The reporting quality of abstracts of randomized controlled trials on melatonin

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THE REPORTING QUALITY OF ABSTRACTS OF RANDOMIZED CONTROLLED TRIALS ON MELATONIN

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LIST OF ABBREVIATIONS

WHO - World Health Organization

ICSD - International Classification of Sleep Disorders

DIS - difficulty initiating sleep

DMS - difficulty maintaining sleep

EMA - early morning awakening

Apo E4 - Apolipoprotein E4,

PER3 - Period Circadian Regulators,

Clock - Clock Circadian Regulator

5-HTTLPR - Serotonin Transporter Linked Polymorphic Region

non-REM - non-rapid eye movement

REM - rapid-eye movement

ARAS - ascending reticular activation system

VLPO - ventrolateral preoptic nucleus

VLPR - ventrolateral preoptic region

GABA - γ-aminobutyric acid

CBT - cognitive behavioral therapy

BZRA - benzodiazepine receptor agonist

FDA - Food and Drug Administration

(5-HT) - 5-hydroxytryptophan

SCN - suprachiasmatic nuclei

RCT - randomized controlled trials

CONSORT - Consolidated Standards for Reporting Trials and

QUORUM - (Quality of Reporting of Meta-Analyses)

1. INTRODUCTION

1.1. Mental health

According to the World Health Organization (WHO), mental health is described as a state of well-being where individuals are capable of coping with the challenges of life, developing their abilities, performing effectively in educational and occupational settings, and contributing to their communities. Additionally, mental health plays a role in our ability to make decisions, establish relationships, and has an impact on our environment. Mental health is an essential human right and important for socio-economic, communal and personal development (1). There are many proposed risk and protective factors for the mental health of an individual. The WHO mentions psychosocial, biological, socio-economic, and genetics as risk factors. Protective factors comprise the distinctive social and emotional abilities and characteristics as well as fulfilling interpersonal connections, quality education, decent job, and safe neighborhoods (1).

The understanding of various medical and psychological conditions now recognizes the substantial influence of individuals' lifestyle choices. Numerous factors related to one's way of living have been acknowledged as having an important effect on the prevention and management of medical and psychiatric conditions, as well as the associated morbidity and mortality. Among these are consuming healthy food, engaging in more physical activity, abstaining from alcohol and other drugs, as well as giving up smoking. A healthy environment, adequate sleep, fun and stress-relieving hobbies, social connections and support, and mentally stimulating activities are some other noted lifestyle factors contributing to the quality of healthy living (2).

1.2. Insomnia

Sleep occupies approximately one third of the human lifespan, amounting to an average of eight hours per night for an average adult. It is suggested that it serves memory consolidation, energy conservation, and restoration. Sleep is defined as a quickly reversible condition of decreased reactivity of motor activity, and metabolism (3). It makes up an essential part of life and contributes to the normal functioning of the brain, metabolism, immune system, hormones, cardiovascular system, and appetite regulation. Healthy sleep should last an adequate amount of time, be of high quality, occur at the right time and regularly, and lack disturbances or disorders (4).

Sleep disturbance can cause clinically significant sleep disorders. According to the International Classification of Sleep Disorders (ICSD), these are sorted into categories as seen in Figure 1 (5). Further in the text, the focus will be directed to Insomnia disorder.

TABLE 1] ICSD-3 Major Diagnostic Sections

Section
Insomnia
Sleep-related breathing disorders
Central disorders of hypersomnolence
Circadian rhythm sleep-wake disorders
Parasomnias
Sleep-related movement disorders
Other sleep disorders

ICSD = *International Classification of Sleep Disorders.*

Figure 1. ICSD-3 Major Diagnostic Sections (5).

Insomnia stands as the prevailing sleep disorder, ranking as the second most frequent neuropsychiatric disorder (6). It is often encountered in medical practice and may occur alone or in association with other physical or mental health conditions, for example, pain and depression. The main characteristics of the disorder are unsatisfactory sleep duration or quality and difficulties falling and staying asleep (7). Commonly used terms for these problems are difficulty initiating sleep (DIS) and difficulty maintaining sleep (DMS). Additionally, early morning awakening (EMA) can also be found in insomnia patients, meaning that the affected awaken at night or earlier than they wanted or needed (6). Unsatisfactory sleep leads to deficits

in diurnal performance seen as fatigue, excessive daytime somnolence, attention deficit, concentration and memory loss, emotional disturbance, and change in behavior. It can also impair occupational, school, and social performance and personal relationships (8). Insomnia needs to be differentiated from acute sleep disturbance, the main difference being the duration. To diagnose insomnia, the before-mentioned symptoms and difficulties are required to occur on a minimum of three nights per week and persist for a duration exceeding three months (7).

If the sleep disturbance lasts for more than three months it is also termed chronic insomnia. Insomnia lasting for less than three months is called short-term and any sleep disturbance not matching the criteria for either long or short-term insomnia is assigned to the category of other Insomnia disorders (9).

There are multiple theories on the development of insomnia. Figure 2 illustrates different contributing factors and possible mechanisms of Insomnia Pathophysiology.

