Research Article

Open Access

Sleeping Pills and Quality of Wake Time: The Missing Link

Sohil A Khan^{1,2,8*}, Treasure M McGuire^{2,5} and Helen S Heussler^{2,6,7}

¹School of Pharmacy, Griffith University, Gold Coast, Australia

²Mater Research Institute, Mater Health Services, South Brisbane, Australia

³Mater Pharmacy Services, Mater Health Services, South Brisbane, Australia

⁴Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia

⁵School of Pharmacy, The University of Queensland, Woolloongabba, Australia

⁶Department of Respiratory and Sleep Medicine, Mater Children's Hospital, Mater Health Services, South Brisbane, Australia

⁷School of Medicine, The University of Queensland, Herston, Australia

⁸Griffith Health Institute, Griffith University, Gold Coast, Australia

Abstract

Background: The rising incidence of insomnia in a 24/7 global society quantifies the burden for the individual, in terms of reduced quality of life (QOL), and for society at large, in terms of work absenteeism, disability, and health care costs.

Aim: To evaluate research on hypnotosedatives (benzodiazepines, non-benzodiazepines) and complementary medicines in paediatric insomnia where quality of wake time is one of the key efficacy outcomes.

Design and setting: Retrospective data analysis of clinical studies in paediatric insomnia

Methods: A systematic review of clinical studies of hypnotosedatives and complementary medicines in paediatric insomnia was conducted. PubMed and Cochrane Central Register of Controlled Trials (January 2002- August 2013) were searched for studies in children aged 3 to 18 years (male or female). Quality of wake time and/or health related QOL parameters were assessed as the outcomes.

Results: From 31 potentially relevant studies, only one, involving melatonin, met the inclusion criteria. One hundred and forty six children (aged 3 to 15 years 8 months) diagnosed with insomnia were evaluated in a 12 week double masked randomised placebo controlled phase III multi-centre trial. Child behaviour and family functioning showed some improvement and favoured use of melatonin but was not statistically significant. There were no controlled clinical studies evaluating the impact of benzodiazepines and non-benzodiazepines hypnotosedatives on quality of wake time in the management of paediatric insomnia.

Conclusion: Data on quality of wake time in children with insomnia are scarce. Research has focused on addressing the metrics of sleep, with quality of wake time notably ignored. QOL measurement provides valuable information about the psychological and social impact of treatment on children with insomnia. Complementary medicines such as melatonin appear to improve the quality of wake time in paediatric insomnia where there are co-morbid conditions; but further research is needed.

Keywords: Insomnia; Benzodiazepines; Non-benzodiazepines; Melatonin; Sleep; Children; Quality of life

Introduction

Human beings spend approximately one-third of their lifetime sleeping [1]. As one of the most fundamental processes of life, sleep has attracted a great deal of attention from ancient philosophers to present day biomedical researchers. The rising incidence of insomnia in a 24/7 global society continues to create increasing demands that pose significant challenges to sleep research and circadian physiology. A recently published epidemiological study [2] quantifies the burden of chronic insomnia for the individual, in terms of reduced Quality of Life (QOL), and for society at large, in terms of work absenteeism, disability and health care costs. The incidence is surprisingly high in the paediatric population, with a quarter of all children experiencing sleep problems. In children with visual impairment and neurodevelopmental disorders, the incidence is as high as 80% [3]. It is likely that this also has an impact on the carers of the affected child.

A sleep disorder exists when a lower quality of sleep results in impaired functioning or excessive sleepiness. For the past four decades, prescription hypnotosedatives (benzodiazepine or non-benzodiazepine) have been widely used in the management of sleep disorders in adults and children. However, the risk associated with their chronic use (dependence, increased abuse potential, withdrawal symptoms) is

alarming [4]. Recently, complementary medicines such as melatonin and valerian have gathered interest in sleep medicine. Prescriptions for sleep problems are common with melatonin, clonidine and antihistamines amongst the most frequent in paediatric practice [5]. There is significant variation in prescribing pharmacotherapeutic options in insomnia with lack of consensus based guidelines in diverse patient population. When novel hypnotosedatives are developed, the focus tends to be on the statistically significant increase in total sleep time (marginal in minutes) during the night instead of the effects on the quality of wakefulness [1]. Pharmaceutical companies are focussed heavily on the metrics of sleep; and have neglected quality of wake time as a key measure of hypnotosedatives efficacy, yet quality of wake

***Corresponding author:** Sohil A Khan, School of Pharmacy, Griffith University, Gold Coast, Australia, Tel: +61 75552 7097; Fax: +61 75552 8804; E-mail: s.khan@griffith.edu.au

Received August 27, 2013; **Accepted** September 12, 2013; **Published** September 17 2013

Citation: Khan SA, McGuire TM, Heussler HS (2013) Sleeping Pills and Quality of Wake Time: The Missing Link. J Sleep Disorders Ther 2: 138. doi:[10.4172/2167-0277.1000138](https://doi.org/10.4172/2167-0277.1000138)

Copyright: © 2013 Khan SA, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Figure 1: Flow chart of study selection process. The characteristics of the excluded studies (after detailed evaluation) are provided in Table 1. The participants' mean age was 8 years. These studies highlighted the impact of sleep problems on health related QOL (HRQOL) in children with various co-morbid conditions (not primary insomniacs).

insomnia and other sleep problems in children are presented in Table 2. It should be noted that administration of such tools in children less than 5 years needed to be completed by their parents/care givers.

