QUALITY OF LIFE IN PRIMARY INSOMNIA: THREE-WEEK TREATMENT WITH ZOLPIDEM VS. LORAZEPAM

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KVALITET ŽIVOTA U PRIMARNOJ NESANICI: POREĐENJE TRONEDELJNOG TRETMANA ZOLPIDEMOM I LORAZEPAMOM

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ABSTRACT

Insomnia is a condition of inadequate quality or quantity of sleep that has extremely adverse effects on daytime activities. The aim of this study was to compare the quality of life in patients with primary insomnia before and after a 3-week treatment with lorazepam (n=20) and zolpidem (n=21) and to compare the potential differences in dysfunctional beliefs and attitudes regarding patients' sleep between the two groups. The diagnosis of primary insomnia was established using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria, and patients had to complete a specially designed sleep log every day; on scheduled visits, we also administered a Visual Analogue Scale for quality of life and a self-evaluation questionnaire about Dysfunctional Beliefs and Attitudes related to Sleep at the beginning and end of this study.

In summary, the examinees in our study had significantly decreased parameters of quality of life, quite lower than expected based on previous findings in this area. However, by the end of the study, quality of life significantly improved with treatment: it improved by approximately 2/3 in the Lorazepam group and more than twice in the Zolpidem group, with a significant difference in favour of Zolpidem (p=0.047). This finding is most likely a consequence of its better safety profile and in part its better efficiency in terms of influence on certain domains of sleep itself, as previously discussed. Further specialized studies in this area with larger samples and a more detailed methodology are clearly warranted.

Keywords: *primary insomnia, zolpidem, quality of life*

SAŽETAK

Nesanica je stanje neadekvatnog kvaliteta ili kvantiteta sna, koje ima izuzetno negativne efekte na dnevne aktivnosti. Cilj ovog istrazivanja je bio da se uporedi kvalitet života pacijenata sa primarnom nesanicom pre i nakon tronedeljnog tretmana lorazepamom (n=20) i zolpidemom (n=21) i da se uporede potencijalna disfunkcionalna verovanja i stavovi o spavanju između ove dve grupe. Dijagnoza primarne nesanice je postavljena korišćenjem kriterijuma Dijagnostičkog i statističkog priručnika za mentalne poremećaje, četvrto izdanje, a pacijent je svakog dana morao da kompletira specijalno dizajniran dnevnik spavanja dok je na zakazanim posetama primenjivana Vizuelna analogna skala za kvalitet života i upitnik samo-evaluacije o Disfunkcionalnim verovanjima i stavovima povezanim sa spavanjem, i to na početku i na kraju ove studije.

Utvrdili smo da su ispitanici u našem ispitivanju imali značajno snižene parametare kvaliteta života, više od očekivanog, ceneći dosadašnje nalaze iz ove oblasti. Međutim, do kraja ispitivanja, kvalitet života je značajno poboljšan uz primenjenu terapiju: kvalitet života je povećan približno za 2/3 u grupi na Lorazepamu, a skoro 2 puta u grupi na Zolpidemu, sa značajnom razlikom u korist Zolpidema (p=0.047). Ovakav nalaz je najverovatnije posledica njegove bolje sigurnosti, a delom i zbog njegove bolje efikasnosti u pogledu uticaja na pojedine oblasti sna, što je prethodno diskutovano.

Dalja istraživanja, specijalizovana u ovoj oblasti, sa većim uzorcima i detaljnijom metodologijom su apsolutno opravdane.

Ključne reči: *primarna nesanica, Zolpidem, kvalitet života*

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INTRODUCTION

Insomnia is a condition of inadequate quality or quantity of sleep (1) that most commonly occurs due to difficulties falling asleep and maintaining sleep and early awakening. Poor sleep does not enable rest, which reflects extremely adversely on daytime activities (2).

To be exact, insomnia is a consequence of numerous illnesses and conditions included under one general term called "sleep disorders". In many individuals with chronic insomnia, it is not possible to determine a clear cause for the condition. The majority of them most likely suffer from primary insomnia, a disorder with a frequency in the general population of 1.3% (3) to 5% (4). Problems with primary insomnia often last over a year (5,6). In some cases, the problems occur early in childhood, while in others, they occur later in life, especially after a stressful event. One study suggested that the average duration of primary insomnia was approximately 14 years, and the onset of complaints was reported to be approximately at the age of 40 years (4). A thorough analysis suggested that primary insomnia is basically a heterogeneous entity that consists of several specific disorders such as psychophysiological insomnia, idiopathic insomnia, and sleep state misperception (7). Chronic stress, inadequate sleep hygiene, and internal distress can also contribute to the onset of primary insomnia (8).

