conducted for Jungquist and colleagues (2010) shows that CBT-I can significantly improve sleep and daily functioning in patients suffering from chronic neck or back pain. After eight weeks, participants reported significant improvements in sleep quality and also a reduction in the extent to which pain interfered in daily activities. Specifically, subjects receiving CBT-I compared with controls (who did not receive directed form of therapy was provided for pain, depression, or sleep disturbance) exhibited significant decreases in sleep latency (time to fall asleep), wake after sleep onset, number of awakenings and significant improvements in sleep efficiency (Jungquist et al., 2010).

However, although our study shows that CBT-I improves sleep quality in FMS patients, evidenced by increased deep sleep and efficiency and decreased light sleep and awakenings, little research has been carried out into the therapeutic potential of CBT-I in these patients. Moreover, sleep problems in FMS are treated, indirectly, with analgesic medication (opioids, tricyclic antidepressants or anticonvulsants) and sedative hypnotics that promote sleep through analgesic and soporific effects (Smith & Haythornthwaite, 2004). These effects may increase sleep quantity but do not usually reduce sleep complaints. Hence, since current medication is unable to improve sleep quality, pain intensity or quality of life, it seems obvious that CBT-I is a promising treatment option for inclusion in current FMS treatments.

It is important to recognize various additional limitations in the interpretation of the results obtained in this study. Firstly, the size of the sample. However, in spite of the small size of the sample, results showed changes in PSG sleep variables. Another limitation is the frequent use of different medication. Most patients in our study took antidepressants, analgesic or anxiolytic medication during treatment. However, and although this may be considered a limitation of the study, it is important to remember that the medication was maintained constant throughout the entire trial. Although there was a random allocation of patients to treatment groups, another limitation of the study is the lack of uniform distribution of employment status in groups (although the differences are not statistically significant). Finally only women were included in this study since prevalence is lower in men.

To summarize, CBT-I may be a promising sleep therapy for FMS patients. However, further research is necessary in the future to replicate these results with larger samples of FMS patients, as well as in patients recruited in other contexts, such as patients' associations. Another future line of research could focus on establishing the relative efficacy of CBT-I compared with common psychological and medical treatment and determining what the study of sleep can contribute to current psychological treatment, in order to improve the symptoms and the quality of life of these patients. Finally, future studies must be carried out using PSG to analyze how treatment can improve different variables, including pain, daily functioning and cognitive function, and their relationships with the improvements observed in sleep parameters.

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DISCUSIÓN GENERAL

Aunque el dolor es el síntoma más destacado en la fibromialgia, la relevancia de los síntomas de sueño en este síndrome ha provocado el aumento de la investigación acerca de este tema. Sin embargo, la fibromialgia es una condición ambigua y controvertida a nivel clínico y los desafíos que se plantean al intentar comprender el trastorno también están presentes en la investigación acerca del sueño en estos pacientes. Esto da lugar a ciertas inconsistencias e incertidumbres en los resultados obtenidos hasta la fecha. El objetivo de esta Tesis Doctoral ha sido clarificar algunos de los interrogantes que aún están presentes en la investigación acerca de los problemas de sueño en los pacientes con fibromialgia. En los estudios reunidos en esta Tesis se realizan nuevas aportaciones al cuerpo de conocimientos sobre sueño y fibromialgia en varias áreas (a saber, caracterización del sueño en este síndrome, el papel del sueño en la clínica de la fibromialgia y su patofisiología y el tratamiento de los problemas de sueño), intentado superar, con nuestra metodología, muchas de las limitaciones de trabajos anteriores.

El rol de los problemas de sueño en la clínica y patofisiología de la fibromialgia

Las quejas de problemas de sueño son muy frecuentes en personas que sufren dolor crónico (Smith y Haythornwaite, 2004) y en otras condiciones reumáticas (Moldofsky, 2010). De hecho, un resultado consistente en investigaciones tanto clínicas como epidemiológicas es la presencia de mala calidad subjetiva de sueño en personas con fibromialgia (Hamilton et al., 2008; Moldofsky, 2008; Theadom, Cropley y Humphrey, 2007). Este hallazgo también está presente en todos los estudios de esta Tesis. Las mujeres que sufren fibromialgia presentan una mala calidad de sueño, lo que se corresponde con quejas de elevada latencia de sueño, baja eficiencia de sueño, pocas horas de sueño nocturno, excesivo número de despertares o disfunción diurna debida a la somnolencia o a la fatiga por un descanso no reparador. Sin embargo, a pesar de que, cuando se evalúa con varios tipos de autoinformes, se comprueba, casi de forma sistemática, que la calidad de sueño está deteriorada en estos pacientes, la presencia y/o cantidad de problemas objetivos de sueño no están tan claras. Los estudios polisomnográficos se realizan en pacientes con dolor crónico desde los años setenta, dado que se sospechaba la presencia de alteraciones objetivas del sueño en estos pacientes. Aunque estos estudios pioneros y otros más recientes han mostrado la

existencia de ciertas alteraciones, como la presencia de intrusiones de ondas α en el sueño no-REM (Drewes, Svendsen, Nielsen, Taagholt y Bjerregård, 1994; Roizenblatt, Moldofsky, Benedito-Silva y Tufik, 2001), muchas de estas alteraciones no son características únicamente de la fibromialgia y están presentes en otras condiciones e, incluso, en personas sin problemas (Manu et al., 1994; Moldofsky, 1989; Shaver et al., 1997). Además, otros estudios no han encontrado diferencias en muchos parámetros polisomnógraficos entre pacientes y controles sanos u otras poblaciones clínicas (por ejemplo, Chervin et al., 2009; Rains y Penzien, 2003; Roehrs et al., 2013). Aunque la polisomnografía es considerada el *gold standard* en la evaluación del sueño porque proporciona información rigurosa y valiosa acerca de la fisiología del sueño, no es una prueba diagnóstica de primera elección ante síntomas de insomnio o sueño no reparador (Kushida et al., 2005) y, además, es un prueba costosa (en términos económicos y temporales). Probablemente, éstas sean algunas de las razones por las que los estudios que han evaluado la arquitectura y microestructura del sueño en estos pacientes presenten datos a partir de muestras muy reducidas y heterogéneas (edad, sexo,…), lo que imposibilita obtener conclusiones claras. En el Estudio 1 de esta Tesis, se evalúa un grupo numeroso de pacientes y de controles sanos, teniendo en cuenta la influencia de la edad y el sexo sobre las características fisiológicas del sueño. Cuando el estudio se realiza de esta manera, se evidencian alteraciones en la organización de los ciclos de sueño (mayor porcentaje de sueño ligero y una baja eficiencia de sueño), así como signos de fragmentación del sueño (mayor número de despertares y de tiempo en vigilia). Aunque hay evidencias de que los datos subjetivos y objetivos de sueño no correlacionan en personas con problemas de sueño (Bianchi, Williams, Mckinney y Ellenbogen, 2013; Harvey y Tang, 2012), nuestros resultados apoyan los hallazgos de Roizenblatt y colaboradores (2001), así como la idea de que las quejas de sueño en pacientes con fibromialgia son consecuencia de problemas en la fisiología del sueño y no son fingidos o exagerados, una acusación muy frecuente hacia estos pacientes (Dick, Verrier, Harker y Rashiq, 2008). En definitiva, los problemas de sueño en esta población son muy frecuentes y se encuentran tanto a nivel subjetivo como objetivo. La existencia de estos problemas de sueño es muy relevante a varios niveles. Por ejemplo, los problemas de sueño provocan un aumento de los costes médicos, directos e indirectos, de estos pacientes (Wagner, Chandran, DiBonaventura y Cappelleri, 2013). Esto está muy relacionado con el hecho de que los pacientes con fibromialgia consideren los problemas de sueño entre los síntomas más problemáticos (Rutledge,

Jones y Jones, 2007), siendo el sueño un factor que magnifica las consecuencias adversas de sufrir dolor crónico (Hamilton et al., 2008), por sus relaciones con síntomas emocionales (Ashworth, Davidson y Espie, 2010; Bigatti, Hernandez, Cronan y Rand, 2008; Díaz-Piedra et al., in press; Miró, Martínez, Sánchez, Prados y Medina; 2011; Munguía-Izquierdo y Legaz-Arrese, 2012; Nicassio, Moxham, Schuman y Gevirtz, 2002), neuropsicológicos (Miró et al., 2011) o de funcionamiento diurno (Korszun et al., 2002). De hecho, en el Estudio 2 de esta Tesis, se evidencia que las características del sueño son variables esenciales para entender el impacto del dolor sobre los niveles de ansiedad y depresión, especialmente elevados en esta población (Consoli et al., 2012). Es más, la variable más importante en estos modelos es una variable objetiva, la eficiencia de sueño. El papel de las variables polisomnográficas nunca ha sido explorado en estudios similares (Miró, Martínez et al., 2011), aun cuando las medidas objetivas aportan información diferente sobre la experiencia de sueño y el rol de las alteraciones objetivas de sueño ha sido enfatizado en varios modelos teóricos acerca de los factores predisponentes, precipitantes y que magnifican los síntomas de la fibromialgia (Hamilton et al., 2012; Moldofsky, 2008). Efectivamente, la contribución más importante de nuestros resultados está relacionada con la idea de un rol fundamental de los problemas de sueño para entender la clínica del trastorno. En estudios previos se ha propuesto que los problemas de sueño disminuirían los recursos afectivos y la habilidad de estos pacientes para afrontar las demandas estresantes consecuencia de sufrir dolor crónico (Hamilton et al., 2008). La combinación de mala calidad de sueño y dolor en pacientes con fibromialgia sería especialmente problemática, dado que un sueño no reparador sería un determinante muy importante de la salud de los pacientes con dolor crónico (Hamilton, Catley y Karlson, 2007), incluyendo una modulación deficiente del dolor (Paul-Savoie et al., 2012) y, como se evidencia en nuestros resultados, la mediación de las respuestas afectivas ante la experiencia de dolor.

Además de caracterizar los problemas de sueño en pacientes con fibromialgia (Estudio 1) y estudiar el papel de estos problemas en la clínica del síndrome (Estudio 2), se pretendía conocer, no sólo si existen alteraciones cerebrales estructurales en estos pacientes, sino el papel de los principales síntomas de la fibromialgia, incluyendo los problemas de sueño, en la patofisiología cerebral del síndrome. En estudios recientes se muestra la existencia de cambios fisiológicos y anatómicos en el Sistema Nervioso

Central de personas con diversos síndromes de dolor crónico. En general, muchas de las alteraciones morfológicas ocurren en regiones cerebrales asociadas la experiencia de dolor (May, 2008). En concreto, en pacientes que sufren fibromialgia se han observado reducciones del volumen de materia gris en diversas zonas (e.g., circunvolución del cíngulo, corteza medial frontal, corteza insular, giro parahipocampal o tálamo) (Burgmer et al., 2009; Kuchinad et al., 2007; Robinson, Craggs, Price, Perlstein y Staud, 2011; Schmidt-Wilcke et al., 2007; Wood, Glabus, Simpson y Patterson, 2009). Al igual que ocurre en los estudios de sueño, estas investigaciones utilizan muestras muy reducidas y heterogéneas. Para ello, se diseñó el Estudio 3 en el que se comparaba los volúmenes de materia cerebral entre mujeres premenopáusicas con fibromialgia y mujeres sanas, sin quejas de dolor, sueño o problemas emocionales. Nuestros resultados, con un número más amplio de participantes, muestran que, efectivamente, las pacientes con fibromialgia tienen un menor volumen de materia gris, replicando toda esta serie de estudios previos. Sin embargo, algunos autores proponen que estos cambios también pueden asociarse a todo el conjunto de comorbilidades frecuentes en esta población (principalmente, depresión, ansiedad, medicación, inactividad, aislamiento social o problemas de sueño) y no sólo a la experiencia de dolor crónico (Henry, Chiodo y Yang, 2011). En nuestro estudio se pone de manifiesto que esta alteración estructural en el cerebro está relacionada, de forma independiente, no sólo con los niveles de dolor, sino también con los niveles de ansiedad y de depresión. Aunque en los Estudios 1 y 2 de esta Tesis se evidencia la relevancia de una mala calidad de sueño en la fibromialgia, en el Estudio 3, los problemas subjetivos de sueño no predicen las alteraciones cerebrales en el volumen de materia gris en estas pacientes. Futuros estudios deben comprobar si las alteraciones fisiológicas del ciclo sueño-vigilia son un factor que contribuya a estas alteraciones cerebrales.

El tratamiento de los problemas de sueño en la fibromialgia

Por otra parte, la heterogeneidad de cuadros clínicos que se presentan bajo el epígrafe de *fibromialgia* ha dado lugar a que varios autores propongan subconjuntos de pacientes (Rehm et al., 2010) que se caracterizarían por la presencia de diferentes síntomas principales. Algunos de esos subtipos se caracterizarían, principalmente, por problemas de sueño y otros problemas asociados a éstos (Hamilton et al., 2012; Rehm et al., 2010). Dado que, además, un mismo paciente puede sufrir variaciones en la presencia, intensidad o gravedad de los síntomas a lo largo del tiempo, esto complejizaría aún más

esta clasificación (Dima, Gillanders y Power, 2013). La clave para entender esta heterogeneidad podría estar en la presencia o ausencia de problemas de sueño. Dado que los problemas de sueño son frecuentes en pacientes con fibromialgia y juegan un papel muy relevante en su relación con los otros síntomas, se ha propuesto que un sueño reparador y de buena calidad podría ser un recurso crucial para aquellas personas que sufren las demandas diarias del dolor crónico y del estrés asociado a esta experiencia (Hamilton et al., 2007). Así, los pacientes que sí tengan un sueño reparador se diferenciarían de aquellos que sufran problemas de sueño tanto en las respuestas cognitivas y afectivas hacia el dolor, como en el afrontamiento de las demandas estresantes que supone vivir con dolor, lo que podría explicar gran parte de la heterogeneidad intra-individual y entre pacientes (Davies et al., 2008). De este modo, si un sueño reparador es crucial para los pacientes con dolor crónico por ser un recurso fundamental para afrontar los problemas que se derivan de la experiencia de dolor, su mejora debería situarse entre las prioridades terapéuticas en fibromialgia. Los tratamientos multidisciplinares, en los que se incluye terapia cognitivo-conductual, suelen recomendarse para el manejo de los síntomas en fibromialgia (Nüesch, Häuser, Bernardy, Barth y Jüni, 2013). Sin embargo, el tratamiento de los problemas de sueño no suele abordarse de forma explícita y, apenas, desde una perspectiva psicológica, aun cuando se ha propuesto que su tratamiento exitoso proporcionaría una reducción de costes a largo plazo (Wagner et al., 2013). En los Estudios 4, 5 y 6, se presentan los resultados relativos a la efectividad de un tratamiento psicológico para los problemas de sueño en la mejora de diversas variables, incluyendo no sólo calidad de sueño y dolor, sino también fatiga, funcionamiento diurno, variables emocionales, cognitivas y neuropsicológicas. Las evidencias acerca de que el TCC-I produce mejoras en las variables subjetivas de sueño en personas con insomnio es consistente a través de los estudios (para una revisión, ver Riemann y Perlis, 2009). Dado que los pacientes con fibromialgia presentan insomnio y, además, no difieren de las personas que sufren de insomnio primario ni en los patrones de sueño ni en la severidad de sus problemas (Tang, Goodchild, Hester y Salkovskis, 2012), el tratamiento cognitivo-conductual para el insomnio (TCC-I) parece una opción adecuada para disminuir los problemas de sueño. Para demostrar su efectividad, la realización de ensayos clínicos aleatorizados y la evaluación de todas las variables de interés en la población con dolor crónico son cruciales (Vitiello, McCurry y Rybarczyk, 2013). Así, en esta Tesis se plantearon tres Estudios para conocer los efectos del TCC-I, no sólo sobre la calidad subjetiva de

sueño, algo ya estudiado por otros autores en muestras de pacientes con dolor crónico (aunque con muestras más pequeñas), sino también sobre parámetros polisomnográficos, sobre otras variables relevantes en la clínica del síndrome y sobre las redes atencionales, variables fundamentales y no siempre exploradas hasta ahora en estos pacientes. En general, la mejora subjetiva de sueño es un resultado consistente a través de los estudios con pacientes con dolor crónico (Currie, Wilson, Pontefract y deLaplante, 2000; Edinger et al., 2005; Jungquist et al., 2010, 2012), tanto cuando se compara el TCC-I con el tratamiento estándar del dolor en estos pacientes, como con un grupo en lista de espera o, como en este Estudio 4, con una intervención educativa en higiene de sueño, que controla el efecto del contacto con el terapeuta. De hecho, nuestro estudio muestra que conocer las pautas de higiene de sueño no es suficiente para mejorar la calidad global de sueño, tanto a corto como medio plazo. Además, los cambios en parámetros polisomnográficos, que se presentan en el Estudio 6, confirman la utilidad del TCC-I para obtener mejoras en el sueño de estas pacientes. No sólo aumenta la eficiencia de sueño, sino que cambia la organización de los ciclos de sueño en favor de un mayor porcentaje de sueño profundo. Como se comentó en el Estudio 2, la eficiencia de sueño es una variable fundamental para explicar el impacto del dolor sobre la ansiedad y la depresión, por lo que su mejora como consecuencia del tratamiento justifica la relevancia de la TCC-I para el manejo de la experiencia de dolor crónico. Por otra parte, la suspensión de la conciencia durante el sueño profundo es una condición necesaria para la ocurrencia de los procesos biológicos restauradores asociados a él (Horovitz et al., 2009). Como se observa en los resultados del Estudio 1, las pacientes con fibromialgia presentan elevados índices de fragmentación de sueño y, además, como informan Tang y colaboradores (2012), un elevado *arousal* previo al sueño. La TCC-I trabaja sobre estos dos elementos a través de, principalmente, la restricción del tiempo en cama, las técnicas de relajación y la discusión de creencias disfuncionales sobre el sueño. El consecuente aumento de sueño profundo como resultado de un sueño no interrumpido permitiría la ocurrencia de estos procesos restauradores. Además de las mejoras en variables de sueño, subjetivas y objetivas, la TCC-I produce mejoras en otras variables clínicas que se presentan en los Estudios 4 y 5. Los beneficios del TCC-I se expanden a mejoras en distintas variables relacionadas con la ejecución y el rendimiento diurno, como son la fatiga, el nivel de funcionamiento diario y la función atencional (en concreto, nivel de alerta y función ejecutiva), y variables emocionales (niveles de ansiedad y depresión) y cognitivas (catastrofización

del dolor). Los problemas en el rendimiento diurno como consecuencia de problemas en funciones neuropsicológicas son quejas frecuentes en pacientes con fibromialgia (sobre todo, problemas de memoria, atención y concentración) (Ambrose, Gracely y Glass, 2012). Esto, unido a los elevados niveles de fatiga, provoca que el funcionamiento diario se vea deteriorado (Wolfe, Hawley y Wilson, 1996). De forma importante, los cambios en la función atencional tras el TCC-I se relacionan con cambios en la calidad de sueño, lo que apoya la idea previa de un sueño reparador potenciaría los recursos del paciente para para enfrentarse a las demandas estresantes provenientes de la experiencia de dolor crónico (Hamilton et al., 2007, 2008). De hecho, la disminución del impacto de la fibromialgia sobre el funcionamiento diario, así como la disminución de los niveles de ansiedad y depresión y de catastrofización del dolor, tras el tratamiento del sueño también apoyarían esta hipótesis. Un resultado que se encuentra en el Estudio 4 y en otros ensayos similares es que la mejora del sueño no lleva aparejada la disminución de la intensidad de dolor (Currie, Wilson, Pontefract y deLaplante, 2000; Edinger et al., 2005; Jungquist et al., 2010, 2012). Pocos estudios han comprobado la efectividad de combinar terapia cognitivo-conductual para el dolor y para el insomnio (Pigeon et al., 2012), aunque los resultados parecen prometedores.

