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Effect of valerian, *Valeriana edulis*, on sleep difficulties in children with intellectual deficits: randomised trial

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Summary

Serious sleep problems are common in children with an intellectual deficit (ID), and are often the source of much distress for both the child and caregivers. As yet, no satisfactory long-term treatment exists for intransigent sleep difficulties in children with an ID. Valerian, Valeriana spp., has been used for thousands of years to induce relaxation and sleep. Scientific investigation of valerian's sleep promoting ability in humans, whilst limited, has yielded promising findings. This initial study aimed to explore valerian's potential for assisting in the treatment of sleep problems in children with an ID. Five children with varying intellectual deficits and different primary sleep problems underwent eight continuous weeks of monitoring via sleep diaries, adhering to a double blind, placebo controlled and randomised design. Compared to baseline and placebo, valerian treatment led to significant reductions in sleep latencies and nocturnal time awake, lengthened total sleep time and improved sleep quality. The treatment was apparently most effective in children with deficits that involved hyperactivity. Although the findings are preliminary and in need of replication, there is evidence to suggest that valerian may be useful in the safe and effective long-term treatment of intransigent sleep difficulties in children with ID's, and therefore warrants further investigation.

Key words: sleep, valerian, herbal drug, intellectual deficit, double blind study

Introduction

Although the functions of sleep are poorly understood, there is little question that adequate sleep is critically important for optimal health and general well being. This may be particularly so for developing children. Aside from any putative contribution that sleep may make to normal physical and cognitive development, research suggests that inadequate sleep undermines a child's capacity to be alert and attentive to educational stimuli, thereby hampering the child's learning potential (Kahn, 1989), increasing daytime behavioural problems (Wiggs and Stores, 1996), and causing considerable distress and frustration for the child, his or her parents, siblings and teachers.

The most common sleep problems in children involve difficulties in initiating and maintaining sleep (Richman, 1986). The incidence of sleep problems is highest in younger children, and steadily decreases with age. In normally developing children, sleep problems may be experienced by as many as 26% of 2 year olds (Richman, 1981) and 14% of 3 year olds (Richman et al., 1975). Investigations of sleep difficulties in children with intellectual deficits (ID) has revealed that the nature of sleep problems are similar, however prevalence figures have been reported as high as 86% for children under 6 years, 81% for those aged 6–11 years, and 77% for children aged 12–16 years (Bartlett et al., 1985). Clearly there is a

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substantial need for effective treatment of sleep problems in children with an ID. Sleep problems in this population impose considerable stress on both child and parents, and typically persist well beyond the age at which such problems cease in normal children.

Extracts of the genus *Valeriana* herbaceous perennial plants, commonly known as valerian, have been recognised for their ability to treat stress and induce relaxation for over 2000 years. Pharmacological tests have consistently verified valerian to have a psychotropic sedative, or tranquillising, effect on the CNS (Capasso et al., 1996; Sakamoto et al., 1992). Clinical and polysomnographic studies of valerian's ability to alleviate poor sleep in humans are sparse but, nonetheless, have shown encouraging results (Balderer and Borbély, 1985; Leathwood and Chauffard, 1985; Lindahl and Lindwall, 1989; Wagner et al., 1998; Gyllenhaal et al., 2000; Donath et al., 2000), comparing favourably with many traditional synthetic sleeping pills, such as the benzodiazepines (Leathwood and Chauffard, 1985; Morazzoni and Bombardelli, 1995).

No significant side effects have been detected with valerian's use (Herberg, 1994), even at 20 times the recommended therapeutic dose (Willey et al., 1995). Valerian has also been shown to have weak anticonvulsive properties (Leuschner et al., 1993). As it is common for children with more severe ID's to experience disturbed sleep due to nocturnal seizure activity (Stores, 1992), some children's sleep may benefit from this additional property of valerian. Extensive research has been directed at determining valerian's mechanism of action, particularly in relation to its suspected interaction with the inhibitory neurotransmitter gamma amino butyric acid (GABA). However, it must be concluded that neither the active constituents nor the effect pathway of valerian have been reliably identified (Leuschner et al., 1993; Blätter and Schoch, 1994).