The social aspects of the illness suggest that insomnia can be related to significant daytime effects such as fatigue, irritability, poor concentration and mood changes, and many life activities are disturbed as well (9). For instance, there is also a belief that insomnia is related to greater work absence (10), and it might be associated with a greater risk of car accidents (11). After relieving any pain, the physician's next obligation is to enable adequate sleep for patients in primary healthcare (12). The results published to date clearly indicate that insomnia has pervasive effects on numerous aspects of health-related quality of life and that this connection, to various extents, occurs independently of the comorbidities present (13).

The combined use of a pharmacologic and non-pharmacologic approach (cognitive-behavioural interventions) to treat insomnia provides better results than each of them separately (14). Among the several medications labelled as benzodiazepine hypnotics, the most suitable candidates include temazepam, estazolam, loprazolam, lormetazepam, oxazepam and lorazepam. However, the first 4 hypnotics are not available in Serbia, and oxazepam penetrates the brain relatively slowly, causing a delayed hypnotic action (15). This pharmacological profile makes lorazepam, similar to temazepam, one of the most prescribed hypnotics (16).

The aim of this study was to compare the quality of life of patients with primary insomnia before and after a 3-week treatment with lorazepam and zolpidem and to compare the potential differences in dysfunctional beliefs and attitudes regarding patients' sleep between the two examined groups.

MATERIAL AND METHODS

Patients and Treatment

The study was conducted at the Psychiatric Clinic of the Clinical Centre Kragujevac from September 2003 until May 2010, and it included patients who met the following inclusion criteria: ambulatory patients of both genders, age 18 to 65 years, with a diagnosis of primary insomnia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (17). Patients' somatic state and laboratory analysis had to be within physiological ranges or clinically insignificant, and patients were not previously treated with any psychotropic medications. Before joining the study, the patient or his or her legal representative had to sign, voluntarily and individually, the written informed consent approved by the independent Ethical Committee of Clinical Centre Kragujevac.

The study included 3 weeks of active treatment for each patient, and during this period, the patients received the investigated medications. The duration of active treatment and the dosage were determined according to guidelines on the rational use of hypnotics. The number of patients evaluated to join the study was 49, 41 of whom were included in active treatment and then randomly divided into the treatment groups by clinical pharmacologist. Treatment groups were prepared in accordance with a randomization code list. Qualified patients were randomly placed into group 1 or group 2: group 1 received a 10 mg oral tablet of zolpidem prior to sleep, and group 2 received a 2 mg oral tablet of lorazepam prior to sleep.

From Visit 1, during week 1 of active treatment, the investigated medications were administered continuously, i.e., every night prior to sleep. Since the continuous use of hypnotics can be related to the development of tolerance, as well as rebound effects, we used an intermittent dosage after Visit 2 (during week 2) and after Visit 3 (during week 3 of active treatment). Specifically, the dose was decreased as follows: in week 2, the patients received 5 capsules each, and in week 3, they received 3 capsules each, which they used during the week according to their own needs, until Visit 4 at the end of the study.

Psychiatric Assessment

A diagnosis of primary insomnia can be established when all obvious causes are carefully excluded (17). DSM-IVTR criteria should be used to confirm the diagnosis: complaints lasting for at least a month and causing significant problems in social, professional and all other aspects of life. It is mandatory to exclude other specific sleep disorders (narcolepsy, difficulty breathing, parasomnias, and disorders of circadian rhythm), mental and somatic illnesses, as well as substance abuse (taking drugs) (18).

The examinees completed a specially designed sleep log every day (obtained by combining the Athena Insomnia Scale, 5 items (AIS-5) (19), and the Visual Analogue

Scale (VAS) for quality of life (20)), while on scheduled visits, we also administered the VAS for quality of life and a self-evaluation questionnaire about Dysfunctional Beliefs and Attitudes related to Sleep (DBAS) at Visit 1 and Visit 4.