En resumen, los problemas de sueño son muy frecuentes en personas que sufren fibromialgia. Tanto los problemas subjetivos como objetivos juegan un papel fundamental en la clínica del trastorno, ya que magnifican la gravedad de otros síntomas. Sin embargo, las quejas subjetivas de calidad de sueño no tienen relación con los cambios estructurales en el Sistema Nervioso Central, aun cuando el dolor y otros síntomas también relevantes en el síndrome sí la tienen. Además, hay evidencias de que un sueño reparador tendría un papel muy importante en el tratamiento exitoso del dolor crónico, por su relación con el funcionamiento diurno y por su potencial para atenuar las respuestas cognitivas y afectivas relacionadas con estrés de sufrir dolor crónico. Por ello, la inclusión del tratamiento de los problemas de sueño entre los objetivos terapéuticos de la fibromialgia parece crucial para mejorar la clínica del síndrome, siendo el TCC-I una alternativa que ha demostrado su efectividad no sólo en pacientes con insomnio, sino también en pacientes con fibromialgia.

CONCLUSIONES GENERALES

- La fibromialgia es un síndrome de dolor crónico cuya etiología es desconocida. La experiencia de dolor en estos pacientes está acompañada de una diversidad de síntomas y comorbilidades, que incluye, entre otros, fatiga, trastornos neuropáticos, trastornos emocionales y problemas de sueño. Estos otros síntomas son altamente incapacitantes y mantienen relaciones complejas entre sí y con el dolor. En particular, el sueño juega un papel fundamental en el síndrome, especialmente en relación al dolor y los trastornos emocionales. De hecho, la eficiencia objetiva de sueño y la calidad subjetiva de sueño median en la relación que se establece entre la intensidad de dolor y los niveles de ansiedad y depresión en pacientes con fibromialgia.
- Las quejas de problemas de sueño son muy habituales en los pacientes con fibromialgia. Estos problemas están considerados entre los más graves, además del dolor. Sin embargo, los estudios disponibles al respecto no ofrecen hallazgos objetivos definitivos en relación a las características del ciclo sueño-vigilia de estos pacientes. Aunque, en general, se tiende a creer que las medidas subjetivas y objetivas de sueño no están relacionadas entre sí en fibromialgia, en la actualidad, la evidencia disponible es discrepante. Si bien ciertos estudios han descrito determinadas alteraciones en la arquitectura y en la microestructura de sueño, así como una mayor prevalencia de trastornos de sueño en esta población, otras investigaciones no han encontrado tales diferencias entre pacientes y personas sanas. Estas incongruencias podrían ser debidas a la omisión en los análisis de ciertas variables confusoras como, por ejemplo, la edad o la presencia de distrés psicológico. Así, cuando se compara el sueño de pacientes con fibromialgia y de personas sanas, teniendo en cuenta el efecto de la edad, se observan, no sólo una peor calidad subjetiva de sueño o una mayor somnolencia diurna, sino también alteraciones objetivas en la organización de los ciclos de sueño durante el descanso y una mayor fragmentación del sueño.
- Los estudios acerca de la patofisiología de la fibromialgia sugieren que este síndrome se relacionaría con alteraciones estructurales y funcionales del sistema nervioso central. En particular, la resonancia magnética permite conocer las alteraciones cerebrales estructurales en pacientes con fibromialgia. Los pacientes con fibromialgia presentan un menor volumen total de materia gris cuando se

comparan con controles sanos. Estas alteraciones en materia gris son explicadas por la intensidad del dolor, así como por los niveles de ansiedad y depresión. La mala calidad de sueño, a pesar de ser muy frecuente entre estos pacientes y asociarse además a cambios cerebrales estructurales en pacientes con insomnio, no explica las alteraciones cerebrales en fibromialgia. No obstante, el tratamiento de los problemas del sueño parece prometedor en la mejora de los pacientes con fibromialgia.

- El tratamiento de los problemas de sueño en pacientes con fibromialgia podría mejorar no sólo las quejas de insomnio, sino también otros síntomas relacionados. La terapia cognitivo-conductual para el insomnio es una alternativa terapéutica que ha demostrado su efectividad frente a los psicofármacos que se suelen prescribir en el tratamiento del insomnio. La aplicación de esta terapia es también más efectiva que la educación en pautas de higiene de sueño, en cuanto a la mejora de los índices polisomnográficos de calidad de sueño. En concreto, aumenta la eficiencia de sueño y el porcentaje de tiempo en sueño profundo, mientras que disminuye la cantidad de sueño ligero. Además, mejora la calidad subjetiva de sueño, el funcionamiento diario y la función atencional, disminuye la fatiga, los niveles de ansiedad y depresión, así como la catastrofización del dolor. En conclusión, el tratamiento de los trastornos del sueño en pacientes con fibromialgia parece ser un componente muy relevante en el abordaje terapéutico de estos pacientes.

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Por lo extraordinario.

...

Cuanto más me contemplo más me aflijo:

cortar este dolor ¿con qué tijeras?

...

Miguel Hernández

Otros poemas

ANEXOS[1]

[1] Los anexos 1, 2, 3 y 4, correspondientes al trabajo *Sleep disturbances of adult women suffering from fibromyalgia: a systematic review of observational studies* se encuentran en el CD adjunto.

ANEXO 5.

Date: Sep 16, 2013
To: "Carolina Diaz-Piedra" dipie@ugr.es
cc: turkdc@u.washington.edu
From: "The Clinical Journal of Pain" JuliePorter529@gmail.com
Subject: CJP Decision

Sep 16, 2013

RE: CJP-D-13-00122R3, entitled "The impact of pain on anxiety and depression is mediated by objective and subjective sleep characteristics in fibromyalgia patients"

Dear Mrs. Diaz-Piedra,

I am pleased to inform you that your work has now been accepted for publication in The Clinical Journal of Pain. All manuscript materials will be forwarded immediately to the production staff for placement in an upcoming issue.

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Dr. Dennis C. Turk
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The Clinical Journal of Pain

Close Resend

ANEXO 6.

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Cognitive-behavioral therapy for insomnia and sleep hygiene in fibromyalgia: a randomized controlled trial

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Abstract Sleep disturbances play an important role in the exacerbation of pain and other troubling symptoms reported by patients with fibromyalgia (FM). The objective of this trial was to analyze the efficacy of a cognitive-behavioral therapy for insomnia (CBT-I) versus a sleep hygiene (SH) education program at improving sleep and other clinical manifestations in FM. Sixty-four FM women with insomnia were randomly assigned to the CBT-I or the SH groups, and 59 completed the treatments (30 in the CBT-I group and 29 in the SH group). Participants completed several self-report questionnaires at pre-, post-treatment and follow-ups. The CBT-I group reported significant improvements at post-treatment in several sleep variables, fatigue, daily functioning, pain catastrophizing, anxiety and depression. The SH group only improved significantly in subjective sleep quality. Patients in the CBT-I group showed significantly greater changes than those in the SH group in most outcome measures. The findings underscore the usefulness of CBT-I in the multidisciplinary management of FM.

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Introduction

Fibromyalgia (FM) is a chronic pain condition characterized by widespread pain for at least 3 months and 11 or more of 18 tender point sites on digital palpation, according to the American College of Rheumatology (ACR; Wolfe et al., 1990). FM is the most common rheumatic disease after low back/neck pain and osteoarthritis (Lawrence et al., 2008) and affects mostly women (the female/male ratio of FM patients is as high as 21:1) (Mas et al., 2008). Annual medical costs per FM patient ($4,065) are significantly higher than those of patients without FM ($2,766) (Lachaine et al., 2010).

Disrupted sleep is a significant problem for many FM patients. Recent studies have shown that 94.7–96 % of such patients are bad sleepers (Bigatti et al., 2008). Yet, although 44 % of FM patients rate their sleep as bad or fairly bad, only 21 % have objective sleep deficits (Stuifbergen et al., 2010). Non-restorative sleep is reported by FM patients as the third symptom experienced with the highest intensity, after stiffness and fatigue (Rutledge et al., 2007), with FM patients suffering more insomnia, less contentment with sleep and more lack of deep and restful sleep in comparison to rheumatoid arthritis patients and subjects of the general population (Belt et al., 2009). Although the physiological evidence for disordered sleep is not completely consistent across studies, several reports have described the anomalies in sleep continuity, architecture and microstructure of FM patients. Many characteristics of sleep dysfunction in FM patients include

reduced total sleep time, greater number of awakenings and arousals, increased latency of sleep onset and of rapid eye movement (REM), more frequent changes of sleep stage, reduced percentage of slow-wave sleep, several manifestations of sleep instability such as alpha-delta activity, K-alpha periodic intrusions, and a cyclic alternating pattern of arousal (see reviews by Moldofsky, 2009, 2010; Prados & Miró, 2012; Spaeth et al., 2011). Consistent with this, unrefreshing sleep has been proposed by the ACR (Wolfe et al., 2010) as one of the most important diagnostic variables in FM in addition to widespread pain, cognitive symptoms, fatigue and a number of somatic symptoms.

It has been suggested that genetic, neurophysiological, neuroendocrine and environmental factors contribute to the development/maintenance of FM. From a psychological approach, the role of conditioning principles and cognitive processes has been considered in chronic pain conditions (see reviews by Gatzounis et al., 2012; Keefe et al., 2004; Leeuw et al., 2007; Meulders et al., 2011). However, the pathogenesis of FM has not been definitely established yet.

Altered function of central pain-processing mechanisms, such as deficient descending analgesic activity and central pain augmentation or sensitization, has been proposed as playing an etiological role in FM (Lee et al., 2011). In addition, several studies using functional magnetic resonance imaging (Cook et al., 2004; Gracely et al., 2002) have documented the relevance of central sensitization in FM patients. In recent years, a promising approach emphasizing the influence of sleep on hyperalgesia in chronic pain syndromes has gradually gained importance. It has been suggested that disordered sleep may contribute to a decrease in the sensory inhibitory function of the central nervous system to the perception of noxious stimuli (see review by Moldofsky, 2009, 2010). Along these lines, a recent prospective study has identified a strong association between sleep problems and risk of FM among adult women (Mork & Nilsen, 2012). Moreover, several clinical studies have evidenced the complex relationship between sleep disturbances and other clinical manifestations of FM, showing that sleep quality may influence pain, fatigue, mood state, cognitive performance and daily functioning (Bigatti et al., 2008; Hamilton et al., 2008, 2012; Nicassio et al., 2002; Miró et al., 2011a, c; Theadom et al., 2007; for a review, see Prados & Miró, 2012). For example, Nicassio et al. (2002) examined the relationship between pain, sleep, fatigue and depression in FM patients, noting that in the cross-sectional assessment greater depression and lower sleep quality were associated with higher fatigue, and in the prospective daily assessment the previous day's pain and sleep quality predicted the next day's fatigue. Interestingly, the paths amongst various FM symptoms are multidirectional. For example, it has been reported that the relationship between pain and emotional distress was mediated by sleep quality (and self-efficacy) (Miró et al., 2011c). In addition, the relationship between sleep and pain was mediated by cognitive processes and the relationship between sleep and disability was mediated by pain (Hamilton et al., 2012). In line with this, several models aimed at explaining FM have considered the role of sleep. For example, the unifying model of central nervous system pathogenesis in FM (Russell & Larson, 2009) indicates that genetic predisposition to brain degeneration and a variety of factors (i.e., age, physical trauma, dysfunctional sleep) lead to neuroendocrine changes that seem to determine an abnormal processing of pain. Thus, the mechanisms of nerve repair of this cortical damage generate increased production of the nerve growth factor, which seems to be associated with a higher concentration of substance P, and this would cause hyperalgesia, insomnia, depression, low levels of biogenic amines and inhibition of the stress response system (Russell & Larson, 2009).

If sleep disturbances play a significant role in the exacerbation of pain and other troubling symptoms associated with FM, achieving restorative sleep is likely to lead to an improvement in all these symptoms. In a prospective study of people with chronic widespread pain, those who reported good-quality sleep were more likely to report the resolution of pain and return to musculoskeletal health (Davies et al., 2008). Recently, some psychological treatments of chronic pain have started to include sleep management, among other components (e.g., Andersson et al., 2012). Yet, few treatment approaches focus on sleep problems of FM patients. To the best of our knowledge, only seven randomized controlled trials have explored the efficacy of cognitive-behavioral therapy for insomnia (CBT-I) in chronic pain syndromes (Currie et al., 2000; Edinger et al., 2005; Jungquist et al., 2010; Miró et al., 2011b; Pigeon et al., 2012; Sánchez et al., 2012; Vitiello et al., 2009). Only three of such studies (Edinger et al., 2005; Miró et al., 2011b; Sánchez et al., 2012) were conducted with FM patients. Edinger et al. (2005) compared CBT-I ($n = 18$), sleep hygiene (SH) ($n = 18$) and usual care (UC) ($n = 11$) in FM patients at baseline, post-treatment and 6-month follow-up using sleep logs and actigraphy to assess various sleep parameters, and questionnaires on insomnia, pain, mood and quality of life. They found that 57 % of participants in the CBT-I group met strict subjective sleep improvement criteria by the end of the intervention (vs. 17 % in the SH group and 0 % in the UC group). The other two studies were done by our research team, and we explored the efficacy of CBT-I in FM using polysomnography (PSG) and neuropsychological tests. In the first study (Miró et al., 2011b), we compared CBT-I ($n = 20$) and SH ($n = 20$) at pre- and post-treatment with questionnaires and neuropsychological tests, and we evidenced the superiority of CBT-I to improve sleep and

attentional functioning. In this study, 85 % of patients in the CBT-I group showed clinically significant changes in sleep quality (vs. 55 % in the SH group). In the second study (Sánchez et al., 2012), we compared the effect of CBT-I ($n = 13$) and SH ($n = 13$) at pre- and post-treatment on sleep parameters using polysomnography (PSG), and we identified improvements in the CBT-I group in time in bed, wake percentage, sleep efficiency, and changes in sleep architecture (an increase in deep sleep time and a decrease in light sleep time), which were not observed in the SH group.

Although the efficacy of CBT-I in FM has been reported using objective measures, data provided by a self-reported measure are more informative than those obtained by an objective measure at identifying patients' perceived distress. It should be noted that complaints of poor sleep are more common than objective sleep deficits (Stuifbergen et al., 2010). Moreover, the usual sleep patterns obtained with subjective measures (e.g., Pittsburgh Sleep Quality Index, PSQI; Buysse et al., 1989) typically differ from those obtained with PSG; in fact, only weak correlations have been found between PSQI and PSG (Backhaus et al., 2002; Buysse et al., 1991). This relative lack of convergence between measures may be explained considering that the PSQI assesses usual patterns of sleep and sleepiness, whereas PSG evaluates sleep and sleepiness on a specific occasion, and that the PSQI assesses aspects of sleep (such as sleep quality) that are not directly captured with PSG (Buysse et al., 2008). Hence, it is relevant to analyze whether the sleep improvements achieved with the CBT-I according to PSG in a small group of FM patients in a previous study (Sánchez et al., 2012) are also observed using self-report measures of sleep quality in a larger sample; it is also interesting to explore whether these changes are also found in other clinical aspects and are maintained at follow-ups.

The evidence-based guidelines for the treatment of FM of the American Pain Society (APS), the European League Against Rheumatism (EULAR) and the Association of the Scientific Medical Societies in Germany (AWMF) propose a multidisciplinary approach. However, the EULAR mostly recommends pharmacological treatment, while the APS and AWMF mostly recommend exercise, CBT, amitriptyline, and multicomponent treatment (Häuser et al., 2010). Surprisingly, none of these guidelines includes specific recommendations for treating sleep problems, although CBT-I can improve the well-being of FM patients. Moreover, although a recent meta-analysis of psychological treatment for FM (Glombiewski et al., 2010) reported that CBT is better than other psychological interventions in reducing pain, studies about the efficacy of CBT focused on insomnia are scarce and the role of sleep in FM symptoms needs further research.

The aim of this trial was to collect additional evidence of the efficacy of CBT-I to treat insomnia in FM. To this end, we compared the effect of a CBT-I program versus an educational SH program on sleep quality and other troubling symptoms in FM women. In order to explore the efficacy of this treatment, the statistical and clinical relevance of the changes was considered. The specific hypotheses proposed were: (1) CBT-I will produce significantly greater statistical and clinical improvements in sleep quality than SH; (2) CBT-I will produce significantly greater statistical and clinical improvements in pain intensity, fatigue and daily functioning than SH; and (3) CBT-I will produce significantly greater statistical and clinical improvements in self-efficacy and pain catastrophizing and emotional distress than SH.

