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Does melatonin help people sleep?

It's a misapplied but probably safe miracle drug

Research p 385

In North America melatonin is a popular wonder drug which has the legal status of a "nutritional supplement," although that is a legal fiction. As a result it is not regulated as a medicine and is advertised and sold widely—in pharmacies, drug stores, health food shops, and on the internet. Many millions of people use it, mostly because they believe it will help them sleep. However, the claims made for melatonin products and their pharmaceutical quality are not controlled, and their safety has not been systematically studied.

The systematic review in this issue by Buscemi and colleagues at the University of Alberta (p 385) examines the value of melatonin in sleep disorders.[1] Such a review is much needed, as the support for this work from the US National Center for Complementary and Alternative Medicine recognises.

A thorough search of the literature yielded 12 mostly small randomised controlled trials of melatonin in secondary sleep disorders associated with medical and neurological disorders and those related to substance misuse. Another set of 13 randomised controlled trials were conducted with people who had sleep disorders arising from "sleep restriction," in which imposed or self imposed lifestyles or work patterns lead to inadequate sleep. The two sets of randomised controlled trials were analysed separately. Nine trials in each group met the criteria for inclusion in the efficacy review.

In the trials in secondary sleep disorder, melatonin had no significant effect on the time taken to fall asleep and caused a small but unimportant increase in the proportion of time in bed spent asleep ("sleep efficiency"). The trials were very heterogeneous—in adults with dementia, schizophrenia, and major depression, and in children with developmental disability, Rett syndrome, and tuberous sclerosis; the duration of trials ranged from one to eight weeks, and doses of melatonin varied. Evidently melatonin does not help such patients to sleep better.

The trials in people with sleep restriction fall into two quite different groups. Jet lag occurs in people who cross five or more time zones in a day or two and then mostly remain at their destination for many days or weeks. Their functions and habits adapt to the new time zone and environment within a few days of travel, so that their own melatonin secretion soon occurs mainly during the hours of darkness. Only people who repeat such trips in quick succession, typically long distance pilots and cabin crew, experience more complicated and intractable jet lag.

Shiftwork disorder differs, in that the time zone and environment remain the same while people are subjected to new rhythms of sleep and wakefulness. These altered rhythms sometimes continue for long periods and often occur in repeated cycles separated by periods of normal working times. In these circumstances melatonin secretion does not adapt in the same way and is much less predictable. To lump jet lag and shiftwork disorder together in a meta-analysis thus makes no sense. The conventional statistical test for heterogeneity (noted by Busecmi and colleagues in figure 3[1]) is too crude and no substitute for considering the trials in detail. For example, jet lag is worst during the first two days after arrival and steadily lessens, so the time course of symptoms must be tracked accurately and compared at several points. Trials differ in this respect, and in the size and timing of doses of melatonin.

The systematic review takes no account of what melatonin does and how it works.[1] The popular misconception underlying the widespread use of this drug is that it induces sleep pharmacologically. It doesn't. Melatonin acts as a regulating switch, pushing the body's circadian phase forward or backward, depending on when the drug is taken. If exogenous melatonin is taken at or after the onset of darkness it substitutes for the endogenous melatonin secretion which normally starts then, and the phase shifts forward, towards the sleep phase. The effect is greater because the doses used are vastly greater than the amount naturally secreted. If exogenous melatonin is taken on waking, phase change is delayed—in physiological terms, the nocturnal period of lowered alertness and performance tends to be prolonged. So, taken in the morning on arrival after a long flight eastwards, melatonin delays circadian adaptation.

The symptoms of jet lag and shiftwork disorder are due to desynchronisation between various body rhythms and environmental rhythms.[2] Sleep disturbance is merely the most prominent symptom and so gets most attention. It is not surprising that melatonin hardly affects it.

The systematic review also summarises the adverse events reported from the 25 trials included, and concludes from these that short term use of melatonin is safe.[1] The trials seem to have met Downs and Black's quality criterion for reporting adverse events.[3] But most randomised controlled trials report adverse events in a cursory and uninformative way,[4] and few reports describe at what time points the adverse events are detected or elicited and how, factors which greatly influ-

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ence what is found. Databases of adverse reactions and types of publications that were excluded from the review should also be considered, as the *Handbook for Systematic Reviews of Interventions* now recommends. The Cochrane review of melatonin for jet lag did this.[5] It found hints of a possible interaction with warfarin and a suggestion of harm in children with severe epilepsy[6]; both these problems remain to be investigated.

