A. 研究背景

本邦一般人口の5人に1人が不眠の訴えを持ち、20人に1人が睡眠薬を使用している。増加の一途を辿って医療経済を圧迫している睡眠薬市場を抑制するために、不眠症に対する非薬物療法の確立と普及は、喫緊の課題である。慢性不眠症の中核は、DSM-IVの原発性不眠症(ICSD-IIの精神生理性不眠症)であり、欧米における原発性不眠症に対する標準的な治療法は、認知行動療法(cognitive behavioral therapy for insomnia; CBT-I)である。CBT-Iによって慢性不眠症患者の70～80%で症状が軽減し、治療終了半年後にも効果が維持され、睡眠薬の減量にも有用であることが実証されている。本邦の『不眠症診断・治療・医療連携ガイドライン』も、治療的初期対応(睡眠衛生指導と適切な薬物療法)で改善が認められない難治例に対して、CBT-Iの導入を推奨している。しかし、その臨床実践は、端緒を開いたに過ぎず、未熟な段階にあると言わざるを得ない。

当院では最近の10年間ほどかけて、慢性の不眠症患者に対してCBT-Iを試行してきた。当初の個人療法のCBT-Iから、2009年以降は集団認知行動療法(group cognitive behavioral therapy for insomnia; g-CBT-I)に移行している。本年度の分担研究は、g-CBT-Iにおける睡眠時間制限法に焦点を当てて、非薬物療法としての意義や適応について検討した。

B. 研究目的

慢性の不眠症(DSM-IVの原発性不眠症、ICSD-2の精神生理性不眠症)に対するg-CBT-Iの効果について、その構成要素である睡眠時間制限法に焦点を当てて、非薬物療法としての意義や適応について検討することを目的とする。

C. 研究方法

対象は、東京慈恵会医科大学付属病院精神神経科睡眠障害専門外来を受診し、g-CBT-I施行した慢性(原発性、精神生理性)不眠症患者33例である。全例とも、主治医からの申し出に対するg-CBT-I施行希望者であり、男性/女性：16/17、平均年齢(以下、±標準偏差)58.4±13.8歳、平均罹病期間6.8±6.2年、ベンゾジアゼピン系睡眠薬の平均投与量1.8±1.0mg(フルニトラゼパム1mg換算)、平均修学期間14.7±1.9年などを背景因子とする(表.1)。

表.1 対 象

精神生理性不眠症 (ICSD-2) 33例
参加に同意した 39名中 6名が脱落
(3名は身体科入院のため / 3名は希望により中止)

CBT導入時年齢 (歳)	性別	罹病期間 (年)	投与薬物量 (mg) FNZ1mg=1	修学期間 (年)
58.4±13.8 [30 - 81]	16/17 M/F	6.8±6.2 [0.1 - 21]	1.8±1.0 [0.3 - 4]	14.7±1.9 [9 - 18]

抗うつ薬併用例：8例 (24.2%)
施行前BDI：9.5±5.8 (極軽症)

g-CBT-I(1グループ3～5人、計2回の講義と討論、1回の個人面接)の構成要素は、刺激調整法、睡眠時間制限法、認知的介入、睡眠衛生指導からなり、施行者は、両群共に睡眠医療を専門とする精神神経科医師であった。

g-CBT-I施行前と施行後1か月時点で、睡眠日誌、ピッツバーグ睡眠質問票(PSQI-J)、睡眠に対する非機能的な信念と態度質問票(DBAS-J)を主観的評価として、腕時計型活動量連続測定計(活動計)を客観的評価として測定

した。対象を、睡眠時間制限法に基づいて施行前1週間の睡眠日誌から算出された総就床時間の主観的評価が、施行後1か月後の測定において、総就床時間±15分の範囲、あるいは、主観的な睡眠効率が85%以上を示した睡眠時間制限法に関する達成群15例と、それ以外の非達成群18例の2群に分類し、背景因子や各評価項目を比較検討した。

統計学的手法として、Fisher's exact probability test、Wilcoxon符号付順位検定、Mann-Whitney's U testを用いて解析した。

[倫理面への配慮]

本研究の研究計画に関して、本学の倫理委員会において審査され、その実施について承諾されている。

D. 研究結果

1. 臨床的特徴 (表2)

達成群は非達成群に比して、有意に男性が多い結果となった。その他、年齢、修学期間、不眠症罹病期間、施行前の睡眠薬投与量及び施行後6ヶ月で判定した治療転帰に両群間で差異は認められなかった。

表.2 達成群と非達成群の比較 ― 臨床的特徴

【性別】

n=33	達成群 (n=15)	非達成群 (n=18)
男 性 (人)*	11	5
女 性 (人)	4	13

【背景因子】

年齢 (歳)	57.4±16.2	59.2±11.8
修学期間 (年)	14.9±2.4	14.6±1.5
罹病期間 (年)	8.2±6.9	5.6±5.4
投薬量 (mg)	2.0±1.4	1.5±0.8

【6か月後治療転帰】

終 結 (人)	6	4
継 続 (人)	9	12
不 明 (人)	0	2

Fisher's exact probability test * :p<0.05

2. 睡眠日誌(主観的睡眠内容) (表3)

達成群では、g-CBT-I施行前に比較して施行後に、有意な離床時刻の前進、総就床時間の短縮、睡眠効率の増加、入眠潜時の短縮が認められた。一方、非達成群では、g-CBT-I施行前に比較して施行後に、有意な離床時刻の前進、総睡眠時間の延長、総就床時間の短縮及び睡眠効率の増加が認められた。

表.3 達成群と非達成群の比較 ― 睡眠日誌

n=33	達成群(n=15)		非達成群(n=18)	
< 睡眠日誌 >	pre-CBT	post-CBT	pre-CBT	post-CBT
就床時刻 (時)	23.8±1.5	23.9±1.1	23.4±1.1	23.6±1.0
離床時刻 (時)	7.4±1.1	6.8±1.1 **	7.3±1.2	7.0±1.3 *
総睡眠時間 (分)	348.2±61.5	359.1±38.9	324.9±58.3	346.2±42.1 *
総就床時間 (分)	458.1±74.6	413.5±43.7 *	472.1±35.1	446.2±38.4 *
睡眠効率 (%)	76.1±8.1	86.9±4.2 ***	68.5±9.6	77.6±6.4 ***
入眠時刻 (時)	24.4±1.3	24.3±1.1	24.5±1.6	24.3±1.1
覚醒時刻 (時)	6.2±1.2	6.4±1.1	6.0±1.7	6.1±1.4
入眠潜時 (分)	36.1±21.2	23.8±12.1 *	62.1±38.4	42.7±16.1

Wilcoxon符号付順位検定 * p<0.05 ** p<0.01 *** p<0.005 **** p<0.001

3. 活動計(客観的睡眠内容) (表4)

達成群では、g-CBT-I施行前に比較して施行後に、睡眠効率の有意な増加が認められた。同一日の睡眠日誌と活動計の乖離に関して、施行前に比較して施行後に、達成群では覚醒時刻と総睡眠時間の乖離が減少し、非達成群では入眠潜時と総睡眠時間の乖離が減少した。

表.4 達成群と非達成群の比較 ― 活動計

n=33	達成群(n=15)		非達成群(n=18)	
<アクチグラフ>	pre-CBT	post-CBT	pre-CBT	post-CBT
TST (min)	388.7±56.4	366.5±41.4	412.2±57.2	396.7±49.2
SE (%)	86.5±6.7	90.8±4.8 *	87.3±8.9	89.0±8.0
SONT (hr)	24.1±1.5	24.3±1.2	23.8±1.2	24.0±1.0
SOFT (hr)	6.8±1.1	6.6±1.1	6.9±1.4	6.8±1.4
SOL (min)	19.9±12.9	17.4±13.1	17.3±9.8	18.2±13.3
NOA (times)	1.6±1.2	1.4±0.8	1.5±0.8	1.2±0.9
WASO (min)	19.0±17.1	14.6±10.9	12.7±5.4	10.3±8.2
MT (counts/min)	9.7±4.5	8.5±3.4	7.0±3.0	7.2±3.5
dissociation SONT (min)	16.4±23.6	4.2±17.5	43.7±30.9	25.5±19.8
dissociation SOFT (min)	-39.3±40.4	-17.2±17.6 *	-50.2±43.6	-36.6±27.8
dissociation SOL (min)	17.9±23.5	6.4±14.2	47.3±29.6	24.2±19.5 *
dissociation TST (min)	-43.0±43.9	-10.9±28.1 **	-89.3±41.2	-52.8±27.6

TST; total sleep time, SE; sleep efficiency, SONT; sleep-onset time, SOFT; sleep-offset time, SOL; sleep onset latency, NOA; the number of awaking episodes lasting more than 5 min, WASO; awaking time after sleep onset, MT; moving time during sleep.