A Visual Analogue Scale was used to assess patient's quality of life related to his or her current health condition. This scale consists of a 100 millimetre line, with the beginning of the line (0 mm) defined as ²I am completely ill, tired and exhausted, and bad health has completely ruined my life² and the end of the line (100 mm) defined as ²I am completely healthy, rested and fresh, and my great health enables me to fully commit to life². The examinees were asked, ²How did your health condition affect your quality of life during the past week?², and they were instructed to mark the line with a vertical dash, corresponding to where they felt was the appropriate answer. The number of millimetres from the beginning of the line to the spot where the examinee had marked the line was measured with a ruler, and the length obtained corresponded to the score. Higher scores represent a better quality of life (21).

As insomnia also implies a disorder in cognitive functioning, we used a list of 30 items (statements) to obtain a self-evaluation of beliefs and attitudes regarding sleep and difficulties maintaining sleep – the Dysfunctional Beliefs and Attitudes about Sleep (DBAS). The examinee rates all items from 0 to 10. The final score is obtained by adding the points from all items and dividing the total sum by the number of items. This questionnaire is used to establish and assess the changes in cognitive functioning due to sleep and insomnia (beliefs, attitudes, expectations, evaluations, characteristics) (22).

To carefully establish the timeline of quality of life affected by the study medications, in our study, we applied the concept of days adjusted by quality of life (Quality-Adjusted Life Days- QALD). This approach was used analogously to the widely accepted and used concept referring to the period of one year (Quality Adjusted Life Years- QALY), which was primarily developed for chronic illnesses (23). Our methodology was determined by the short-term study period and was also based on similar previous studies that referred to illnesses and conditions with a limited time duration, such as antibiotic prophylaxis (24), prevention of acute respiratory infections (25) and therapy of acute pyelonephritis (26). The basis for the QALD assessment was the previously mentioned utility scores established using the VAS.

Statistical Analysis

All statistical tests were performed using appropriate software (SPSS, 22.0, Chicago, IL, USA). The following descriptive methods were used: measures of central tendency (x), measures of variability (SD) and relative numbers (indicators of structure). Regarding methods for hypothesis testing, the following tests were used: Chi-square test, t-test, Mann-Whitney test, Wilcoxon test, Analysis of variance and Friedman test. Statistical hypotheses were tested at a level of significance of $p<0.05$.

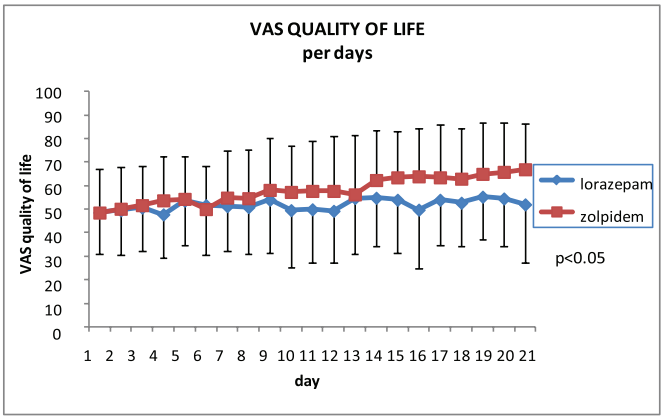

Figure 1. VAS quality of life per day

Based on the daily assessment of quality of life, using the VAS scale as part of the sleep log, we calculated the percentage differences in quality of life (utility score = VAS per day/100), as well as the number of days of quality life (QALD, Quality-adjusted life days = utility score * 21).

RESULTS

Demographic Data

The majority of patients, approximately 2/3, were middle-aged, at the beginning of the fifth decade of their life. A significantly smaller number of patients was younger than 30 years of age (approximately every fifth examinee) or older than 60 years (approximately every 10th examinee). Two-thirds of the investigated population were female. Additionally, approximately 2/3 patients were from an urban environment, whereas every 6th was from a rural setting. Regarding age, gender, place of birth and place of residence, there were no statistically significant differences between the investigated groups.