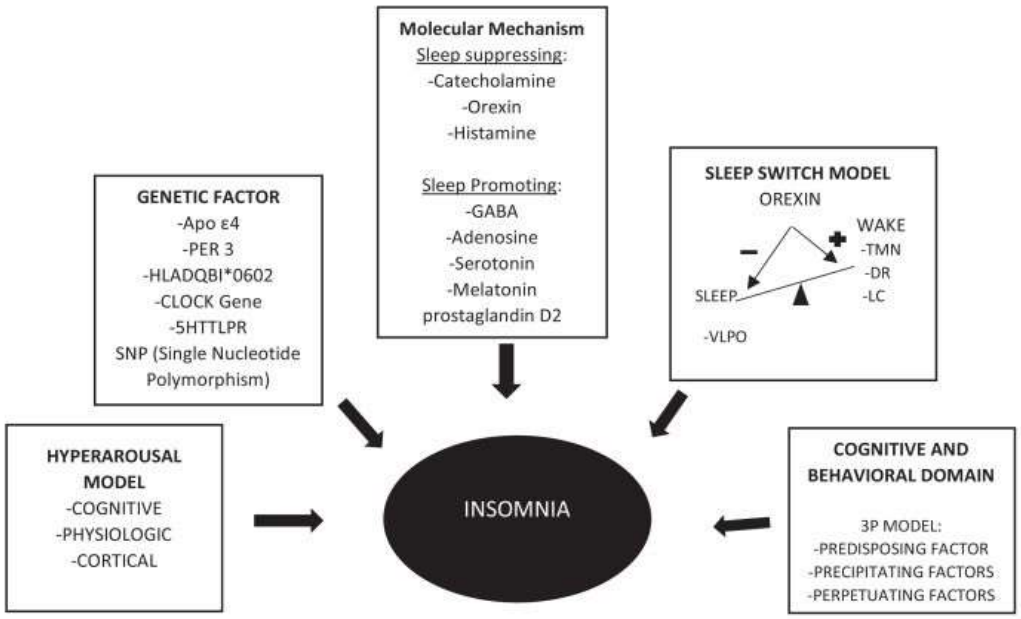

Figure 2. Pathophysiology of Insomnia (DR: dorsal raphe; TMN: Tuberomamillary nucleus; GABA: gamma-aminobutyric acid; LC: Locus coeruleus; VLPO: ventrolateral preoptic nucleus) (9).

The following genetic factors were found to influence the development of Insomnia: Apolipoprotein E4 (Apo E4), Clock Circadian Regulator (Clock), Serotonin Transporter Linked Polymorphic Region (5-HTTLPR), and Period Circadian Regulators (PER3) (9).

Sleeping can be divided into four stages. The first three belong to non-rapid eye movement (non-REM) sleep, shown by slower activity on the EEG. During stages one and two

a person loses their conscious awareness and stage three corresponds to deep sleep. Stage four is characterized by rapid-eye movement (REM) sleep and dreaming (10,11).

The state of wakefulness is attained through the activation of ascending reticular activation system (ARAS) in the brain, which consists of multiple brainstem and posterior hypothalamic nuclei (11). Molecular factors can be divided into sleep-suppressing and sleep-promoting, as seen in Figure 2. Orexin is one of the Sleep suppressing molecules that reinforces the ARAS activity and is suggested to have a function in the Sleep switch Model (9,11). The name Sleep switch model is derived from the fact that sleep and wakefulness cannot occur at the same time, but one needs to be switched off for the other to occur (11).

Orexin causes increased neuronal activity in the dorsal raphe, locus coeruleus, and tuberomammillary nucleus, which belong to the wake-promoting areas, but it inhibits the median preoptic nucleus and ventrolateral preoptic nucleus (VLPO), the sleep-promoting areas (9). Together with norepinephrine and dopamine, orexin achieves wakefulness by inhibition of the ventrolateral preoptic region (VLPR). On the other hand, the VLPR's neurotransmitter γ-aminobutyric acid (GABA), is mostly responsible for inhibiting the ARAS during sleep. The same mechanism of switching is also responsible for the change between REM and non-REM sleep (11).

In some literature, insomnia is described as a result of hyperarousal, which can mean cognitive, physiologic, or cortical overactivity. Physiological hyperarousal refers to the overactivity of autonomic or cortical nervous systems, while cognitive hyperarousal is linked to emotional well-being and psychological factors. The theory leans on the 3P Model of the behavioral domain (12,13). This model, established by Spielmann, outlines three elements that contribute to the emergence of insomnia. Genetic factors, a confirmed positive family history and personality traits are considered predisposing factors. Precipitating factors describe the elements that contributed to the initiation of sleep disruption. For example, many women experience sleep issues for the first time during pregnancy or menopause. Occupational or social changes such as shift work, divorce, or deaths in the family can also trigger insomnia. Perpetuating factors are behaviors, that are adapted to combat insomnia but actually worsen or stabilize it. Examples of this include using alcohol as a sleeping aid or daytime napping, which negatively influence sleep quality and onset at night, respectively. Perpetuating factors are signs of insomnia becoming a long-term issue (11,14).

The described relationship between precipitating and perpetuating factors by the example of trauma-induced insomnia is shown in Figure 3. A precipitating factor, for example, a car accident, leads to an emotional reaction, which can cause dysfunctional thoughts and/or dysregulated brain function. The dysregulated amygdala causes REM sleep disturbance, reduced deep sleep, and sleep fragmentation, while dysfunctional thoughts lead to nightmares. All of this constitutes acute trauma-induced insomnia. To combat Insomnia, the affected uses, for example, coffee to handle daytime sleepiness or alcohol to fall asleep, which worsens Insomnia and facilitates progression to the chronic form. Predisposing factors are thought to influence this process at multiple points since an affected person without the aforementioned factors is less likely to develop any of the shown reactions following trauma (15).

