Submission to the Medicines Classification Committee, Medsafe NZ

Chris King – Emeritus University of Auckland
[redacted]

31st January 2018

Purpose:

This submission seeks that the Committee:

(a) Return oral melatonin in doses of 3 mg or less to over the counter use as a food supplement, from which it was summarily removed in the 16th meeting of the then Committee on 24 April 1996. or to allow it to be purchased under the instruction of a chemist, as with doxylamine and diphenhydramine.
and/or

(b) Instruct Medsafe to allow the mail order of up to three months supply of 3mg tablets for personal use from countries such as the US, where it is legal to purchase as a dietary supplement, to bring NZ legislation into line with that of countries such as Australia, Canada, and several European countries such as Denmark, where it is regulated by prescription but personal importation from jurisdictions where it is a food supplement is permitted.

I am not a representative of a drug company, or the food additives industry, but a mathematician with a research interest in neuroscience, neurotransmitter function and the mechanisms of cerebral processing, with scientific and ethical concerns about the way melatonin has been incorrectly classified. I have included relevant research data that bears on this question, including the broader context of insomnia treatment in New Zealand, and have compiled it as a research review, so that it can be published as a research and discovery source on melatonin in insomnia treatment.

As the author of this submission I am acting in the good faith that the current Committee has the capacity and ethical commitment to consider this submission reasonably on its merits, without prejudice, notwithstanding any critical comments made about the historical actions of past Committee decisions.

Melatonin in Other Jurisdictions and the New Zealand Context

In the US, melatonin is classified as a dietary supplement under the Dietary Supplement Health and Education Act of 1994. The DSHEA defines the term "dietary supplement" to mean a product (other than tobacco) intended to supplement the diet that bears or contains one or more dietary ingredients, including a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any of the aforementioned ingredients.

David Kessler, commissioner of the FDA when DSHEA was approved, has stated that "The 1994 Dietary Supplement Act does not require that dietary supplements (defined broadly to include many substances, such as herbs and amino acids, that have no nutritive value) be shown to be safe or effective before they are marketed. The FDA does not scrutinize a dietary supplement before it enters the marketplace. The agency is permitted to restrict a substance if it poses a 'significant and unreasonable risk' under the conditions of use on the label or as commonly consumed".

This definition is completely consistent with the facts of melatonin, since it is an essential substance common to all organisms, which is produced by the human body and is widely present in both plant and animal food products.

In the author's view it is completely within the powers of this committee to resolve this by simply allowing 3 mg tablets to be purchased over the counter, possibly under the direction of a pharmacist, as is doxylamine succinate, and to be ordered by mail order from the US, for personal use, as in other countries (see below).

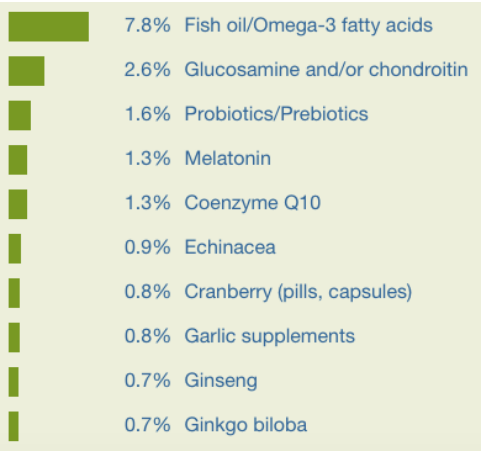


Fig 1: Data from the CDC study (right) shows 3.1 million people in the US use melatonin as a dietary supplement.

A Centers for Disease Control study (Clarke et al. 2015) finds that melatonin is the fourth most used dietary supplement in the US surveyed in the study after Omega 3 (right). The study notes that melatonin use has more than doubled between 2007 and 2012, constituting 1.3% of the then population of 314 million so that now more than 3 million people in the US are using melatonin as a food supplement on a regular basis, including 419,000 children as of February 2015 (van Winkles 2015).

During the period since the enactment of the DSHEA, the FDA has never sought to have melatonin more tightly regulated, nor has there been any evidence to support such a move. This has to be accepted by the committee as prima facie evidence of lack of manifest harm on a huge demographic scale. One would point out that the FDA is vigilant enough about food additives to place a ban when there is evidence of possible harm, as was the case with L-tryptophan between 1989 and 2001 due to processing contamination leading to eosinophilia-myalgia syndrome which was later linked to one Japanese company using genetically modified bacteria.

While debates over the use of the DSHEA including the context of melatonin continue (van Winkles 2015), the fact that the US is a major source of internet health products on a global scale means that this status needs to be respected in NZ as large scale evidence of relative lack of harm and a prevailing reason for not impounding products legally purchased in the US by mail order, given the increasingly high volume of such trade.