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Clinical course of infection with hepatitis C

Is still poorly understood

Although around 170 million people worldwide are currently infected with hepatitis C virus (HCV), its course is still not well understood. Predicting the course of infection is essential to deciding who and when to treat with the powerful available drugs—pegylated interferons and ribavirin—and anticipating the need for liver transplants and other interventions for end stage liver disease.

Several factors influence the clinical course of HCV infection. Being older than 40 at the time of infection, male sex, coinfection with hepatitis B virus or HIV, steatohepatitis, immunosuppression, and predisposing human leukocyte antigen (HLA) haplotypes have all been associated with progression of fibrosis and possible development of cirrhosis. The main risk factor for faster progression to cirrhosis in HCV infection remains, however, the consumption of alcohol.[1 2] Moreover, many intravenous drug users, the main population still at risk of HCV infection in developed countries, consume alcohol regularly.

Despite this evidence about risk factors, studies of the course of HCV infection have so far led to conflicting conclusions, and the two most recent studies are no exceptions. Wiese et al extended the follow-up of a cohort of 1980 women infected in the former East Germany from a single source (anti-D immunoglobulin contaminated by HCV genotype 1b) in 1978 and 1979 and found that, after 25 years, only 48% of untreated women still had HCV RNA in their blood. Of those untreated women who developed chronic hepatitis C, 1.3% had cirrhosis, 4.4% had marked hepatic fibrosis, and 0.1% had hepatocellular carcinoma.[3] Liver associated mortality was 0.5% in viraemic women (half of them had serious comorbidities).

Another recent study gives an entirely different picture of prognosis. D'Souza et al studied 206 first generation and second generation adult Asian immigrants to northeast London who were, according to history and extrapolation of linear regression analyses, most probably infected with HCV in childhood or by the age of 20. The investigators selected 143 patients for analysis and compared them with 239 white patients. Liver biopsies showed cirrhosis in 11% of Asians aged 26-40, 33% of those aged 41-60, and 78% of those older than 60.[4] Although only 25% of white patients aged 61-80 had cirrhosis, on the basis of multivariable linear analysis the authors concluded that prolonged infection for over 50 years leads to cirrhosis in most patients in other populations too. Can we then conclude that white European women are almost immune from cirrhosis induced by HCV, whereas the prognosis is very poor for Asians likely to be infected in childhood? We cannot.

The clinic based, cross sectional study by D'Souza et al looked at a highly selected group of individuals who were ascertained because they had HCV infection. Prone to detection bias and largely depending on extrapolation of regression lines, the study overestimates the risk of cirrhosis and reports the highest rate ever recorded for any such population of patients. Still, the data by D'Souza et al confirm that people can survive for more than 60 years with HCV infection, even when they have developed cirrhosis.

How should we put into context these two conflicting reports? Studies of the clinical course of HCV infection transmitted vertically or acquired early in life clearly show that progression of the disease is usually very slow, at least in the first three decades of life.[5] The study by D'Souza et al is therefore exceptional in showing rapid progression in 11% of patients aged under 40.[4] On the other hand, cohort studies with long term follow-up of people who acquired HCV in adulthood[6] confirm and extend in time the data of Wiese et al.[3] Finally, although the progression of hepatic fibrosis in hepatitis C seems to be non-linear,[7] and the virus seems to be more fibrogenic in older people,[8] population based studies show that infection with HCV is highly prevalent in asymptomatic people who live to old age.[9 10] Overall, the study by D'Souza et al adds little to our knowledge of the course of HCV infection. The cohort study by Wiese et al is more robust, but it may underestimate the occurrence and progression of liver disease because it is confined to young, healthy women, who are already at reduced risk of liver disease related to HCV. Most low income countries cannot afford antiviral drugs. Worldwide, antiviral treatment for HCV infection is therefore underused, and treatment does not have a marked impact on the course of this infection in populations.[11] We should urgently aim to reduce the spread of HCV infection by strictly avoiding reuse of syringes and needles (still practised in many poor countries), and to

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