Wilcoxon符号付順位検定 * p<0.05 ** p<0.01 *** p<0.005

4. PSQI-J、DBAS-J、投薬量 （表 5）

達成群、非達成群ともに、施行前に比較して施行後には、睡眠薬投与量が有意に減少し、DBAS-J の下位項目のいくつかで有意な低下が認められた。一方で、PSQI-J 総得点は、達成群のみで、施行前に比較して施行後の有意な減少が認められた。

表.5 達成群と非達成群の比較 ― PSQI/DBAS/投薬量

n=33	達成群(n=15)		非達成群(n=18)	
	pre-CBT	post-CBT	pre-CBT	post-CBT
PSQI-J Total	11.4±2.3	8.5±3.5 ***	13.1±2.8	11.6±3.1
DBAS-J				
不眠の影響に対する不安	55.0±18.1	47.3±23.9	58.9±24.4	46.7±23.0
睡眠を制御できない不安	43.5±15.0	33.9±18.4 ***	51.4±18.6	41.7±21.8 *
睡眠に対する適切な期待	35.5±13.3	32.8±13.4	39.4±20.5	30.4±19.3 *
不眠の原因に対する誤解	30.8±23.1	32.1±21.5	36.6±26.7	31.5±22.0
眠るための適切な努力	29.8±13.7	24.5±16.0 *	33.9±14.7	30.8±14.8
投薬量（mg）	2.0±1.4	1.6±1.7 *	1.5±0.8	1.1±0.6 ***

Wilcoxon符号付順位検定 * p<0.05 *** p<0.005

5. g-CBT-I 施行前における両群間の比較

（表 6）

g-CBT-I 施行前における各指標について、達成群は非達成群に比較して、男性が多く、主観的入眠潜時が短く、客観的夜間体動量が多く、また、入眠潜時と総睡眠時間に関する主観的評価と客観的評価の乖離度が少ない、などの所見が得られた。

表.6 達成群と非達成群の比較の比較 ― CBT施行前

< pre-CBT > n=33	達成群（n=15）	非達成群（n=18）
男性（人） *	11	5
女性（人）	4	13
罹病期間（年）	8.2±6.9	5.6±5.4
投薬量（mg）FNZ1mg=1	2.0±1.4	1.5±0.8
睡眠効率（%）	76.1±8.1	68.5±9.6
SE（%）	86.5±6.7	87.3±8.9
入眠潜時（分）*	36.1±21.2	62.1±38.4
SOL（min）	19.9±12.9	17.3±9.8
dissociation SOL（min）*	17.9±23.5	47.3±29.6
dissociation TST（min）*	-43.0±43.9	-89.3±41.2
WASO（min）	19.0±17.1	12.7±5.4
MT（counts/min）*	9.7±4.5	7.0±3.0

Fisher's exact probability test, Mann-Whitney's U test *p<0.05

E. 考察

CBT-I の構成要素の中で、行動療法的技法である睡眠時間制限法は中核的な存在であり、その効果サイズの高さが指摘されている。今回の検討では、漸進的筋弛緩法を含まない g-CBT-I 施行後の主観的および客観的睡眠指標の変化を睡眠時間制限療法の実施状況の可否で分類して比較検討した。

睡眠時間制限療法に基づいて睡眠スケジュールを修正することができた達成群は、施行後 6 ヶ月時点で判定された治療転帰には非達成群と差異を認めなかったが、施行後 1 ヶ月時点での PSQI-J は、達成群においてのみ施行前に比較して有意な減少を認めた。g-CBT-I の短期治療成績として、達成群における有意な不眠症状の軽減が示唆された。

g-CBT-I 施行前の各種指標の両群間比較として、達成群において男性が多かった点について、対象の男性はほとんどが有職者であり、専業主婦を主体とする女性に比較して、日中の定期的な活動性が保たれた結果、睡眠時間制限療法の原則を遂行しやすかった可能性は想像される。ただし、性差に関する詳細な評価は不明な点が多いと考えられた。

一方、g-CBT-I 施行前の各種指標の両群間比較として、達成群において、入眠潜時や総睡眠時間に関するに主観的評価と客観的評価の乖離度が小さかったことについて、施行前における睡眠に関する誤認の程度が少ない程、施行者が指示した睡眠スケジュール通りに睡眠時間帯を修正しやすかった可能性が示唆された。

今回の結果は、CBT-I における睡眠時間制限法の重要性を示すと共に、CBT-I の構成要素の設定や適応症例選択に際しての参考になり得

ると考えられた。

F. 結論

g-CBT-I における睡眠時間制限法は技法の中核であり、その有効性が指摘されているが、今回の結果は、適応症例を選択する際の指標の1つになりうると考えられた。

G. 健康危険情報

なし

H. 研究発表

1. 論文発表

1) Yamadera W, Harada D. Short term efficacy of group cognitive behavioral therapy for primary insomnia. Sleep and Biological Rhythms, 2014; 12(4): 239.

2) 山寺 亘. 睡眠衛生教育－健やかな睡眠のために知っておくべきこと－. 産業精神保健, 2014 ; 22(1) : 8－13.

3) 山寺 亘. 睡眠時無呼吸症候群における合併疾患と併存疾患. 睡眠医療, 2014 ; 8(1) : 63－67.

4) 山寺 亘. 旅と睡眠と時差対策. 日本旅行医学会学会誌 2014 ; 11(1) : 30－33.

5) 山寺 亘、伊藤洋. 睡眠障害の診断と治療. 東京都病院薬剤師会雑誌 2014 ; 63(6) : 491－497.

2. 学会発表

1) 山寺 亘、原田大輔. 不眠症に対する認知行動療法における睡眠時間制限療法. (シンポジウム)睡眠障害に対する非薬物療法の本質. 日本睡眠学会第39回定期学術集会. 徳島. 2014年. 7月.

2) 山寺 亘. 睡眠衛生指導. (ワークショップ)不眠症の認知行動療法. 日本睡眠学会第39回定期学術集会. 徳島. 2014年. 7月.

3) 山寺 亘. 慢性不眠症に対する認知行動療法の効果－個人療法と集団療法の比較－. (シンポジウム)睡眠障害に対する認知行動療法の理論と実践. 第14回日本認知療法学会第18回日本摂食障害学術集会合同学会. 大阪. 2014年. 9月.

4) 山寺 亘. (ランチョンセミナー)不眠症の診断と治療－最近のガイドラインから－. 第14回日本認知療法学会第18回日本摂食障害学術集会合同学会. 大阪. 2014年. 9月.

5) Yamadera W, Harada D. The role of sleep restriction methods in group cognitive-behavioral therapy for psychophysiological insomnia. (Symposium5) Non-pharmacological treatments for insomniacs in Japan. The 8th Asian Sleep Research Society Congress. India. 2014. Sep.

6) 青木亮、小林伸行、山寺 亘、岩下正幸、近藤一博、伊藤洋、中山和彦. 客観的疲労評価測定による閉塞型睡眠時無呼吸症候群の重症度評価に関する検討. 日本睡眠学会第39回定期学術集会. 徳島. 2014年. 7月.