Many other countries which do have prescription restrictions on melatonin allow for such exceptions, rather than impounding product and forcing the purchaser to seek medical consultation in NZ to release the shipment. The examples below were found in an internet search as informal supporting evidence:

Australia: *The Therapeutic Goods Administration has categorized melatonin as a restricted item, which means that it is not available over the counter in Australia. In order to purchase it legally, it must be prescribed by a doctor. Australian residents are allowed to import therapeutic goods – like melatonin – for personal use. For this reason, many Australians buy this supplement online and ship it to their homes (https://nootriment.com/melatonin-australia/).*

Canada: *Health Canada officials say that it is legal for Canadians to bring melatonin across the border, or to obtain it abroad by mail order, but only in amounts that are suitable for personal use - no more than a 60-tablet bottle (https://www.thecanadianencyclopedia.ca/en/article/melatonin-banned/).*

Denmark: *I live in Denmark where melatonin requires a prescription. I contacted the authorities (lægemiddelstyrelsen), and apparently I'm allowed to import it from a country in the EU as long as it is legally purchased in that country. I imported some from Italy via ebay (https://www.reddit.com/r/Nootropics/comments/3quvrl/purchasing_melatonin_in_the_eu/).*

Netherlands: *I live in the Netherlands, it's no problem to find it here (ibid).*

The situation in New Zealand is a dysfunctional compromise between trying to stop importation with or without a prior medical prescription while recognizing that a person acting legally to purchase a food additive online in the US, cannot be fairly held to be acting illegally by making such an order. The compromise is dysfunctional for several reasons. The person may not have a medical condition, but is mandated to have to seek a medical consultation for a “sleep disorder”. Even if they have been to a doctor and had a prescription issued, this does not suffice either, because of arcane procedures in the regulations which would mean a second visit to the doctor to get them to issue the correct form to Medsafe. This is an obstructive compromise that is also expensive to police and a waste of public money. It is a situation that has evolved with the increase of internet purchasing and needs an efficient and reasonable adjustment. It involves a whack-a-mole exercise on the part of Medsafe, because many diverse food additive products contain melatonin under other names such as “chocolate sleep bites”.

It is manifestly inconsistent that visitors to New Zealand are legally entitled to bring in quantities of melatonin for personal use purchased in the US, or in Australia by mail order from the US according to their rules, but New Zealand citizens are denied the same rights. One can also compare the pragmatic needs of this situation with a decision recently announced by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) that Britain is to become the first country where Viagra can be bought over the counter. It said it hopes the move will stop men seeking to buy it from unregulated websites (Siddique 2017).

Committee History on Melatonin:

Background: The minutes of the 47th meeting 1 May 2012, notes the following:

Melatonin was classified urgently as a prescription medicine at the 16th meeting on 24 April 1996. Before classification a number of supplements had appeared on the New Zealand market bearing therapeutic claims. Melatonin was classified because it is a hormone and at the time there was insufficient data available regarding its effects and safety profile.

Comment: This “urgent” response was both highly inappropriate and potentially unlawful. There was no manifest issue of public health, but one of false advertising, which should have been dealt with by the appropriate government body dealing with false commercial claims. Far more serious issues have arisen with other natural supplements, such as vitamin A and no such action has been taken, despite studies confirming an up to 30% increase in cancer rates for

people taking such supplements. To turn a natural substance into a prescription poison simply on the basis of false advertising is an unjustified intrusion into civil rights by medical professionals with a primary interest in ensuring they have maintained a vigilant enough control over human behavior to void any claims of professional irresponsibility.

The claim that melatonin was “urgently” classified because it is a “hormone” and there was insufficient safety data available raises two further ethical issues. The claim that it is a “hormone” is corrected scientifically in the discussion below. At whose behest did this reclassification take place? Melatonin bears no comparison to steroid hormones and falls much more closely in line with serotonin and glutamic acid, which are amine-based neurotransmitters. One could of course argue that mono-sodium glutamate should be made a prescription drug on the same basis.

The second claim is specious because melatonin is not a designer drug, but a natural substance. A person consuming 1.5-3mg is only raising their natural melatonin levels by a marginal amount since a normal daily serum level is between 0.3 and 0.8 mg, and oral availability of melatonin by mouth is around 15%, so requiring exhaustive and financially prohibitive research to allow it to be consumed is counterproductive to public health.

47th Committee Meeting 1 May 2012 Item 6.2

(Circadin, Pharmacy Retailing (NZ) Limited trading as Healthcare Logistics)
This was a company submission for the reclassification of melatonin 2 mg prolonged release tablets from prescription medicine to restricted medicine, in a pack of up to 30 tablets, when used as monotherapy for the short term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 and over.

The committee noted that *classification of melatonin was highly variable in other overseas jurisdictions. The data provided with the submission showed that melatonin had an acceptable safety profile and had sufficient evidence of efficacy to support its approval by several medicines regulators including Medsafe.* The Committee also agreed that *the short term side effect profile of melatonin may be considered safer than the sedating anti-histamines which are often used to treat insomnia.*

However the position then taken by the committee made it difficult or impossible for the company to proceed. It cited an EU criterion to free a prescription drug for general use despite it being a natural substance already in the body:

The Committee uses the following definition adopted in 1990 by the Commission of the European Communities for suitability for non-prescription sale: 'Medical products which may be available without prescription shall show a substantial safety in use in the treatment of minor ailments or symptoms, usually capable of rapid and spontaneous relief, which are easily identifiable by users and do not justify a medical consultation'. The Committee felt that the use of melatonin in the elderly did not quite meet these criteria.