The previous studies (Miró et al., 2011b; and Sánchez et al., 2012) and the present study are part of the same research. The present study, compared to the previous studies, included a larger sample, PSQI subscales, self-report measures about fatigue, pain catastrophizing and self-efficacy for coping pain, and assessment at 3 and 6-month follow-up.

Methods

Design and participants

The guidelines of the CONSORT 2010 (Moher et al., 2010) were considered. An individually randomized, 2-group, parallel trial design was used. Fifty-nine adult women with FM participated in the study. Patients were recruited from the Rheumatology Service and Pain Unit of Virgen de las Nieves University Hospital (Granada, Spain) and referred to the Clinical Psychology Unit of the University of Granada, where the psychological assessment and treatment sessions were conducted.

Inclusion criteria to participate in the study were: (1) being a woman aged between 25 and 60; (2) meeting the diagnostic criteria for FM (ACR, Wolfe et al., 1990); (3) having had this disorder for more than 6 months so that adaptation to the impact of the diagnosis had already occurred; (4) being stable as regards the intake of analgesics, antidepressants or other drugs at least 1 month before the study; and (5) meeting the diagnostic criteria for insomnia (DSM-IV-TR, American Psychiatric Association, APA, 2000). Exclusion criteria were as follows: (1) being pregnant; (2) having a medical history of significant head injury or neurological disorder; (3) having major concomitant medical conditions; (4) having major depressive disorder with suicide ideation or other major Axis I diagnoses (APA, 2000); (5) having symptoms of sleep-disruptive comorbidities with insomnia; (6) having an apnea-

hypopnea index or periodic limb movement-related arousal index of 15 or more per hour of sleep; (7) having a severe hypnotic dependence; and (8) being treated with another psychological or physical therapy at the time of the study.

One hundred and twelve eligible FM women from 25 to 60 years old were screened using a brief interview administered by a psychologist via telephone. Of these patients, 77 women with FM who fulfilled the inclusion criteria were admitted for psychological assessment. The subjects completed a semi-structured interview in two sessions. Session 1 focused on the onset and course of FM and insomnia, biographical history, lifestyle, work activity, family and social relations, and psychological state. After the interview the patients were given several self-report questionnaires and a sleep diary to complete at home. Session 2 was devoted to completing additional data on insomnia, collecting questionnaires, and applying a neuropsychological test. Within 1 week after Session 2, a PSG recording was performed to exclude patients with sleep disorders other than insomnia. All patients completed the sleep diary for 2 weeks before treatment and during the time of intervention. A subgroup of patients was also assessed with PSG and a neuropsychological test at post-treatment (changes in these measures were reported in Miró et al., 2011b, and Sánchez et al., 2012).

After the initial assessment, 64 women with FM were randomly assigned to either a cognitive-behavioral treatment for insomnia (CBT-I, $n = 32$) or a sleep hygiene educational program (SH, $n = 32$). For random allocation of the patients to the treatments (simple randomization, 1:1) a computerized number generator was applied by a researcher blinded to the implementation of the trial. Finally, 30 patients in the CBT-I group and 29 patients in the SH group completed the treatments and were included in the analyses (see Fig. 1 for the flowchart of this study). Patients were instructed to strictly follow their treatment while participating in the study. All subjects received detailed information about the study and signed an informed consent form. The present research received ethical approval from the University of Granada Ethics Committee.

Measures

The questionnaires were applied at pre-, post-treatment and follow-up performed at 3 and 6 months after the intervention. The patients completed the questionnaires on these assessment moments, considering how they had felt in the previous week. The measures were assessed by a sleep expert (C.D.P.) who was blinded to group assignment. Sleep quality was considered as the primary outcome measure, and pain, fatigue, daily functioning, self-efficacy, catastrophizing, anxiety and depression were considered as secondary outcome measures.

Pittsburgh Sleep Quality Index (PSQI, Buysse et al., 1989): The PSQI includes 19 items that explore *Subjective sleep quality, Sleep latency, Sleep duration, Habitual sleep efficiency, Sleep disturbances, Use of sleeping medication,* and *Daytime dysfunction.* The subscale scores ranged from 0 to 3 and the Sleep quality-Total score ranged from 0 to 21, with high scores indicating disturbance. The Spanish version showed acceptable validity and internal consistency (Royuela & Macías, 1997). The PSQI was selected as a primary measure considering the following aspects: (a) it is a reliable and valid instrument to measure sleep quality in insomnia patients (Backhaus et al., 2002) and to characterize and quantify sleep disturbances in FM patients (Osorio et al., 2006); (b) it is frequently used in clinical trials of pain treatment and is well suited to measure aspects of sleep that are of particular importance in the study of pain (Cole et al., 2007); and (c) the psychometric characteristics of the Spanish adaptation of PSQI are well established (Jiménez-Genchi et al., 2008; Royuela & Macías, 1997).

McGill Pain Questionnaire-Short Form (MPQ-SF, Melzack, 1987): This questionnaire assesses several dimensions of pain experience using 15 verbal pain descriptors, a current pain intensity index, and a visual analogue scale (VAS) to assess pain intensity in the last week (from 1 to 10). The present study used the VAS. Several studies have reported the reliability and validity of the Spanish version of the MPQ (e.g., Lázaro et al., 2001).

Multidimensional Fatigue Inventory (MFI, Smets et al., 1995; adaptation by Fillion et al., 2003): It consists of 20 items that assess several aspects of fatigue: *General fatigue, Physical fatigue, Mental fatigue, Reduced motivation* and *Reduced activity*. Items are assessed on a Likert scale ranging from 1 to 5. General fatigue subscale was selected for this study. The MFI showed adequate internal consistency, construct validity and convergent validity (Smets et al., 1995).

Fibromyalgia Impact Questionnaire (FIQ, Burckhardt et al., 1991): The FIQ includes 10 items that evaluate health status in FM. Item 1 assesses functional capacity for daily living (ranging from 0 to 3). Items 2 and 3 ask patients to mark the number of days they felt well/unable to work. Items 4 through 10 are scales that rate work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression from 0 to 10. The Spanish version was reliable, valid and responsive to changes (Rivera & González, 2004).

Chronic Pain Self-efficacy Scale (CPSS, Anderson et al., 1995): The CPSS explores patients' self-efficacy expectations regarding pain management, coping with symptoms, and physical function. This instrument includes 19 items that are assessed on a Likert scale ranging from 0 to 10. The Spanish version showed good construct validity and internal consistency (Martín-Aragón et al., 1999).

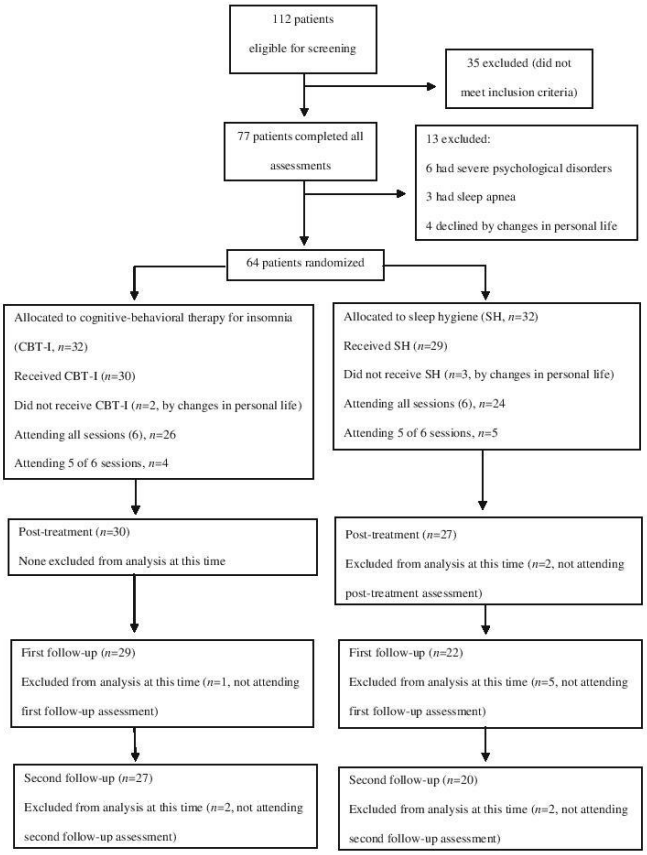

Fig. 1 Flow diagram of participants through the phases of the trial

Pain Catastrophizing Scale (PCS, Sullivan et al., 1995): This instrument assesses rumination, magnification and helplessness associated to pain. It includes 13 items measured on a Likert scale ranging from 0 to 4. The Spanish version showed adequate internal consistency, test–retest reliability and sensitivity to change (García-Campayo et al., 2008).

Symptom Checklist-90-Revised (SCL-90-R, Derogatis, 2002): It contains 90 items grouped into 9 dimensions: *Somatization, Obsessive–compulsive, Interpersonal sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation* and *Psychoticism*. Each item is rated on a Likert scale ranging from 0 to 4. The Anxiety and Depression subscales were selected. The Spanish version showed good internal consistency and a factor structure that was similar to the original version.

Treatment protocols

The protocol-based psychological treatments (CBT-I and SH) were provided by three female therapists (M.P.M., E.M., and A.I.S.) with experience in the management of chronic pain and sleep disorders. All sessions were conducted in group format (5–6 participants) once a week for 6 weeks and lasted about an hour and a half. Patients in the CBT-I and SH groups continued with their usual medical

care for FM (on stable doses of medication) during the study. Patients also agreed not to participate in other interventions until the trial ended.

CBT-I program: This intervention was designed following the trial by Edinger et al. (2005) and met the recommendations of the American Academy of Sleep Medicine (Morgenthaler et al., 2006). Session 1 was focused on providing information about the relationship between sleep and FM, basic notions about sleep, and sleep hygiene education. In Session 2, participants were given instructions for applying sleep restriction and stimulus control. Patients were asked to complete the sleep diary before applying sleep restriction. Sleep efficiency was calculated considering the sleep diary data, restriction of time in bed was established, bedtime and time to get up were set, and the sleep schedule was reviewed every 3–4 days by increasing bedtime as sleep efficiency was improving. Session 3 was aimed at training physiological deactivation procedures (slow breathing, passive relaxation and imagery training). Sessions 4 and 5 were focused on cognitive therapy to change negative thoughts about insomnia through verbal discussion and behavioral experiments. Session 6 was devoted to maintaining achievements and preventing relapses.

SH program: The aim of this intervention was only to provide training about sleep hygiene rules. In Session 1, participants were given the same information about sleep as those in the CBT-I program. Session 2 was devoted to sleep hygiene rules related to environmental factors (e.g., noise, temperature, light). Session 3 was focused on learning about lifestyle factors that influence sleep (use of stimulants and other substances). Sessions 4 and 5 were aimed at providing information about diet and physical exercise, respectively. Session 6 was devoted to maintaining achievements and preventing relapses, as in the CBT-I program. Throughout the sessions, the educational content of sleep hygiene was illustrated and discussed in detail with active involvement of patients. After the follow-ups, patients in the SH group were given the possibility of receiving CBT-I.

The integrity of the interventions was ensured as follows: (a) the therapists had a high level of professional training and experience in the treatments applied; (b) a written therapy manual with detailed information about each session was used; and (c) the therapists had regular clinical meetings with the research group to monitor the implementation of the therapies and to follow the progress of patients.

Data analyses

Statistical analyses were performed using IBM SPSS Statistics 19 software. Probabilities less than or equal to .05 were used as the level of significance. Student's t, Mann–Whitney U, and χ^2 tests were used to compare baseline measures between the CBT-I and SH groups. After that, 2 (Group; CBT-I vs. SH) $\times$ 4 (Time; Pre-treatment vs. Post-treatment vs. First follow-up vs. Second follow-up) ANCOVAs were performed considering pre-treatment values as a covariate to verify whether both groups differed in the outcome measures. Mauchly's test of sphericity and the Greenhouse-Geiser correction were computed. Additionally, unpaired and paired two-samples Student's t tests were computed. The Bonferroni-Holm method for controlling Type I errors in multiple comparisons was applied in the PSQI analyses. In significant statistics, effect sizes were calculated via the partial η^2 and Cohen's d. According to Cohen's guidelines (1988), d .2 is a small effect, .5 is a medium effect and .8 is a large effect; in the η^2, .01 is a small effect, .06 is a medium effect and .14 is a large effect.

Following the recommendations made by Lambert and Ogles (2009) in psychotherapy outcome research, the estimate of clinical significance was based on the Jacobson-Truax method (Reliable Change Index, RCI; Jacobson & Truax, 1991). Patients were classified into different categories according to this index (Salaberría et al., 1996): *Same*, with no positive nor negative changes; *Deterioration*, negative change; *Improvement without complete recuperation*, positive change but <1; *Somewhat positive change*, higher than 1 but <1.96; and *Very positive change*, higher than 1.96. In the present study we considered the last three categories together.

Considering the criteria used by Edinger et al. (2005), patients were classified as having improved sleep if at post-treatment they showed a mean total sleep time of 6.5 h or longer, a mean total wake time of <60 min, or a mean sleep efficiency of 85 % or greater. Patients who met the improvement criteria at pre-treatment were excluded from these analyses.

Results

Characteristics of the FM sample

The CBT-I and SH groups were similar in the baseline measures (all p's $>$ .144; see Table 1). The mean age of the FM sample was 47.58 years (SD = 6.82; range = 33–60). Most participants were married (84.7 %) and had basic education (29.5 %), high school (25 %), professional instruction (22.7 %), or university studies (22.7 %). Almost half of the subjects had an inactive work situation. The mean duration of FM diagnosis was 5.10 years (SD = 4.23), and the mean duration of the sleep problem was 9.17 years (SD = 7.82). Almost all subjects (91.52 %) were receiving medication.

Table 1 Demographic and clinical characteristics of the FM subjects who completed the treatments

Variables	Total sample ($n = 59$)	CBT-I group ($n = 30$)	SH group ($n = 29$)	CBT-I vs. SH	
				$t/U/\chi^2$	p
Age, *M* (SD)	47.58 (6.82)	46.53 (6.31)	48.66 (7.27)	−1.19	.236
Education (%)					
Basic education	29.5	21.7	38.1	217.00	.552
High school	25.0	34.8	14.3		
Professional instruction	22.7	17.4	28.6		
University studies	22.7	26.1	19.0		
Marital status (%)					
Married	84.7	76.7	93.1	3.30	.347
Single	6.8	10.0	3.4		
Divorced	6.8	10.0	3.4		
Widowed	1.7	3.3	.0		
Work status (%)					
Currently employed	51.0	62.5	40.0	3.39	.335
Retired	6.1	4.2	8.0		
Unemployed	16.3	8.3	24.0		
Disabled	26.5	25.0	28.0		
Duration of FM diagnosis (years), *M* (SD)	5.10 (4.23)	4.25 (3.26)	5.92 (4.92)	−1.48	.144
Duration of FM symptoms (years), *M* (SD)	14.33 (9.17)	15.32 (10.13)	13.37 (8.22)	.76	.445
Duration of sleep problem (years), *M* (SD)	9.17 (7.82)	9.67 (8.76)	8.58 (6.77)	.41	.680
Sleep latency (h), *M* (SD)	1.12 (.59)	1.12 (1.07)	1.11 (.47)	.06	.947
Number of awakenings per night, *M* (SD)	2.82 (1.30)	2.57 (1.19)	3.04 (1.37)	−1.28	.206
Sleeping hours per night, *M* (SD)	4.50 (1.25)	5.03 (1.30)	4.37 (1.18)	1.04	.300
Drug intake (%)					
Antidepressants	57.1	53.6	60.7	.29	.589
Anxiolytics	64.3	60.7	67.9	.31	.577
Anti-inflammatory drugs	64.3	60.7	67.9	.31	.577
Analgesics	60.7	64.3	57.1	.29	.584

Changes in sleep quality

The ANCOVA for Sleep quality-Total revealed a significant effect of Group (see Table 2). Whereas the Sleep quality of the CBT-I group improved from pre- to post-treatment, the SH group showed no significant improvement. The CBT-I group reported better Sleep quality than the SH group at post-treatment and first follow-up.

In Sleep disturbances significant effects of Group, Time and Group × Time were found. Sleep disturbances improved from pre- to post-treatment in the CBT-I group but not in the SH group. The CBT-I group showed a greater reduction in Sleep disturbances than the SH group at post-treatment and first follow-up. In Subjective sleep quality, a significant effect of Time and an effect close to significance of Group × Time were observed. Both groups improved in Subjective sleep quality from pre- to post-treatment. The CBT-I group showed better Subjective sleep quality than the SH group at all times except the second follow-up. In Habitual sleep efficiency a significant effect of Time was observed. The CBT-I group showed a significant improvement in Habitual sleep efficiency from pre- to post-treatment and the SH group showed an improvement close to significance. The CBT-I group showed better Habitual sleep efficiency than the SH group at post-treatment.