VAS - Quality of life per day

The comparison of changes in VAS quality of life scores obtained through the 21 days of the study in both groups of patients is presented in Table 1 and Figure 1. There were some significant changes in VAS score over time in both groups of examinees, i.e., the Lorazepam group ($p=0.002$) and Zolpidem group ($p<0.001$). There was a statistically significant difference in VAS quality of life scores between the investigated groups for Day 20 ($p=0.049$) and Day 21 ($p=0.043$), with examinees from the Zolpidem group having significantly better quality of life on those days than the Lorazepam group.

VAS - Quality of life per visit

Repeated-measures single factor analysis of variance was used to compare the changes in VAS scores of quality of life obtained during Visits 1, 2, 3 and 4 in both the

Table 1. VAS quality of life per day

VAS Patient self-evaluation	lorazepam (n=20)	zolpidem (n=21)	p lorazepam vs zolpidem
	$\bar{x}$±SD	$\bar{x}$±SD	
Day 1	48,6±17,61	48,52±18,34	0,896
Day 2	49,45±18,78	50,14±17,78	0,904
Day 3	50,65±18,44	51,66±16,43	0,853
Day 4	47,75±18,33	53,71±18,76	0,31
Day 5	53,55±18,87	54,33±18,13	0,927
Day 6	51,65±21,1	50±18,35	0,79
Day 7	51,25±19,1	54,86±19,8	0,556
Day 8	50,85±19,89	54,62±20,76	0,557
Day 9	53,95±22,67	58,14±22,1	0,522
Day 10	49,55±24,32	57,28±19,66	0,269
Day 11	49,9±22,7	57,71±21,27	0,239
Day 12	49,25±21,98	57,71±23,29	0,188
Day 13	54,7±23,66	56,24±25,3	0,774
Day 14	54,8±20,4	62,33±21,14	0,253
Day 15	53,95±22,65	63,47±19,37	0,155
Day 16	49,75±24,84	63,9±20,53	0,053
Day 17	53,95±19,11	63,48±22,57	0,144
Day 18	52,7±18,57	62,9±21,21	0,064
Day 19	55,25±18,3	64,95±21,58	0,144
Day 20	54,5±20,1	65,8±20,99	0,049
Day 21	52±24,9	66,9±19,22	0,043
p change in time	0,002	0,001	

VAS- Visual Analog Scale; n- number of patients; $\bar{x}$- mean value; SD – standard deviation;

Table 2. VAS - quality of life per visits

Visit	lorazepam (n=20)	zolpidem (n=21)	p lorazepam vs zolpidem
	$\bar{x}$±SD	$\bar{x}$±SD	
Visit 1	32,6±16,24	30,76±15,15	0,676
Visit 2	49,5±17	56,19±18,84	0,134
Visit 3	53,5±17,79	62,76±19,64	0,14
Visit 4	54,95±19,29	67,85±20,1	0,025
p change in time	p<0,001	p<0,001	

VAS- Visual Analog Scale, n- number of patients; $\bar{x}$- mean value; SD – standard deviation

Lorazepam and Zolpidem groups (Table 2). Significant changes over time were identified in the Lorazepam group (p<0.001), as well as in the Zolpidem group (p<0.001).

There was a significant difference in VAS quality of life scores between the investigated groups at Visit 4 (p=0.025), indicating that Zolpidem patients had a better quality of life than Lorazepam patients at that visit. The changes in scores of the VAS quality of life item between visits in both groups of examinees (lorazepam and zolpidem), as well as their statistical significance, are shown in Table 3.

There were significant changes in the Lorazepam group, p<0.05, at Visit 1 compared to Visit 2 (p=0.001), Visit 3 (p<0.001) and Visit 4 (p<0.001). There were also significant changes in the Zolpidem group during Visit 1 compared to Visit 2 (p<0.001), Visit 3 (p<0.001) and Visit 4 (p<0.001) and during Visit 2 compared to Visit 3 (p=0.001) and Visit 4 (p=0.001).

Overall assessment of quality of life

The mean values, standard deviations and significance of changes in total scores for the VAS item- quality of life obtained in the daily evaluations with sleep logs and weekly evaluations during the visits are shown in Table 4.

There were no significant differences based on the daily evaluations, but there was a significant difference in the change in VAS score per day of quality of life between groups in favour of the Zolpidem group (p=0.047) according to the evaluations at visits, which means that the Zolpidem patients had an overall better quality of life.