The committee then goes on to spell out the conditions that it imagines might meet these criteria:

To qualify for a shift from prescription to non-prescription status, a prescription medicine should have been marketed for three years or more in a market with a sophisticated adverse reactions reporting scheme, have had wide use during those three years, have a low adverse reaction profile with serious reactions occurring only rarely and be suitable for non-prescription sale. It was noted that Circadin has been marketed for over four years so it does meet this criterion.

The two **pre-meeting comments** also supported this reclassification:

The interested parties commented that New Zealand's aging population, and that insomnia can become more common with age, makes the need for appropriate treatment especially pertinent. Some studies have shown that Circadin does not induce tolerance over time and that patients do not suffer withdrawal effects. Pharmacists are well placed to educate patients and provide advice on dealing with insomnia. It is extensively used as a dietary supplement in the United States. With appropriate advice and labelling melatonin was suitable for reclassification.

Overall the Committee felt that the labelling, algorithm and training material for pharmacists needed more work and that there was not enough data at present supporting the proposed indication to overcome the main concerns about the product i.e. misdiagnosis and the possible adverse effects of delaying consultation with a doctor for a maximum of 13 weeks. In the end the meeting allowed for **a revised submission to be presented at a future meeting**.

48th Committee Meeting 30 Oct 2012 Item 6.4

Two pre-meeting comments were received during the consultation period. These comments supported the reclassification proposal for the following reasons:

a. melatonin, accompanied by appropriate written instructions on the packaging, is believed to be an appropriate medicine for reclassification to restricted medicine in New Zealand

b. prolonged release melatonin may be a preferable treatment for insomnia compared to prescription hypnotics or sedating antihistamines
c. pharmacists are experienced at refusing sales when the patient does not meet the set criteria for using a medicine
d. pharmacies are regulated regarding keeping accurate records of restricted medicine sales
e. community pharmacists already offer a wide range of personal and public health services (eg, emergency contraception consultations, smoking cessation advice)
f. it is already common for pharmacists to provide advice about insomnia
g. having a wider range of effective products available in a pharmacy increases the chances of patients coming to a pharmacy and therefore increases the chances of patients being referred to another health professional for other health concerns (eg, depression, chronic pain)
h. melatonin has a documented safety profile
i. melatonin is used extensively in the United States as a dietary supplement.

The committee's response despite this can be summarized in two paragraphs:

The supporting documentation and references provided with the submission referred to 13 week use of melatonin whereas the submission for reclassification was for a pack up to 30 tablets. I
Although the potential for adverse effects could be dealt with by labelling, concerns remained over the
a. risk of use in children
b. difficulty in diagnosing primary insomnia correctly, particularly in the elderly
c. likelihood and impact of an important diagnosis being missed.

Although melatonin had been used extensively in the United States, the experience had not been with a prolonged release formulation. So although that data was relevant it was not directly applicable to the submission for reclassification.

Despite the prevailing evidence being positive, the committee refused to release Circadin from controlled status:

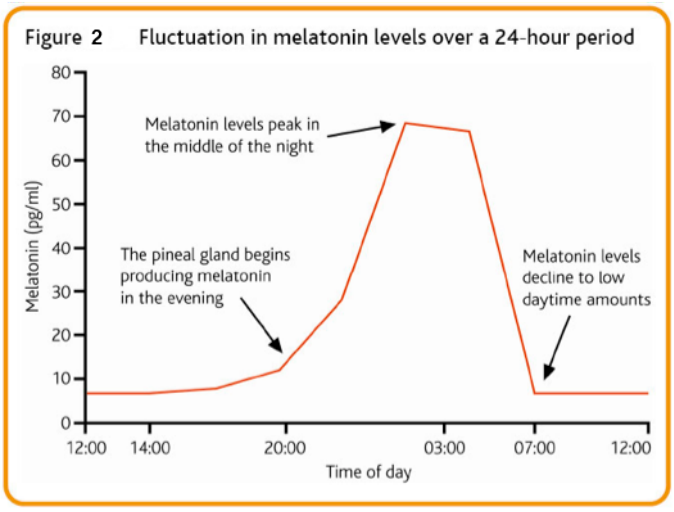
Decision: *That melatonin 2 mg prolonged release tablets should not be reclassified from prescription medicine to restricted medicine, in a pack of up to 30 tablets, when used as monotherapy for the short term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 and over.*

Comments: In the author's view this is clear evidence of an inability on the part of the then committee to act in the best interests both of public health and the general public's civil rights, by ignoring both the balance of the evidence and the supporting recommendations and instead inventing convoluted medical arguments to make any form of release of the prescription status unfeasible:

a. Not allowing its deregulation because it might confuse medical diagnosis of primary insomnia or some other condition. This is a deceptive argument, because the committee already allows over the counter sleep aids such as diphenhydramine and doxylamine cause just such an issue and have manifest side effects in addition. Therefore the decision is selectively unfair. We will deal with the question of primary insomnia in a later section.
b. There is no evidence of risk to children. No evidence has been presented to support it and use in the US confirms a good safety profile in children (see safety later).
c. The question of impeding the application because it is a slow release formulation is again unfairly obstructive. The slow release formulation was clearly designed to allow a very low dose formulation to track natural nightly fluctuations of melatonin more closely that the simple tablets the committee accepted were safe.