7) 鈴木貴子、山寺 亘、岩下正幸、青木亮、原田大輔、尾作恵理、黒田彩子、森田道明、伊藤洋、中山和彦. 高齢者の慢性不眠症に対するCBT-Iの治療経験―若年症例との比較―. 第30回不眠研究会研究発表会. 東京. 2014年. 12月.

I. 知的財産権の出願・登録状況

なし

Ⅲ．　研究成果の刊行に関する一覧表

1．書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
松井健太郎，井上雄一	不眠症	松永寿人	抗不安薬プラクティカルガイド	中外医学社	東京	2015	93-102
山下英尚，山脇成人	うつ状態	小林祥泰/水澤英洋/山口修平	神経疾患　最新の治療2015-2017	南江堂	東京	2015	269-270

２．雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Okajima I, Nakajima S, Ochi M, Inoue Y.	Reducing dysfunctional beliefs about sleep does not significantly improve insomnia in cognitive behavioral therapy	PLoS One	9(7)	e102565	2014
Takaesu Y, Komada Y, Asaoka S, Kagimura T, Inoue Y.	Factors associated with long-term Use of hypnotics among patients with chronic insomnia	PLoS One	9(11)	e113753	2014
井上雄一	不眠症	日本医師会雑誌	143(12)	2529-2533	2015
Späti J, Aritake S, Meyer AH, Kitamura S, Hida A, Higuchi S, Moriguchi Y, Mishima K.	Modeling circadian and sleep-homeostatic effects on short-term interval timing.	Frontiers in Integrative Neuroscience	9	15	2015
Mishima K, DiBonaventura Md, Gross H.	The burden of insomnia in Japan	Nat Sci Sleep	7	1-11	2015
Nakazaki K, Kitamura S, Motomura Y, Hida A, Kamei Y, Miura N, Mishima K.	Validity of an algorithm for determining sleep/wake states using a new actigraph.	J Physiol Anthropol	33 (1)	31	2014
Hida A, Kitamura S, Katayose Y, Kato M, Ono H, Kadotani H, Uchiyama M, Ebisawa T, Inoue Y, Kamei Y, Okawa M, Takahashi K, Mishima K.	Screening of clock gene polymorphisms demonstrates association of a PER3 polymorphism with morningness-eveningness preference and circadian rhythm sleep disorder.	Sci Rep	4	6309	2014

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Motomura Y, Kitamura S, Oba K, Terasawa Y, Enomoto M, Katayose Y, Hida A, Moriguchi Y, Higuchi S, Mishima K.	Sleepiness induced by sleep-debt enhanced amygdala activity for subliminal signals of fear.	BMC Neurosci	15 (1)	97	2014
Ikeda M, Kaneita Y, Uchiyama M, Mishima K, Uchimura N, Nakaji S, Akashiba T, Itani O, Aono H, Ohida T.	Epidemiological study of the associations between sleep complaints and metabolic syndrome in Japan.	Sleep and Biological Rhythms	12 (4)	269-278	2014
Kitamura S, Hida A, Aritake S, Higuchi S, Enomoto M, Kato M, Vetter C, Roenneberg T, Mishima K.	Validity of the Japanese version of the Munich ChronoType Questionnaire.	Chronobiol Int	31 (7)	845-850	2014
Lee SI, Hida A, Kitamura S, Mishima K, Higuchi S.	Association between the melanopsin gene polymorphism OPN4*Ile394Thr and sleep/wake timing in Japanese university students.	J Physiol Anthropol	33 (1)	9	2014
Ohnishi T, Murata T, Watanabe A, Hida A, Ohba H, Iwayama Y, Mishima K, Gondo Y, Yoshikawa T.	Defective craniofacial development and brain function in a mouse model for depletion of intracellular inositol synthesis.	J Biol Chem	289 (15)	10785-10796	2014
Motomura Y, Kitamura S, Oba K, Terasawa Y, Enomoto M, Katayose Y, Hida A, Moriguchi Y, Higuchi S, Mishima K	Sleep Debt Elicits Negative Emotional Reaction through Diminished Amygdala-Anterior Cingulate Functional Connectivity.	PloS one	8(2)	e56578	2013

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
元村祐貴, 三島和夫	特集 日常生活の脳科学 睡眠と情動ー情動調節における睡眠の役割.	BRAIN and NERVE	66 (1)	15-23	2014
Miyagawa T, Toyoda H, Hirataka A, Kanbayashi T, Imanishi A, Sagawa Y, Kotorii N, Kotorii T, Hashizume Y, Ogi K, Hiejima H, Kamei Y, Hida A, Miyamoto M, Imai M, Fujimura Y, Tamura Y, Ikegami A, Wada Y, Moriya S, Furuya H, Kato M, Omata N, Kojima H, Kashiwase K, Saji H, Khor SS, Yamasaki M, Wada Y, Ishigooka J, Kuroda K, Kume K, Chiba S, Yamada N, Okawa M, Hirata K, Uchimura N, Shimizu T, Inoue Y, Honda Y, Mishima K, Honda M, Tokunaga K.	New susceptibility variants to narcolepsy identified in HLA class II region.	Hum Mol Genet.	24(3)	891-8	2015
Kikuchi YS, Ataka K, Yagisawa K, Omori Y, Kanbayashi T, Shimizu T.	Clozapine administration and the risk of drug-related pure red cell aplasia: a novel case report.	J Clin Psychopharmacol.	34(6)	763-4	2014
Kikuchi YS, Sato W, Ataka K, Yagisawa K, Omori Y, Kanbayashi T, Shimizu T.	Clozapine-induced seizures, electroencephalography abnormalities, and clinical responses in Japanese patients with schizophrenia.	Neuropsychiatr Dis Treat.	10	1973-8	2014

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Sato M, Sagawa Y, Hirai N, Sato S, Okuro M, Kumar S, Kanbayashi T, Shimizu T, Sakai N, Nishino S.	Noninvasive detection of sleep/wake changes and cataplexy-like behaviors in orexin/ataxin-3 transgenic narcoleptic mice across the disease onset.	Exp Neurol.	261	744-51	2014
Kondo H, Ozone M, Ohki N, Sagawa Y, Yamamichi K, Fukuju M, Yoshida T, Nishi C, Kawasaki A, Mori K, Kanbayashi T, Izumi M, Hishikawa Y, Nishino S, Shimizu T.	Association between heart rate variability, blood pressure and autonomic activity in cyclic alternating pattern during sleep.	Sleep	37(1)	187-94	2014
Takeshima M, Echizenya M, Inomata Y, Shimizu T.	Scurvy in an alcohol-dependent patient with a severely unbalanced diet.	Psychiatry Clin Neurosci.	68(3)	242-3	2014
清水徹男	認知症と生活習慣病：睡眠障害の観点から	分子精神医学	14(3)	217-9	2014
清水 徹男	DSM-5による睡眠障害と睡眠障害国際分類(ICSD-2)との関係	臨床精神医	43(7)	965-70	2014
清水 徹男	体内時計,睡眠,代謝における動的恒常性維持機構	睡眠医療	8(4)	706-8	2014
清水 徹男	不眠症の疫学と治療意義（オレキシン受容体拮抗薬の登場と不眠症治療のパラダイムシフト）-- (不眠症とその治療の現状)	睡眠医療	8(34増刊)	444-8	2014