This study had a single exploratory aim, which was to examine the effectiveness of valerian for alleviating sleep difficulties in children with a variety of intellectual and neurologic deficits. It was expected that statistically and clinically significant improvements would be observed in primary outcome measures of sleep latency, nocturnal time awake, and subjectively reported sleep quality.

Materials and Methods

Five males aged between 7 and 14 years, and with significant sleep problems, were recruited (with parental consent) through schools and organizations for children with intellectual disabilities. All children had an IQ of less than 70, as measured by the Weschler Intelligence Scale for Children (WISC). Further details of participants are provided in the case studies, below. Prior to formal inclusion in the study, participants underwent a medical exam and screening interview to determine the nature and history of the child's sleep difficulty. When asked to rate, on a ten point scale, the extent to which their child's sleep difficulties were 'a problem', all parents rated the severity as '10'.

A repeated measures, double-blind, cross-over design was used. At recruitment, subjects were randomly assigned on an individual basis to initial valerian or placebo treatment using a table of random numbers. Random allocation and blinding of treatments were carried out by the senior investigator, who had no contact with either the subjects or their parents. The codes for these procedures were maintained in a locked filing cabinet to which only the senior investigator held a key. The codes were broken only after all subjects had completed the trial.

Valerian and placebo tablets were prepared and donated by MediHerb, PTY., LTD. (Brisbane, Australia). Valerian tablets contained 500 mg (100%) of dried and crushed whole root from *Valeriana edulis* plants. Each tablet contained 5.52 mg of valtrate/isovaltrate. This was determined by HPLC using the method of Bos et al (1996). No Didrovaltrate or Acevaltrate were present in the products analysed. To give the same appearance and distinctive odour, placebo tablets contained 25 mg (5%; not pharmacologically significant) of whole root *V. edulis* extract. The accepted standard dose of *V. edulis* for a 60 kg adult is 1500 mg/day. During the treatment phase of the study, parents administered a pro rata dosage of 20 mg/kilogram of body weight to their child, in a single nightly dose at least one hour before preferred bed-time.

An eight-week diary consisting of 21 daily questions (completed by parents) was used to assess general behaviour and sleep patterns in the children (copies of the diary are available from the authors). All measurements were made in the children's normal living environment. Primary outcome measures were sleep latency (time taken to fall asleep), time spent awake during the night, and sleep quality (visual analogue scale). Parents were instructed in the use of the sleep rating scales prior to the commencement of the study. Whilst the accuracy of sleep diaries might be questionable, in the current experiment they provided the best means of obtaining information on basic sleep parameters over an extended period of time, and with minimal disturbance or constraint being placed on the child. Parents would check their child every 15 minutes following placement in bed for sleep onset, or base their judgment on lack of audible verbal behaviour (which is often a reliable indicator of alertness for a disabled child). Where nighttime awakenings for the child fell in the parent's sleep period, only those which disturbed

the parent to awakening were recorded. Therefore, the data for nighttime awakenings must be regarded conservative.

Each child underwent the following procedures:

Baseline measurement: No treatment, for a two-week period.

Treatment A: Double-blind, randomised assignment to either valerian or placebo tablet administration for a two-week period.

Washout period 1: A seven-day post-treatment period with continued monitoring via sleep diary.

Treatment B: Double-blind assignment to the alternative treatment from that received in the treatment A phase for a two week period.

Washout period 2: A seven-day post-treatment period with continued monitoring via sleep diary. At the completion of the study parents participated in an 'end of study' interview, which retrospectively examined their child's involvement in the study. Questions explored areas relating to: estimation of the valerian and placebo conditions, perceived changes in their child's sleep behaviour, observed changes in daytime behaviour, possible adverse side effects, and whether they believed it worthwhile for their child to continue using valerian. For group analyses, means of important sleep parameters during each condition were calculated and compared using Analysis Of Variance (ANOVA) procedures, followed by post-hoc testing. For individual analyses, descriptive analyses and 24hr actograms of sleep-wake activity (constructed in the conventional manner for chronobiologic studies) were used.