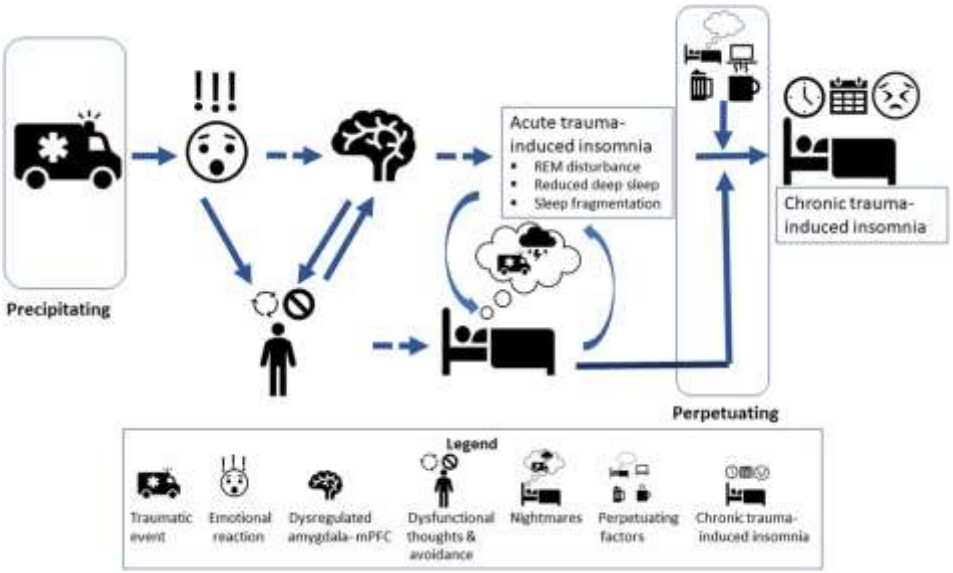

Figure 3. Integrated model of chronic trauma-induced insomnia (15).

Long-term insomnia has the potential to negatively impact one's life satisfaction and disrupt both mental and physical well-being (7). It was found that patients affected by insomnia are at a heightened risk of developing conditions such as hypertension, acute myocardial infarction, heart failure, diabetes, and death, especially if the sleep duration is less than 6 hours per night. Furthermore, the likelihood of experiencing major depression also becomes elevated (8). Therefore, it is crucial to recognize and treat every affected person appropriately.

1.3. Pharmacotherapy

Acute Insomnia caused by a stressor is common and usually subsides after the disappearance of the stressor. As per the guidelines of the European Sleep Research Society of insomnia, cognitive behavioral therapy (CBT) is considered the primary treatment for chronic insomnia in adults. This therapeutic approach encompasses a range of techniques and strategies, which are not elaborated upon in this particular thesis (16). Treatment for insomnia aims to correct the mismatched homeostatic and circadian drives that are responsible for the underlying sleep disorder (17). In Europe, there are seven primary categories of medications employed for the treatment of insomnia, those are listed in Figure 4.

BZ	Diazepam, flunitrazepam, flurazepam, lormetazepam, nitrazepam, oxazepam, temazepam, triazolam
BZRA	Zaleplone, zolpidem, zopiclone
Antidepressants	Agomelatine, amitriptyline, doxepin, mianserin, mirtazapine, trazodone, trimipramine
Antipsychotics	Chlorprothixene, levomepromazine, melperone, olanzapine, pipamperone, prothipendyl, quetiapine
Antihistamines	Diphenhydramine, doxylamine, hydroxyzine, promethazine
Phytotherapeutics	Hops, melissa, passiflora, valerian
Melatonin receptor agonists	Melatonin, ramelteon, slow-release melatonin

BZ, benzodiazepines; BZRA, benzodiazepine receptor agonists.

Figure 4. Major drug classes used to treat insomnia in Europe (16)

Benzodiazepine and non-benzodiazepine BZRAs, also called Z-drugs, both act on the GABAergic system, and potentiate its effect, which promotes sleep (18). Drugs in this class have different pharmacokinetic properties, which influence their therapeutic and adverse effects. Especially important for the treatment of Insomnia are the half-lives. This can be shown in the example of zaleplon, a Z-drug, and temazepam, a traditional benzodiazepine. Zaleplon, with a half-life of one hour, is effective in reducing the time it takes to fall asleep (sleep latency) but it does not typically extend the duration of sleep. On the other hand, temazepam, which has a longer onset of action, has a limited impact on sleep latency but helps reduce the time spent awake. Traditional benzodiazepines, when used, can alter the sleep stages by reducing or

delaying REM sleep, while zaleplon and zolpidem do not show the same effect. When prescribing BZRAs special attention should be directed toward patients with lung diseases since long-acting benzodiazepines can suppress breathing (19). Another problem of long-acting benzodiazepines is the emergence of tolerance and challenging withdrawal, which may become fatal if done rapidly. Headaches, dizziness, sleepiness during the day, and psychomotor and cognitive problems, belong to the common adverse reactions of BSRAs, which can lead to falls, injuries, and accidents, especially in the elderly population (19,20).

Doxepin stands out as the sole tricyclic antidepressant authorized by the United States Food and Drug Administration (FDA) for managing sleep maintenance insomnia, while other sedating antidepressants such as trazodone are used off-label. They should not be the first choice because there is insufficient evidence to support their usage in the treatment of insomnia. (21). At the low dosage of doxepin used in Insomnia treatment, no anticholinergic or cognitive adverse effects were seen (20). Trazodone can cause hypotension and priapism (19).