Based on the daily assessments with sleep logs, the percentage differences in quality of life (utility score), as well as the number of quality life days (QALD) were calculated. The mean values, deviations and significance of the scores of these variables are shown in Table 5.

There were no statistically significant differences in the change in total VAS score, utility score or QALD value between the investigated groups. However, the results showed that there was a difference in VAS quality of life score in favour of Zolpidem patients. During the 3 weeks of treatment, Zolpidem patients had 1.3 more days of quality life than the Lorazepam patients.

DBAS assessment

Changes in cognitive sleep experience at the beginning and at the end of the study were assessed by the DBAS. The results obtained are presented in Table 6.

There was a significant change in DBAS score in the Lorazepam group at p<0.05 on Day 0 compared to Day 21 (p=0.006). A significant change in DBAS score was also present in the Zolpidem group (p<0.001). There was no statistically significant difference in the change in DBAS score between the investigated groups at Visit 1 (p=0.173) and Visit 4 (p=0.392).

DISCUSSION

The concept of quality of life is becoming very important in modern medicine (27). Although there is no universal, generally accepted definition of this term, it most often comprises a subjective and objective assessment of an individual's current level of functioning compared to what that individual perceives is possible or ideal (28).

The effect of a disease on quality of life is determined using different instruments of clinical assessment (29).

Table 3. VAS quality of life between visits

VAS Quality of life	lorazepam (n=20)	zolpidem (n=21)
	p	
V1-V2	0,001	0,001
V1-V3	0,001	0,001
V1-V4	0,001	0,001
V2-V3	0,297	0,001
V2-V4	0,767	0,001
V3-V4	1	0,073

VAS- Visual Analog Scale; n- number of patients; x;¯- mean value; SD – standard deviation;

Table 4. VAS per day of quality of life

Type of assessment	lorazepam (n=20)	zolpidem (n=21)	p
	x;¯±SD	x;¯±SD	
Evaluation at visits	52,78±16,78	62,55±18,16	0,047
Everyday evaluation	51,81±17,47	58±18,79	0,278

VAS- Visual Analog Scale; n- number of patients; x;¯- mean value; SD – standard deviation;

Table 5. VAS score, utility score and QALD of investigated groups

Quality of life variable	lorazepam (n=20)	zolpidem (n=21)	p
	x;¯±SD	x;¯±SD	
VAS total score	1088±366,98	1218,71±394,48	0,197
Utility score*	0,52±0,17	0,58±0,18	0,197
QALD**	10,88±3,67	12,18±3,94	0,196

VAS- Visual Analog Scale; n- number of patients; x;¯- mean value; SD- standard deviation;
*Utility score = VAS per day/100;
**Quality adjusted life days = utility score • 21

Table 6. DBAS score at the first and at the final visit

DBAS	lorazepam (n=20)	zolpidem (n=21)	Statistical significance among groups
	x;¯±SD	x;¯±SD	
Visit 1	5,18±0,98	5,59±0,89	p=0,173
Visit 4	4,4±1,27	4,1±1,01	p=0,392
Statistical significance of changes in time	p=0,006	p<0,001	

VAS- Visual Analog Scale; DBAS- Dysfunctional Beliefs and Attitudes related to Sleep; n- number of patients; x;¯- mean value; SD- standard deviation

Considering the numerous modalities of living and the absence of a unique definition and classification in this area, the precise objectification of quality of life remains a significant investigational challenge. However, by using different methodological approaches and compiling the known findings, relatively good insight into the influence of many diseases on quality of life has been achieved.

There are few studies on insomnia that have investigated quality of life, especially considering the conditions studied in randomized clinical studies. Some of the potential reasons for this scarcity of research are as follows: the large number of different clinical manifestations of sleep disorders, the presence of comorbidity especially from the group of mental illnesses, the absence of a unique classification of treatment, the significant number of different therapeutic approaches, and the demographic, social, economic and cultural differences in different environments. However, based on previously developed instruments such as the QOLI (Quality of Life of Insomniacs) and Leeds Sleep Evaluation Questionnaire, it has been indicated that the presence of insomnia significantly disturbs many domains of quality of life (30,31). Subsequent methodological improvements, such as the SF-36 questionnaire (Medical Outcomes Study Short-Form Health Survey 36), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), Hotel Dieu 16 (HD-16) and others, have enabled further insight into the relationship between insomnia and quality of life.