Results

Group Analyses

Means and standard deviations of important sleep parameters across all five children during each condition of the study are shown in Table 1. Repeated measures ANOVAs were conducted to test the significance of differences between these means. Significant treatment effects were found for time spent awake during the night, $F(2,8) = 9.298$, $p = 0.008$, total sleep time, $F(2,8) = 5.594$, $p = 0.030$, and parent-rated sleep quality, $F(2,8) = 15.611$, $p = 0.002$, but not for sleep latency, $F(2,8) = 2.077$, $p = 0.188$. Post-hoc Least Significant Difference (LSD) comparisons were conducted to examine differences between the means, and significance levels for these comparisons are also shown in Table 1. In relation to sleep latency, although the ANOVA treatment effect was not significant, given the small sample and obvious differences in the means, LSD comparisons were conducted for exploratory purposes.

Compared to baseline, under valerian treatment significant decreases in sleep latency and nocturnal time awake were observed, and there was also a significant lengthening of total sleep time. No significant changes in these parameters were observed under placebo treatment compared to baseline. Significant increments in sleep quality were observed under both valerian and placebo treatment, although the increase was greater under valerian treatment.

Case Descriptions

Case 1: This 12-year old boy had a moderate intellectual disability and nocturnal epilepsy, for which he received 1000 mg of Epilum nightly. He appeared to have no significant problems with sleep initiation or co-sleeping (unless ill), however he had serious difficulties in maintaining sleep; waking irregularly between 1 and 3 times a night. These wakening episodes would last between 10 minutes and one hour. The mother reported her son's sleep pattern as having been erratic and problematic for the past 7 years, and was often the source of considerable distress. Inspection of the sleep-wake record and parameter means for this child (not presented here) indicated a reduction in nocturnal awakenings during both placebo and valerian conditions, with the largest improvement occurring during the valerian condition. There was also a notable decrease in sleep latency during the valerian condition, when compared to baseline and placebo. The mother indicated she had noticed an improvement in both her

Table 1. Means, standard deviations and LSD significance for four parameters of sleep.

Sleep parameter	Baseline		Placebo		Valerian		Significance	
	M	SD	**M**	SD	**M**	SD	Baseln. vs. placebo	Baseln. vs. valerian
Latency (min.)	**41.14**	20.99	**39.14**	34.68	**23.49**	13.42	.87	.05*
Time awake (min.)	**17.92**	8.21	**8.38**	9.07	**6.85**	7.16	.06	.02*
Total sleep time (hrs)	**9.93**	0.56	**9.94**	0.70	**10.28**	0.43	.89	<.01*
Sleep quality	**5.34**	1.49	**6.71**	1.29	**7.54**	1.47	.04*	<.01*

*Statistically significant

own and her son's sleep during the valerian condition. In addition, the mother reported that during the valerian condition her son appeared "more well rested and calmer during the day", as well as being "more happily cooperative" and "more cheerful".

Case 2: This 14-year old boy had a genetic disorder known as hypertelorism-hypospasius, a moderate intellectual disability, and episodic fibril convulsions. The only medication that this child received was 20 ml of Epilum daily. The nature of this child's sleep difficulty was similar to that of Case 1, although more severe, in that his sleep problem was primarily one of sleep maintenance, characterised by consistently waking between 1 and 4 (typically 3) times a night. Generally these waking episodes lasted no longer than 10 minutes, as the child would return to sleep following parental intervention. The mother reported her son's sleep problem as having been present since age three, and could not remember the last time that he had slept for a full night without wakening. Inspection of the actogram (not presented here) revealed a decrease in sleep disruptions for the first several nights of the valerian condition, after which however, no further improvement could be detected. Means for different treatment conditions indicated reductions in average time awake and sleep latency, as well as an increase in rated sleep quality during valerian treatment. The child's mother reported that, during the first few nights of the valerian condition, she had her "best nights sleep in years." She also indicated that he reverted back to his normal problematic sleep pattern towards the end of the first week of the valerian period.