In the clinic, sedating atypical antipsychotics, especially quetiapine, are frequently used to treat insomnia that co-occurs with psychiatric illness. They are beneficial in the treatment of bipolar and psychiatric illnesses but don't show effectiveness in insomnia treatment, which is why it is not recommended to prescribe them (22). Olanzapine and quetiapine both act as antagonists to alpha-1, dopamine, histamine, serotonin, cholinergic and muscarinic receptors which is reflected in the reported adverse effects, such as weight gain, nocturnal leg movements, orthostatic hypotension, and anticholinergic symptoms (19).

Diphenhydramine is a first-generation antihistamine, which was primarily used for the treatment of allergies. But it was discovered that it causes drowsiness and sleepiness as a side effect, through inhibition of postsynaptic H1 receptors. Considering its extended half-life and anticholinergic properties, the usage of doxepin is not advised for elderly patients. Potential adverse reactions can be grogginess dry mouth, difficulties urinating, and cognitive impairment (19,20).

Additionally, a new class of drugs was recently discovered, acting on the hypocretin/orexin system. The first FDA-approved drug of this class was suvorexant in 2014, which is a dual orexin receptor antagonist. As explained above, orexin promotes arousal and wakefulness. Orexin-A and -B are two orexin neuropeptides. Suvorexant binds reversibly to both and thereby inhibits the activation of the arousal system. At lower doses, it seems to have a different side effect profile, than conventionally used drugs for Insomnia, but it is still new and needs to be further evaluated for effectiveness and adverse events (18,23).

Due to the large number of side effects of conventional pharmacotherapy, more people are trying to use phytotherapeutics, meaning herbal medicine, as an aid in psychiatric disorders, among them insomnia (24). Lemon balm (*Melissa officinalis*), Ashwagandha, German chamomile, hops, and valerian are some of the herbs that have been utilized for centuries by herbal medicine practitioners and indigenous societies to manage sleep problems. Based on empirical data, it was shown that certain plants have the potential to aid in the treatment of insomnia by reducing the time it takes to fall asleep and enhancing the duration of sleep. This effect is believed to be achieved by actions on glutamic acid decarboxylase or GABA and 5-hydroxytryptophan (5-HT) receptors. This shows that it is physiologically possible to alleviate insomnia using herbal remedies, but further studies are needed to conclude effectiveness and safety (25).

1.3.1. Melatonin

Mammals have a central circadian clock that synchronizes internal body functions and behaviors with the external 24-hour light-dark course. This clock lies in the suprachiasmatic nuclei (SCN), belonging to the hypothalamus. When deprived of light, the SCN activates the synthesis of melatonin within the pineal gland (26). Melatonin itself then acts as a messenger, relaying the information about night time, for other systems in the body, which have melatonin receptors. This contributes to the regulation of the immune system, blood pressure, and bone metabolism and also functions regulated by the SCN as temperature, sleep-wake state, and cortisol. The relationship between melatonin and the last three factors was demonstrated in long-sleepers, which show a decreased body temperature and increased melatonin and cortisol levels longer than short sleepers. Furthermore, studies showed melatonin's sleep-inducing properties, upon administration at day and night time, although higher doses were needed at night (27). An interesting factor pointing towards the connection between melatonin and sleep is that melatonin levels decrease from childhood until adulthood and old age. The potential connection between pineal gland calcification and aging could contribute to reduced melatonin levels. This decline in melatonin among the elderly is also the basis for utilizing it in the management of insomnia in this population (27,28).

Melatonin, as exogenous substance, can be found in the form of a dietary supplement commercially, and its regulation falls outside the purview of the FDA. Despite the absence of FDA approval, the American Academy of Family Physicians recommends melatonin as the primary pharmacological management of insomnia. (29).

It is available in various forms for different routes of administration. There are tablets and liquid for oral use, rectal suppositories and transdermal patches. Three distinct formulations exist depending on the timing of their release: immediate-release, extended-release and a combination of immediate and extended-release (29). Controlled-release melatonin supplements should be avoided in older people since they may induce prolonged melatonin levels (30).

Due to the lack of strict FDA regulation in the United States, compared to other new drugs, the dosage marked on the products may not be the actual one. Doses can vary from 0.3 mg up to 60 mg. Europe on the other hand has regulated numerous formulations. Immediate-release tablets come in doses of 0.3 to 0.5 mg, while prolonged-release tablets come in 2 mg (20).

Studies revealed reduced sleep latency as a consistent result of melatonin use, while the effect on wakefulness was unclear. Melatonin had no impact on sleep duration (19).

In the short term, using exogenous melatonin was not linked to any major side effects, according to a systematic review from 2019. Headaches, dizziness, hypothermia, exhaustion, sleepiness during the day, and other issues concerning sleep emerged as most prevalent side effects. The mild rise in headache frequency and daytime tiredness is supported by the most evidence. The absence of data from long standing randomized controlled trials (RCTs) hinders the ability to draw conclusions about long-term safety and tolerability, which suggests a need for more research (31).

1.4. Quality of Research

Dietary supplements like Melatonin are not under strict FDA regulation. As a physician it is necessary to be informed about the supplements patients are taking or planning to take to be able to recommend them or not. Therefore, it is important to find relevant and high-quality information about research done on the subject.

Using the best available evidence to guide a physician’s practice is crucial for improving patient care. Today a lot of publications are available on the internet, but it is hard to filter out the research with the best quality, supporting the author's claims. As an example, a common reason why research would be considered invalid is the study size being too small (32).