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
清水 徹男	意外と多い?むずむず脚症候群	心とからだのオアシス	7(4)	18-23	2014
山下英尚、濱聖司、村上太郎、町野彰彦、志々田一宏、小早川誠、淵上学、土岐茂、吉野敦雄、岡本泰昌、山脇成人	血管障害とうつ病・アパシー	老年精神医学雑誌			印刷中
山下 英尚, 町野 彰彦, 志々田 一宏, 吉野 敦雄, 土岐 茂, 淵上 学, 小早川 誠, 岡本 泰昌, 山脇 成人	不眠症の薬物療法の今日的問題点　代替薬物療法にエビデンスはあるか	精神科	25(1)	72-77	2014
山下 英尚, 濱 聖司, 村上 太郎, 福本 拓治, 町野 彰彦, 志々田 一宏, 小早川 誠, 淵上 学, 吉野 敦雄, 岡本 泰昌, 山脇 成人	脳卒中後うつ病の診断と治療	精神科治療学	29(3)	289-294	2014
大村 淳, 淵上 学, 山下 英尚, 岡本 泰昌, 山脇 成人	抗生剤治療によって精神症状が可逆的であった神経梅毒の1例	精神科	25(3)	356-362	2014
Yoshimura Y, Okamoto Y, Onoda K, Okada G, Toki S, Yoshino A, Yamashita H, Yamawaki S.	Psychosocial functioning is correlated with activation in the anterior cingulate cortex and left lateral prefrontal cortex during a verbal fluency task in euthymic bipolar disorder: a preliminary fMRI study.	Psychiatry Clin Neurosci	68	188-196	2014
Hayashi A, Okamoto Y, Yoshimura S, Yoshino A, Toki S, Yamashita H, Matsuda F, Yamawaki S.	Visual imagery while reading concrete and abstract Japanese kanji words: An fMRI study.	Neurosci Res	79	61-66	2014

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yoshino A, Okamoto Y, Kunisato Y, Yoshimura S, Jinnin R, Hayashi Y, Kobayakawa M, Doi M, Oshita K, Nakamura R, Tanaka K, Yamashita H, Kawamoto M, Yamawaki S.	Distinctive spontaneous regional neural activity in patients with somatoform pain disorder: A preliminary resting-state fMRI study.	Psychiatry Res	221	246-248	2014
Yamadera W, Harada D	Short term efficacy of group cognitive behavioral therapy for primary insomnia	Sleep and Biological Rhythms	12(4)	239	2014
山寺亘	睡眠衛生教育－健やかな睡眠のために知っておくべきこと－	産業精神保健	22(1)	8-13	2014
山寺亘	睡眠時無呼吸症候群における合併疾患と併存疾患	睡眠医療	8(1)	63－67	2014
山寺亘	旅と睡眠と時差対策	日本旅行医学会学会誌	11(1)	30-33	2014
山寺亘，伊藤洋	睡眠障害の診断と治療	東京都病院薬剤師会雑誌	63(6)	491-497	2014

Ⅳ. 研究成果の刊行物・別冊

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Reducing Dysfunctional Beliefs about Sleep Does Not Significantly Improve Insomnia in Cognitive Behavioral Therapy

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Abstract

The present study examined to examine whether improvement of insomnia is mediated by a reduction in sleep-related dysfunctional beliefs through cognitive behavioral therapy for insomnia. In total, 64 patients with chronic insomnia received cognitive behavioral therapy for insomnia consisting of 6 biweekly individual treatment sessions of 50 minutes in length. Participants were asked to complete the Athens Insomnia Scale and the Dysfunctional Beliefs and Attitudes about Sleep scale both at the baseline and at the end of treatment. The results showed that although cognitive behavioral therapy for insomnia greatly reduced individuals' scores on both scales, the decrease in dysfunctional beliefs and attitudes about sleep with treatment did not seem to mediate improvement in insomnia. The findings suggest that sleep-related dysfunctional beliefs endorsed by patients with chronic insomnia may be attenuated by cognitive behavioral therapy for insomnia, but changes in such beliefs are not likely to play a crucial role in reducing the severity of insomnia.

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Introduction

Insomnia is defined as having difficulty initiating or maintaining sleep, waking up too early, or sleep that is chronically nonrestorative or poor in quality, causing daytime impairments such as decreased attention and worries concerning sleep [1]. Nearly 20% of the general adult population has been reported to suffer from insomnia [2], [3], and 10–15% of the individuals with insomnia show a chronic course [4], [5]. Chronic insomnia is associated with the development, treatment resistance to, and relapse of depression [4], [5], [6], [7].

Cognitive behavioral therapy for insomnia (CBT-I) is commonly used for treatment of the disorder. CBT-I has been shown to be effective for improving insomnia symptoms in 70–80% of patients with chronic insomnia [8], and to have long-term preventive effects on symptom recurrence [9]. Although a number of treatment outcome studies focusing on the CBT-I have been conducted [8], [10], [11], [12], only a few have investigated the underlying mechanisms or actual processes through which improvements after CBT-I occur [13], [14], [15]. Therefore, the specific reasons as to why CBT-I is effective for treating insomnia remain unclear.

Schwartz and Carney [15] reviewed theoretical models of insomnia and proposed several mediators of the treatment effectiveness of CBT-I. According to their hypothesis, behavioral (e.g., decreased time in bed), cognitive (e.g., decreased maladaptive beliefs about sleep), and hyperarousal (e.g., decreased physiological arousal) mediators are believed to account for therapeutic change via this intervention. There has been a surge of interest, in particular, in the role of sleep-related dysfunctional beliefs as potential perpetuating factor of insomnia. Some findings have suggested that such beliefs may be involved in exacerbation of the vicious cycle of insomnia [16]. Consequently, sleep-related dysfunctional beliefs have been incorporated into prominent cognitive behavioral models of insomnia [17].

Previous studies have examined the relationship between sleep-related dysfunctional beliefs and treatment outcomes with CBT-I [11], [13], [14], [18]. Based on these study results, Schwartz and Carney suggested that participants receiving CBT-I experienced (a) changes in their Dysfunctional Beliefs and Attitudes about Sleep (DBAS) from the baseline to the conclusion of treatment, as well as (b) greater reductions in DBAS scores as compared to the control group. They also proposed that (c) these reductions were associated with a range of subjective and objective sleep outcomes at the end of treatment and during the follow-up period [15]. This hypothesis implies that reductions in sleep-related dysfunctional beliefs are associated with positive changes in sleep outcomes with CBT-I. However, researchers have yet to examine if changes in sleep-related dysfunctional beliefs during CBT-I have a direct impact on improvement of insomnia. The cause-and-effect relationship between the reduction in DBAS and improvement of insomnia thus needs elucidating. Furthermore, although sleep efficiency and quality as determined from sleep diary data have been used as outcome variables in previous investigations [13],

[14], [18], standardized measures of insomnia severity have not been examined in this regard. Therefore, the relationship between change in sleep-related dysfunctional beliefs and severity of insomnia has yet to be ascertained.

Considering these issues, the present study set out to clarify whether improvement of insomnia, as evaluated with the Athens Insomnia Scale (AIS), is mediated by a reduction in sleep-related dysfunctional beliefs through CBT-I.

Materials and Methods

Participants

Individuals were eligible for this study if they were 20 years old or above and met criteria for psychophisiological insomnia (i.e., chronic insomnia) according to the second edition of the International Classification of Sleep Disorders [1]. The participants of this study were outpatients who visited the Yoyogi Sleep Disorder Center seeking treatment for chronic insomnia between October 2011 and October 2012. Most of the patients were referred to the center by local psychiatrists or general practitioners. Participants' disturbed sleep met all of the following additional criteria: (1) difficulties in initiating and/or maintaining sleep, defined as subjective sleep onset latency and/or waking after sleep onset greater than 30 minutes at least three nights per week, respectively [19]; (2) insomnia morbidity for over 6 months [19]; and (3) a score of 6 points or greater for severity of insomnia as measured with the AIS [20], [21]. Exclusion criteria were (1) insomnia due to medical or psychiatric disorders [22] or pharmaceutical use, and (2) the existence of other sleep disorders, such as obstructive sleep apnea syndrome, restless legs syndrome, periodic limb movement disorder, or circadian rhythm sleep disorders. In order to exclude these sleep disorders, after assessment by board-certified sleep disorder specialist physicians, eligible patients underwent nocturnal polysomnography (PSG) and/or provided self-checked sleep logs for more than 2 weeks, if necessary.

In all, 64 patients participated in the study; however, 11 patients answered at least one of the above-indicated scales incompletely. Therefore, the total number of participants with sufficient data for analysis was 53 (26 men, 27 women; mean [SD] age = 48.6 [15.1] years; mean [SD] duration of insomnia morbidity = 8.4 [11.4] years).