Circadin product formulation states clearly that it has a terminal half-life of 3.5 to 4 hours. The formulation thus effectively lowered the bar of the 2mg dose to a lower dose spread very appropriately over the natural peak period. To say this formulation simply by being released more gradually posed unacceptable risks when melatonin was considered safe was unscientific and obstructive. I am not making this as an argument for giving Circadin an exclusive licence for graduated release formulations, but to emphasize the committee's decision was unreasonably restrictive.

This raises a fundamental question about how the precautionary principle should be applied. Is it



satisfactory to make the precautionary principle so severe that a natural substance conserved by evolution throughout the spread of all natural life forms is defined to be too dangerous for the pubic to use without supervision unless exhaustive and expensive medical research is performed to prove otherwise?

49th Committee Meeting 17 Jun 2013 Item 6.4

At their request, two representatives of the company were given the opportunity to ask questions and observe the discussion. It was understood by the company that more safety data was required. The lack of safety data was the main reason for the Committee recommending not to reclassify at the last meeting. However, a number of questions were asked specifically around the risk of use in children and the screening tool. The Committee made a number of suggestions for any future submission. For example, the next submission should also try and quantify the importance of an important diagnosis of primary insomnia being missed, what the impact of this would be and how this risk could be mitigated. The Committee agreed that it would not be possible to repeat this request for future submissions for reclassification because of time constraints on the agenda.

So the end result, after months of applications, the admitted safety of melatonin, universally supportive pre-meeting comments from others, the low dose formulation spread with the natural circadian rhythm, is that the committee invented its own concerns, stranding a valid initiative conducive to public health and imposed such stringent conditions as to make the application unsustainable for the applicant, as evidenced in the subsequent 2016 meeting below.

49th Committee Meeting 1 November 2016 Item 5.8

6.2 Melatonin (Luminarie Healthcare Ltd)
This submission was withdrawn by the submitter prior to the meeting.
6.3 Melatonin (Natalie Gauld Ltd and Pharmacy Retailing (NZ) Ltd trading as Healthcare Logistics)
This submission was withdrawn by the submitter prior to the meeting.

The Biology of Melatonin

Melatonin, N-acetyl-5-methoxy tryptamine, is a highly conserved molecule present throughout the domains of life, whose presence can be traced back to ancient photosynthetic prokaryotes. It is an ambiphilic antioxidant that can easily cross cell membranes, and in animals, the blood-brain barrier. It is a direct scavenger of radical oxygen and nitrogen species. In many less-complex life forms, this is its central function (Tan et al. 2007).

Melatonin is also produced in plants where it functions as a first line of defense against oxidative stress (Tan et al. 2012). Until its identification in plants in 1987, melatonin was for decades thought to be primarily an animal neurohormone. Melatonin has subsequently been found in all plants that have been investigated. It is present in all the different parts of plants, including leaves, stems, roots, fruits, and seeds in varying proportions.

Melatonin is widely present across animal phyla, being present in insects (Richter et al. 2000). The physiological effects of melatonin on various periodic processes such as rhythmic contractions in coelenterates, fissioning of asexual planarians and reproductive events in flies have been reported in the literature (Vivien-Roels and Pevet 1993).

In vertebrates, melatonin is a neuro-transmitter/hormone produced by the pineal gland that regulates sleep and wakefulness, being involved in the entrainment (synchronization) of the circadian rhythms including sleep-wake timing, blood pressure regulation, seasonal reproduction, and many other functions. Many of its biological effects in animals are produced through activation of melatonin receptors, while others are due to its role as an antioxidant, with a particular role in the protection of nuclear and mitochondrial DNA.

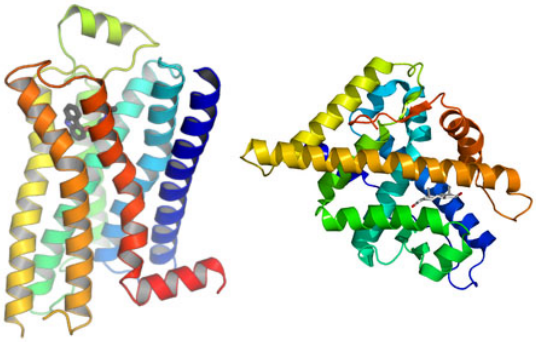


Fig 3:The melatonin receptor (left) is a membrane bound hepta-helical G-protein linked receptor like that of the beta-2-adrenergic receptor illustrated and every metabotropic neuro-receptor, but the androgen receptor (right) is a cytoplasmic transcription factor that binds directly to DNA in the nucleus.

Melatonin as a 'Hormone'

Although the literature describes melatonin as a 'hormone', this is fundamentally incorrect in terms of the molecular physiology. The classical steroid hormones such as testosterone act directly on cells by traversing the cell membrane (cholesterol is a membrane component) and binding to receptors in the cytoplasm that interact directly with DNA as transcription factors in the nucleus (e.g. the androgen receptor). Melatonin is basically an ambiphilic neurotransmitter, which binds to a membrane-bound G-protein linked receptor.

In mammals, melatonin binds to two receptors with complementary functions:

MT1 (or Mel1A) is a G protein-coupled, 7-transmembrane receptor that is responsible for melatonin effects on mammalian circadian rhythm and reproductive alterations affected by day length. The receptor is an integral membrane protein that is readily detectable and localized to two specific regions of the brain. The hypothalamic suprachiasmatic nucleus appears to be involved in circadian rhythm while the hypophysial pars tuberalis may be responsible for the reproductive effects of melatonin.