Case 3: This 11-year old boy was diagnosed with a mild to moderate intellectual disability accompanied with hyperactivity and day-time behaviour problems. His sleep problems involved difficulties in both initiating and maintaining sleep, and were reported as having been present since birth. This child's problematic sleep pattern involved sleep latencies of between 30 and 120 minutes, at least one sleep disturbance most nights, and difficulty associated with waking in the morning. Parents reported that their son's sleep difficulties had caused considerable distress for them both, particularly when they began allowing their son to co-sleep with them. The mother believed that his often irritable behaviour, violent temper tantrums, and generally difficult nature were largely due to sleep inadequacies. Analysis of the actogram (not presented here) indicated sleep latencies and nighttime awakenings were markedly improved from the onset of valerian treatment. Average sleep latencies decreased from 56 minutes during baseline to 20 minutes during placebo and, except for one 5 minute awakening, there was no evidence of sleep disturbance during the valerian period. This improvement in sleep appears to have largely persisted through the subsequent washout week and placebo treatment for this case, as indicated by both parental reports and actogram data. The mother reported a variety of changes in her son's behaviour under valerian treatment, including "no more temper tantrums", "he is easier to live with", "the whole household has seen an improvement", "his behaviour is more relaxed", and "his life skills seem to have improved".

Case 4: This 7-year old boy had attention deficit disorder (ADD) with hyperactivity and aggressive behaviour tendencies. He was receiving 10 mg of dexamphetamine throughout the day to stem his hyperactivity and 5 mg of Catapres at night to assist with sleep. This case displayed a number of sleep associated problems, the most prominent of which was protracted sleep latencies. Other sleep complaints included semi-frequent nighttime awakenings, co-sleeping with parents (beside their bed), and morning waking difficulties. Parents believed these sleep problems were due to their child's 'over active' mind, and "his inability to relax". The actogram for this case is presented in Figure 1. There is a substantial reduction in sleep latencies during valerian treatment, particularly in the second week. Mean sleep latency for this child was 60 minutes during baseline, almost 100 minutes during placebo, and 46 minutes during valerian treatment. Mean sleep latencies increased again when valerian was withdrawn. In the end of study interview, the mother reported she was "simply amazed" at the improvement in her son's sleep and behaviour during the valerian treatment condition, adding that "he has never slept that well since birth".

Case 5: This 10-year-old boy had received a diagnosis of attention deficit hyperactivity disorder (ADHD) accompanied by a non-specific learning disorder. During the study he received 30 mg of Ritalin on school days for his hyperactivity, and 10 mg of Catapres at night to assist with his sleep difficulties. He was reported to have a variety of sleep problems, which included problematic bedtime behaviour, long sleep latencies, and nighttime awakenings. The actogram for this child is presented in Figure 2. Co-sleeping was identified as a prominent sleep problem, tending to follow nighttime awakenings. The parents felt that the entire family experienced distress that stemmed from their son's sleep difficulties. There was a marked decrease in co-sleeping during the valerian treatment condition, and the means for this child indicating decreases in sleep latency, nocturnal time awake and co-sleeping, and an increase in total sleep time and rated sleep quality. The mother reported that she had seen an improvement in not only her son's sleep and well being, but also in her own. She believed that her son was sleeping longer and experiencing fewer sleep disturbances. Regarding her son's general behaviour, his mother stated that there appeared to be "more maturity" in his interactions and exchanges with family members.

