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Reflections on melatonin: focus on child mental health

AIMS AND METHOD

To examine the propriety of the use of melatonin in child and adolescent psychiatry based on findings retrieved from multiple electronic databases including the Cochrane Library resource, covering 1950–2007.

RESULTS

There is evidence for the effectiveness of melatonin in the initiation of sleep in children with a variety of neurodevelopmental disorders but its value in improving quality of sleep is doubtful. Like hormones in general, melatonin has multifarious action sites and hence potential for many side-effects. Posological issues and long-term side-effects are yet to be validly determined.

CLINICAL IMPLICATIONS

Sleep hygiene should be a major component of the routine intervention programme for insomnia and melatonin judiciously prescribed until the safety of long-term use is known.

Melatonin (*N*-acetyl-5-methoxytryptamine) is widely prescribed in child psychiatric practice for symptomatic treatment of 'insomnia' in the UK (Armour & Paton, 2004; Waldron *et al*, 2005) and perhaps in several other countries of western Europe despite the paucity of evidence of its long-term safety and some vagary of its clinical usefulness in children and adolescents. In this article we examine the propriety of its use in the light of more recent studies and propose guidelines pending valid definition of its pharmacotherapeutic status.

Method

With keywords, melatonin, circadian rhythm, child and adolescents, we searched two databases namely MEDLINE and the Educational Resources Information Centre (ERIC) for 'any publications': journal articles, research reports and monographs, for the period 1950–2007. Cochrane Library reviews were perused for additional information on the effect of melatonin on jet lag (Herxheimer & Petrie, 2002) and related themes. Our searches yielded 168 hits out of which 33 have hard-core neurobiological content and with their insignificant relevance to our clinical interest they were excluded. The remaining 135 papers (inclusive of 57 duplications) on clinical trials and systemic analyses that specifically addressed the use of melatonin in paediatric and psychiatric practice were critically reviewed. We endeavoured to cover a wide bibliography but we might have missed some non-English publications as well as those that did not fit into the classified subheadings (search grouping of keywords).

Mode of action

Melatonin is the major hormone of the pineal gland produced from the amino acid tryptophan and it is known from animal studies (Armstrong, 1989; Bartness & Goldman, 1989; Rusak & Bina, 1990) to elevate the concentration of aminobutyric acid, dopamine and serotonin in the mid-brain and hypothalamus.

In humans, melatonin is synthesised from serotonin in a reaction that is entrained to the light–dark 24 h cycle (Brzezinski, 1997) via a neural pathway from the eye relaying in the suprachiasmatic and paraventricular nuclei of the hypothalamus then descending to the thoracic spinal cord and superior cervical ganglion to innervate the pineal gland (Moller *et al*, 1996) (Fig. 1). At night, its production is stimulated by noradrenaline released by post-ganglionic sympathetic nerve fibres from the superior ganglia and through cyclic adenosine monophospate (cAMP) norardrenaline stimulates the synthesis and activity of *N*-acetyl transferase, which is one of the major enzymes involved in the synthesis of melatonin (Fig. 2). During the daytime, light suppresses norardrenaline release by the post-ganglionic sympathetic nerve fibres innervating the pineal gland and melatonin synthesis decreases (Webb & Puig-Domingo, 1995). Therefore, melatonin secretion has a diurnal pattern with blood level rising around 21.00 h and remaining elevated for 12 h then receding to a trough during the daytime.

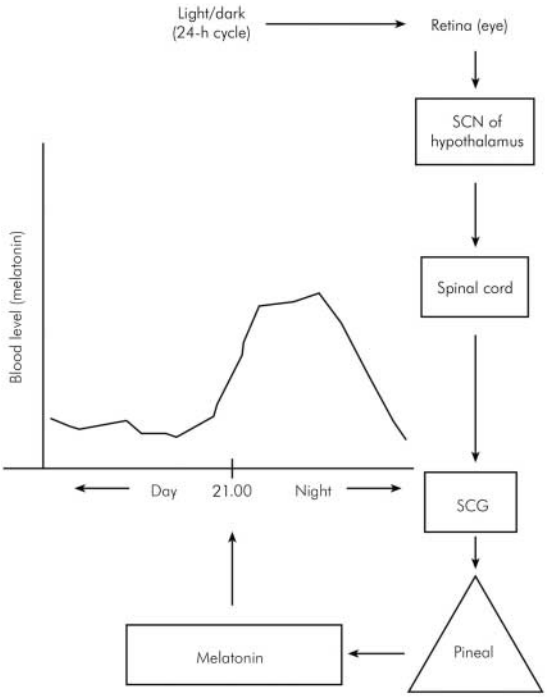

Fig. 1. Schematic neural link between the pineal gland and the light–dark environment. SCN, suprachiasmatic nucleus; SCG, superior cervical ganglion.