Good clinical research should be based on an original and meaningful research question, which should be testable and answerable. The hypothesis should be clear from the beginning and followed by study planning and execution (33).

A methodology appropriate for the research question should be chosen, ensuring the collection and correct analysis of important data. Additionally, previously done research on the chosen topic should be reviewed and taken into consideration. Criteria for good research also include external validity, replicability, reproducibility, transparency, and representativeness (34).

But regardless of the study's outcome or validity, authors can increase the usefulness of their research, by proper reporting and making it transparent to readers or peer reviewers. When reporting their research, CONSORT (Consolidated Standards for Reporting Trials) and QUORUM (Quality of Reporting of Meta-Analyses) are two established protocols, that have been devised to assist researchers and enhance the caliber of research documentation. CONSORT focuses on the reporting of trials, while QUORUM is a guideline for the reporting of meta-analyses (32,33).

1.4.1. CONSORT

A well-designed and appropriate RCT stands as the benchmark for assessing the effectiveness of new treatments. The accurate reporting of RCTs holds equal significance to robust science and methodology, enabling readers to assess the credibility of trial results. The initial presentation of the CONSORT statement occurred in 1996, with subsequent revisions in the years 2001 and 2010 (35). It consists of a checklist of important elements that should be present in RCT reports, as well as a visual representation illustrating the progression of participants through a trial. In addition to aiding authors in writing reports, it is also meant to help readers, experts in the researched fields (peer reviewers), as well as journal editors in interpretation. Initially, CONSORT was meant for RCTs with two group parallel designs, but lately, extensions have been added to optimize its use for various other trial designs, data, and intervention types, seen in Figure 5 (36).

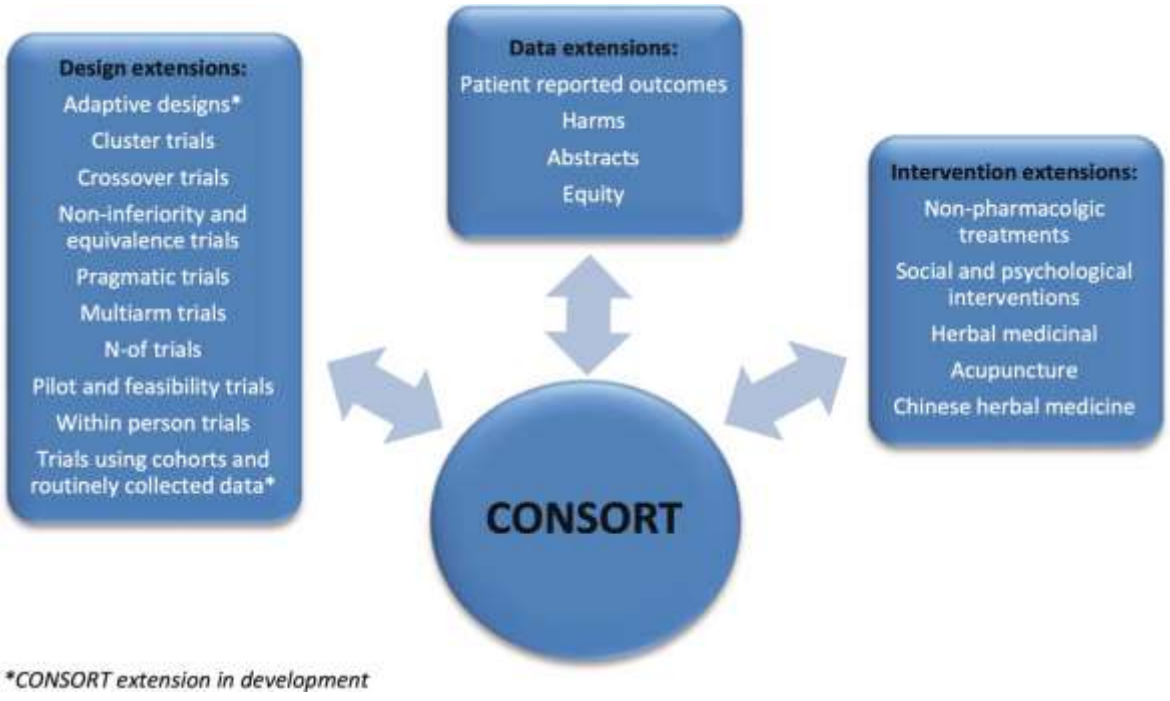

Figure 5. Extensions of the CONSORT statement (36).

CONSORT also provides a checklist of items to include in abstracts of RCTs, as seen in Figure 6, because abstracts are often used to make a first assessment of the trial and decide whether to read it. For some healthcare professionals, the full versions of the articles might not be accessible, which is why the abstracts should contain enough information to make a judgment about validity and applicability (37).

Item	Description
Title	Identification of the study as randomized
Authors *	Contact details for the corresponding author
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)
Methods	
Participants	Eligibility criteria for participants and the settings where the data were collected
Interventions	Interventions intended for each group
Objective	Specific objective or hypothesis
Outcome	Clearly defined primary outcome for this report
Randomization	How participants were allocated to interventions
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment
Results	
Numbers randomized	Number of participants randomized to each group
Recruitment	Trial status
Numbers analysed	Number of participants analysed in each group
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision
Harms	Important adverse events or side effects
Conclusions	General interpretation of the results
Trial registration	Registration number and name of trial register
Funding	Source of funding

*This item is specific to conference abstracts.
doi:10.1371/journal.pmed.0050020.t001

Figure 6. Items to include when reporting a randomized trial in a journal or conference abstract (37).