MT2 (or Mel1B) is found primarily in the retina and brain. It is thought to participate in light-dependent functions in the retina and may be involved in the neurobiological effects of melatonin. Besides the brain and retina this receptor is expressed on bone forming cells where it regulates their function in depositing bone.

The trick is that melatonin is ambiphilic enough to be released by the pineal and both have effects through the blood stream and cross the blood-brain barrier back to the receptors in the suprachiasmatic nucleus. Melatonin is not a hormone in the sense that it is a metabolic driver e.g. of sexual metabolism, but simply a circadian primer in response to light with a day-length priming effect on sexual functions in some animals. It is not habit forming, does not cause 'droid rage' like steroids, or addiction, like opiates, and manifests additional health benefits to cellular metabolism, in contrast, for example with the tendency for testosterone to significantly lower immunity, leading to buck deer sporting antlers becoming infested with parasites. Thus using the term "hormone" is qualitatively inaccurate and an unjustified rationalization for declaring melatonin a prescription drug.

General Health Benefits of Melatonin

Both animal and human studies have shown melatonin to protect against radiation-induced cellular damage. Melatonin and its metabolites protect organisms from oxidative stress by scavenging reactive oxygen species, which are generated during exposure. It is a broadly protective, readily available, orally self-administered antioxidant that is without major known side effects. An important characteristic of melatonin that distinguishes it from other classic radical scavengers is that its metabolites are also scavengers in what is referred to as the cascade reaction. Preliminary evidence suggests that it may help strengthen the immune system.

Naturally-occurring melatonin has been reported in foods including tart cherries, bananas and grapes, rice and cereals, herbs, plums, olive oil, wine and beer. When humans consume foods rich in melatonin such as banana, pineapple and orange, the blood levels of melatonin increase significantly (Sae-Teaw et al. 2012). In New Zealand both tart cherries (Howatson et al. 2012) and powder generated from night-milked cows has been marketed specifically as a natural source of melatonin in quantities claimed to help induce sleep in subject trials with exports to Korea (http://www.nzherald.co.nz/the-country/news/article.cfm?c_id=16&objectid=11440476). In fact there appears to be an international race with Brazil in this respect (Milagres et al. 2014). This provides clear evidence that melatonin is rightly regarded as a food supplement in the US and that the NZ classification as a prescription medicine is incorrect and inappropriate. How can it be reasonable that an Otago research firm can be encouraged to produce high-melatonin export milk for sleep while "chocolate sleep bites" legitimately purchased by mail-order in the US by NZers are being summarily seized by Medsafe in Auckland?

Cited health benefits from the Universities of Maryland and Michigan include: Supplementing with melatonin may reduce nighttime systolic blood pressure. It has been shown to help regulate gastrointestinal function and sensation. In one trial, people with irritable bowel syndrome who took melatonin experienced significantly less severe abdominal pain. In one trial, melatonin improved eye abnormalities in the majority of cases. It appears to work by regulating eye pigmentation and by functioning as an antioxidant. Supplementing with melatonin lowered intraocular pressure of healthy people in one study. Pineal gland function and melatonin secretion may be disturbed in people with migraine headaches. Taking melatonin may correct this problem and reduce symptoms. It may also reduce the frequency of cluster headaches. Melatonin has also been used to treat infertility. Melatonin also helps control the timing and release of female reproductive hormones. It helps determine when a woman starts to menstruate, the frequency and duration of menstrual cycles, and menopause. The AAAS also reported in 2015 that melatonin helps in the treatment of multiple sclerosis (Armitage 2015). Lowered melatonin levels have also been cited as an underlying basis for chronic insomnia in elderly people. Melatonin has been cited as being cardio-protective and neuro-protective, encouraging hippocampal neuronal regeneration, protecting against neurodegenerative diseases, and protective in perinatal hypoxia/ischemia and stroke (Srinivasan et al. 2014). Bubenik et al. (2010) have even gone so far as to suggest on the basis of a research review that melatonin supplementation at bedtime may constitute an alternative route to to increase human lifespan, avoiding the need for caloric restriction to achieve a similar effect.

But by far the most clear and obvious direct health benefit of melatonin is enabling people who have any issues with circadian rhythms to get a good, refreshing night's sleep and maintain a healthy active life style under the stresses of modern civilization. These take many forms. Light pollution, particularly of blue light in the evening from monitors and cool white light sources inhibit production of melatonin. The world is entering a phase of rapid transport across time zones where many people suffer from fatigue caused by "jet-lag". Shift workers also suffer repeated time zone changes which are known to be broadly harmful to health. Sedative sleeping tablets is not an appropriate remedy for these impacts of modern society on human physiology, but melatonin is.