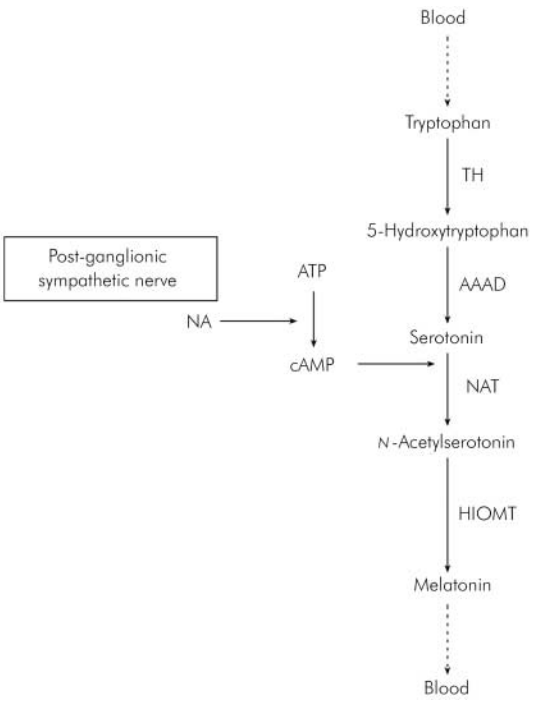

Fig. 2. Synthesis of melatonin in the pineal gland. AAAD, 1-aromatic-aminoacid-decarboxylase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophospate; HIOMT, hydroxyindole-O-methyltransferase; NA, noradrenaline; NAT, N-acetyltransferase; TH, tyroxine hydroxylase.

Pharmacotherapy

A major limitation of the appraisal of the effect of melatonin on sleep was the failure of several authors to explicitly define insomnia. Furthermore, different definitions focused on different aspects of sleep pathology such as disturbance of: initiation, sustenance, termination or poor quality. However, it would appear that, generally, the term is used in a generic sense to mean difficulty in falling asleep or remaining asleep or poor quality sleep.

Regarding clinical benefit, there is evidence that one of the main actions of melatonin is reduction of sleep-onset latency, i.e. duration of time falling asleep (Zhdanova *et al*, 1995; Nagtegaal *et al*, 2000) and this feature, which is a component of its diurnal secretory pattern, constitutes the basis of its use in the treatment of insomnia owing to altered light–dark circadian rhythm such as occurs in jet lag (Herxheimer & Petrie, 2002). However, a rigorous and more recent systematic review (Buscemi *et al*, 2006) concludes that exogenous melatonin did not exert significant effect on jet lag or shift work in adults. Stimulated by studies on adults, considerable attention has been paid in the past decade to clinical utility in child mental healthcare. Details of the most recent systematic studies of melatonin use in children and adolescents can be found in Table 1.

For instance, melatonin was found in a placebo-controlled trial to be effective in improving delayed sleep-onset unassociated with a specific disorder in children (Smits *et al*, 2003) and in adolescents (Szeinberg *et al*, 2006). A similar finding was obtained in relation to sleep-onset disorder in a variety of neuropsychiatric disorders such as autism (Giannotti *et al*, 2006), multiple disabilities (Sajith & Clarke, 2007), neurodevelopmental disabilities (Phillips & Appleton, 2004) and intellectual disability (Jan, 2000; Coppola *et al*, 2004). However, it should be borne in mind that the clinical features of these underlying disorders in the studies might mask veritable side-effects and, moreover, the dose of melatonin varied considerably – a point highlighted in a survey of prescribing practices of paediatricians that found doses ranging widely from 0.5 mg to 24 mg (Waldron *et al*, 2005). Furthermore, lack of control and the fact that efficacy (i.e. the extent to which a drug produced the desired therapeutic effect) was assessed in the short term, such that a placebo response (the law of initial effect) could contribute significantly to a false positive outcome.

Some other studies (Tjon Pian Gi *et al*, 2003; Golan *et al*, 2004) highlighted the usefulness of melatonin in control of prolonged sleep-latency known to be the most common sleep disturbance in children with attention-deficit hyperactivity disorder (ADHD) (Barkley *et al*, 1990) and not surprisingly, therefore, prescription of sleep medication was found to be two- to fourfold more frequent in children with this disorder than in those without (Owens *et al*, 2003). A related issue that should be considered in an evaluation of the effect of melatonin in ADHD is the fact that stimulant medication can further increase initial insomnia (Schwartz *et al*, 2004).

Reviewing the evidence findings on clinical benefit from randomised placebo-controlled studies (Weiss *et al*, 2006; Van der Heijden *et al*, 2007) favour the inference that melatonin is effective in treating sleep-onset insomnia in ADHD and may be useful in this type of insomnia associated with a variety of neurodevelopmental disorders.