Procedure

This study was approved by the ethical review board of the Neuropsychiatric Research Institute, Tokyo, Japan. Written informed consent was obtained from all participants. After diagnoses were made by board-certified sleep disorder specialist physicians, eligible participants were offered CBT-I [23]. Measures of insomnia severity and dysfunctional beliefs and attitudes about sleep were administered to patients during their first visit and immediately after treatment concluded.

Measures

Athens Insomnia Scale (AIS) [20], [21], [24]. The AIS was used to assess the severity of insomnia according to criteria for insomnia outlined in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) [25]. The AIS is an inventory consisting of eight items. The first five items assess nocturnal sleep problems (e.g., difficulty in sleep initiation, awakening during the night, early morning awakening), and the remaining three assess daytime dysfunction brought about by insomnia (e.g., overall functioning, sleepiness during the day). Responses are made on a 4-point scale ranging from 0 (*no problem at all*) to 3 (*very serious problem*). Participants were asked to rate corresponding items (e.g., awakenings during the night) as positive (i.e., to choose among rating options 1, 2, and 3) when they had experienced sleep difficulty at least three nights per week during the previous month. This scale was also used to measure concomitant change in insomnia symptoms over the course of treatment with CBT-I. A score of 6 points or greater on this scale indicates clinical levels of insomnia [20], [24].

Dysfunctional Beliefs and Attitudes about Sleep scale-16 (DBAS-16) [26], [27]. The DBAS has been utilized in previous mediation analyses, making it an effective tool for assessing the sleep-related dysfunctional beliefs of participants in our study. The DBAS-16 is a self-rating inventory consisting of 16 items (e.g., I am worried that I may lose control over my abilities to sleep) with 10-point scales, ranging from 0 (*strongly disagree*) to 10 (*strongly agree*). The total score is calculated from the average score of all the items on the scale and could range from 0 to 10, with higher scores indicating higher levels of dysfunctional beliefs about sleep.

Treatment

The patients attended six biweekly individual treatment sessions, each lasting approximately 50 minutes. The first session began after the initial intake interview and case formulation. Core treatment components of CBT-I included sleep education and hygiene (Session 2), progressive muscle relaxation (Session 3), sleep scheduling (comprising sleep restriction and stimulus control, Sessions 4 and 5), and coping with worry (Session 6) based on the manual of a previous study [23]. Patients were asked to practice what they had learned and to track their results according to the treatment protocol between sessions.

Data management and statistical analysis

Descriptive and inferential statistics were computed using SPSS version 19.0 (IBM Inc., Tokyo, Japan). The relationships between the scales at baseline and at the end of treatment were evaluated using paired t-tests and correlation analysis. The effect size (Cohen's d) was used to investigate the extent of differences in scale scores between survey points (baseline vs. endpoint) in order to evaluate treatment effect. In general, Cohen's d values of 0.2 or lower, around 0.5, and 0.8 or more indicate small, moderate, and large effect sizes [28]. Effects of sleep-related dysfunctional beliefs on improvement of insomnia were assessed using path analyses following the steps outlined [29]. The severity of insomnia at baseline (AIS-T1) was adopted as the candidate predictor variable, change in sleep-related dysfunctional beliefs (i.e., difference in DBAS scores between baseline and endpoint) as the candidate mediator variable, and severity of insomnia after treatment (AIS-T2) as the criterion variable. We computed three regression analyses: First, we regressed AIS-T2 alone on AIS-T1; second, we regressed change in DBAS alone on AIS-T1; third, we regressed AIS-T2 on AIS-T1 simultaneously with change in DBAS. Typically, an effect size of 0.02 or below (coefficient of determination, R^2) is considered small, whereas one around 0.13 is deemed moderate. One of 0.26 or greater is generally considered large [28]. Path analysis requires the usual assumptions of regression. Therefore, we assumed linear relationships among all variables and normally distributed error variables.

Results

Means and standard deviations for clinical measures at baseline and at the end of the treatment are presented in Table 1. The results of paired t-tests showed significant decreases in participants' AIS ($t_{52} = 10.21$, $p<0.01$) and DBAS ($t_{52} = 3.69$, $p<0.01$) scores at

Table 1. Summary of self-reported measures of insomnia severity and sleep beliefs.

	Mean (SE)		Mean Difference score (*SE*)	*t* (*df*)	*p*	Effect size (95% CI)
	Baseline	End of treatment				
DBAS total	5.65 (0.18)	4.71 (0.25)	0.94 (0.25)	3.69 (52)	<0.01	0.72 (0.33, 1.11)
AIS total	11.96 (0.69)	5.89 (0.57)	6.08 (0.60)	10.21 (52)	<0.01	1.21 (0.80, 1.62)

Note. AIS = Athens Insomnia Scale; DBAS = Dysfunctional Beliefs and Attitudes about Sleep scale; SE = standard error; 95% CI = 95% Confidence Interval.
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the end of treatment as compared to when they began. The effect sizes (*d*) were 1.21 and 0.72, respectively (see Table 1).

The results of correlation analyses showed significant correlations between: (1) the AIS and DBAS at baseline ($r = 0.33$, $p < 0.05$), (2) AIS scores at baseline and at the end of treatment ($r = 0.48$, $p < 0.01$), and (3) DBAS scores at baseline and at the end of treatment ($r = 0.27$, $p < 0.05$) (refer to Table 2).

The first regression analysis revealed that AIS-T1 had a standardized direct effect on AIS-T2, with a β-value of 0.57 ($p = 0.00$; Model 1), but did not have a direct effect on change in DBAS ($p = 0.41$; Model 2). In the multiple regression equation with dysfunctional beliefs as the second independent variable (Model 3), the β-value of the AIS-T1 increased to 0.55 ($p = 0.00$), while change in DBAS did not show a direct effect on AIS-T2 (β-value = 0.15, $p = 0.20$; see Table 3). Path models using these variables are shown in Figure 1. Change in DBAS did not seem to mediate the effect of AIS-T1 on AIS-T2. The standardized path coefficient of 0.57 (Figure 1, Direct Model) decreased to 0.55 when change in DBAS was used as a mediator (Figure 1, Mediated Model). When change in DBAS was used as the second independent variable, the change in R^2 from 0.32 to 0.35 was significant ($\Delta R^2 = 0.03$, $F_{2,50} = 12.00$, $p = 0.00$).

Discussion

The present study examined whether improvement in insomnia is mediated by a reduction in sleep-related dysfunctional beliefs as manifested by a decrease in DBAS score after CBT-I. The results suggest that DBAS scores decreased after CBT-I, but the change in these beliefs did not seem to play a crucial role in improving insomnia.

We compared the DBAS scores of insomnia patients in this study with those of good sleepers ($n = 335$, mean score = 2.96, $SD = 0.13$) and individuals with insomnia ($n = 1049$, mean score = 5.23, $SD = 1.60$) in a previous study involving a large sample [30]. We found that the scores of insomnia patients in the present study were significantly higher than those of the good sleepers ($t_{386} = -14.34$, $p < 0.01$), but were not significantly different from those of the insomnia patients ($t_{1100} = -1.88$, *n.s.*). Therefore, the DBAS scores of our study sample were thought to not differ significantly from those of insomnia patients in general.

Previous studies have demonstrated a relationship between sleep-related dysfunctional beliefs and sleep variables (e.g., sleep quality and sleep efficiency) and that reductions in maladaptive beliefs lead to improved sleep [13], [14]. Similarly, the present study revealed a significant correlation between DBAS and AIS scores, but the association between these two variables was observed only at baseline. These results are somewhat in line with those of a previous cross-sectional study [26]. DBAS scores also decreased after CBT-I, but analyses such as these inevitably lead to the question of whether changes in sleep-related dysfunctional beliefs play a pivotal role in improving insomnia with CBT-I.