Daytime dysfunction showed a significant effect of Time and an effect close to significance of Group, but no specific

Table 2 Changes in sleep quality (PSQI) in the treatment groups

Variables	Group	Pre-treatment *M* (SD)	Post-treatment *M* (SD)	First follow-up *M* (SD)	Second follow-up *M* (SD)	Group F (η^2)	Time F (η^2)	Group × Time F (η^2)	T1 vs. T2 t (d)	T2 vs. T3 t (d)	T3 vs. T4 t (d)
Sleep quality-total											
	CBT-I	15.30 (3.03)	11.33 (4.03)	11.00 (3.88)	11.63 (4.63)	5.64* (.11)	1.87	2.11	6.63*** (1.25)	.55	−.55
	SH	14.93 (3.35)	13.48 (2.88)	13.18 (3.73)	13.30 (4.15)				1.43	1.65	−.73
	CBT-I vs. SH, t (d)	.44	−2.22* (−.61)	−2.02* (−.57)	−1.27						
Subjective sleep quality											
	CBT-I	2.07 (.52)	1.40 (.81)	1.44 (.68)	1.74 (.71)	1.48	2.77* (.06)	2.49, $p = .06$ (.05)	5.13*** (1.0)	−.23	−1.89
	SH	2.45 (.63)	2.08 (.57)	1.95 (.78)	1.85 (1.04)				2.09* (.43)	1.56	.62
	CBT-I vs. SH, t (d)	−2.52* (−.69)	−3.62** (−.97)	−2.45* (−.69)	−.42						
Sleep latency											
	CBT-I	2.30 (.83)	1.70 (.79)	1.79 (.94)	1.93 (.91)	.01	1.21	1.03	4.26*** (.78)	−.49	−.59
	SH	1.97 (.94)	1.64 (1.15)	1.68 (1.04)	1.65 (1.18)				1.54	1.42	−.56
	CBT-I vs. SH, t (d)	1.44	.22	.40	.86						
Sleep duration											
	CBT-I	2.23 (.81)	1.46 (.86)	1.37 (.90)	1.63 (.96)	2.17	2.14	.85	4.67*** (.85)	.49	−1.41
	SH	2.00 (1.00)	1.72 (.93)	1.68 (.89)	1.75 (.96)				.70	.32	−.56
	CBT-I vs. SH, t (d)	.98	−1.04	−1.19	−.42						
Habitual sleep efficiency											
	CBT-I	2.07 (1.01)	.96 (.99)	1.17 (1.13)	1.48 (1.08)	1.26	4.86** (.10)	1.65	5.35*** (.98)	−1.02	−1.03
	SH	2.14 (1.18)	1.60 (1.15)	1.54 (1.01)	1.65 (1.18)				1.83, $p = .07$ (.37)	.64	−.90
	CBT-I vs. SH, t (d)	−.24	−2.18* (−.59)	−1.21	−.50						
Sleep disturbances											
	CBT-I	2.20 (.48)	1.93 (.73)	1.89 (.55)	2.04 (.64)	7.30** (.14)	5.09** (.10)	2.71* (.06)	1.97* (.38)	.57	−1.14
	SH	2.24 (.51)	2.40 (.57)	2.45 (.50)	2.30 (.47)				−1.44	.00	1.37
	CBT-I vs. SH, t (d)	−.31	−2.56* (−.71)	−3.67** (−1.06)	−1.53						
Use of sleeping medication											
	CBT-I	2.20 (1.12)	1.90 (1.32)	1.55 (1.29)	1.48 (1.25)	1.67	1.95	.57	1.43	1.43	−.15
	SH	2.07 (1.36)	2.04 (1.27)	1.77 (1.23)	1.90 (1.33)				−.48	.58	−.89
	CBT-I vs. SH, t (d)	.40	−.39	−.61	−1.10						

Table 2 continued

Variables	Group	Pre-treatment *M* (SD)	Post-treatment *M* (SD)	First follow-up *M* (SD)	Second follow-up *M* (SD)	Group F (η^2)	Time F (η^2)	Group × Time F (η^2)	T1 vs. T2 t (*d*)	T2 vs. T3 t (*d*)	T3 vs. T4 t (*d*)
Daytime dysfunction											
	CBT-I	2.23 (.81)	1.96 (.99)	1.75 (.91)	1.81 (.92)	3.02, $p = .08$ (.06)	6.83*** (.14)	1.62	1.39	1.68	.27
	SH	2.07 (.96)	2.00 (.95)	2.09 (.81)	2.20 (.83)				−.27	−.29	−.56
	CBT-I vs. SH, t (*d*)	.70	−.12	−1.35	−1.47						

CBT-I = cognitive-behavioral therapy for insomnia, SH = sleep hygiene, T1 = pre-treatment, T2 = post-treatment, T3 = first follow-up, T4 = second follow-up

* $p < .05$; ** $p < .01$; *** $p < .001$

between-subject or within-subject changes were identified. No significant effects were found in any factors regarding Sleep latency and Sleep duration. Both parameters improved from pre- to post-treatment in the CBT -I group but not in the SH group. Both the CBT-I and SH groups showed the same results over time in Sleep latency and Sleep duration. Neither significant effects nor specific changes were identified in Use of sleeping medication.

Applying the Bonferroni-Holm correction the Time factor in Habitual sleep efficiency, Sleep disturbances and Daytime dysfunction, the comparison pre vs. post-treatment in the CBT-I group in Sleep quality-Total, Subjective sleep quality, Sleep latency, Sleep duration, and Habitual sleep efficiency, and the comparison CBT-I vs. SH at post-treatment in Subjective sleep quality and at first follow-up in Sleep disturbances, were significant.

According to the RCI, 87 % of CBT-I patients and 45 % of SH patients showed clinically significant changes in Sleep quality-Total. Considering sleep improvement criteria, 33.33 % of the patients in the CBT-I group reported a mean total wake time of <60 min (vs. 7.40 % in the SH group), 33.33 % reported a mean total sleep time of 6.5 h

Table 3 Changes in pain intensity, fatigue and daily functioning in the treatment groups

Variables	Group	Pre-treatment *M* (SD)	Post-treatment *M* (SD)	First follow-up *M* (SD)	Second follow-up *M* (SD)	Group F (η^2)	Time F (η^2)	Group × Time F (η^2)	T1 vs. T2 t (*d*)	T2 vs. T3 t (*d*)	T3 vs. T4 t (*d*)
Pain intensity (MPQ)											
	CBT-I	7.32 (1.94)	6.72 (2.08)	7.05 (1.70)	6.90 (2.12)	.02	1.99	.43	1.79, $p = .08$ (.31)	−.73	.26
	SH	8.46 (1.10)	8.23 (1.34)	7.84 (2.05)	7.60 (2.34)				.98	.70	.38
	CBT-I vs. SH, t (*d*)	−2.73** (−.72)	−3.16** (−.86)	−1.43	−.96						
General fatigue (MFI)											
	CBT-I	4.47 (.58)	4.05 (.79)	4.26 (.55)	4.16 (.68)	3.87* (.08)	8.92*** (.18)	2.34	2.50* (.44)	−1.30	1.05
	SH	4.65 (.53)	4.45 (.63)	4.51 (.64)	4.39 (.74)				1.07	.94	.66
	CBT-I vs. SH, t (*d*)	−1.21	−2.04* (−.56)	−1.43	−1.07						
Daily functioning (FIQ)											
	CBT-I	60.71 (11.83)	50.47 (18.43)	54.03 (15.76)	52.61 (15.65)	8.71** (.17)	4.62** (.10)	3.65* (.08)	2.47* (.50)	−.76	.51
	SH	64.09 (13.61)	64.46 (15.23)	63.52 (16.01)	62.39 (17.38)				−1.26	1.35	.33
	CBT-I vs. SH, t (*d*)	−1.02	−2.98** (−.82)	−2.09* (−.59)	−2.02* (−.59)						

CBT-I = cognitive-behavioral therapy for insomnia, SH = sleep hygiene, T1 = pre-treatment, T2 = post-treatment, T3 = first follow-up, T4 = second follow-up

* $p < .05$, ** $p < .01$, *** $p < .001$

or longer (vs. 25.92 % in SH), and 36.66 % reported a mean sleep efficiency of 85 % or greater (vs. 18.51 % in SH).

Changes in pain intensity, fatigue and daily functioning

As regards Pain intensity, the ANCOVA showed no significant effects on any factor. However, the CBT-I group showed significantly lower Pain intensity than the SH group at pre- and post-treatment, and only the CBT-I group showed a reduction in Pain intensity close to significance between both times (see Table 3). The ANCOVA for General fatigue revealed a significant effect of Group and Time. General fatigue decreased from pre- to post-treatment in the CBT-I group but not in the SH group. The CBT-I group showed lower General fatigue than the SH group at post-treatment. As regards Daily functioning, the ANCOVA showed a significant effect of Group, Time and Group × Time. Daily functioning improved from pre- to post-treatment in the CBT-I group but not in the SH group. The CBT-I reported better Daily functioning than the SH group at post-treatment and first and second follow-up.

According to the RCI, 43 % of the patients in the CBT-I group showed significant improvements in Pain intensity, 50 % showed improvements in General fatigue and 63 % showed improvements in Daily functioning, compared to 31, 41 and 21 % of patients in the SH group, respectively.

Changes in self-efficacy, pain catastrophizing and emotional distress

The ANCOVA for Self-efficacy indicated significant effects of Group, Time and Group × Time (see Table 4). In the CBT-I group, Self-efficacy increased to a level close to significance from pre- to post-treatment. The CBT-I group showed higher Self-efficacy than the SH group at post-treatment, first- and second follow-up. In Pain catastrophizing, the ANCOVA showed an effect close to significance of Time. Pain catastrophizing significantly decreased from pre- to post-treatment in the CBT-I but not in the SH group. The CBT-I group showed significantly lower Pain catastrophizing than SH group at post-treatment.

Table 4 Changes in self-efficacy, pain catastrophizing, and emotional distress in the treatment groups

Variables	Group	Pre-treatment *M* (SD)	Post-treatment *M* (SD)	First follow-up *M* (SD)	Second follow-up *M* (SD)	Group F (η^2)	Time F (η^2)	Group × Time F (η^2)	T1 vs. T2 t (d)	T2 vs. T3 t (d)	T3 vs. T4 t (d)
Self-efficacy (CPSS)	CBT-I	86.50 (36.63)	93.96 (33.60)	98.89 (33.81)	101.52 (31.51)	4.63* (.09)	4.93** (.10)	2.82* (.06)	−1.83, p = .07 (−.33)	−1.00	−1.52
	SH	71.59 (35.39)	70.48 (37.81)	74.77 (39.73)	71.95 (41.85)				.65	−.38	1.05
	CBT-I vs. SH, t (d)	1.59	2.43* (.65)	2.34* (.65)	2.65* (.79)						
Pain catastrophizing (PCS)	CBT	26.23 (13.91)	20.36 (11.50)	22.34 (14.85)	21.41 (13.65)	.59	2.51, p = .06 (.05)	.95	2.87** (.53)	−.93	1.64
	SH	31.00 (11.57)	27.28 (10.67)	26.77 (11.31)	25.85 (14.18)				1.41	.75	.40
	CBT-I vs. SH, t (d)	−1.42	−2.29* (−.62)	−1.20	−1.08						
Anxiety (SCL-90-R)	CBT-I	1.49 (.96)	1.23 (.79)	1.38 (1.07)	1.50 (1.02)	.19	1.06	1.20	2.58* (.52)	−1.28	−.81
	SH	1.75 (.86)	1.62 (.92)	1.53 (.80)	1.55 (.68)				1.64	.57	.26
	CBT-I vs. SH, t (d)	−1.09	−1.68	−.52	−.21						
Depression (SCL-90-R)	CBT-I	2.09 (.84)	1.63 (.84)	1.58 (.87)	1.78 (.88)	3.09, p = .08 (.07)	1.46	2.21	3.44** (.75)	1.12	−1.71
	SH	2.37 (.74)	2.29 (.77)	2.22 (.80)	2.11 (.88)				.68	.72	1.08
	CBT-I vs. SH, t (d)	−1.31	−2.97 ** (−.82)	−2.63* (−.76)	−1.24						

CBT-I = cognitive-behavioral therapy for insomnia, SH = sleep hygiene, T1 = pre-treatment, T2 = post-treatment, T3 = first follow-up, T4 = second follow-up

* $p < .05$; ** $p < .01$; *** $p < .001$

As regards Anxiety, the ANCOVA revealed no significant effects on any factor. Anxiety decreased from pre- to post-treatment in the CBT-I group but not in the SH group. In Depression, the ANCOVA indicated an effect close to significance of Group. Depression decreased from pre- to post-treatment in the CBT-I group but not in the SH group. The CBT-I group reported a higher improvement in Depression than the SH group at post-treatment and first follow-up.

According to the RCI, 63 % of the CBT-I patients and 28 % of the SH patients obtained significant clinical changes in Self-efficacy. The rate of patient improvement in the CBT-I group was 60 % in Pain catastrophizing, 57 % in Anxiety and 57 % in Depression, and 48 %, 55 % and 41 % of patients in the SH group, respectively.

Discussion

This trial explored the efficacy of the CBT-I in comparison to the SH in FM patients with comorbid insomnia and found that the former was better at improving sleep, daily functioning, and psychological well-being. Patients who received CBT-I reported significant and positive changes at post-treatment in subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency and sleep disturbances; these therapeutic gains were maintained at follow-ups. By contrast, patients in the SH group only reported a significant improvement in subjective sleep quality and a trend towards improvement in sleep efficiency. The CBT-I group obtained significantly higher changes than the SH group at post-treatment or follow-ups in several indices of sleep. The percentage of patients who showed clinical improvement in sleep quality according to the RCI was higher in the CBT-I group (87 %) than in the SH group (45 %). Considering sleep improvement criteria, in the CBT-I group 33.3 % of patients reported a mean total wake time of <60 min (vs. 7.4 % in the SH group), 33.3 % showed a mean total sleep time of 6.5 h or longer (vs. 25.9 % in the SH group), and 36.7 % showed a mean sleep efficiency of 85 % or greater (vs. 18.5 % in SH). These results support the first hypothesis.

These findings are also in line with previous research in FM patients. In the study by Edinger et al. (2005) the CBT-I and SH groups did not differ at post-treatment or follow-ups in sleep parameters (sleep logs and actigraphy); nevertheless, the CBT-I group showed lower total wake time and sleep latency and higher sleep efficiency than the UC group. As reflected in the sleep logs, 57 % of CBT-I participants met strict subjective sleep improvement criteria (vs. 17 % in the SH group and 0 % in the UC group). The CBT-I and SH groups did not differ at post-treatment and follow-ups in insomnia (questionnaire); however, both groups showed a greater improvement than the UC group. In one of our studies (Miró et al., 2011b) the CBT-I group showed an improvement in sleep quality (questionnaire) from pre- to post-treatment, but the SH group did not show any changes between both moments. Additionally, 85 % of the patients in the CBT-I group showed clinically significant changes in sleep quality (vs. 55 % in the SH group). In another of our studies using PSG (Sánchez et al., 2012), the CBT-I group showed improvements in time in bed, wake percentage and sleep efficiency, as well as a decrease in light sleep and an increase in deep sleep that were not observed in the SH group.

The results of the present trial are also similar to those of studies that have explored the efficacy of CBT-I in non-fibromyalgia samples. The study by Currie et al. (2000) was conducted with 60 patients with chronic pain that were assigned to a CBT-I ($n = 32$) or a self-monitoring/waiting-list control condition ($n = 28$). The CBT-I group obtained higher improvements than the control group at post-treatment in sleep onset latency, sleep efficiency and wake time after sleep onset (sleep diary), and sleep quality (questionnaire), which were maintained at follow-ups. The control group only reported changes in sleep quality that were not maintained at follow-ups. In addition, 16 % of the CBT-I patients fulfilled the criteria for good sleep (vs. 0 % of controls). The study by Vitiello et al. (2009) included older adults with osteoarthritis that were assigned to CBT-I ($n = 23$) or an attention-control stress management and wellness intervention ($n = 28$). The CBT-I patients reported improvements in sleep latency, wake after sleep onset and sleep efficiency (sleep log) after the intervention that were maintained at follow-up, but patients in the control condition reported no changes. In the study by Jungquist et al. (2010), 28 subjects with chronic pain were assigned to CBT-I ($n = 19$) or a contact control condition ($n = 9$). The CBT-I group showed improvements in sleep latency, wake after sleep onset, number of awakenings and sleep efficiency (sleep diary), and in insomnia severity (questionnaire); however, the control condition did not exhibit changes in these aspects of sleep. Moreover, 42 % of patients who received CBT-I achieved normal sleep (vs. 11 % of controls).The study by Pigeon et al. (2012) included 21 chronic pain patients that were randomized to CBT for pain (CBT-P) ($n = 5$), CBT-I ($n = 6$), combined CBT-I/P ($n = 6$), or a waiting-list control condition ($n = 4$). The CBT-I and the CBT-I/P were better than CBT-P at decreasing insomnia severity (questionnaire). In the present study, pre vs. post-treatment size effects of CBT-I in sleep latency and efficiency were similar to those reported by previous studies (Currie et al., 2000; Edinger et al., 2005; Vitiello et al., 2009).

Patients receiving CBT-I in the present study showed significant improvement in fatigue and daily functioning at

post-treatment and maintained the gains at follow-ups; however, only a trend towards relief of pain intensity was identified. These findings are in contrast with the failure of the SH to produce significant changes. The CBT-I group obtained significantly higher changes than the SH group at post-treatment or follow-ups in these measures. According to the RCI, 43 % of the CBT-I subjects obtained clinically significant improvements in pain intensity, 50 % in fatigue and 63 % in daily functioning (vs. 31, 41, and 21 %, respectively, in the SH group). The second hypothesis of the study was only partially supported. Contrary to our prediction, the CBT-I did not change pain intensity significantly. It may be necessary for sleep to be normalized for a longer time before an effective change in pain can be observed.

Most studies on chronic pain have reported that CBT-I did not have a substantial impact on reducing pain, and data about adjustment are mixed. Edinger et al. (2005) observed that the CBT-I and SH groups did not differ at post-treatment and follow-ups in pain and quality of life; yet, the SH group reported less pain than the UC group, and the CBT-I and SH groups reported greater quality of life than the UC group. In a previous study (Miró et al., 2011b), we reported that the CBT-I group did not report any changes in pain intensity but showed a trend towards improvement in daily functioning after the intervention, whereas the SH group showed no changes in these measures. Currie et al. (2000) found that neither the CBT-I nor the control condition produced significant effects on pain severity at post-treatment and follow-up. Vitiello et al. (2009) showed that the CBT-I reduced pain at post-treatment, but this effect disappeared at follow-up. Jungquist et al. (2010) reported that the CBT-I led to a decrease of interference at post-treatment but not of pain severity and pain disability. The control group did not improve in these parameters. Pigeon et al. (2012) reported that the CBT-I and the CBT-I/P obtained better changes in fatigue than the CBT-P, the CBT-P showed a greater effect on pain than CBT-I, and all therapies led to improvements in pain disability.

Patients receiving CBT-I in the present trial reported significant and positive changes at post-treatment in anxiety, depression and pain catastrophizing, and a trend towards improvement in self-efficacy for coping pain. These gains were maintained at follow-ups. Patients receiving SH did not show any changes in the above-mentioned parameters. The CBT-I group displayed significantly higher changes than the SH group at post-treatment or follow-ups in these measures, including a trend towards lower anxiety at post-treatment. According to the RCI, 63 % of CBT-I patients obtained significant clinical changes in self-efficacy (vs. 28 % in SH), 60 % in pain catastrophizing (vs. 48 % in SH), 57 % in anxiety (vs. 55 % in SH) and 57 % in depression (vs. 41 % in SH). The third hypothesis of the trial was partially supported.