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Table 1. Clinical trials of melatonin in children and adolescents[1]

Author(s)	Type of study	Sample size, *n*	Age, years	Diagnosis	Dose, mg	Duration	Outcome
Van der Heijden, *et al* (2007)	Randomised, double-blind placebo-controlled	105	6–12	ADHD	3 or 6	4 weeks	Increased total sleep duration
Gianotti, *et al* (2006)	Controlled	25	2.5–9.5	Autism	5	24 weeks	Sleep improved in all participants
Weiss, *et al* (2006)	Randomised, placebo-controlled	27	6–14	ADHD	5	30 days	Effective in all participants (+sleep hygiene)
Smits, *et al* (2003)	Randomised, double-blind placebo-controlled	62	6–12	Idiopathic insomnia	5	4 weeks	Better than placebo
Camfield *et al* (1996)	Controlled	6	6–12	Developmental disorders	0.5–1	4 weeks	None improved
Coppola, *et al* (2004)	Randomised, double-blind placebo-controlled	25	4–26	Intellectual disability+epilepsy	3–9	8 weeks	Significant improvement
Tjon Pian Gi, *et al* (2003)	Open label uncontrolled	24	Not stated	ADHD	3	12 weeks	Significantly effective
Szeinberg, *et al* (2006)	Retrospective	33	10–18	Delayed sleep-phase syndrome	3–5	24 weeks	Significant improvement

ADHD, attention-deficit hyperactivity disorder.

1. More recent systematic studies only. No study reported side-effects.

Dose and side-effects

The therapeutic dose in children and adolescents is yet to be determined by consensus; consequently, doses vary significantly among clinicians. The initial dose generally recommended is 2–3 mg to be taken half an hour before usual bedtime and can be increased 4–6 mg if there was no benefit after 2 weeks. The maximum dose should not exceed 10 mg. Regular review is important and a decision on the desirability of continued administration should be taken after 6 months.

A major issue for due consideration is the intensity and protean pharmacological actions of melatonin which involves multiple organ systems. For example, it modulates immune functions (Besedovsky & Rey, 1996; Sutherland *et al*, 2003), inhibits gonadal activity (Weaver, 1997), is a powerful antioxidant and a free radical scavenger (Pierie *et al*, 1994), may have oncostatic properties (Lamberg, 1996) and because of its reciprocal relationship to β-adrenergic receptor activity, may worsen depression in some individuals (Peselow, 2005).

We found no single study that reported any significant side-effects of melatonin in the short term, but it is pertinent to note that among the controlled clinical trials in the past 20 years or so, the longest follow-up evaluation period in a study (Giannotti *et al*, 2006) was 24 weeks, a finding which obviously can diminish confidence regarding the safety of long-term prescribing. However, from anecdotal evidence, three side-effects, epileptiform seizures in neurologically disordered children (Sheldon, 1998), asthmatic attacks (Sutherland *et al*, 2003) and contraceptive effect (Weaver, 1997), have been recognised.

Another point of note is that theoretically the wide pharmacological action spectrum indicated above, which is attributable to multiplicity of active sites, as with hormones in general, constitutes significant potential for probable side-effects.

Sleep hygiene

In view of the uncertainty of long-term side-effects, some attention should be paid to the application of sleep hygiene defined as the 'regulation of those daily activities and environmental factors consistent with the maintenance of good quality sleep and daytime alertness' (American Sleep Disorders Association, 1997). The key rules of sleep hygiene include: sleeping on a comfortable bed in a cool and quiet room, regular sleep time scheduling, avoidance of stimulants and late night recreations (e.g. television and computer games and for children this should be supported by positive reinforcements by parents).

As a sole treatment in young adults, sleep hygiene was not found to be as effective as other treatments (Morin *et al*, 1994). Interestingly, in a study of adults, there was no difference in knowledge about sleep hygiene in good sleepers compared with people with insomnia and in people with insomnia engaged in more unhealthy habits than good sleepers (Lacks & Roterts, 1986). Unfortunately, controlled studies that compare sleep hygiene with pharmacological treatment in children are very few.

A recent randomised, placebo-controlled trial (Weiss *et al*, 2006) investigated the relative merits of melatonin (dose 5 mg) and sleep hygiene for delayed sleep-onset insomnia in children and adolescents, (average age 10.4 years, range 6.5–14.7) with ADHD who were on stimulants. Sleep was evaluated with use of actigraphy (a process of continuing monitoring of body movements and other indicators of quantity and quality of sleep) and somnolog (a detailed structured record of sleep pattern).

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The authors concluded that melatonin was clinically superior to placebo in decreasing sleep-onset latency and that a combination of sleep hygiene and melatonin could obviate the need for a hypnotic.