Schwartz and Carney [15] have alluded to the possibility that mediational analyses could yield further directions in ascertaining whether improvement of insomnia is in fact a result of changes in sleep-related beliefs. The present study was the first of its kind to analytically examine the cause-and-effect relationship between symptoms of insomnia and dysfunctional beliefs about sleep. The results indicated that change in sleep-related dysfunctional beliefs did not seem to mediate improvement in insomnia. Thus, reductions in these dysfunctional beliefs likely do not contribute significantly to improving insomnia. Given this, we speculated that changes we observed in dysfunctional beliefs about sleep might not necessarily have been the result of CBT-I, and that improvements in insomnia could have been mediated by other factors, such as change in behavior or hyperarousal states [15].

Our study had several limitations. First, the present study only examined the association between change in DBAS scores and improvement in AIS scores. As mentioned earlier, several candidate mediators of the persistence of insomnia exist other than dysfunctional beliefs, and significant interactions have been found between symptoms of insomnia and behavioral, cognitive, and hyperarousal variables [15]. Individuals receiving CBT-I are known to experience greater improvements in these aspects/variables relative to comparison groups [31], [32]. Future

Table 2. Correlations between self-reported measures.

	DBAS_pre	AIS_post	DBAS_post
AIS_pre	0.33*	0.48**	0.19 n.s.
DBAS_pre	–	0.17 n.s.	0.27*
AIS_post		–	0.10 n.s.
DBAS_post			–

Note. AIS = Athens Insomnia Scale; DBAS = Dysfunctional Beliefs and Attitudes about Sleep scale; Pre = at baseline; Post = at the end of treatment;
**$p < 0.01$,
*$p < 0.05$.
doi:10.1371/journal.pone.0102565.t002

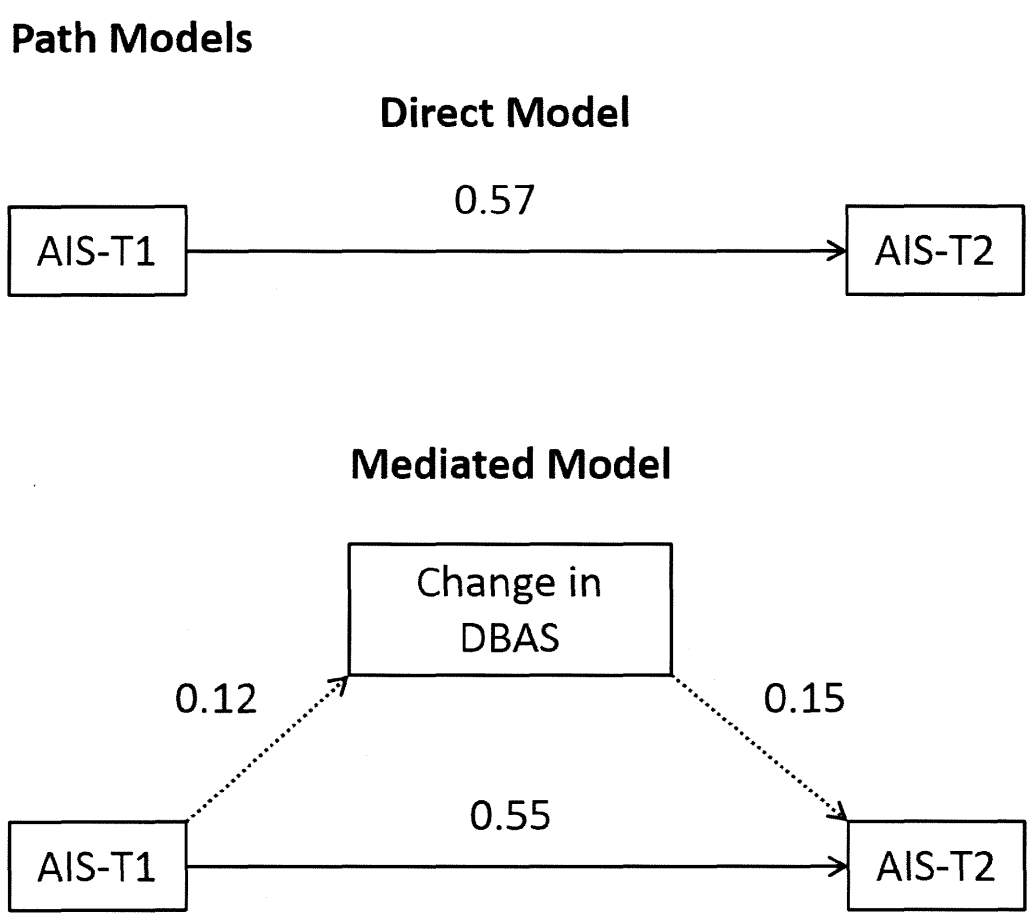

Figure 1. Two alternate path models. *Figure 1.* Two alternative path models, with severity of insomnia at baseline as the predictive variable of severity (of insomnia) at the end of treatment: a direct model, in which AIS-T1 has a direct effect on AIS-T2; and a mediated model, in which the effects of AIS-T1 on AIS-T2 are exerted via a change in dysfunctional sleep-related beliefs. Standardized regression coefficients (β) are listed for each path. The paths expressed with solid arrows are statistically significant ($p<0.01$), and those expressed with dashed arrows are not significant. AIS-T1 = Athens Insomnia Scale scores at baseline; AIS-T2 = Athens Insomnia Scale scores at the end of the treatment.
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Table 3. Summary of path analyses.

Regression for AIS-T2 with AIS-T1 (Model 1)						
Model 1	β	*t*	*P*	R^2	ΔR^2	*p* (ΔR^2)
AIS-T1	0.57	4.92	0.00	0.32	_	0.00
Regression for dysfunctional beliefs[a] with AIS-T1 (Model 2)						
Model 2	β	*t*	*p*	R^2	ΔR^2	*p* (ΔR^2)
AIS-T1	0.12	0.82	0.41	0.01	_	0.41
Multiple regression for AIS-T2 with AIS-T1 and dysfunctional beliefs (Model 3)						
Model 3[b]	β	*t*	*p*	R^2	ΔR^2 **(M3–M1)**	*p* (ΔR^2)
AIS-T1	0.55	4.77	0.00	0.35	0.03	0.00
Dysfunctional beliefs	0.15	1.31	0.20			

Note. AIS = Athens Insomnia Scale; M = Model; *p* (ΔR^2) = significance of change;
[a]indicates difference between DBAS scores at baseline and at the end of treatment;
[b]analysis of variance for Model 3 showed that multiple *R* was 0.57, multiple R^2 (adj.) was 0.30, and *F* ratio was 12.00 ($df_1 = 2$, $df_2 = 50$, $p = 0.00$).
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mediational analyses should be conducted on these variables to clarify this important issue. Second, the number of participants in this study was relatively small. Further research should be conducted with a larger sample. Third, although participants underwent PSG and/or provided self-checked sleep logs when sleep disorders other than insomnia were suspected, it is possible that some patients with a sleep-related breathing disorder or periodic limb movement disorder may have been overlooked and included in the study sample.

Finally, all participants were drawn from a single sleep disorder clinic. Therefore, the participants of our study might not be representative of the general chronic insomniac population, although the demographic data and effect size of insomnia severity were quite similar to those of previous studies [13], [33], [34].

In summary, the sleep-related dysfunctional beliefs endorsed by patients with chronic insomnia were decreased through CBT-I, but changes in these beliefs did not play a crucial role in reducing the severity of insomnia. Therefore, the impact of cognitive-behavioral approaches such as the CBT-I on behavioral and hyperarousal aspects should be studied in greater detail in order to clarify underlying mechanisms by which insomnia is significantly improved. It would also be important to examine potential long-term mediating effects of dysfunctional beliefs and attitudes about sleep on AIS scores and whether CBT-I outcomes in individual therapy setting differ from those of group therapy settings in future research.

Author Contributions

Conceived and designed the experiments: IO YI. Performed the experiments: IO SN MO. Analyzed the data: IO MO. Contributed reagents/materials/analysis tools: IO SN. Contributed to the writing of the manuscript: IO YI.