Results about emotional distress differed from those of previous studies. Edinger et al. (2005) found that the CBT-I and SH groups did not differ at post-treatment and follow-ups in mood, but the CBT-I group showed more favorable changes than the UC group. In one of our studies (Miró et al., 2011b), we reported that the CBT-I and SH groups did not differ in the improvements obtained after the intervention in anxiety and depression. Currie et al. (2000) did not observe any differences between CBT-I and the control condition in depression at post-treatment and follow-up. Vitiello et al. (2009) and Jungquist et al. (2010) reported no changes in either the CBT-I or the control groups in depression from pre- to post-treatment. However, Pigeon et al. (2012) reported that CBT-I and CBT-I/P were better than CBT-P at reducing depression. Similarly to the present study, Jungquist et al. (2010) identified positive changes in self-efficacy in CBT-I (but not in the control condition) at post-treatment. None of these studies used measures about pain catastrophizing thoughts.

Note that some of the discrepancies between the findings of the present study and those of the previous ones may be due to differences in the methodology used. For example, unlike this study, Edinger et al. (2005), Jungquist et al. (2010) and Pigeon et al. (2012) used an individual therapy format, Vitiello et al. (2009) included a sample of older adults, and all studies (except our previous studies, Miró et al., 2011b, and Sánchez et al., 2012) included samples of men and women, considered different control conditions, and used partially different measures to assess sleep, pain, adjustment and mental well-being. Also, the estimated range for remission/improvement was defined differently among the trials. It is necessary to consider that sex differences can play a significant role. Women experience greater clinical pain, suffer greater pain-related distress, and show heightened sensitivity to experimentally induced pain compared to men (Paller et al., 2009); these differences may also be reflected in the differences in therapeutic gains between men and women in the CBT-I.

The results of the present trial should be considered with caution because of its limitations. Sleep quality (pre-, post-treatment, and follow-ups) was self-reported. Objective measures (PSG and actigraphy) applied at different stages of the clinical trial are needed to obtain a more complete assessment of sleep. However, it should be noted that a recent study has reported that FM-related symptoms were related to participants' subjective report (electronic diary) of how refreshed they were upon waking and the number of times they woke during the night but were not related to objective sleep (actigraphy) (Okifuji & Hare, 2011). Therefore, self-report measures are particularly relevant to assess sleep complaints in FM. It would also be desirable to include a sleep diary during the clinical trial allowing a more continuous evaluation of sleep characteristics and to

compare these findings with those obtained with other subjective measures such as the PSQI. Since the PSQI only provides data on sleep quality, it would have been very valuable to include a self-report questionnaire focused on insomnia. Pain intensity was also self-reported. Although the MPQ has good psychometric properties, for future research it would be advisable to use a pressure algometer, which measures pain threshold and tolerance and may complete the information provided by self-reports. There is some overlap between FIQ, SLC-90-R and MFI, which might explain the correlations among outcome variables. Patients came from specialized medical settings and may have had different clinical characteristics from those observed in primary care patients and those in other community contexts (e.g., FM associations). The integrity of the interventions was not verified using a procedure in which audiotapes were assessed by at least two independent raters. The data were analyzed considering only short-term changes. Despite the randomization, the SH group had higher pain scores at baseline that remained high at post-treatment compared to the CBT-I group, thus inflating post-treatment pain scores. Overall, the effect size was medium in both primary and secondary measures.

Future research has some important issues to address in this area. For example, whether there are any sex differences among FM patients in the response to CBT-I, and whether CBT-I also improves the sleep of FM patients with psychological and/or medical comorbid problems and patients from different care settings. Dismantling studies to identify which components of CBT-I contribute most to the efficacy of treatment is also necessary. Finally, it is of great interest to examine whether a treatment approach focused on disturbed sleep such as the CBT-I can increase the efficacy of multi-component therapeutic programs, and whether this combination contributes to a better quality of life in FM patients than standard medical treatment.

The present study shows that CBT-I is useful to treat non-restorative sleep in FM patients. Our findings extend those of previous research by suggesting the positive effect of the CBT-I not only on sleep, daily functioning and emotional distress, but also on other symptoms such as fatigue and cognitive aspects such as catastrophic cognitions about pain. Nevertheless, these changes were not accompanied by significant reductions in pain severity, although changes in the expected direction were observed. Experimental and clinical reports show that non-restorative sleep worsens pain intensity. However, reversing this relationship in therapeutic contexts is difficult, and so far psychological interventions focused on insomnia have achieved limited improvements in reduction of pain. Moreover, several studies have reported that CBT improves pain and several adjustment variables in FM patients (see reviews by Glombiewski et al., 2010; Hassett & Gevirtz, 2009) but has a limited positive impact on sleep in chronic pain syndromes including FM (see review by Tang, 2009). Since CBT-I is effective at improving sleep but has limited effects on pain, and pain management programs based on CBT provide appropriate skills to cope with pain, it is suggested that a hybrid treatment is necessary to address both pain and sleep in patients with chronic pain (Tang, 2009). The pilot study by Pigeon et al. (2012) provides recent evidence of the usefulness of this hybrid approach. The typical components of CBT-I can be combined with other elements of CBT for chronic pain (pain education, balanced combination of activity and rest, emotions management, training of communication skills, training for problem solving, and cognitive therapy for negative thoughts about pain), providing potentially greater therapeutic benefits that each option separately. This is a promising issue that needs to be studied because of its potential to enhance the current multi-component programs for FM.

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ANEXO 7.

Article

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Cognitive-behavioral therapy for insomnia improves attentional function in fibromyalgia syndrome: A pilot, randomized controlled trial

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Abstract

This pilot, randomized controlled trial analyzed the effects of a cognitive behavioral therapy (CBT, n = 20) for insomnia vs a sleep hygiene (SH, n = 20) program on the three attentional networks (alertness, orienting, and executive function) and other additional outcome measures (sleep, pain, depression, anxiety, and daily functioning) of fibromyalgia patients. The CBT group showed significant improvement in alertness ($F(1, 28) = 11.84$, $p = .0018$), executive functioning ($F(1, 28) = 15.76$, $p = .00059$), sleep quality ($F(1, 38) = 6.33$, $p = .016$), and a trend to improvement in daily functioning ($p > .06$), as compared with the SH group. The improvement in executive functioning was significantly related to the changes in sleep ($r = 0.40$, $p = .026$). A CBT for insomnia represents a useful intervention in fibromyalgia patients not only regarding sleep disturbance but also attentional dysfunction and probably daily functioning.

Keywords

attentional function, cognitive behavioral therapy, fibromyalgia, insomnia, randomized controlled trial

Introduction

Fibromyalgia (FM) is a chronic pain syndrome characterized by widespread musculoskeletal pain and multiple tender points (Wolfe et al., 1990). FM is estimated to appear in 2–5 percent of the population (female/male ratio 9:1) and can severely affect the individual's quality of life, leading to substantial social and economic costs (Spaeth and Briley, 2009).

Cognitive complaints may affect up to 70 percent of individuals with FM and contribute to the global disability associated to the syndrome (Leavitt and Katz, 2009). Patients often complain of forgetfulness, blurring of mental activity, and diminished ability to concentrate or follow conversations, which are sufficient to impair life quality or occupational functioning.

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Overall, FM patients seem to have problems in working memory, episodic memory, and semantic memory access as compared to healthy controls (see Glass, 2009 for a review). Attention and concentration have also been analyzed in FM patients, with contradictory results (Glass, 2009). A main limitation of existing studies is that attention has been broadly defined and the tasks used to measure attention are not designed to cover all the main components of the attentional system.

Research on attention has identified three primary functions of attention, known as alerting, orienting, and executive functioning (Posner and Rothbart, 2007). The alerting network is in charge of keeping the cognitive system properly activated. The orienting network selectively allocates attention to a potentially relevant area of the visual field and/or object to enhance its perceptual processing. The executive component of attention is active in situations that involve planning, maintaining goal-relevant priorities and avoiding interference, making a decision, detecting an error, or overcoming habitual actions (Fan et al., 2002). In a recent study designed to analyze the three attentional networks in FM, observed impaired alertness (reduced vigilance) and executive control (greater interference) were observed in FM patients as compared to healthy controls (Miró et al., 2010). The ability to control distraction is part of the executive component of attention. In fact, it has been recently suggested that FM patients seem especially sensitive to distraction (Glass, 2009; Leavitt and Katz, 2009) and have some impairment in executive processes (Verdejo-García et al., 2009).

Cognitive problems are a real and troubling symptom for FM patients. However, very few studies have addressed whether cognitive dysfunction could be improved in FM. From a pharmacological approach, it is not yet known whether any of the medications used in FM are helpful to improve cognitive function. In a study with chronic pain patients, Dick and Rashiq (2007) found that cognitive function was not improved by short-term local analgesia in several tests of working memory and attention. Two recent studies have shown that exercise in a warm-water pool improves cognitive function in FM patients. Munguía-Izquierdo and Legaz-Arrese (2007) performed a randomized controlled trial comparing an exercise training group vs a control group. Their outcome measures included several memory tasks, attention and working memory assessed with the Paced Auditory Serial Addition Task (PASAT) and executive function in the Trail Making Test (TMT). After training, exercise improved all neuropsychological tests, pain, and severity of FM, while differences were not significant in the control group. In a later publication, Munguía-Izquierdo and Legaz-Arrese (2008) reported similar results, also finding that physical condition and subjective sleep quality improved in the exercise group, while anxiety remained unchanged during the trial.

However, to our knowledge, no study to date has analyzed the impact of a psychological therapy on cognitive function in FM. Since the etiology of FM is unknown, the relationship between its different symptoms is currently not well understood and there is no definitive treatment for the condition (Häuser et al., 2010). It is not clear whether cognitive deficits can be attributed to central nervous system dysfunction or may instead be due to the influence of psychological variables such as emotional distress or pain (see Glass, 2009 for a review).

The relationship between sleep and cognitive deficit has not been generally assessed. This is surprising, if we consider that fatigue and sleep disturbances may affect up to 99 percent of FM patients and are particularly distressing to them (Hamilton et al., 2008). The inability to obtain restorative sleep produces an impairment in the cortical function (Lim and Dinges, 2010), especially in the prefrontal cortex involved in alertness and executive functioning (Jones and Harrison, 2001). In our previous research, sleep dysfunction was the measure that correlated the strongest with attention (Miró et al., 2010). Thus, a therapy focused on sleep may improve cognitive function. Accumulating evidence supports

the idea that sleep disturbances have a reciprocal influence on pain, fatigue, mood, and cognitive functioning in FM patients (see Moldofsky, 2010 for a review). A randomized clinical trial with FM patients suffering from chronic insomnia showed that a cognitive-behavioral therapy (CBT) for insomnia significantly improves sleep quality (57 percent of improvement) as compared with sleep hygiene (SH) instructions (17%) and usual care (0%) (Edinger et al., 2005). In addition, the CBT group showed improvement in mood state as compared with the other groups. Non-pharmacological therapies currently recommended in the evidence-based guidelines for the management of FM are aerobic exercise, cognitive-behavioral therapy, and multicomponent treatment (Häuser et al., 2010). However, in CBT, sleep disturbances in FM are ignored or only deal with SH at the most.

In this trial we analyzed the effects of a CBT for insomnia on the cognitive function of FM patients. The objectives of the study were the following: (1) to compare the effect of a CBT for insomnia vs an SH education program on our primary outcomes (overall reaction time, alertness, orienting, and executive function) and other secondary outcomes (sleep, pain, depression, anxiety, and daily functioning) in FM patients with chronic insomnia; and (2) to determine the relationships between possible changes observed over time as a result of the therapy in the different outcome measures.

Method

Design and participants

The clinical sample was selected from the Rheumatology Service and Pain Unit of Virgen de las Nieves Hospital in Granada, Spain. Since FM is infrequent in males and it is not clear whether FM has differential characteristics depending on gender, only women were recruited. Women who fulfilled the inclusion criteria to participate in the pilot study were referred from the hospital to the Clinical Psychology Unit of the School of Psychology. All patients met the diagnostic criteria for FM (Wolfe et al., 1990) and the criteria for insomnia (APA, 2000).

Exclusion criteria, designed to exclude patients whose insomnia and/or cognitive dysfunction were better explained by other comorbid conditions were as follows: (1) being pregnant; (2) having a medical history of significant head injury or neurological disorder; (3) having major concomitant medical conditions; (4) having major depressive disorder with suicide ideation or other major Axis I diagnoses (APA, 2000); (5) having symptoms of sleep-disruptive comorbidities with insomnia; (6) having an apnea-hypopnea index or periodic limb movement-related arousal index of 15 or more per hour of sleep; (7) having a severe hypnotic dependence, suggested by the use of a hypnotic in a higher than recommended dosage or repeated episodes of rebound insomnia on withdrawal (Edinger et al., 2005); and (8) being treated with another psychological or physical therapy at the moment of the study.

The study flow of participants is shown in Fig. 1. Eighty-two eligible Spanish-speaking women from 25 to 60 years old with FM were initially screened by a psychologist just before the medical examination. From these patients, 53 women with FM who fulfilled the inclusion criteria were admitted for evaluation. The complete evaluation was carried out by CD and included, in this order, interviews (two sessions), questionnaires (to be completed at home after the first interview), a neuropsychological test (performed at the end of the second session), and a polysomnographic study. After the evaluation, a final sample of 44 women with FM was randomly assigned to either a cognitive-behavioral treatment (CBT, $n = 22$) for insomnia, or a sleep hygiene (SH, $n = 22$) group. Simple randomization (1:1) was implemented by a computerized number generator designed by a researcher with no clinical involvement in the trial. Finally, 16 patients in the CBT group and 15 patients in the SH group completed the whole trial and were included in the analysis of the ANT-I. All participants

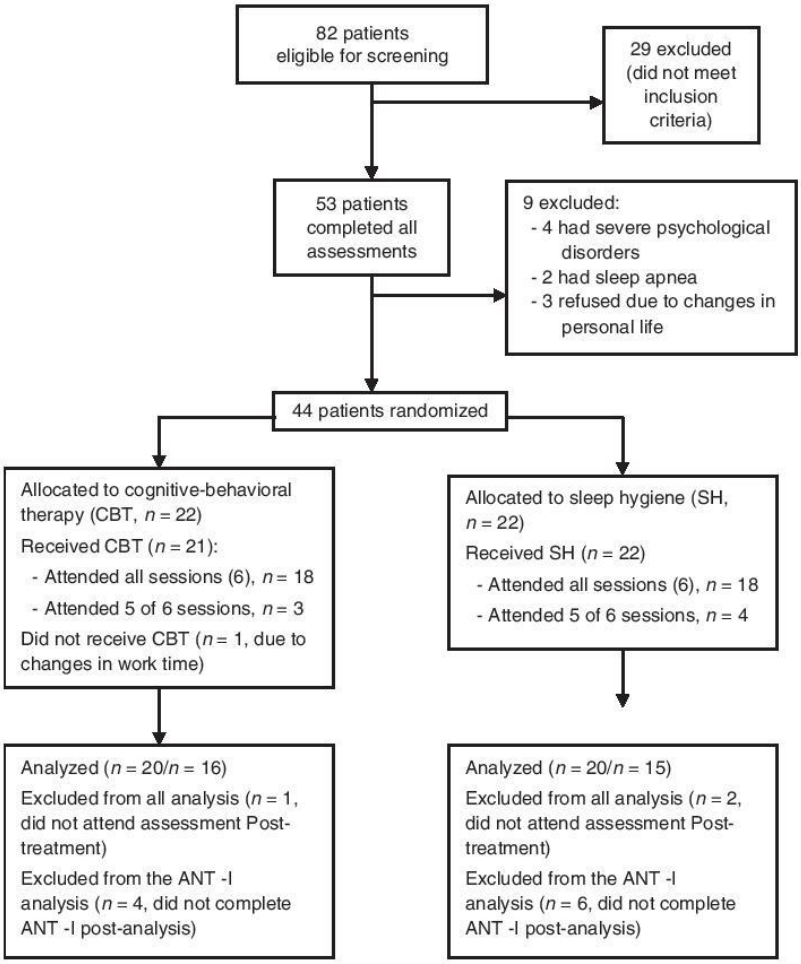

Figure 1. Flow of participants throughout the study.

gave their informed consent prior to their inclusion in the study. The study received ethical approval from the University of Granada Ethics Committee.

Treatments

Three female CBT experts with experience in FM (EM, MPM, and AIS) provided the therapy guided by a treatment manual designed for the study. Each therapist applied both CBT and SH. All sessions were delivered in groups (five to six participants) once a week for six weeks, and lasted about 90 minutes. Patients in the CBT and SH therapy groups continued with their usual medical treatment for FM. All participants were on stable doses of medication during the trial (see Table 1).

The contents and format of the CBT program were designed according the work of Edinger et al. (2005) and met the recommendations of the American Academy of Sleep Medicine (Morgenthaler et al., 2006). In the first session, patients received information about the relationship between sleep and FM, basic notions about sleep (sleep stages, sleep functions, circadian rhythms, sleep needs, effects of sleep deprivation on wake functioning, and explanation of insomnia) and sleep hygiene education. In the second session, the therapist provided sleep restriction and stimulus control instructions. The third session was devoted to relaxation training (a combination of passive relaxation and imagery training). The fourth and fifth sessions focused on cognitive therapy for the dysfunctional beliefs related to insomnia. Finally, the sixth session was devoted to maintaining achievements and preventing relapses. The SH group worked only with sleep hygiene rules. In the first session, participants were given the same information about sleep as the CBT group. The second session was devoted to sleep hygiene rules related to environmental factors. The third session focused on some lifestyle factors that influence sleep (consumption of stimulants and other substances). The fourth and fifth sessions were devoted to providing information about diet and physical exercise, respectively. The sixth session was similar in both groups.

At the beginning of the first session (CBT and SH groups), the therapist provided patients with a written manual with a summary of the information presented in every session and homework. Participants in the SH group were offered CBT after their Post-treatment assessment.

Measures

The assessment of the outcome measures was performed within one week after the intervention by an examiner (CD) who was blinded to group assignment.