General Safety of Melatonin

Two attached systematic reviews found no adverse effects of exogenous melatonin in several clinical trials and comparative trials found the adverse effects – headaches, dizziness, nausea, and drowsiness were reported about equally for both melatonin and placebo (Buscemi et al. 2005, 2006). Prolonged-release melatonin is safe with long-term use of up to 12 months. The National Institutes of Health in the US state that here have been no reports of significant side effects of melatonin in children (https://nccih.nih.gov/health/melatonin#hed4). Its use has been suggested as beneficial for ADHD and for a rare child seizure condition. Melatonin may increase REM sleep, or lead to nightmares or dizziness, in larger doses then the 3 mg proposed, and to lowered body temperature in the elderly. One study has reported a reduction in sperm quality in 2 of 8 subject in a melatonin trial, possibly due to effects of FSH levels. But there is no verified evidence of withdrawal symptoms, postural instability, or of side effects continuing after cessation of use.

Bone Remodelling, Fractures and Osteoporosis Treatment

The fact that melatonin MT2 receptors also reside in bone-forming cells raises the question of the effects of melatonin on bone growth and remodeling. A significant number of research studies have found that bone remodeling is modulated in positive ways by melatonin. Bones are dynamically remodeled by the opposing actions of osteoblasts, which generate bone by weaving dense collagen mats in coordinated groups and depositing hydroxyapatite. Osteoclasts are the iconoclasts of bone, breaking down bone tissue, disassembling and digesting the composite of hydrated protein and mineral at a molecular level by secreting acid and a collagenase.

Roth et al. (1999) demonstrated that melatonin promotes osteoblast differentiation and bone formation. Han et al. (2017) elucidate that melatonin directly regulates the late stage of osteoblast differentiation by enhancing Osterix expression and conclude that this provides further evidence of melatonin as a potent agent for treating osteoporosis. Sanchez-Barcelo et al. (2010) in a review, note that a variety of in vitro and in vivo experimental studies, although with some controversial results, point toward a possible role of melatonin deficits in the etiology of osteoporosis and adolescent idiopathic scoliosis and open a new field related to the possible therapeutic use of melatonin in these bone diseases.

Osteoclasts on the other hand generate free radicals, which are responsible for bone degradation and resorption. Melatonin appears to inhibit the osteoclast RANK/RANKL system, aiding bone consolidation (Srinivasan 2014), although not necessarily directly through the membrane receptors (Kim et al. 2017). Osteoporosis is also associated with reactive oxygen species. Koyama et al. (2002) note that melatonin at pharmacologic doses increases bone mass by suppressing resorption through down-regulation of the RANKL-mediated osteoclast formation and activation.

Amstrup et al. (2013) note that in vitro, melatonin reduces oxidative stress on bone cells by acting as an antioxidant. Furthermore, melatonin improves bone formation by promoting differentiation of human mesenchymal stem cell (hMSC) into the osteoblastic cell linage. Bone resorption is reduced by increased synthesis of osteoprogeterin (OPG), a decoy receptor that prevents receptor activator of NK-κB ligand (RANKL) in binding to its receptor. Moreover, melatonin is believed to reduce the synthesis of RANKL preventing further bone resorption. In ovariectomized as well as nonovariectomized rodents, melatonin has shown beneficial effects on bone as assessed by biochemical bone turnover markers, DXA, and μCT scans. Furthermore, in pinealectomized animals, bone mineral density (BMD) is significantly decreased compared to controls, supporting the importance of sufficient melatonin levels In a wide-ranging review, Liu et al.(2013) consider that due to its ability of regulating bone metabolism, enhancing bone formation, promoting osseo-integration of dental plant and cell and tissue protection, melatonin may used as a novel mode of therapy for augmenting bone mass in bone diseases characterized by low bone mass and increased fragility.

One widely reported study in mice given a huge dose of 50mg/kg of melatonin found reduced bone remodeling accompanied by less bone stiffness and greater callusing at 2 weeks accompanied by a reduction in osteoclasts and RANKL suppression (Histing et al. 2012). However a second study in which 5 mg and 10 mg / kg and controls were used, the low dose showed improved bone recovery, but the high dose retarded recovery, implying that low dose supplementation may aid recovery from fractures (Kim et al. 2013). Another study of young women and girls with anorexia nervosa where natural melatonin fluctuations are abnormal and bone mass loss occurs claimed RANKL suppression was phased with natural elevated nocturnal levels of melatonin in these individuals, but bone loss in anorexics is likely to be primarily a consequence of dietary starvation (Ostorowska et al. 2010).

The overall upshot of these many studies is that melatonin plays an active and functional role in bone stabilization and presents a possible strategy for treating a variety of conditions related to bone loss such as osteoporosis, but that people should be advised to avoid high dose melatonin after an accident to encourage bone remodeling, while low dose supplementation may actually be beneficial.

We now come to the question of melatonin and fracture incidence. There is one widely reported study (Frisher et al. 2016) from the UK in which medical records were retrospectively used to infer fracture rates in cohorts of people

prescribed benzodiazepines (nitrazepam or temazepam), Z-drugs (zolpidem or zopiclone), or melatonin, in which these groups had higher rates of fracture than controls who received none of these drugs.