References

1. American Academy of Sleep Medicine (2005) The international classification of sleep disorders: Diagnostic and coding manual. Westchester, IL: American Academy of Sleep Medicine. xviii, 297.
2. Ancoli-Israel S, Roth T (1999) Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. Sleep 22: S347–353.
3. Kim K, Uchiyama M, Okawa M, Liu X, Ogihara R (2000) An epidemiological study of insomnia among the Japanese general population. Sleep 23: 41–47.
4. Ford DE, Kamerow DB (1989) Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? JAMA 262: 1479–1484.
5. Ohayon MM (2002) Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 6: 97–111.
6. Buysse DJ, Angst J, Gamma A, Ajdacic V, Eich D, et al. (2008) Prevalence, course, and comorbidity of insomnia and depression in young adults. Sleep 31: 473–480.
7. Okajima I, Komada Y, Nomura T, Nakashima K, Inoue Y (2012) Insomnia as a risk for depression: a longitudinal epidemiologic study on a Japanese rural cohort. J Clin Psychiatry 73: 377–383.
8. Morin CM, Hauri PJ, Espie CA, Spielman AJ, Buysse DJ, et al. (1999) Nonpharmacologic treatment of chronic insomnia. An American Academy of Sleep Medicine review. Sleep 22: 1134–1156.
9. Morin CM, Colecchi C, Stone J, Sood R, Brink D (1999) Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. JAMA 281: 991–999.
10. Bastien CH, Morin CM, Ouellet MC, Blais FC, Bouchard S (2004) Cognitive-behavioral therapy for insomnia: comparison of individual therapy, group therapy, and telephone consultations. J Consult Clin Psychol 72: 653.
11. Edinger JD, Wohlgemuth WK, Radtke RA, Marsh GR, Quillian RE (2001) Does cognitive-behavioral insomnia therapy alter dysfunctional beliefs about sleep? Sleep 24: 591–599.
12. van Straten A, Cuijpers P (2009) Self-help therapy for insomnia: a meta-analysis. Sleep Med Rev 13: 61–71.
13. Jansson-Frojmark M, Linton SJ (2008) The role of sleep-related beliefs to improvement in early cognitive behavioral therapy for insomnia. Cogn Behav Ther 37: 5–13.
14. Morin CM, Blais F, Savard J (2002) Are changes in beliefs and attitudes about sleep related to sleep improvements in the treatment of insomnia? Behav Res Ther 40: 741–752.
15. Schwartz DR, Carney CE (2012) Mediators of cognitive-behavioral therapy for insomnia: a review of randomized controlled trials and secondary analysis studies. Clin Psychol Rev 32: 664–675.
16. Edinger JD, Fins AI, Glenn DM, Sullivan RJ Jr, Bastian LA, et al. (2000) Insomnia and the eye of the beholder: are there clinical markers of objective sleep disturbances among adults with and without insomnia complaints? J Consult Clin Psychol 68: 586–593.
17. Harvey AG (2002) A cognitive model of insomnia. Behav Res Ther 40: 869–893.
18. Espie CA, Inglis SJ, Harvey L (2001) Predicting clinically significant response to cognitive behavior therapy for chronic insomnia in general medical practice: analysis of outcome data at 12 months posttreatment. J Consult Clin Psychol 69: 58–66.
19. Lichstein KL, Durrence HH, Taylor DJ, Bush AJ, Riedel BW (2003) Quantitative criteria for insomnia. Behav Res Ther 41: 427–445.
20. Okajima I, Nakajima S, Kobayashi M, Inoue Y (2013) Development and validation of the Japanese version of the Athens Insomnia Scale. Psychiatry Clin Neurosci 67: 420–425.
21. Soldatos CR, Dikeos DG, Paparrigopoulos TJ (2000) Athens Insomnia Scale: validation of an instrument based on ICD-10 criteria. J Psychosom Res 48: 555–560.
22. American Psychiatric Association (2000) Diagnostic criteria from DSM-IV-TR. Washington, D.C.: American Psychiatric Association. xii, 370.
23. Okajima I, Nakamura M, Nishida S, Usui A, Hayashida K, et al. (2013) Cognitive behavioural therapy with behavioural analysis for pharmacological treatment-resistant chronic insomnia. Psychiatry Res 210: 515–521.
24. Soldatos CR, Dikeos DG, Paparrigopoulos TJ (2003) The diagnostic validity of the Athens Insomnia Scale. J Psychosom Res 55: 263–267.
25. World Health Organization (1992) The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines. Geneva: World Health Organization. xii, 362.
26. Morin CM, Vallieres A, Ivers H (2007) Dysfunctional beliefs and attitudes about sleep (DBAS): validation of a brief version (DBAS-16). Sleep 30: 1547–1554.
27. Munezawa T, Morin CM, Inoue Y, Nedate K (2009) Development of the Japanese version of Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS-J). Jpn J Sleep Med 3: 396–403 (in Japanese).
28. Cohen J (1988) Statistical power analysis for the behavioral sciences. Hillsdale, NJ: L. Erlbaum Associates. xxi, 567.
29. Baron RM, Kenny DA (1986) The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 51: 1173–1182.
30. Carney CE, Edinger JD, Morin CM, Manber R, Rybarczyk B, et al. (2010) Examining maladaptive beliefs about sleep across insomnia patient groups. J Psychosom Res 68: 57–65.
31. Edinger JD, Wohlgemuth WK, Radtke RA, Marsh GR, Quillian RE (2001) Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. JAMA 285: 1856–1864.
32. Wu R, Bao J, Zhang C, Deng J, Long C (2006) Comparison of sleep condition and sleep-related psychological activity after cognitive-behavior and pharmacological therapy for chronic insomnia. Psychother Psychosom 75: 220–228.
33. Edinger JD, Carney CE, Wohlgemuth WK (2008) Pretherapy cognitive dispositions and treatment outcome in cognitive behavior therapy for insomnia. Behav Ther 39: 406–416.
34. Okajima I, Komada Y, Inoue Y (2011) A meta-analysis on the treatment effectiveness of cognitive behavioral therapy for primary insomnia. Sleep Biol Rhythms 9: 24–34.

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Factors Associated with Long-Term Use of Hypnotics among Patients with Chronic Insomnia

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Abstract

This study investigated factors associated with long-term use of benzodiazepines (BZDs) or benzodiazepine receptor agonists (BzRAs) as hypnotics in patients with chronic insomnia. Consecutive patients (n = 140) with chronic insomnia were enrolled in this study (68 men and 72 women; mean age, 53.8±10.8 years). All patients filled out a self-assessment questionnaire asking clinical descriptive variables at the baseline of the treatment period; patients received the usual dose of a single type of BZD or BzRA. The Pittsburgh Sleep Quality Index (PSQI) and the Zung Self-Rating Depression Scale were self-assessed at the baseline, and the former was re-evaluated at the time of cessation of medication or at the end of the 6-month treatment period. The PSQI included the following sub-items: evaluating sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), frequency of sleep disturbance (C5), use of sleeping medication (C6), and daytime dysfunction (C7). Among the patients, 54.6% needed to continue hypnotics for a 6-month treatment period. Logistic regression analysis revealed that, among descriptive variables, only the PSQI score appeared as a significant factor associated with long-term use {odds ratio (OR) = 2.8, 95% confidence interval (CI) = 2.0–4.0}. The receiver operating curve (ROC) analysis identified that the cut-off PSQI total score at the baseline for predicting long-term use was estimated at 13.5 points (area under the curve = 0.86, 95% CI = 0.8–0.92). Among the sub-items of PSQI, the increases in C1: (OR = 8.4, 95% CI = 2.4–30.0), C3: (OR = 3.6, 95% CI = 1.1–11.5), C4: (OR = 11.1, 95% CI = 3.6–33.9), and C6: (OR = 3.4, 95% CI = 1.9–6.2) scores were associated with long-term use. This study revealed that a high PSQI score at the baseline, particularly in the sub-items relating to sleep maintenance disturbance, is predictive of long-term hypnotic treatment. Our results imply the limitation of the effectiveness of hypnotic treatment alone for chronic insomnia.