Polysomnography (PSG). A domiciliary PSG recording (with a SomnoScreen PSG-Tele, SomnoMedics) was used to exclude subjects with sleep-disruptive comorbidities. The recording included electroencephalography in the frontal, central, parietal, and occipital regions (FZ/A1, CZ/A1, PZ/A1, OZ/A1), bilateral electrooculography, bilateral submental and anterior tibial electromyography, and respiratory variables (nasal/oral airflow, thoracic effort, snoring, and pulse oximetry). Sleep stages were scored visually according to Rechtschaffen and Kales' (1968) standard criteria.

Neuropsychological task. The ANT-I (Attentional Network Test-Interactions) task developed by Callejas et al. (2004) explores the efficiency and interactions of the three attentional networks (alertness, orienting, and executive functioning). The ANT-I task was performed with a laptop computer with a 15" color screen monitor, with Windows Vista and E-Prime 2 software. Participants were instructed to respond to the direction of the target stimulus by pressing one of two possible keys on the keyboard. A fixation point was followed by the 50 ms alerting signal (a 2000 Hz sound), presented only in half of the trials. The orienting cue (an asterisk) was presented 400 ms later for 50 ms above or below the fixation point in two-thirds of the trials. After another 50 ms ISI, the target and flankers were shown at the same location of the previous orienting cue in 50 percent of the trials and at the opposite location in the remaining 50 percent of cue-present trials. Participants were to press the 'C' key on the keyboard if the central arrow pointed to the left and the 'M' key if it pointed to the right, while ignoring the flanking arrows. Target and flankers were congruent (i.e. showed the same direction) in 50 percent of the trials and incongruent (i.e. pointed in opposite directions) in the remaining 50 percent.

Participants performed two practice trials followed by four blocks of 48 experimental trials each, which amounted to 16 trials per experimental condition. The test session lasted for about 40 m. with similar test conditions for all subjects. All participants' self-reported chronotypes were estimated and participants were

tested at their optimal time (e.g. evening types in the evening).

The task had a 2 (Alerting Signal) × 3 (Orienting Cue) × 2 (Congruency) design. The Alerting Signal, used as an index of Attention-Alerting, had two levels: presence vs absence of the sound. The Orienting Cue, which measured Attention-Orienting, had three levels: no-cue trials (no orienting cue was presented, i.e. neutral trials), cued location trials (an orienting cue was presented at the same location as the subsequent target, i.e. valid trials), and uncued location trials (the orienting cue was presented but at the opposite side to the target, i.e. invalid trials). Lastly, Congruency was used to measure Attention-Executive functioning and had two levels: congruent trials (the target was flanked by arrows pointing in the same direction as the target) and incongruent trials (the flanker arrows pointed in the direction opposite to that of the target).

Questionnaires

Pittsburgh Sleep Quality Index, PSQI (Spanish version of Royuela and Macías (1997)). The PSQI includes 19 items that explore Sleep Quality, Sleep Latency, Sleep Duration, Habitual Sleep Efficiency, Sleep Disturbances, Use of Sleeping Medication, and Daytime Dysfunction. The present study used the total score (ranging from 0 = absence of perturbation to 21 = severe perturbation). The internal consistency of the PSQI ranged between .67 and .81 (Royuela and Macías, 1997).

McGill Pain Questionnaire, MPQ (Spanish version of Lázaro et al. (2001)). The MPQ assesses pain experience using 15 verbal pain descriptors (sensory and affective), a current pain index, and a visual analogue scale to assess pain intensity in the last week (from 1 = no pain to 10 = extreme pain). The present study used this last score. The Cronbach's alpha of the MPQ was .74 (Lázaro et al., 2001).

Hospital Anxiety and Depression Scale, HAD (Spanish version of Herrero et al. (2003)). The HAD assesses anxiety and depression symptoms in non-psychiatric hospital contexts. The HAD includes 14 items (grouped into *Anxiety* and *Depression* dimensions) that are scored from 0 to 3. The Cronbach's alpha was .84 for the Depression subscale and .85 for the Anxiety scale (Herrero et al., 2003).

Fibromyalgia Impact Questionnaire, FIQ (Spanish version of Rivera and González (2004)). The FIQ is composed of 10 items. The first item assesses functional capacity for daily living (ranging from 0 to 3). Items 2 and 3 ask the patients to mark the number of days they felt well/unable to work. Items 4 through 10 are scales marked in 10 levels which rate work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. The internal consistency of the FIQ showed an alpha coefficient of .82 (Rivera and González, 2004).

Results

Table 1 shows the demographic and clinical characteristics of the FM sample. The Student's *t*-test, the Mann-Whitney U, and the X^2 tests were used to compare baseline measures between the CBT and SH groups. The two groups completing the ANT-I task (CBT; $n = 16$ vs SH; $n = 15$) differed significantly in terms of age ($t(29) = -3.31$, $p = .002$), but were similar in educational level, marital status, work status, and clinical variables such as years since the diagnosis of FM, and insomnia, or type of insomnia problem ($p > .2$ for all effects). The CBT ($n = 20$) and SH ($n = 20$) groups completing self-reported measures were similar in all demographic and clinical variables (all $ps > .37$).

Attentional measures

Previous analyses showed that the main effects of each variable as well as the expected interactions were significant in the first session of the FM sample. Thus, the same results obtained with the original task were perfectly replicated (Callejas et al., 2004).

Table 1. Demographic and clinical characteristics of the FM sample completing the ANT-I task

Variable	Total sample (n = 31)	CBT group (n = 16)	SH group (n = 15)	p value
Age, mean (SD)	46.45 (7.03)	43.94 (6.06)	50.20 (6.12)	.002
Education (%)				.215
Basic education	35.5	32.5	30	
High school	19.4	21.3	16.7	
Professional instruction	16.1	14.5	18.0	
University studies	29	32.8	25.3	
Marital status (%)				.396
Married	90.3	87.5	93.3	
Single	3.2	6.3	0	
Divorced or widowed	6.4	6.3	6.7	
Work status (%)				.184
Currently employed	45.2	62.5	26.7	
Retired	3.2	0	6.7	
Unemployed	19.4	12.5	26.7	
Disabled	32.2	25.1	40	
Duration of FM (years), mean (SD)	4.47 (3.83)	4.23 (3.44)	4.70 (4.30)	.744
Duration of sleep problem (years), mean (SD)	10.70 (8.62)	11.41 (9.24)	9.85 (8.23)	.682
Nature of sleep problem				
Onset (%)	74.3	75	73.3	.425
Maintenance (%)	90.3	87.6	93.4	.505
Early awakening (%)	71	62.5	80	.130
Sleep latency (hours), mean (SD)	1.16 (1.13)	1.12 (1.23)	1.23 (0.53)	.742
Number of awakenings per night, mean (SD)	2.93 (1.12)	2.71 (0.99)	3.14 (1.23)	.320
Sleeping hours per night, mean (SD)	4.42 (1.03)	4.48 (1.05)	4.36 (1.03)	.652
Drug intake (%)				
Antidepressants	64.4	64.2	64.3	.622
Anxiolytics	60.7	64.3	57.1	.699
Anti-inflammatory drugs	64.3	57.1	71.4	.430
Analgesics	64.3	64.2	64.3	.589

Group and treatment effects

Mean and standard deviations of outcome measures are shown in Table 2 and Figure 2. A first analysis showed that attentional measures at baseline were no different between the CBT and SH groups (all $p > .2$). After that, a 2 (Alerting Signal) × 3 (Orienting Cue) × 2 (Congruency) × 2 (Time; Pre- vs Post-treatment) × 2 (Group; CBT vs SH) repeated measures ANCOVA was performed on the data from the two sessions to check whether the two groups differed across sessions in attentional functioning. Age was introduced in this analysis as a covariate to take into account age differences between the two groups. Age did not reach statistical significance in the ANCOVA, ($F(1, 28) = 2.31$, $p = .1401$). The analysis showed a significant interaction between Alerting Signal, Time, and Group ($F(1, 28) = 4.88$, $p = .0355$). It revealed that, whereas the CBT group reduced the alertness effect from the Pre- (63 ms) to the Post-treatment (31 ms)

Table 2. Mean (M) and standard deviations (SD) of the clinical variables obtained by the therapy groups at Pre- and Post-treatment

	CBT group ($n = 20$)		SH group ($n = 20$)	
	Pre-treatment M (SD)	Post-treatment M (SD)	Pre-treatment M (SD)	Post-treatment M (SD)
MeanRT (1)	717.45 (124.82)	617.00 (78.39)	703.68 (111.73)	653.60 (88.57)
Control (1)	113.97 (33.74)	87.92 (29.13)	114.20 (49.81)	104.70 (33.84)
Orienting (2)	54.88 (43.25)	66.17 (24.26)	59.70 (20.34)	58.15 (38.16)
Alerting (1)	92.03 (74.17)	51.85 (31.33)	69.48 (47.39)	68.98 (44.81)
Sleep Quality (PSQI) (1)	15.05 (3.39)	11.55 (4.29)	14.15 (3.11)	13.20 (3.12)
Pain Intensity (MPQ) (1)	7.02 (1.92)	6.50 (2.46)	8.26 (1.70)	8.26 (1.48)
Anxiety (HAD) (1)	10.60 (4.13)	10.95 (4.26)	11.60 (4.12)	11.55 (3.84)
Depression (HAD) (1)	10.50 (3.69)	9.65 (4.39)	12.20 (3.73)	11.30 (4.61)
Daily Functioning (FIQ) (1)	59.66 (12.83)	49.25 (21.38)	62.19 (13.97)	63.67 (16.08)

Note: (1) High scores indicate worse functioning; (2) High scores indicate better functioning

session ($F(1, 28) = 11.84$, $p = .0018$), the SH group showed similar alertness effects in both sessions (47 and 46 ms, $F < 1$). Similarly, the interaction between Congruency, Group, and Time was significant ($F(1, 28) = 5.27$, $p = .0294$). Again, whereas the CBT group showed reduced interference from the Pre- (114 ms) to the Post-treatment (88 ms) session, ($F(1, 28) = 15.76$, $p = .0005$), the SH group showed similar congruency effects in both sessions (114 ms and 104 ms, respectively, $F < 1$).

The CBT group reduced overall reaction time (RT) in the second session to a greater extent than the SH group, although the Time × Group interaction only approached significance ($F(1, 28) = 2.97$, $p = .0956$). Whereas the CBT group reduced overall RT significantly from the Pre- (717 ms) to the Post-treatment (617 ms) session ($F(1, 28) = 16.37$, $p = .0004$), the SH group showed rather similar overall RT in both sessions (704 ms and 654 ms, respectively, $F(1, 28) = 1.74$, $p = .1984$). No other interaction involving the factor Group approached significance. In summary, the CBT group showed a significantly greater improvement than the SH group in Attention-Executive functioning (i.e. greater reduction in interference), Attention-Alerting (i.e. greater reduction in alertness), and a marginally significant larger reduction in overall RT.

Attentional indexes

Indexes of the efficiency of each attentional network were computed as the following subtractions (Callejas et al., 2004): Attention-Alerting = NoTone–Tone conditions (restricted to the no-cue condition); Attention-Orienting = Uncued location–Cued location trials, and Attention-Executive functioning = Incongruent–Congruent. These indexes were computed for both the Pre- and Post-treatment sessions. Overall RT in each session was also taken as an index of overall performance. Furthermore, differences between the Pre- and Post-treatment sessions were computed as an index of improvement in each measure. Specific *t*-tests comparing each Pre-Post attentional index against 0 for each group were computed to test whether the functioning of each attentional network changed after treatment for each group.

In the SH group, there was no change after treatment in any of the attentional indexes (all $ps > .45$). In the CBT group, only the Alertness and Executive functioning attention indexes changed after treatment ($t(16) = 2.16$, $p = .0470$, $d = .70$ and $t(16) = 2.65$, $p < .0183$, $d = .82$, respectively), whereas no change was observed in the Attention-Orienting index ($t(16) = –.82$, $p = .4271$).

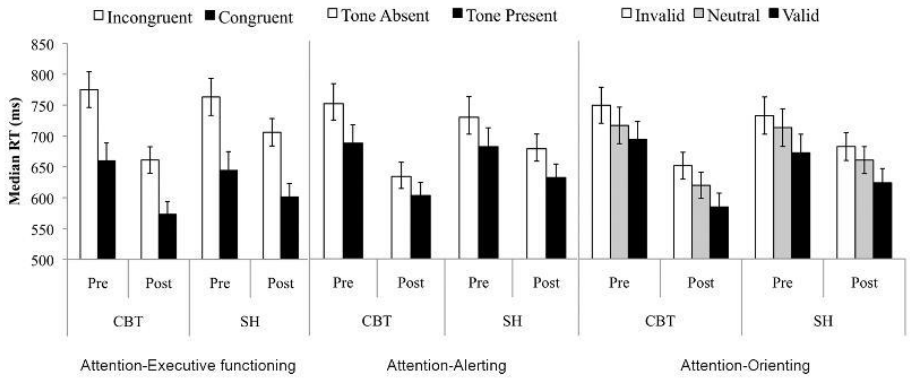

Figure 2. Attentional functioning of the CBT and SH groups in the Pre- and Post-Treatment sessions. Note that the CBT group showed a larger improvement in the Post-Treatment session, in Attention-Executive functioning (i.e. larger reduction in interference) and Attention-Alerting, as compared with the SH Group.

Self-report measures

Differences in self-reported measures between the CBT and SH therapy groups across sessions were compared using repeated-measures ANOVAs (Group; CBT vs SH × Time; Pre vs Post-treatment). Effect sizes were calculated via the partial η^2. For significant effects, Student's *t* test was computed for paired comparisons and Cohen *d* was used to examine the effect sizes (small .2, medium .5, and large .8) (Cohen, 1988). The statistical power of the analysis performed with the self-report measures was 70 percent.

Repeated-measures ANOVAs for Sleep Quality (PSQI) showed a significant effect for Time (($F(1, 38) = 19.29$, $p = .000$, $\eta^2 = .33$)) and for Time × Group interaction (($F(1, 38) = 6.33$, $p = .016$, $\eta^2 = .14$)) but no significant effect for Group. Whereas the CBT group reduced sleep dysfunction from the Pre- (15.05) to the Post-treatment (11.55) session (($t(19) = 5.01$, $p = .000$, $d = .90$, large effect size)), the SH group showed no differences in sleep dysfunction between both sessions (14.15 and 13.20, respectively, ($t = 1.29$, $p = .211$)). The ANOVA for Daily Functioning (FIQ) showed a significant Time × Group interaction (($F(1, 38) = 4.09$, $p = .050$, $\eta^2 = .09$)), whereas the effect of Group or Time factors was not significant. CBT group changed the Daily Functioning (FIQ) from the Pre- (59.66) to the Post-treatment (49.25) sessions at a level that approached significance (($t(19) = 1.94$, $p = .067$, $d = .59$, medium effect size)), whereas the SH group did not change (62.19 and 63.67, respectively). In short, 85 percent of the patients in the CBT group and 55 percent in the SH group showed significant clinical changes in Sleep quality (PSQI). Similarly, 60 percent of the patients in the CBT group and 30 percent in the SH group improved Daily Functioning (FIQ) to a clinically significant level. ANOVAs for Pain intensity (MPQ) and Anxiety and Depression (HADS) did not show any significant effects for Time, Group, and Time × Treatment interaction factors ((between $F(1, 38) = .002$, $p = .961$ and $F(1, 38) = 2.93$, $p = .095$)). Overall, these results show that the CBT group obtained greater improvement than the HS group in both Sleep Quality and Daily Functioning.

Relationships between outcome measures

For clinical variables that changed over time as a result of the therapy (CBT or HS), individual

changes were calculated with the Reliable Change Index (RCI) (Jacobson and Truax, 1991; Salaberría et al., 1996). Pearson's analysis was performed to examine relations between changes (Reliable Change Index) in Sleep Quality (PSQI) and Daily Functioning (FIQ) and changes (rate of change) in subtraction indexes of the ANT-I. Results revealed a significant correlation between the Attention-Executive functioning and the Reliable Change Index of Sleep quality (PSQI) (r = .40, p = .026). No significant correlations were observed between the Reliable Change Index of Sleep quality (PSQI) and Daily Functioning (FIQ) and the remaining indexes of the ANT-I (MeanRT, Alerting and Orienting) either at Pre- or Post-treatment (r between .29, p = .104, and –0.24, p = .181), nor subtraction indexes of the ANT-I (r between .19, p = .300 and –.25, p = .162). These results show that the change in sleep quality was related to the improvement in executive functioning.

Discussion

This is the first study to our knowledge that demonstrates the positive effect of a CBT for insomnia on cognitive function of patients with FM. The CBT group showed significant improvement in alertness and executive functioning as compared with the SH group. In addition, the CBT group showed significant improvement in sleep quality and a trend to improvement in daily functioning, in contrast to the SH group. The analysis of relationships between changes in the ANT-I measures (alertness and control) and changes in psychological measures (sleep and daily functioning) showed that the improvement in executive functioning was significantly related to changes in sleep.

At Pre-treatment, participants with FM showed the expected impairment in Attention-Alerting and Attention-Executive functioning reported in our previous study (Miró et al., 2010). The two FM groups in the current study showed 115 and 119 ms Attention-Executive functioning, and 63 and 48 ms Attention-Alerting effects, while the control group in our previous study (Miró et al., 2010) showed 82 and 29 ms effects, respectively. The larger alerting effect is usually observed in populations with attentional deficits, and suggests that these subjects take greater advantage of the tone signal than healthy controls because they have difficulties in maintaining alertness without an external signal (Fan et al., 2002). After the treatment, the CBT group showed a significant reduction in the alertness effect as compared with the SH group. This seems to reflect an improvement in the capacity to endogenously maintain the level of activation that is necessary to perform the task, that is, an improvement in vigilance. This conclusion is somehow supported by the fact that, after treatment, the CBT also seems to decrease overall RT, a measure that is usually taken as an index of vigilance.

With regard to executive functioning, after the intervention, the CBT group showed a reduction in the interference effect as compared with the SH group. Sleep processes have strong relationships with executive functioning and attention (Lim and Dinges, 2010), and there is evidence that sleep therapy can lead to an improvement in most of these cognitive domains, as happens in people with sleep apnea or with insomnia (Altena et al., 2008).