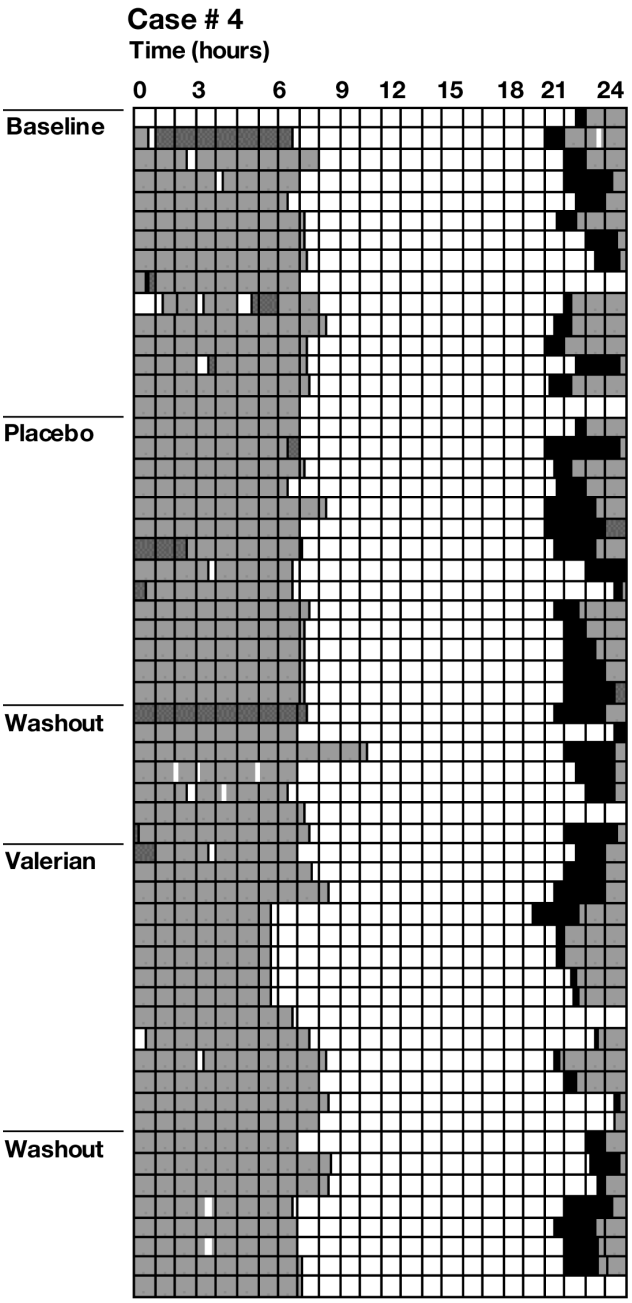

Fig. 1. Actogram for case 4. Each line represents one day, and each square one hour. Shaded areas represent the following: light grey – sleep; white – awake; black – sleep latency; dark grey – co-sleeping with a parent (in own or parent's bed).