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Introduction

Insomnia is a common disorder with a remarkably high prevalence [1–3]. It has been reported that one-fifth of the general population in Japan has symptoms associated with insomnia [4]. Chronic insomnia is known to be associated with subjective daytime fatigue, low energy, difficulties in cognitive performance, and deteriorated quality of life [5]. The disorder has also been known to be a risk factor for the development of somatic diseases such as hypertension and diabetes mellitus [6–8]. Furthermore, chronic insomnia is suspected as one of the risk factors for the development of psychiatric disorders, particularly depression and anxiety disorders [9,10]. Thus, establishment of a better treatment strategy for achieving sufficient improvement of the disorder is desirable.

Benzodiazepines (BZDs) or benzodiazepine receptor agonists (BzRAs) have long been accepted as one of the important treatment choices for insomnia. However, the disadvantages of the long-term use of these kinds of hypnotics, such as the risk of tolerance [11] and dependence [12], have been indicated. Based on this, clinical guidelines of the American Academy of Sleep Medicine suggested that long-term hypnotic treatment can be indicated only for the patients with severe or refractory insomnia or chronic illness [13]. It is also suggested that BZDs should only be used for a short-term period of up to 4 weeks to prevent the occurrence of the disadvantages associated with long-term use [14]. However, there are considerably large numbers of patients with chronic insomnia who require long-term medication with hypnotics due to poor response to treatment [15].

To avoid the long-term use of BZDs or BzRAs as hypnotics, it is necessary to highlight the factors associated with long-term treatment with these types of drugs. However, thus far, there have been apparently no studies to clarify this issue. We therefore investigated the factors associated with long-term treatment with hypnotics among patients with chronic insomnia in order to contribute to the development of an effective treatment strategy for this disorder.

Materials and Methods

This study was approved by the Ethics Committee of the Neuropsychiatric Research Institute, Tokyo, Japan, and written informed consent was obtained from all the enrolled patients.

Among the consecutive patients who visited the outpatient clinic of the Japan Somnology Center seeking treatment of their sleep problems from May 2003 to December 2009, the subjects for this study were selected from the patients who met the diagnostic criteria for primary insomnia according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR). The diagnosis of primary insomnia for all selected patients was confirmed by at least 2 psychiatrists who specialize in sleep disorders. None of the patients had or were previously affected with any other psychiatric disorders, such as major depression, anxiety disorders, or substance abuse. Patients who received antidepressants, antipsychotics, or more than 2 types or unusually high doses of hypnotics were excluded from the study. In cases of the suspected presence of other sleep disorders, 1 night polysomnography and more than 2 weeks of sleep logs were recorded for making differential diagnoses. As a result, 140 consecutive patients with primary insomnia, who met the criteria of chronic insomnia with persistence of insomnia symptoms for at least 6 months [16], were enrolled in this study (68 men and 72 women; mean age, 53.8±10.8 years).

All these patients filled out a self-assessment questionnaire before starting the treatment with the usual dose of BZD or BzRA hypnotic. The questionnaire requested information regarding sex, age at the time of investigation, age at the onset of subjective insomnia, duration of morbidity, marital status (married/unmarried), occupation (employed/unemployed), and educational background (college educated/not). The Pittsburgh Sleep Quality Index (PSQI) was self-assessed for estimating the severity of their insomnia symptoms before starting the treatment [17,18]. The PSQI included the following sub-items: evaluating sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), frequency of sleep disturbance (C5), use of sleeping medication (C6), and daytime dysfunction (C7). The scores of these sub-items range from 0 (no difficulty) to 3 (severe difficulty) and are summed to produce a global measure of sleep disturbance, with a higher score denoting poorer sleep quality (range: 0–21). Simultaneously, all patients completed the Zung Self-Rating Depression Scale (SDS) [19].

At the start of hypnotic treatment for each patient, sleep specialist physicians set a goal to finish the treatment within 6 months since increasing occurrence of dependence and withdrawal symptoms of BZDs or BzRAs are reportedly likely to increase over 6 months of consecutive medication [20,21]. Based on this, sleep specialist physicians instructed the subject patients to reduce the amount of hypnotics by one-quarter tablet during the treatment period, if their insomnia symptoms improved sufficiently. During the treatment period, all patients visited the outpatient clinic once per month regularly to receive a prescription of BZD or BzRA together with general sleep hygiene education [22]; none of them received any psychotherapy, including cognitive behavioral therapy (CBT).

We divided the patients into 2 groups, namely, those who achieved sufficient improvement of symptoms resulting in the discontinuation of BZD or BzRA medication within a 6-month treatment period (discontinuation group), and those who continued to be treated with those hypnotics even at the end of the treatment period (long-term use group). PSQI was self-assessed at two time points by all the subject patients. In the discontinuation group, PSQI was re-evaluated at the time of cessation of treatment with hypnotics to confirm a sufficient improvement; in the long-term use group, PSQI was re-evaluated 6 months after the start of the treatment.

Statistical analysis

The Mann-Whitney U test and chi-square test were used for comparison of descriptive variables between the discontinuation group and the long-term use group. The Mann-Whitney U test was also used for the comparison between the 2 groups of the changes in PSQI total and sub-item scores from the baseline to the end of the treatment period. The Wilcoxon signed rank test was used for the comparison of PSQI total and sub-item scores between the baseline and the end of the treatment period.

The factors associated with the discontinuation group were examined by logistic regression analyses including the above-indicated independent variables (sex, age at the time of investigation, age at onset of insomnia, duration of morbidity, marital status, educational background, occupation, SDS scores, and PSQI scores). All variables were initially examined in univariate models. To control for confounding factors and to determine the main correlates, we then performed multivariate logistic regression analysis for all variables that showed a significant correlation ($p<0.05$) in the univariate models.

Receiver operating characteristic (ROC) curves [23] were plotted and the mean estimated area under the curve (AUC) with 95% confidence interval (CI) for the PSQI score at the baseline was calculated for predicting discontinuation of hypnotics. When the slope of the tangent line of the ROC curve was statistically equal to 1 (i.e., AUC = 0.5), the ROC curve was regarded as inaccurate for prediction. The best cut-off value for predicting the discontinuation of hypnotics was determined on the basis of sensitivity, specificity, and positive likelihood ratio (LR+) and negative likelihood ratio (LR−). According to an established method [24], the cut-off value was assessed as adequate when LR+ was 2.0 or higher and LR− was 0.5 or lower.

SPSS version 11.5.1J software for Windows (SPSS Inc., Tokyo) was used for the above statistical analyses. A p-value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Patients' characteristics are shown in Table 1. For the total number of patients (n = 140), the mean age at onset was 50.8±11.0 (mean±SD) years, the mean age at the time of investigation was 53.8±10.8 years, the mean duration of self-reported insomnia morbidity was 2.9±2.3 years (all patients indicated longer than 6 months), and the mean SDS score was 39.7±8.9 points. The male/female ratio was 48.6%/51.4%, 72.1% of the patients were married, 34.3% had a college education, and 56.4% were employed (Table 1).

Of all the patients, 35.0% received an ultrashort elimination half-life BZD or BzRA, 45.7% received a short elimination half-life BZD, 13.6% received an intermediate elimination half-life BZD, and 5.7% received a long elimination half-life BZD. The amount of BZD or BzRA manifested as diazepam equivalent doses was 6.1±2.2 mg in the discontinued group and 5.9±2.1 mg in the long-term use group.

There were 64 patients (45.4%) in the discontinuation group, and the remaining 76 patients (54.6%) were in the long-term use group. Among the long-term use group, 28 patients continued to receive the same dose of BZD or BzRA as the baseline dose, 41 were prescribed a higher dose of the same BZD or BzRA than the baseline dose, or other types of BZDs or BzRAs additionally because of the ineffectiveness of treatment, and 7 were prescribed