Previously, two studies have shown that exercise in a warm-water pool improved attentional function and executive control in FM patients (Munguía-Izquierdo & Legaz-Arrese, 2007, 2008). This training in a warm-water pool included three sessions a week and lasted for 16 weeks, while our CBT program is composed of six sessions, one every week for six weeks. However, before concluding that CBT is more efficient than exercise therapy a detailed cost–benefit analysis is mandatory. As regards the self-reported measures, after treatment FM patients in the CBT group showed a significant improvement in sleep and showed a trend to improvement in daily functioning, as compared with subjects in the SH group. This finding is consistent with Edinger's work, which showed a significant improvement in sleep quality in a

CBT group as compared with SH instructions and usual care (Edinger et al., 2005). Also, Munguía-Izquierdo and Legaz-Arrese (2008) reported an improvement in sleep quality in their exercise group vs the control group. Sleep disturbances in FM are usually treated with tricyclic antidepressants or sleep medications which provide very limited effects and often have adverse consequences (Häuser et al., 2010). Again, our results suggest that a CBT that includes sleep education and cognitive-behavioral strategies for insomnia may be both effective and efficient to improve sleep quality as compared with medications or the longer duration exercise therapy. However, much more research is needed before reaching conclusions about the efficacy of these treatments.

Our data suggest that improvement in cognitive function seems to be related to a positive impact in daily functioning, although the effect was only marginally significant. No significant changes were found in anxiety, depression, or pain between both groups. In Edinger's work, the CBT group showed an improvement in mood state as compared with the remaining groups, but Edinger used the Profile of Mood States while we used the HADS. As in the present study, Munguía-Izquierdo and Legaz-Arrese (2008) did not find any differences in anxiety either after their treatment using the State Trait Anxiety Inventory. The difference seems to lie in testing state vs trait. Improvements in trait rather than state may only appear after a longer period after treatment.

The absence of changes in pain may also be related to the instrument used to measure pain (MPQ). An objective measure of pain may be more sensitive to our intervention. Dick and Rashiq (2007) did not find any changes in the MPQ after procedures resulting in analgesia, while studies that have assessed pain with objective methods (dolorimeter) have found significant changes in the pain threshold after exercise training (Munguía-Izquierdo and Legaz-Arrese, 2007, 2008).

In addition, most studies of CBT that have achieved major psychological improvements in emotional distress and pain have used longer programs and include a much greater intervention (Hassett and Gevirtz, 2009). Moreover, it is important to consider that our results were obtained comparing a group of FM patients who received CBT vs a group of FM patients who received SH. Note that psycho-education is a feature of both interventions. If we had compared our outcome results with a control group, the benefits would probably have been greater. It is known that education conditions such as SH lead to greater improvement than a waiting-list control group (Edinger et al., 2005; Yang et al., 2010).

Regarding the relationships between attentional deficits and psychological measures, we found that changes in executive functioning – but not in alertness – were correlated with the improvement in sleep quality. The improvement in alertness may relate better with other sleep parameters that we have not considered in our study. Further research is needed to understand the relationships between sleep processes and cognitive functioning in FM. Accumulating evidence suggests that FM appears in response to chronic stressors (Oliveira and Costa, 2009) and is associated with a disorder of the neuroendocrine stress response that may influence cognitive function through effects of hypocortisolism on the brain (Sephton et al., 2003). Also, for example, chronic stress produces alterations in prefrontal cortical morphology that may underlie the observed deficits in executive control (Liston et al., 2006). In addition, chronic stress relates strongly to poor sleep quality (Hamilton et al., 2008; Moldofsky, 2010), and the inability to obtain a restorative sleep has been related with prefrontal cortex dysfunction (Jones and Harrison, 2001; Lim and Dinges, 2010).

Several methodological limitations of the present study should be taken into account in future research. First, our findings should be replicated with a larger sample recruited from other contexts. Although the diagnostic reliability of a sample collected from a hospital may be greater, these subjects may also have greater impairment than the participants recruited from

FM associations. Also, requiring participants to undergo many procedures and tests may have reduced the attendance to Post-treatment assessments (e.g. ANT-I). Follow-up assessments are necessary to clarify whether the observed benefits remain over time. In addition, it would be interesting for future trials to include objective measures of pain, a wide range of measures of emotional distress, and monitoring of therapy sessions to ensure fidelity of therapists to treatment protocols.

Furthermore, an added complication of the study of cognitive function in FM is the frequent use in the sample of multiple drugs. Although this might be considered a limitation of the study, it makes our study more representative of a general clinical population. It is important to note that medication was kept constant through all the trial. Nevertheless, the results of the present study should be treated with caution, and replication is called for.

In short, the present study showed that a CBT for insomnia represents a promising intervention not only for sleep disturbance in FM patients but also for attentional dysfunction, and probably for daily functioning. Our trial provides additional evidence for the relevance of sleep in FM. The results of the present study should encourage the use of a more structured intervention for insomnia such as CBT. Similarly, further research should address more specifically whether the combination of the usual CBT treatment with a CBT therapy for sleep may improve current management of FM syndrome.

Competing Interests

None declared.

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ANEXO 8.

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Effects of cognitive-behavioral therapy for insomnia on polysomnographic parameters in fibromyalgia patients[1]

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ABSTRACT. This study aimed to evaluate the efficacy of cognitive-behavioral therapy for insomnia (CBT-I) on polysomnographic parameters in patients with fibromyalgia (FM). Twenty-six women with FM participated in the study and were randomly assigned to a CBT-I (n = 13) group or sleep hygiene (SH) condition (n = 13). The evaluation consisted in two interview sessions and domiciliary polysomnography study before and after treatment. The results show that time-in-bed and wake percentage diminish after CBT-I. Improvements were also observed in sleep efficiency, which was close to normal levels. The percentage of NREM stage 1 sleep decreased and NREM stages 3 sleep and 4 increased. Similarly, light sleep (stages 1 and 2) diminished and deep sleep increased (stages 3 and 4) after CBT-I. No improvements were observed in any of these parameters in the individuals undergoing SH therapy. This randomized controlled trial provides new evidence that the use of CBT-I in FM patients can significantly improve objective sleep parameters.

KEYWORDS. Fibromyalgia. Insomnia. Cognitive-behavioral therapy. Domiciliary polisomnography. Randomized controlled trial.

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RESUMEN. El objetivo de este estudio fue evaluar la eficacia de la terapia cognitivo-conductual para el insomnio (TCC-I) en los parámetros polisomnográficos de pacientes con fibromialgia (FM). Veintiséis mujeres con FM participaron en el estudio y fueron asignadas al azar a un grupo de TCC-I (n = 13) o a una condición de higiene del sueño (HS) (n = 13). La evaluación consistió en dos sesiones de entrevista y un estudio polisomnográfico domiciliario antes y después del tratamiento. Los resultados mostraron que el tiempo en cama y el porcentaje de vigilia disminuyeron después de la TCC-I. Se observaron mejorías en la eficiencia del sueño, acercándose a niveles normales. El porcentaje de etapa 1 del sueño NREM disminuyó y se observó un aumento en las etapas 3 y 4 del sueño NREM. Del mismo modo, el sueño ligero (etapas 1 y 2) disminuyó y el sueño profundo aumentó (etapas 3 y 4) después de la TCC-I. Los sujetos que participaron en la terapia de HS no mostraron ninguna mejoría en ninguno de estos parámetros. Este ensayo controlado aleatorizado proporciona nueva evidencia de que el uso de la TCC-I en pacientes con FM puede mejorar significativamente los parámetros objetivos del sueño.

PALABRAS CLAVE. Fibromialgia. Insomnio. Terapia cognitivo-conductual. Polisomnografía domiciliaria. Ensayo controlado aleatorizado.

Fibromyalgia (FM) is a disorder characterized by widespread musculoskeletal chronic pain and multiple tender points (11 of 18 tender points) (Wolfe *et al.,* 1990). The symptoms of FM are very heterogeneous. Besides pain, up to 96-99% of patients with FM describe fatigue and sleep dysfunction (Lineberger, Means, and Edinger, 2007). They also complain of anxiety, depression, cognitive dysfunction, stiffness, cold sensitivity, irritable bowel syndrome and headaches (Gormsen, Rosenberg, Bach, and Jensen, 2010; Miró *et al.,* in press; Miró, Martínez, Sánchez, Prados, and Medina, 2011; Pérez-Pareja, Sesé, González-Ordi, and Palmer, 2010), with significant negative repercussions on the patient's quality of life (Lledó-Boyer *et al.,* 2010; Sánchez, Martínez, Miró, and Medina, 2011).

The etiology of FM is unknown. Thus, it is currently difficult to have an in-depth understanding of the role of, and relationships between, pain and other symptoms that may accompany this syndrome, and effective treatment is therefore lacking (Häuser, Thieme, and Turk, 2010). A number of hypotheses have been proposed regarding the pathophysiology of FM, including central nervous system dysfunction affecting pain sensitivity, viral infections, immunological causes, neuroendocrine dysfunction, neuromuscular, metabolic or immune system issues, and it has even been suggested that FM is associated with a history of trauma or other psychological disorders (Bradley, McKendree-Smith, Alarcón, and Cianfrini, 2002; Broderick, Junghaenel, and Schwartz, 2005; Gur and Oktayoglu, 2008).

Some authors suggest that sleep disturbances may have an important role in the maintenance of pain and other symptoms of FM (for a review see Moldofsky, 2001, 2002, 2008, 2010). Moreover, Nicassio, Moxham, Schuman, and Gevirtz (2002) analyzed the influence of pain, depression and sleep disorders on fatigue in FM using questionnaires and self-records, and observed multiple relationships between pain, sleep and fatigue,

beyond the prevailing notion that pain is responsible for the other symptoms. Recently, Hamilton *et al.* (2008) reported that sleep duration and sleep quality are prospectively related to affect and fatigue. In addition, inadequate sleep has a cumulative effect on negative mood. In this line, recent clinical and experimental research shows that sleep disturbances have a reciprocal influence on musculoskeletal pain and fatigue (Moldofsky, 2008, 2010). In fact, the American College of Rheumatology has developed diagnostic criteria for FM in which unrefreshing sleep is included as one of the most important diagnostic variables (Wolfe *et al.,* 2010).

Although the presence of abnormal nocturnal sleep in FM has been reported and recognized, its significance with respect to the pathophysiology of the syndrome is debated. Also, sleep recordings are rarely used for evaluation in these patients and sleep disturbance is often considered a consequence of pain (Spitzer and Broadman, 2010).

Most research studies that have used subjective measures of sleep (mainly self-reports) mention the poor subjective quality of sleep in FM patients. Thus, for example, 99% of FM patients in the study by Theadom, Cropley, and Humphrey (2007) reported poor sleep quality measured using the Pittsburgh Sleep Quality Index (PSQI). Also, in this study sleep quality was significantly predictive of pain, fatigue, and social functioning in patients with FM. Osorio, Gallinaro, Lorenzi-Filho, and Lage (2006), also using the PSQI, observed that patients with FM achieved higher scores than healthy controls in all the PSQI components except *Use of sleep medications*.

Different alterations have been identified by polysomnography (PSG) in patients with FM, although not all research results are consistent. Specifically, it has been described that these patients display shorter total sleep time, greater sleep latency, more awakenings, less sleep efficiency, higher percentages of non-rapid eye movement (NREM) stage 1 sleep, greater fragmentation of sleep, lower percentages of REM (rapid eye movement) sleep and shorter NREM sleep stages 3 and 4 compared with healthy controls (Besteiro *et al.,* 2011; Dauvilliers and Carlander, 2007; Moldofsky, 2001, 2008; Roizenblatt, Moldofsky, Benedito-Silva, and Tufik, 2001). A recent study used actigraphy, showing that female FM patients with objective sleep deficits (less than 6 hours of sleep) presented significantly lower sleep efficiency, significantly longer sleep onset latency and significantly shorter nighttime sleep times than women without sleep deficits (Stuifbergen, Phillips, Carter, Morrison, and Todd, 2010).

In terms of the microstructure of sleep in FM, observed alterations include alpha-delta intrusions, as well as regular K-alpha intrusions, decreased sleep spindles, larger number of oxygen desaturations per hour of sleep and twice as many arousals per hour of sleep than controls, with an alternating cyclic pattern associated with severity of pain and low sleep efficiency (Lineberger *et al.*, 2007; Rizzi *et al.*, 2004). Moldofsky in 1975 was the first to suggest, through polysomnography, that the presence of alpha intrusions in deep delta sleep could be related with the set of symptoms known as FM. Other studies have also reported these alpha intrusions in slow-wave or NREM sleep, as well as different changes indicative of sleep fragmentation (Lineberger *et al.*, 2007; Moldofsky, 2001; Roizenblatt *et al.*, 2001). The alpha sleep pattern in FM has been associated with longer duration of pain symptoms, a perception of generally unrestful sleep and the

presence of pain when getting up in the morning (Lineberger *et al.*, 2007; Moldofsky, 2008).

As regards treatment, a recent review of the latest Clinical Practice Guidelines on the treatment of FM of the American Pain Society (APS) (Burckhardt *et al.*, 2005), the European League Against Rheumatism (EULAR) (Carville *et al.*, 2008) and the Association of the Scientific Medical Societies in Germany (AWMF) (2008) (Häuser *et al.,* 2010), recommend that FM be treated using a multidisciplinary approach combining aerobic exercise, cognitive-behavioral therapy (CBT), amitriptyline and multicomponent treatments (Häuser *et al.*, 2010). However, although it is accepted that sleep alteration is one key symptom of FM, the treatment of sleep alterations is not covered in current clinical guidelines on this syndrome. In most cases, such guidelines only include sleep hygiene (SH) instructions and pharmacological therapies to treat such alterations, but other much more effective cognitive-behavioral therapy for insomnia techniques (CBT-I) are not applied (Edinger, Wohlgemuth, Krystal, and Rice, 2005; Miró, Sánchez, and Buela-Casal, 2003; Pigeon, 2010).

In existing literature, two pilot studies have shown that CBT-I may improve sleep (Edinger *et al.*, 2005; Miró, Lupiañez *et al.,* 2011). In this first study, Edinger *et al.* (2005) compared sleep and other symptom improvements in FM patients who received CBT-I, sleep hygiene (SH) or only usual care: 57% of the CBT-I group reported significantly improved sleep quality and mood, compared with 20% of the SH group and 3.5% of the medication therapy group. However, Edinger *et al.* (2005) used different subjective scales and actigraphy, which are less reliable than polysomnography (PSG). Recently, Miró, Lupiañez *et al.* (2011) compared CBT-I with SH and observed greater improvements not only in sleep quality but also in attention function and daily functioning in the CBT-I group. However, these studies did not use PSG records to evaluate changes in sleep quality.

In summary, sleep alterations are one of the most prevalent symptoms in FM. Several studies have suggested that an improvement in sleep quality could be associated with a positive change in pain, fatigue and daily functioning. Therefore, determining whether CBT-I can improve not only subjective sleep quality but also objective sleep parameters is crucial to establish the clinical utility of this intervention. Thus, the aim of this study was to evaluate the efficacy of CBT-I on polysomnographic parameters in patients with FM compared to a control group that received SH.

Method

Participants

Twenty-six women with FM (M = 46.79 years of age, SD = 5.15) participated in the study and were assigned to a CBT-I group (n = 13; M = 44.83, SD = 5.30) or a sleep hygiene (SH) condition (n = 13; M = 48.75, SD = 4.37). Simple randomization (1:1) was implemented by a computerized number generator designed by an investigator with no clinical involvement in the trial. The clinical sample was selected from the Rheumatology Service and Pain Unit of the *Hospital Universitario Virgen de las Nieves* in Granada

(Spain). The mean duration of the illness was 5.02 years ($SD = 4.28$), although the mean onset of symptoms was greater ($M = 12.96$ years; $SD = 8.33$). The women who were fulfilling the inclusion criteria to participate in the study (see Table 1) were referred from the hospital at the Clinical Psychology Unit of the Faculty of Psychology (University of Granada), where three psychologist therapists conducted both assessment and treatment (CBT-I and SH) to patients with FM. All participants were informed about the characteristics of the study and an informed consent was obtained. The study received ethical approval from the University of Granada Ethics Committee.

TABLE 1. Inclusion and exclusion criteria established for participation in the study.

Inclusion criteria
1. Age between 25 and 60 years old.
2. Met the diagnostic criteria for FM as defined by the American College of Rheumatology (ACR) (Wolfe *et al.*, 1990).
3. Have chronic insomnia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, American Psychiatric Association, 2000).
Exclusion criteria
1. Currently pregnant.
2. Medical history of significant head injury or neurological disorder.
3. Concomitant major medical conditions (e.g., inflammatory rheumatic diseases, endocrine disturbances).
4. Major depressive disorder with severe symptoms or suicide ideation, or other major Axis I diagnoses of the DSM-IV-TR (American Psychiatric Association, 2000).
5. Severe hypnotic dependence.
6. Having symptoms of sleep-disruptive comorbidities with insomnia.
7. Having an apnea-hypopnea index or periodic limb movement (PLM) related arousal index of 15 or more per hour on a polisomnography (PSG) recording.
8. To be receiving another psychological or physical therapy at the time of the study.

Measures. Polysomnography (PSG)

A domiciliary PSG recording (with a SomnoScreen PSG-Tele, SomnoMedics) was used to collect information from key sleep parameters in patients with FM. The PSG recordings included electroencephalography in the frontal, central, parietal, and occipital regions (F_Z/A1, C_Z/A1, P_Z/A1, O_Z/A1), bilateral electrooculography, bilateral submental and anterior tibial electromyography and respiratory variables (chest belt, respiratory thermistance and oximetry). Sleep stages were scored visually according to the criteria of Rechtschaffen and Kales (1968) using 30 seconds' epochs. Table 2 contains a brief description of the sleep variables analysis.

TABLE 2. Sleep variables analysis in the PSG.