Discussion

In recent times, measurement of QOL has added a new dimension to clinical trials and the drug development process. Results of epidemiological studies have demonstrated the increasing burden of chronic disease and its social impact, based on disability and not mortality. QOL measurement provides valuable information about the psychological and social impact of treatment on children, especially where differences in survival rates are anticipated. Despite the lack of a pharmacotherapeutic intervention in the four studies excluded from this systematic review, they serve to highlight the adverse impact of paediatric sleep disorders on HRQOL.

To the best of our knowledge, there is only one controlled trial that has evaluated the impact of a pharmacotherapeutic intervention on quality of wake time in paediatric insomnia. This study assessed the impact of melatonin on QOL and daytime functioning in children with neurodevelopmental disorders suffering from severe sleep problems [11]. Findings from measures of child behaviour and family QOL tended to favour melatonin but were not statistically significant. The authors justify this as the outcome measures were not sensitive enough over the study time period (12 weeks). The lack of studies addressing this issue with benzodiazepine or non-benzodiazepine hypnotosedatives is surprising, considering their extensive use. Nonetheless, the melatonin study provides a baseline for future trials to focus on this neglected but an important parameter in sleep medicine – the quality of wake time.

A similar search in adult insomniacs with co-morbid conditions also retrieved only one placebo-controlled trial [18]. Claimed to be the first of its kind, the study demonstrated that long-term nightly treatment of primary insomnia with eszopiclone was able to enhance QOL, reduce work limitations, and reduce global insomnia severity, in addition to improving patient-reported sleep variables. Patient-reported sleep and daytime function were improved more with the hypnotosedative than with placebo at months 1-6 (duration: 6 months)

($P < 0.001$). Furthermore, statistically significant improvements were observed with eszopiclone compared with placebo for the SF-36 domains of Physical Functioning, Vitality, and Social Functioning ($P < 0.05$), and all domains of the work limitations questionnaire ($P < 0.05$). As this trial was conducted in primary insomniacs, impact of quality of wake time from the findings may not be extrapolated to patients with co-morbid conditions.

The use of medication to manage insomnia often follows a 'one-size-fits-all' approach. Yet the nature of the sleep problem experienced by those with insomnia varies. At present, daytime performance is considered as an absence of impairment — improvement of function with benzodiazepines or benzodiazepine receptor agonists has never been demonstrated. There are a number of barriers in evaluating quality of wake time. One is the lack of subjective and objective parameters to evaluate the clinical effect. Validated tools designed to assess HRQOL (Table 2) would be suitable for evaluating daytime performance and QOL in paediatric sleep pharmacotherapy.

Insomniacs with co-morbid conditions (e.g. neurodevelopmental disorders or circadian rhythm sleep disorders) are presented with challenging therapeutic decisions. A recently published therapeutic guideline [19] highlighted the need for studies to identify how to optimally manage insomnia in patients with co-morbid conditions. Newer strategies such as chronobiotic therapies are under trial. Melatonin seems one of the promising options to address this unexplored yet an important clinical domain of sleep medicine.

Implications for practice and research

- Despite their long history in the management of sleep disorders, there are no controlled clinical studies evaluating the impact of benzodiazepines and non-benzodiazepines hypnotosedatives on quality of wake time in the management of paediatric insomnia.
- Complementary medicines such as melatonin appear to improve the quality of wake time in paediatric insomnia where there are co-morbid conditions (e.g. neurodevelopmental disorders, visual impairment and circadian rhythm sleep disorders). Further long term studies (more than 6 months) are needed.