In this study, we performed a global assessment of quality of life using the Visual Analogue Scale on a daily basis (using the sleep log) as well as weekly at study visits. At the beginning of the study, it was established that insomnia has an extremely negative influence on quality of life (quality of life was rated at only 1/3 of the ideal). However, by the end of the study, quality of life had significantly improved with treatment, by approximately 2/3 in the Lorazepam group and more than twice in the Zolpidem group, with significant difference in favour of Zolpidem. Similar results were achieved in the daily assessments of quality of life.

The estimated quality of life was significantly lower than those of other similar studies. For instance, in a sample of 35,527 Ontario residents in Canada, the utility index for mental illnesses (indirect measure of quality of life) was estimated to be between 0.846 and 0.850 out of a maximum score of 1.0, while the lowest values were recorded in individuals who survived a traumatic event (0.765 - 0.790) (32). In a different study, quality of life was evaluated as relatively good in individuals with insomnia: 70% in individuals with chronic insomnia, 81% in individuals with occasional sleep disturbances, and 96% in individuals without insomnia (9). The lower quality of life in our study can be explained by the influence of at least 3 factors. First, the specific social-economic conditions in our country in previous decades had a significant influence, leading to a decrease in quality of both health and living compared to other, more developed countries, as shown by many domestic studies (33,34,35) and as recognized by the international public as well (36,37).

Second, there is a certain degree of methodological limitations to our research regarding the measurement of quality of life. Although the VAS scale, which was used in our study, is a widely used instrument, it does have some significant shortcomings (38). Accordingly, the simultaneous use of several techniques such as Time-to-Trade Off (TTO),

Standard-Gamble (SG) or generic questionnaires such as the SF-36 is recommended for a more precise assessment of quality of life. In studies of patients with insomnia treated with zolpidem, the SF-36 scale showed a significant improvement in quality of life (39,40). However, our study was not specifically directed and designed to evaluate quality of life. Instead, that part of the analysis was primarily predicted by the needs of an economic model, i.e., the identification of utility scores for a subsequent analysis of cost-utility. Indeed, there are almost no valid studies for individuals with insomnia that have established the exact values of utility scores, especially in therapeutic trials (41).

Third, it is known that quality life is negatively correlated with the severity of insomnia (42). The inclusion of the general population in the assessment of the index, that is, utility scores, and the heterogeneity in terms of various clinical forms of insomnia represent significant methodological differences between our research and other studies, and thus a more reliable comparison of results is needed. Our study sample was strictly limited to individuals with primary insomnia, and the presence of more than two-thirds of those with a severe form of insomnia might be the reason for the significantly worse quality of life scores than expected.

In our study, the group that received zolpidem had higher QALD scores; more precisely, every zolpidem examinee had 1-2 more days of quality living than individuals in the control group. Although this difference was not statistically significant and seems relatively modest, it could be of greater interest over a longer period of time. For example, a six-month duration of insomnia is the minimum period for diagnosing chronic primary insomnia beyond any doubt (43). If individuals are treated with zolpidem throughout this entire period, as in previous clinical studies (44,45), then they could have at least 8 to 16 more days of quality life than if they were not taking any hypnotic medication or were treated with lorazepam or similar benzodiazepines. As chronic insomnias usually last a year, even longer (6), this gain would become progressively larger over a longer period of time.

CONCLUSION

In summary, the examinees in our study had a significantly decreased quality of life, quite lower than expected based on previous findings in this area. Generally, individuals treated with zolpidem showed a trend of improving quality of life, which reached statistical significance in some aspects by the end of the study monitoring period. This finding is most likely a consequence of its better safety profile and partially its better efficiency in terms of influence on certain domains of sleep itself, as discussed previously. The small study sample, methodological limitations of evaluating quality of life, as well as the relatively short period of time are probable reasons the superiority of zolpidem in this domain of clinical efficiency was not definitively proven. Furthermore, specialized studies in this area with larger sample sizes and a more detailed methodology are clearly necessary. Based on our results, treating insomnia can improve quality of life domains to a significant extent, although the final effects depend on many factors such as the investigated population, the assessment method used, and the therapeutic modality.

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Conflict of Interest
None.

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