According to CONSORT the title of the report should state, that it's a randomized control trial, so it can be indexed properly in the databases. Authors should also include contact details making it possible for readers to access additional data on the RCT. Describing the trial design also helps with indexing and avoiding misinterpretation by readers. For readers to evaluate the trial's external validity and determine whether it is applicable to their own context, a thorough explanation of the trial participants and the environment in which they were investigated is required. Interventions should be fully explained and one or multiple objectives stated. In the case of multiple objectives, the main and key secondary objectives should be shown. The primary outcome of the experiment should be stated precisely by the authors, along with when it was evaluated. Randomization and Masking in RCTs prevent investigators and participants from influencing the trial and causing bias. Stating the methods used for both helps readers judge the probability of selection bias or overestimated effects due to lack of blinding. Results shown in the abstract should include, the total count of randomized participants within

each group, the trial's status, meaning whether it is active or has concluded in terms of participant recruitment and follow-up, the outcomes observed, and important side effects. The use of trial registration numbers aid in conducting proper systematic reviews, avoiding the inclusion of the same study results multiple times. Since the pharmacological industry has an interest in their products showing favorable results, funding should always be disclosed (37).

CONSORT for abstracts was formally recommended to all authors by the International Committee of medical journal editors and many more editors and journals (38). But despite CONSORT reporting guidelines being endorsed by them, research is still not being published properly. Reasons for this could be the lack of proper instructions for authors or their lack of knowledge about the existing guidelines for research and reporting or the use of inappropriate checklist extensions (35).

2. OBJECTIVES

The goal of this study was to analyze the quality of abstracts of RCTs regarding melatonin and sleep disorders.

3. MATERIALS AND METHODS

This cross-sectional study aimed to evaluate the reporting quality of abstracts available on PubMed regarding RCTs on melatonin and sleep. In December 2022 a PubMed search including the terms “melatonin” and “sleep” was performed and the filter for RCTs was used. The search was limited to articles published between the years 2012 and 2021. There were 232 Abstracts found and 13 were excluded. The reason for the exclusion was they either not qualifying as RCT or not being available.

To evaluate the quality of the found abstracts, the CONSORT for abstracts checklist was used.

First, the title of the article, publication year, and the journal name were analyzed.

The checklist further guides the evaluation of the article title (whether or not it contains randomization), the author’s contact information, and the description of the trial design (whether it is parallel, cluster, or non-inferiority), methods, results, and conclusions.

When analyzing the three latter items it needed to be established whether the following information was given or not: participants’ eligibility criteria and setting, interventions intended for each group, specific objectives, clearly defined primary outcome, allocation of participants, blinding, numbers randomized (number of participants randomized to each group), recruitment (trial status), numbers analyzed (number of participants analyzed in each group), the primary outcome for each group, important adverse events or side effects and a general interpretation of results.

The abstract was also checked for a trial registration number and a source of funding.

Additionally, the number of participants, country of study conduction, whether it is a pharmacological trial, multicentricity, significance of results, financing, place of study, number of authors, and structure were evaluated.

The collected data from the abstracts was documented in a Microsoft Office Excel table and analyzed using MedCalc software for Windows (v.11.5.1.0, MedCalc Software, Ostend Belgium).

4. RESULTS

In total, 232 abstracts were found on the MEDLINE data search engine using melatonin as a keyword. Out of 232 abstracts, 5 were animal studies, 4 were not randomized controlled trials and 4 did not include melatonin as an intervention. Therefore, these 13 abstracts were not eligible to be included in this study and 219 abstracts were included in the final analysis.

The abstract with the lowest CONSORT total score did not include any of the 17 items, and the abstract with the highest CONSORT total score included 16 items. The median value of CONSORT total score of melatonin research abstracts was 7, and the interquartile range 6-9. The difference in median value between abstracts published in different journal categories is presented in Figure 7. Quartile 0 includes journals that are not categorized in quartiles according to Journal Citation Reports. The highest CONSORT total score was observed in abstracts published in the first quartile, and the lowest median value in abstracts published in journals without the quartile.

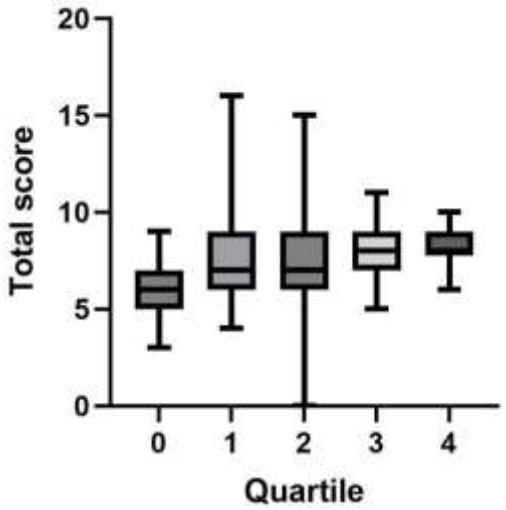

Figure 7. Difference in CONSORT total score between different journal categories

A very low proportion, 4.1%, of published studies were conducted as multiple centers. Significant results for primary outcomes were reported in 167 (76.3%) of melatonin abstracts. The majority of abstracts, 62.1%, had structure. The proportion of reported CONSORT checklist items is shown in Table 1. The CONSORT item most frequently reported, in 216 (98.6%) abstracts, was the objective of the study. The CONSORT item least frequently reported was funding, reported in only 8 (3.7%) abstracts.