Time in bed (TIB) (hours)	Period of time between bedtime and awakening in the morning.
Total sleep time (TST) (hours)	Equal to total sleep period less movement and awake time.
Wake percentage	Percentage of time awake scored from bedtime to the final wake-up.
% REM	Total time spent in REM sleep as a percentage of TST.
Stage 1, 2 3 and 4 percentages	Total time spent in stage 1, stage 2, stage 3 and stage 4 sleep as a percentage of TST.
Light sleep	(stages 1+2).
Deep sleep	(stages 3+4).
Sleep efficiency	The proportion of sleep in the period potentially filled by sleep: ratio of TST to TIB as a percentage.
NREM sleep latency	The time period measured from bedtime to the beginning of sleep.
REM latency	The period of time from sleep onset to the first appearance of REM sleep.
REM density	Average rate of the whole REM phase with mini REM epochs (3 sec.).
Number of awakenings > 3 minute (index)	Number of wake periods longer than 3 minute during TIB (index: per hour of sleep).
Wake after sleep onset	Time spent awake after sleep onset had occurred.
Arousals index	The average number of arousals per hour of sleep.

Procedure

The evaluation and therapeutic treatment (CBT-I and SH) of sleep disorders in patients with FM was carried out at the Clinical Psychology Unit of the Faculty of Psychology. The whole evaluation consisted of two sessions of individual interviews focusing on the origin and evolution of the problem and domiciliary PSG. Three female CBT experts with experience in FM provided the therapy guided by a treatment manual designed for the study. Each therapist applied both treatments (CBT-I and SH). Therapists delivered CBT-I and SH treatment in 6 weekly groups sessions. Each session included 5-6 participants and lasted around 90 minutes. The CBT-I program was designed according the works of Edinger *et al.* (2005), and met the recommendations of the American Academy of Sleep Medicine (Morgenthaler *et al.,* 2006). Subjects who participated in SH therapy just received sleep hygiene instructions and were offered CBT-I after their post-treatment assessment. The contents of the SH therapy can be seen in Table 3. Also, all patients continued with their usual medical treatment for FM. All participants were on stable doses of medication during the trial (see Table 4). On the consumption of medicaments, 4 patients in the CBT-I group and 2 patients in the SH group consumed occasionally benzodiazepines (less than once a week). Moreover, most patients in both groups consumed regularly non-benzodiazepine anxiolytics (those patients with severe hypnotics dependence were excluded from the study), and antidepressants. In relation to the latter category of medicaments, although they can affect sleep, we must specify that patients had taken these medicaments for months before the psychological interventions, so we think that the possible effect on sleep was controlled.

TABLE 3. Contents of the CBT-I treatment and SH therapy.

	CBT-I sessions	*SH sessions*
Session 1	Information about the relationship between sleep and FM, basic notions about sleep (*e.g.*, sleep stages, sleep functions, effects of sleep deprivation on wake functioning, explanation of insomnia) and SH education.	Participants were given the same information about sleep as the CBT-I group.
Session 2	Sleep restriction therapy combined with stimulus control instructions.	Sleep hygiene rules related to environmental factors.
Session 3	Relaxation training (a combination of passive relaxation and imagery training).	Lifestyle factors that influence sleep (consumption of stimulants and other substances).
Session 4 and 5	Cognitive therapy for the dysfunctional beliefs related to insomnia.	Information about diet and physical exercise, respectively.
Session 6	Maintaining achievements and preventing relapses.	Similiar as the CBT-I group.

Study desing and statistical analysis

This was a controlled randomized trial or "experimental design with an independent variable (IV) and random groups" in which the IV was the type of treatment to be received by the subjects (CBT-I and SH). Statistical analysis was performed using SPSS 15.0 for Windows. Non-parametric statistical tests were used because they are recommended when the sample size is less than 15 (Bryman and Cramer, 1990). To compare the groups on demographic and clinical variables at baseline the Mann-Whitney's *U* test for interval data and the Pearson chi-square (χ^2) test for nominal data were computed. In order to examine the therapeutic changes between-group in PSG parameters the Mann-Whitney's *U* test was used. Finally, the therapeutic changes intra-group in PSG parameters were analyzed via the Wilcoxon test.

Results

Table 4 shows the demographic and clinical characteristics of the FM sample. The results of the non-parametric tests performed (Mann-Whitney's *U* and the Pearson chi-square test, showed that the two groups (CBT-I *vs*. SH) did not differ significantly in terms of age, marital status and work, education, and clinical variables such as years since diagnosis of FM, insomnia or type of insomnia problem and drug intake (all $p > .05$).

TABLE 4. Demographic and clinical characteristics of the FM sample completing the domiciliary PSG study.

Variable	*Total sample (n=26)*	*CBT-I group (n=13)*	*SH group (n=13)*	*p value*
Age, mean (SD)	46.79 (5.15)	44.83 (5.30)	48.75 (4.37)	.07
Education (%)				.08
Basic education	31.8	18.2	45.5	
High school	27.3	45.5	9.1	
Professional instruction	22.7	9.1	36.4	
University studies	18.2	27.3	9.1	
Marital status (%)				.386
Married	92.3	92.3	92.3	
Single	3.8	0	7.7	
Divorced or widowed	3.8	7.7	0	
Work status (%)				.094
Currently employed	50.0	69.2	30.8	
Unemployed	23.1	7.7	38.5	
Disabled	26.9	23.1	30.8	
Duration of FM (years), mean (SD)	5.02 (4.28)	4.67 (3.66)	5.34 (4.91)	.913
Duration of sleep problem (years), mean (SD)	11.25 (9.08)	11.41 (9.24)	9.85 (8.23)	.682
Nature of sleep problem				
Onset (%)	69.3	69.3	69.5	.884
Maintenance (%)	84.6	84.7	84.6	.836
Early awakening (%)	76.9	69.3	84.6	.661
Drug intake (%)				
Antidepressants	50.0	45.5	53.8	.682
Anxiolytics	63.6	61.5	62.5	.916
Anti-inflammatory	63.6	69.2	66.7	.772
Analgesics	72.7	69.2	70.8	.851

Table 5 shows PSG variables before and after CBT-I or SH therapy. As can be seen, the results of the Mann-Whitney's *U* test indicate that prior to treatment there were no statistically significant differences in any of the PSG variables between the two groups (CBT-I and SH) (*U* values between 75.00 and 84.00, $p > .05$). Secondly, a Wilcoxon test was carried out to determine whether there were any differences in the PSG variables analyzed pre-post treatment in each treatment group (CBT-I and the SH). The results for the active treatment group receiving CBT-I showed a decrease in time-in-bed [$z = -2.62$, $p < .01$] and wake percentage [$z = -2.41$, $p < .05$] after treatment. Thus, sleep efficiency [$z = -2.41$, $p < .05$] improved, almost reaching normal levels. As regards sleep architecture, the results revealed a decrease in the percentage of non-rapid eye movement (NREM) stage 1 sleep [$z = -2.90$, $p < .01$] and an increase in the percentage of NREM stage 3 sleep [$z = -2.20$, $p < .05$] and NREM stage 4 sleep [$z = -2.19$, $p < .05$]. No differences were observed between pre-post treatment in the percentage of REM sleep [$z = -.17$, $p = .86$] and NREM stage 2 sleep [$z = -1.15$, $p = .24$]. In addition, the results showed light sleep (NREM stages 1 and 2) decreased [$z = -2.20$, $p < .05$] and deep sleep (NREM stages 3 and 4) increased [$z = -2.55$, $p < .01$] after CBT-I. No differences were observed in sleep duration (hours) [$z = -1.37$, $p = .12$], NREM sleep latency [$z = -1.49$, $p = .136$], REM latency

[z = -1.17, p= .23], % REM density [z = -.31, p= .75], wake after sleep onset [z = -.31, p= .75], number of awakenings greater than 3 minutes [z = -1.67, p = .09] and arousal index [z = -.80, p = .42]. Subjects participating in SH group therapy showed no significant improvements (z values between -1.50 and -.15, p > .05). Finally, we checked for significant differences in PSG sleep parameters post-treatment between the CBT-I group *vs.* HS group. The Mann-Whitney's U test revealed statistically significant differences in three of the PSG variables analyzed, namely % NREM stage 1 sleep [U = 44.50, p < .05], % stage 4 sleep [U = 48.00, p < .05] and deep sleep (NREM stages 3 and 4) [U = 44.50, p <.05]. As can be seen in the mean scores (table 5), in the CBT-I group, a lower percentage of NREM stage 1, and a higher percentage of NREM stage 4 and deep sleep (stage 3 and 4) were observed, compared with the group that received only HS.

TABLE 5. Polysomnographic measures of the group assigned a cognitive-behavioral therapy for insomnia (CBT-I) and the group sleep hygiene (SH).

	CBT-I group			*SH group*			*CBT-I vs. HS*	*CBT-I vs. HS*
	Mean (Standard deviation)			*Mean (Standard deviation)*			*Pre-treatment*	*Post-treatment*
PSG variables	*Pre-treatment*	*Post-treatment*	*Z*	*Pre-treatment*	*Post-treatment*	*Z*	*U*	*U*
Total sleep time (hours)	7:03 (1:04)	6:53 (2:19)	-1.37	7:31 (0:54)	6:57 (0:55)	-1.21	84.00	77.00
Time in bed (hours)	8:54 (0:40)	8:21 (0:53)	-2.62**	8:31 (0:53)	7:45 (1:10)	-1.50	68.00	68.00
Wake percentage	15.51 (9.38)	12.51 (9.47)	-2.41*	11.56 (6.18)	10.06 (3.67)	-.52	64.00	77.00
% REM	23.88 (6.22)	23.83 (5.66)	-.17	22.02 (6.30)	25.43 (9.72)	-1.50	75.00	76.00
% Stage 1	6.89 (4.20)	4.55 (2.23)	-2.90**	6.50 (3.02)	7.00 (2.87)	-.80	80.00	44.50*
% Stage 2	54.05 (9.44)	50.74 (9.28)	-1.15	52.71 (7.50)	52.51 (7.78)	-.80	77.00	70.50
% Stage 3	10.20 (3.93)	13.17 (4.75)	-2.20*	11.24 (4.40)	11.36 (5.91)	-.21	77.00	72.00
% Stage 4	4.81 (3.67)	7.43 (5.56)	-2.19*	4.51 (4.55)	3.62 (3.82)	-.96	78.00	48.00*
Light sleep	60.95 (9.88)	55.26 (9.64)	-2.20*	62.20(7.78)	59.53 (8.24)	-.94	72.00	57.50
Deep sleep	15.03 (5.68)	20.58 (8.41)	-2.55**	15.76 (6.53)	14.97 (7.36)	-.31	81.00	44.50*
Sleep efficiency	84.48 (9.39)	87.48 (9.47)	-2.41*	88.43 (6.18)	89.29 (3.67)	-.52	64.00	77.00
NREM sleep latency	0:27 (0:24)	0:24 (0:45)	-1.49	0:19 (0:16)	0:15 (0:13)	-.80	58.00	74.00
REM latency	1:53 (0:55)	1:35 (0:56)	-1.17	2:05 (1:15)	1.55 (1.34)	-.15	64.00	83.00
% REM density	13.00 (8.57)	13.00 (6.32)	-.31	9.46 (9.78)	9.85 (6.40)	-.26	64.50	56.55
Nº of awakenings > 3 min.	3.33 (2.09)	2.15 (2.37)	-1.67	2.15 (1.62)	1.77 (1.92)	-.73	61.50	77.50
Wake after sleep onset	0:40 (0:18)	0:36 (0:23)	-.31	0.31 (0.22)	0.31 (0.20)	-.94	79.00	76.00
Arousals	10.55 (4.34)	13.18 (15.35)	-.80	13.86 (9.28)	13.56 (13.82)	-.94	74.00	80.00

* p < .05; ** p < .01

Discussion

This clinical trial provides new evidence that the use of CBT-I in women with FM can improve objective sleep disturbance parameters. The few studies identified in the literature that have used PSG to evaluate sleep in patients with FM have reported relevant findings, including shorter total sleep time, greater sleep fragmentation, greater sleep latency, less sleep efficiency, an increase in NREM stage 1 sleep and a reduction of the quantity of NREM stage 3 and 4 sleep compared with healthy controls (Besteiro *et al.*, 2011; Moldofsky, 2001, 2008; Roizenblatt *et al.*, 2001). Moldofsky's studies in the seventies showed that patients with FM did not reach NREM sleep stages 3 and 4, *i.e.* the deepest and most restful phases of sleep. Research comparing sleep problems in patients with FM with those observed in other chronic pain diseases, including rheumatoid arthritis, have found that FM patients reported more insomnia, less contentment with sleep and more lack of deep and restful sleep in comparison to rheumatoid arthritis patients (Belt, Kronholm, and Kauppi, 2009).

In the present study, patients with FM showed at pre-treatment sleep onset insomnia, maintenance and early awakening (see Table 4). However, upon completion of treatment, the CBT-I group evidenced improvements in sleep efficiency to almost normal levels and a decrease in wake percentage and time-in-bed. Significant changes were also observed in sleep architecture; specifically, a decrease in the percentage of NREM stage 1 sleep and an increase in the percentage of NREM stages 3 and 4 sleep. Similarly, light sleep (NREM stages 1 and 2) decreased, accompanied by increased deep sleep (NREM stages 3 and 4). Despite the small size of the sample, the results showed objective evidence of a change in sleep features. Therefore, although no changes were observed in the total sleep time of patients with FM, significant differences were observed in the percentages of deepest sleep, which increased after intervention, and a decrease the percentage of wake that provided the most restful sleep. Although both sleep quality and sleep quantity parameters are relevant, the association with different health indicators is stronger in the case of the former (Miró, Cano Lozano, and Buela Casal, 2005; Pilcher and Ott, 1998). Deep sleep (stages 3 and 4) has been related with corporal and neurological restoration, and these stages are closely related to the correct immune system functioning (Buela-Casal and Miró, 2001). The improvement in these phases observed in this study could have a great positive impact on other symptoms of FM and on the actual severity of the syndrome. However, further research is necessary in order to determine how these changes in objective sleep parameters are related to the improvement of other FM symptoms. Moreover, time-in-bed decreases and sleep efficiency increases, indicating an improvement in SH. These clinical parameters are normally used as evidence of improvements in sleep in insomnia treatment studies (Morin and Espie, 2003).

In this study, the patients in the SH therapy group showed no improvements in any parameter. These findings do not coincide with those reported elsewhere in the literature. For example, in a recent study Miró, Lupiañez *et al.* (2011) reported that 55% of the subjects in their SH group displayd significant clinical changes in sleep quality compared with 85% in the CBT-I group. Edinger *et al.* (2005) also reported that the participants receiving SH therapy had reduced their nocturnal wake time by nearly 20% at the end of the study, compared with a 50% decrease in patients receiving CBT-I therapy. Patients receiving CBT-I also showed a higher rate of sleep improvement (57%) compared with patients in SH therapy (17%). A possible explanation for these results may be the evaluation instruments used. In our study, the pre- and post-treatment changes observed in sleep variables after the application of CBT-I and SH therapy were evaluated using polysomnographic measurements, whereas in the aforementioned studies measurements were taken using actigraphy and subjective measurements that provided different and complementary information to polysomnography. Many studies in the literature argue that therapy groups based on education (*e.g.*, sleep hygiene) produce improvements, albeit more modest than those obtained with more structured therapy groups. SH may slightly improve the subjective sensation of sleeping better but it is not a sufficiently powerful treatment to change objective sleep parameters (for review about use of sleep hygiene in the treatment of insomnia see Stepanski and Wyatt, 2003).

Moreover, some studies have also examined CBT-I with chronic pain patients and obtained positive results, but basically using questionnaires. Previous studies have suggested that improving sleep quality (rapid sleep onset, absence of early awakening and restorative sleep) in chronic widespread pain subjects could decrease pain (Davies *et al.*, 2008), as well as impact on daily life functioning and depression. In osteoarthritis patients, Vitiello, Rybarczyk, Von Korff, and Stepanski (2009) observed that patients receiving CBT-I reported significantly decreased sleep latency and wake after sleep onset and increased sleep efficiency after treatment, compared with before treatment. They also reported significantly reduced pain. One-year follow-up found maintenance of improved sleep (in sleep latency and wake after sleep onset and increased sleep efficiency and total sleep time) and reduced pain in the CBT-I group. Finally, a recent study conducted for Jungquist *et al.* (2010) shows that CBT-I can significantly improve sleep and daily functioning in patients suffering from chronic neck or back pain. After eight weeks, participants reported significant improvements in sleep quality and also a reduction in the extent to which pain interfered in daily activities. Specifically, subjects receiving CBT-I compared with controls (who did not receive directed form of therapy was provided for pain, depression, or sleep disturbance) exhibited significant decreases in sleep latency (time to fall asleep), wake after sleep onset, number of awakenings and significant improvements in sleep efficiency (Jungquist *et al.*, 2010).

However, although our study shows that CBT-I improves sleep quality in FM patients, evidenced by increased deep sleep and efficiency and decreased light sleep and awakenings, little research has been carried out into the therapeutic potential of CBT-I in these patients. Moreover, sleep problems in FM are treated, indirectly, with analgesic medication (opioids, tricyclic antidepressants or anticonvulsants) and sedative hypnotics that promote sleep through analgesic and soporific effects (Smith and Haythornthwaite, 2004). These effects may increase sleep quantity but do not usually reduce sleep complaints. Hence, since current medication is unable to improve sleep quality, pain intensity or quality of life, it seems obvious that CBT-I is a promising treatment option for inclusion in current FM treatments.

It is important to recognize various additional limitations in the interpretation of the results obtained in this study. Firstly, the size of the sample. However, in spite of the small size of the sample, results showed changes in PSG sleep variables. Another limitation is the frequent use of different medication. Most patients in our study took antidepressants, analgesic or anxiolytic medication during treatment. However, and although this may be considered a limitation of the study, it is important to remember that the medication was maintained constant throughout the entire trial. Although there was a random allocation of patients to treatment groups, another limitation of the study is the lack of uniform distribution of employment status in groups (although the differences are not statistically significant). Finally only women were included in this study since prevalence is lower in men.

To summarize, CBT-I may be a promising sleep therapy for FM patients. However, further research is necessary in the future to replicate these results with larger samples

of FM patients, as well as in patients recruited in other contexts, such as patients' associations. Another future line of research could focus on establishing the relative efficacy of CBT-I compared with common psychological and medical treatment and determining what the study of sleep can contribute to current psychological treatment, in order to improve the symptoms and the quality of life of these patients. Finally, future studies must be carried out using PSG to analyze how treatment can improve different variables, including pain, daily functioning and cognitive function, and their relationships with the improvements observed in sleep parameters.

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