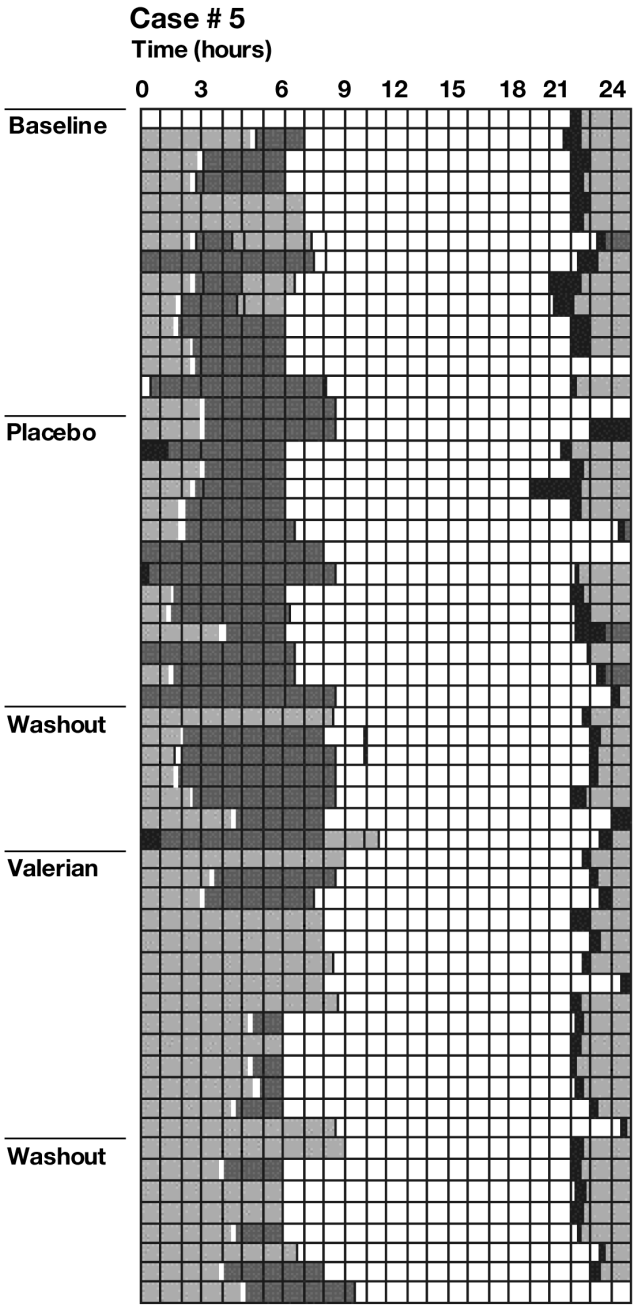

Fig. 2. Actogram for case 5. Conventions as for Figure 1.

Discussion

Valerian was effective in producing significant improvements in important sleep parameters. As a group, the children exhibited reduced sleep latency and time spent awake at night, and increased total sleep time and sleep quality under valerian treatment compared to baseline. Only in the case of parent-rated sleep quality was there a significant improvement under placebo treatment. The reasons for this are unclear, however since this was the most subjective parameter measured in the study, the result may reflect a real 'placebo effect' in parental ratings of their child's sleep quality.

Whilst the present study is the first of its kind, and involved a limited number of participants, the positive nature of the results warrant further investigation in this and other specific populations with sleep problems; including various disability groups and the aged. As Stevinson and Ernst (2000) have noted, the size of a treatment effect often reflects the available scope for improvement. The strong treatment effect observed probably reflects the severity of presenting problems in the participants of this study. It is encouraging to observe that the positive, although limited, effects of valerian on sleep problems observed in 'normal' populations (Balderer and Borbély, 1985; Leathwood and Chauffard, 1985; Lindahl and Lindwall, 1989; Morazzoni and Bombardelli, 1995; Wagner et al., 1998; Gyllenhaal et al., 2000; Donath et al., 2000) are also demonstrable in disabled populations, where the need for resolution is often greater. Although, as Stevinson and Ernst (2000) argue, there is a need for further rigorous trials in this area of research using appropriate protocol and methodological controls.

In order to ensure compliance, and because of time constraints, the treatment phases for the current study were limited to two weeks, with three cases showing the greatest improvement in sleep during the second week of the valerian treatment. Future studies might find more substantive effects if the treatments were extended to at least four weeks. The lack of any reported significant adverse side-effects in the current study, or past literature, does not preclude such extended treatment regimes. Whilst parental reports on children's sleep was considered to be reliable and accurate in the current study, where possible the inclusion of an unobtrusive objective measure of sleep such as wrist worn activity meters would increase the objectivity of measurements in future studies. Subsequent research might also explore the efficacy of valerian as an adjunct to behavioural techniques. Ultimately, all treatments of sleep problems require some degree of behaviour modification, even if it is the bare minimum of a well-structured bedtime routine. The effects of valerian may provide enough assistance to parents to enable the freeing of time and energy resources that can be re-directed toward implementing more sophisticated and effective behavioural modification programs. The use of valerian in conjunction with behavioural approaches to managing sleep difficulties is likely to bring about a more rapid and lasting improvement in sleep.

Sleep problems in children with intellectual deficits are a significant and widespread problem that has long been neglected. Although sleep disturbances in these children are particularly common, and substantially impinge upon the functioning and well-being of the child and family, little progress has been made in procuring an effective and satisfactory treatment. This initial study has employed the powerful double-blind, placebo-controlled single-case methodology to examine the effectiveness of valerian in ameliorating problematic sleep in children with an intellectual deficit. This population is difficult to recruit from, and future trials may also be limited by sample size considerations. However, although preliminary and in need of replication, the present findings indicate valerian has considerable potential for assisting intellectually impaired children with sleep difficulties, and thus warrants further investigation.

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