Table 1. Frequency of CONSORT items in melatonin abstracts

	N (%)
1. Title	120 (54.8)
2. Authors	117 (53.4)
3. Trial design	73 (33.5)
4. Participants	69 (31.5)
5. Interventions	214 (97.7)
6. Objective	216 (98.6)
7. Outcomes	211 (96.3)
8. Randomization type	9 (4.1)
9. Blinding	108 (49.3)
10. Numbers randomized	83 (37.9)
11. Recruitment	116 (53.0)
12. Numbers analyzed	13 (5.9)
13. Trial outcome	42 (19.2)
14. Harms	38 (17.3)
15. Conclusion	209 (95.4)
16. Trial registration	7 (6.5)
17. Funding	8 (3.7)

Data are presented as whole number (percentage)

A comparison of abstracts that included significant or non-significant results (Table 2) for primary outcome revealed a significant difference between several CONSORT items. The randomization was mentioned in the title of non-significant results more frequently than in the title aim of the abstracts of significant outcomes, 69.2% vs. 50.3%, P=0.025. Another statistically significant difference between these two groups was found in the participants' category (inclusion criteria and study setting), 40.4% vs. 28.7%, P=0.035.

However, the conclusion was more frequently reported in abstracts with significant results, all 100% of them, compared to 80.8% of abstracts with non-significant results.

Table 2. Comparison of CONSORT items in abstracts of different significance

	N (%) N=167	N (%) N=52	P value*
	Significant results	Non-significant results	
1. Title	84 (50.3)	36 (69.2)	**0.025**
2. Authors	84 (50.3)	31 (59.6)	0.387
3. Trial design	54 (32.5)	19 (36.5)	0.134
4. Participants	48 (28.7)	21 (40.4)	**0.035**
5. Interventions	162 (97.0)	52 (100.0)	0.465
6. Objective	164 (98.2)	52 (100.0)	0.771
7. Outcomes	159 (95.2)	52 (100.0)	0.236
8. Randomization type	4 (2.4)	5 (9.6)	0.048
9. Blinding	73 (43.7)	35 (67.3)	0.005
10. Numbers randomized	66 (39.5)	17 (32.7)	0.469
11. Recruitment	90 (53.9)	26 (50.0)	0.739
12. Numbers analyzed	12 (7.2)	1 (1.9)	0.286
13. Trial outcome	32 (19.2)	10 (19.2)	0.849
14. Harms	31 (18.6)	7 (13.5)	0.523
15. Conclusion	167 (100.0)	42 (80.8)	**<0.001**
16. Trial registration	28 (16.8)	18 (34.6)	**0.010**
17. Funding	6 (3.6)	2 (3.8)	0.735

*chi-squared test
Data are presented as whole number (percentage)

5. DISCUSSION

In general, the randomized controlled trials included in this study scored in the medium range of the CONSORT total score suggesting that there is partial adherence to the CONSORT checklist. However, it is worth noting that there remains potential for further enhancement in meeting the checklist's requirements. It is important to highlight that all articles with a significant outcome included conclusions in their abstracts. Conversely in 20% of articles without significant results, conclusions were missing, which could be intentional attempt to conceal the lack of results or just non-qualitative reporting. An interesting result of the study is that the journals ranked in the first quartile showed highest total scores while the ones not indexed in Web of Science (without quartile) showed the lowest. This observation indicates that esteemed journals of higher ranking, may place greater emphasis on the significance of high-quality reporting.

A study conducted in 2022 by the University of Split School of Medicine aimed to determine the reporting quality of abstracts of RCTs about *Helicobacter Pylori*, after introduction of CONSORT guidelines. It shows slightly better results than this study. Both studies showed that no abstract reported all 17 items. The lowest number of items included in the *H. pylori* abstracts was 3 out of 17, while it was 0 in the melatonin reports. In the abstracts about *H. pylori,* there were eight adequately reported items on average with an interquartile range of 7 to 9, while for melatonin the median value was 7 and the interquartile range was 6 to 9. When comparing the percentages of different items included in the abstracts, interestingly there are some similarities in the very high and very low scoring items. In both studies interventions, objective, outcomes and conclusions were stated in most abstracts, while participants, trial registration, and funding were not reported in most articles. Thus, it might indicate that there is a need for a greater explanation of these items and their significance in the CONSORT statement, as well as better regulations for trial registration and disclosure of funding. Surprisingly trial design and blinding methods were reported better in the melatonin studies. Percentages of numbers randomized and analyzed were a lot smaller in the abstracts concerning melatonin (39).

In general, it would be reasonable to anticipate a higher level of reporting quality in studies related to *H. pylori*, considering its status as an extensively researched topic addressed in everyday hospital and outpatient practices, as well as an abundance of therapeutic options that have been explored. This is in contrast to melatonin, which is primarily marketed as a dietary supplement and often falls outside the scope of regulatory requirements for medications.

Aaron Lerner, a dermatologist, discovered melatonin in 1958 and was able to isolate it. Later Alfred Lewy's finding that intense nighttime light inhibited melatonin production, advanced chronobiology and melatonin studies. Melatonin's influence on body functions drew attention to the hormone in the early 1990s and it's still studied until this day (40).

The first time a melatonin formulation appeared on the market was in 1996 and since 2005 a number of melatonin-related substances, like Ramelteon, which has a longer half-life than melatonin, were first made available. Unlike the dietary supplement, melatonin formulations, its use is authorized by the FDA and can only be prescribed by medical doctors in the USA (41,42,43).