This observational study found that in people aged 45 years and over, receiving prescriptions for melatonin was associated with an increased risk of fracture. The study also found that in a matched population group receiving 2 or more prescriptions for 'Z drug' hypnotics was also associated with a similarly increased fracture risk. The study authors reported that an increased risk of fracture was only seen in people who received 3 or more melatonin prescriptions (average 11.9). This is longer than the recommended duration of treatment in the UK, which is an initial 3 weeks, followed by a further 10 weeks if a response is seen. Over the observation period 6.0% of participants in the melatonin cohort, 5.8% of participants in the hypnotic benzodiazepine cohort, 5.9% of participants in the 'Z drug' cohort, and 3.2% of participants in the control group had a fracture. After adjusting for covariates, both the melatonin cohort and the 'Z drugs' cohort were associated with an increased risk of fracture (adjusted hazard ratio [HR] 1.44 and 1.52. However, after this adjustment the hypnotic benzodiazepine cohort was not associated with an increased risk of fracture (adjusted HR 1.26).

The conclusion about the benzodiazepines is manifestly contradictory to all other evidence on a drug that has manifest propensities for loss of coordination and injury, especially falls. Risks associated with the long-term use of hypnotic drugs have been well recognised for many years. These include falls, accidents, cognitive impairment, dependence and withdrawal symptoms. Falls and fall-related injuries are a common and serious problem for older people with 30% of people older than 65 and 50% of people older than 80 falling at least once a year. Falls are the leading cause of fatal and nonfatal unintentional injury among older adults worldwide. There is also a significant skew in the melatonin data. The majority of the melatonin prescriptions (71%) were for the prolonged-release formulation and 79% of those prescribed melatonin were prescribed it once or twice. For the 21% of participants who received 3 or more melatonin prescriptions, the average number of prescriptions was 11.9. An average of nearly 12 prescriptions for the over three group is way beyond any prescription guidelines for melatonin prescription in the UK so fundamental questions have to be asked about this cohort, which also displayed other anomalies likely to bias the results.

Commentary provided by Narinder Bhalla, Consultant Pharmacist – Medication Safety, Cambridge University Hospitals NHS Foundation Trust highlghts some of these issues: *This was an observational study so it is prone to confounding and bias, in that any outcome (in this case fracture risk) may be due to the particular characteristics of the study population rather than the treatment being studied. For instance, the melatonin, 'Z drug' and hypnotic benzodiazepine cohorts had a higher prevalence of mental health conditions and other co-morbidities compared with the control group. In addition, the melatonin cohort had a higher prevalence of sleep disorders and dementia than the 'Z drug' and hypnotic benzodiazepines groups. However, the study aimed to reduce the risk of confounding by adjusting for several covariates and potential confounding factors including age, body weight, gender, pre-study fractures, concomitant medication, sleep disorders and a variety of co-morbidities.*

This is a study that rightly causes considerable concern from many points of view. Benzodiazepines are known to make people unsteady, particularly on awakening from sleep in the night and prone to falls. Z-drugs have also been shown to be prone to postural instability as discussed below. Yet this study firstly finds increases in all three of benzodiazepines, chronic melatonin use and Z-drugs, in equal measure suggesting a common underlying cause rather than the treatment, but in attempting to adjust for confounds has managed to whitewash benzodiazepines altogether. The inconsistency of this evidence with known experience of the risks of benzodiazepines in elderly people raises fundamental questions about the cohort comparability and the data on melatonin, where 79% of the cohort had no effect, but the high melatonin cohort of 21% had both higher incidence of sleep disorder and dementia than either of the two sedatives cohorts, both factors which could affect fracture rates. Having found no effect in 79% of melatonin users, the study has focused on the upper statistical tail of melatonin users with a chronic profile and then found an effect ranging from nil to a doubling with 95% confidence. Neither are the source, or severity of the fractures known, so we don't know if they resulted from falls or other unrelated factors. There is no direct assessment of any of the patients in terms of their use of the drugs, the condition they were prescribed for or the causes of injury. If the sedatives were not given for sleep disorders, what were they given for? The authors' claim that there is no relationship between sleep disorders and fractures also flies in the face of known realities.

Given the manifest inconsistencies with all other streams of information on both melatonin and sedatives, one has to take the scientific position that the essence of good science is replicability and this is an unreplicated study with significant design flaws. There is no evidence of an increase of fractures in the moderate 79% of melatonin users, so the study doesn't imply moderate melatonin use itself carries a significant fracture risk. Nor have other agencies such as the FDA sought to take action over this report.

The thrust of the study is also contradicted by a study of postural instability of melatonin and zolpidem (Otmani et al. 2012), which has found that melatonin causes no postural instabilities on being awakened from sleep but that zolpidem causes profound such disturbances. This contrasts with the previous study in that it is actually dealing directly with live subjects, and real drug effects upon them, rather than medical records alone.

Twenty-four healthy volunteers (12 women, 12 men, aged 55–64 years) completed a randomized, double-blind, single-dose, three-way crossover study of postural stability of prolonged release melatonin 2 mg, zolpidem 10 mg, or placebo. Subjects were tested for body sway 30 min before, 1.5 and 4 h after dosing given at bedtime on body sway during the night in healthy men and women aged 55–64years. The main finding of this study is that melatonin has no effect on body sway upon mid-sleep awakening as expressed in A95, the area of the 95% confidence ellipse enclosing the COP. In contrast, zolpidem was found to significantly increase the A95 values, which indicate an increase in body sway at all time points in both “eyes closed” and “eyes open” conditions in the 55- to 65-year old subjects. The effects of zolpidem at 4 h post-dose was smaller than at 1 h 30 min but still significantly higher than that of placebo or PR-M. Post hoc analysis indicated that zolpidem significantly increased body sway compared with placebo in both “eyes closed” and “eyes open” conditions, at both time points (1 h 30 min and 4 h post-dose). This effect was highly significant and with a high magnitude (380% increase in “eyes closed” and 230% in “eyes open” condition at 1.5h and 72% increase in “eyes closed” and 98% in “eyes open” condition at 4 h post- dose