Availability

Finally, in the USA, melatonin is the only hormone available without a prescription and its sale as a food supplement is allowed legally but manufacturing procedures are not standardised so that the dose in each tablet varies between packages. In current clinical practice, melatonin is administered orally only and the two major formulations are immediate release and extended release. Several strengths varying from 1.0 mg to 7.5 mg are available and the most common presentations include tablets, capsules, sublingual lozenges and liquid. In the UK, the Medicines and Health Care Regulatory Agency has declared melatonin a medicinal product rather than a nutritional supplement hence over-the-counter dispensing is not permitted and it is yet to be licensed. However, its popularity apparently predicates on the reported clinical effectiveness in sleep-onset disturbance coupled with the fact that no significant side-effects in the short term have been reported, but the non-existence of agreed posological guidelines remains a problem in clinical practice in that it can result in under-treatment or overdosing.

Conclusion

There is evidence that melatonin is effective in the control of delayed sleep-onset as a primary problem or associated with some neuropsychiatric disorders; but it should be prescribed judiciously and combined with sleep hygiene so that optimum results can be achieved (Weiss *et al*, 2006). To date, no serious side-effects have been reported. None the less, clinicians should be mindful of the possibility of fatal side-effects with prolonged use.

Declaration of interest

None.

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CATHERINE ITZIN, SUSAN BAILEY AND ARNON BENTOVIM

The effects of domestic violence and sexual abuse on mental health

SUMMARY

The Department of Health and National Institute for Mental Health in England have undertaken a programme of research and policy development since spring 2004 in partnership with the Home Office which has important implications for the practice of psychiatry. This article looks at the Victims of Violence and Abuse Prevention Programme (VVAPP) guide 'Tackling the Health and Mental Health Effects of Domestic and Sexual Violence and Abuse' launched in 2006, supported by Department of Health and Home Office ministers and national clinical directors.

The Department of Health and the National Institute for Mental Health in England in partnership with the Home Office have undertaken a 4-year programme of research and policy development (spring 2004) which has important implications for the practice of psychiatry. The Victims of Violence and Abuse Prevention Programme (VVAPP) guide 'Tackling the Health and Mental Health Effects of Domestic and Sexual Violence and Abuse' was launched in 2006, supported by health and Home Office ministers and national clinical directors (Box 1). The VVAPP has reported to the Inter-Departmental Ministerial Group on domestic violence, sexual offending and human trafficking.

Prevalence rates for this type of violence and abuse are high and its effects can be lifelong and debilitating (Boxes 2 and 3). The intention behind the VVAPP has been to assist professionals and services to identify and respond to the needs of individuals affected by domestic violence, child sexual abuse, rape and sexual assault, and sexual exploitation in prostitution, pornography and trafficking; involving victims, survivors and abusers, children, adolescents and adults.

The VVAPP was established to develop national service guidelines based on research commissioned, reviewed and conducted under the direction of the VVAPP Director to document what is known about the nature, extent and effects of victimisation, the needs of those victimised, and the treatment and care most appropriate to their needs. The programme has been advised by six panels of 150 multidisciplinary, multi-agency, cross-sector expert professionals, service providers and leading academics. Three research projects were designed to provide a triangulation of findings and evidence. A systematic literature review across all areas and groups has covered epidemiology, impact, therapeutic interventions, protection and prevention of mental health-related violence and abuse.

A Delphi expert consultation on the subject was conducted involving 285 individuals completing 586 questionnaires (Taket *et al*, in press). This included leading academics and professionals from all disciplines, service providers from all sectors and organisations representing mental health service users. The consultation focused on a number of aspects concerning mental health and violence such as service providers' principles, values, core beliefs, theoretical models and therapeutic approaches, as well as prevention, managing safety and risk, training, overcoming obstacles and improving outcomes of treatment.

A violence and abuse care pathway mapping research project has been conducted with victims of extreme and chronic abuse, and organisations providing preventive interventions with abusers. These include individuals with learning and physical disabilities and those from black and minority ethnic communities. Publication of the three research reports (Department of Health; Itzin *et al*; Trevillion *et al*; all in press) and the VVAPP guidelines is scheduled for 2008.

The VVAPP has also mapped services and produced a survey and directory of the 180 voluntary and community sector organisations providing counselling and other therapeutic interventions (in mental health) for adult victims of rape and sexual assault, adult survivors of childhood sexual abuse and young people who sexually abuse. The Home Office are using this to establish an interactive website with the potential to support the introduction of a national rape helpline, modelled on the Women's Aid and Refuge online services and national domestic violence helpline. From 2008, the child health, child and adolescent mental health services, and children's services will routinely collect data on child abuse.

A national scoping of therapeutic services for sexually abused children took place in 2007 involving the