The dietary supplement is not properly monitored which was shown in a study from 2017. The majority of melatonin supplements exhibited a notable disparity between the actual melatonin content and the stated quantity on their labels. Approximately a quarter of those tested also contained potentially harmful serotonin (44). The United Kingdom, Japan, and European Union have all outlawed melatonin sales without prescription (45). In the past in Germany, melatonin was a prescription-only medication, which has recently changed, because of an unclear judicial definition of melatonin, making melatonin in the form of sprays and liquids freely available for everyone (46). As mentioned before, there is also a lack of data about the long-term effects of melatonin on the human body. All of this shows that there is a demand for more and higher quality research about melatonin. The results need to be reported clearly and made available to the public since there is an increase in use of this supplement and a decrease in regulation.

One of the significant limitations of studies is that there is the absence of comparison between studies conducted before and after the initial publication of the CONSORT statement for RCTs in 2008, as has been undertaken in other research. In this particular study, only abstracts from the time period between 2012 to 2021 were taken into account, not allowing any conclusions regarding the potential advancements or progress made since the release of CONSORT (47). An additional valuable analysis for this study would have been an assessment of the journal endorsement status of CONSORT abstracts and its comparison with the total scores of the studies and journal quartiles. This analysis could have provided insights into the extent to which journal endorsement enhances reporting quality. This study examined abstracts obtained from PubMed, which presents a conflicting limitation. On one hand, PubMed serves as a freely accessible platform, serving as primary source of information for physicians who do not have access to subscription-based research databases. On the other hand, relying solely on

PubMed as the search engine means that information from abstracts in other databases, which may or may not adhere to CONSORT guidelines, is not included. Consequently, this restricts the ability to draw conclusions about all abstracts pertaining to the topic.

6. CONCLUSIONS

- The median value of CONSORT total score of melatonin research abstracts was 7, and interquartile range 6-9.
- The 3 highest ranking items, most often included in the abstract were objective (98.6%), intervention (97.7%) and outcome (96.3%), in this order.
- The lowest ranking items were funding (3.7%), randomization type (4.1%), numbers analyzed (5,9%) and trial registration (6.5%).
- The abstracts published in the first quartile had the highest CONSORT total score, and the ones in journals without quartile had the lowest median value.

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8. SUMMARY

Diploma Thesis Title: The Reporting Quality of Abstracts of Randomized Controlled Trials on Melatonin

Objectives: The goal of this study was to analyze the quality of abstracts of RCTs regarding melatonin and sleep disorders.

Materials and methods: This study assessed the reporting quality of abstracts on PubMed for melatonin and sleep RCTs. A search yielded 232 abstracts, with 13 exclusions. The CONSORT for abstracts checklist was used to assess various aspects including study design, methods, results and conclusions. Data was analyzed using MedCalc software.

Results: Of the 232 abstracts initially found, 13 were excluded, leaving 219 abstracts for analysis. The median CONSORT score was 7, with a range of 6-9. Abstracts from higher ranked journals had higher scores. Significant differences in reporting were found between abstracts with significant and non-significant results. The most common components found in the abstracts were the objective, intervention and outcome, demonstrating their inherent importance. Conversely, aspects such as funding, type of randomization and trial registration were under-reported, suggesting opportunities for improvement.

Conclusion: The review of abstracts from a PubMed search on melatonin and sleep revealed moderate reporting quality according to CONSORT. Notably, abstracts published in the top quartile had the highest CONSORT scores, while those in journals not indexed in the Web of Science (without quartile) had comparatively lower scores, highlighting the influence of journal prestige on reporting standards.

9. CROATIAN SUMMARY

Naslov: Analiza kvalitete sažetaka randomiziranih kontroliranih istraživanja melatonina

Cilj istraživanja: Cilj ovog istraživanja bio je analizirati kvalitetu sažetaka RCT-ova koji se odnose na melatonin i poremećaje spavanja.

Materijal i metode: Ova studija procijenila je kvalitetu izvješćivanja sažetaka na PubMedu za melatonin i RCT-ove spavanja. Pretraživanje je dalo 232 sažetka, s 13 isključenja. Kontrolni popis CONSORT za sažetke korišten je za procjenu različitih aspekata uključujući dizajn studije, metode, rezultate i zaključke. Podaci su analizirani pomoću softvera MedCalc.

Rezultati: Od ukupno pronađenih 232 sažetka, isključeno je 13, ostavljajući 219 sažetaka za analizu. Medijan CONSORT bodova bio je 7, s rasponom od 6 do 9. Sažetci iz časopisa višeg ranga imali su više bodova. Utvrđene su značajne razlike u izvještavanju između sažetaka s značajnim i nesignifikantnim rezultatima. Najčešći elementi u sažecima bili su cilj, intervencija i ishod, što ukazuje na njihovu inherentnu važnost. Nasuprot tome, aspekti poput financiranja, vrste randomizacije i registracije ispitivanja bili su nedovoljno prikazani, što ukazuje na mogućnosti za poboljšanje.

Zaključak: Pregled sažetaka dobivenih pretragom na PubMedu o melatoninu i spavanju otkrio je umjereni kvaliteta izvještavanja prema CONSORT-u. Posebno se ističe da su sažetci objavljeni u prvom kvartilu imali najviše CONSORT bodova, dok su oni u časopisima koji nisu indeksirani u *Web of Science*-u (bez kvartila) imali relativno niže bodove, što naglašava utjecaj ugleda časopisa na standarde izvještavanja.

10. CURRICULUM VITAE

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10/2019 – 07/2023 University of Split School of Medicine, Split, Croatia

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