Measure	Age range (years)	Concept	Child (self) Report	Parent (proxy) Report	Domain	Time to complete (min)	Reliability data	Validity data
Child Health and Illness Profile [12]	6-11 and 12-17	Measure based on a broad concept that includes evaluation of perception of well being and illness, participation in developmentally appropriate tasks, and activities or behaviours that promote or threaten health	X		6 domain; Child edition (6-11 years); Adolescent edition (12-17 years)	30	X	X
Child Health Questionnaire [13]	5-18	Measures health with regard to physical, psychological and social domains	X	X	11 domains; Self and Parent version	20	X	X
Dartmouth Coop Functional Health Assessment Charts [14]	15 (median)	Measures exclusive dimensions of health and social problems through picture/word charts	X		6 charts (pictures and words)	15-20	X	
KINDL [15]	4-16	Describes physical, psychological, social, and functional aspects of well-being and functioning from patient's perspective	X	X	6 domains	10	X	X
Pediatric Quality of Life Questionnaire [16]	2-18	Evaluates physical, mental and social health of children and adolescents	X	X	4 domain, 23 items	5-10	X	X
Quality of Life Profile – Adolescent Version [16]	14-20	Evaluates physical, psychological and spiritual parameters through being, belonging and becoming options	X		3 domains, 54 items	40	X	
Warwick Child Health and Morbidity Profile [17]	0-5	Evaluates general, acute, chronic and functional health status and QOL	X	X	10 domains	10	X	

Table 2: Summary of generic measures of health-related QOL used in paediatric sleep disorders.

- Inclusion of quality of wake time as a secondary outcome in pharmacotherapeutic studies will be a key step in addressing this neglected but significant aspect of sleep medicine.

There are number of good quality validated tools (outcome measures) to study the quality of wake time for therapeutic trials in insomnia although some of these may not be suitable where children are affected by disability.

References

- Wafford KA, Ebert B (2008) Emerging anti-insomnia drugs: tackling sleeplessness and the quality of wake time. *Nat Rev Drug Discov* 7: 530-540.
- Morin C, Jarrin DC (2013) Epidemiology of insomnia: prevalence, course, risk factors, and public health burden. *Sleep Medicine Clinics*.
- Khan S, Heussler H, McGuire T, Dakin C, Pache D, et al. (2011) Melatonin for non-respiratory sleep disorders in visually impaired children. *Cochrane Database Syst Rev*: CD008473.
- Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE (2005) Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 331: 1169.
- Heussler H, Chan P, Price AM, Waters K, Davey MJ, et al. (2013) Pharmacological and non-pharmacological management of sleep disturbance in children: an Australian Paediatric Research Network survey. *Sleep Med* 14: 189-194.
- American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders (5th edn.). Arlington, VA: American Psychiatric Publishing: 5-25.
- De Serres LM, Derkay C, Sie K, Biavati M, Jones J, et al. (2002) Impact of adenotonsillectomy on quality of life in children with obstructive sleep disorders. *Arch Otolaryngol Head Neck Surg* 128: 489-496.
- Rosen CL, Palermo TM, Larkin EK, Redline S (2002) Health-related quality of life and sleep-disordered breathing in children. *Sleep* 25: 657-666.
- Hart CN, Palermo TM, Rosen CL (2005) Health-related quality of life among children presenting to a pediatric sleep disorders clinic. *Behav Sleep Med* 3: 4-17.
- Díez-Montiel A, de Diego JI, Prim MP, Martín-Martínez MA, Pérez-Fernández E, et al. (2006) Quality of life after surgical treatment of children with obstructive sleep apnea: long-term results. *International Journal of Pediatric Otorhinolaryngology* 70: 1575-1579.
- Gringras P, Gamble C, Jones AP, Wiggs L, Williamson PR, et al. (2012) Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. *BMJ* 345: e6664.
- Child health and illness profile – a comprehensive assessment of health and functioning for children and adolescents.
- Waters E, Salmon L, Wake M, Hesketh K, Wright M (2000) The Child Health Questionnaire in Australia: reliability, validity and population means. *Aust N Z J Public Health* 24: 207-210.
- Dartmouth COOP functional health assessment charts: brief measures for clinical practice (1995) Quality of life and pharmacoeconomics. In: Spilker B, editor *Clinical Trials 2nd edition* Philadelphia, PA: Lippincott-Raven Publishers, 161-168.
- KINDL: Information. Available from <http://kindl.org/english/information/>.
- The PedsQL: Measurement model for pediatric quality of life inventory.
- Spencer NJ, Coe C (2000) Validation of the Warwick Child Health and Morbidity profile in routine child health surveillance. *Child Care Health Dev* 26: 323-336.
- Walsh JK, Krystal AD, Amato DA, Rubens R, Caron J, et al. (2007) Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. *Sleep* 30: 959-968.
- Minkel J, Krystal AD (2013) Optimizing the Pharmacologic Treatment of Insomnia: Current Status and Future Horizons. *Sleep Med Clin* 8: 333-350.

Citation: Khan SA, McGuire TM, Heussler HS (2013) Sleeping Pills and Quality of Wake Time: The Missing Link. *J Sleep Disorders Ther* 2: 138.
doi:[10.4172/2167-0277.1000138](https://doi.org/10.4172/2167-0277.1000138)