Clinical Insomnia, Circadian Arrythmia, Urban Lifestyle and Public Health

In previous Circadin applications, the then Committee brought up arguments that deregulating melatonin might confuse, or mask medical, diagnosis of primary insomnia. This is thus an issue that needs to be dealt with directly with some honesty in assessing an appropriate response on the Committee’s part. In fact the problem isn’t diagnosis of insomnia, as the medical profession well knows, but what to do about it – i.e. adequate treatment of insomnia. The next section therefore provides an in-depth discussion of the actual state of play concerning treatment of insomnia in the New Zealand context, to highlight the importance of melatonin being freely available to the general public as a safety valve against more untoward potential outcomes of drug therapy for insomnia.

The current situation is highly counterproductive, because while Medsafe classifies melatonin as a prescription poison, Pharmac declines to subsidize it. This means that access to it is restricted both legally and financially, effectively filtering it unreasonably as an effective therapy. One can mail order 90 melatonin for less than $20 NZ from the US but the standard price for three months supply in New Zealand amounts to around $150 ($50-$75 for a doctor’s appointment plus a price of around $30 for a month’s supply of 3 mg tablets). By contrast a patient can go to their doctor and get 20 temazepam or zopiclone for around $5 a pack as long as a doctor is prepared to prescribe it. This is pricing melatonin in the same ballpark as Viagra. Either Pharmac needs to subsidize it at government cost, or the Committee needs to recognize the contradiction brought about by its own previous actions and free at least 3 mg tablets from prescription regulation, saving Medsafe policing costs better applied elsewhere, the government prescriptions subsidies and the individual needless costs and impediments to protecting their own welfare.

Insomnia as an Epidemic of Civilized Life

According to US statistics, insomnia affects 20% of the population. Insomnia also presents itself in varied forms, which require differing strategies to treat effectively. Many people, including some with anxiety symptoms, find they wake early from a troubled sleep, resulting in a form of chronic insomnia where they are getting between 4 and 5 hours sleep and feel tired and seek medical help. Others, with an acute spell of sleep-onset insomnia, often due to a real life family, relationship, or financial crisis, find they cannot get to sleep at all, perhaps even on two or three nights in a row, resulting in an acute syndrome seriously affecting their brain and bodily functions and rendering them unable to carry out normal tasks, resulting in a serious medical episode unless they receive some immediate respite from sedatives to give them a chance for recuperation. At an extreme we have fatal familial insomnia, a genetic prion-related condition in which people are reduced to a catatonic coma of several months duration before death sets in.

Thus, from all points of view, the medical treatment of insomnia needs to be taken seriously as a debilitating condition which is a primary threat to good health. Insomnia and sleep arrhythmias are also a feature of the demands of modern civilization. While gatherer-hunter societies lived by the light of the sun and moon and many biological processes, from the circadian rhythm to the menstrual period were readily primed by the natural cycles, those living in urban societies face massive conflicting demands on their evolutionary physiology. Many people have to do shift work on sliding time scales that give them no consistent sleep biorhythm. Urban lighting, particularly of the blue light that photoreceptors in the retina independent of the visual system register, leads to suppression of melatonin production. Developed societies have also entered an era of transnational activity in which many people have to regularly traverse times zones on long flights and recover from jet lag. These are not medical conditions as such, but occupational hazards of otherwise healthy individuals, so it is fundamentally wrong for the medical profession to treat them as such. Critically, many of these social imperatives indicate a direct relationship with disruption of circadian cycles.

Loss of sleep has a diverse array of negative effects, both on the brain and bodily functions. Recent studies have shown that sleep enables the brain to reset synapses, which during daily activity gradually become over-excitable, back to physiological baseline levels, so that effective cognition can take place with much less expenditure of energy. This kind of problem is subjectively manifest in the fatigue and irritation over-tired people feel. Regular lack of sleep also predisposes to a significant risk of cancer (Fang et al. 2015), hypertension (Vgontzas, et al. 2009), metabolic disorders, including both diabetes mellitus (Gottleib et al. 2005) and acute gestational diabetes (Reutrakul et al. 2017). Persistent insomnia is associated with increased risk of death, as well as increased inflammation (Parthasarathy et al.

2014). Men with insomnia have a fourfold higher death rate than normal sleepers who get at least 6 hours sleep a night (Vgontzas, et al. 2010). In a large cohort of older, mostly male veterans, investigators found that any sleep disturbance was associated with a 30% increased risk for dementia and that this risk increased to 80% if individuals also had posttraumatic stress disorder (PTSD).

Given these costs to individual welfare and public health, it is imperative that the medical profession takes insomnia seriously and provides all the means at our disposal to facilitate treatment of conditions rising from lack of sleep without prejudice or paying more attention to protecting medical interests that public health. However, in both the current New Zealand context, and in trends in medical treatment over time, what we find is a very confused picture. GP dependence on GABA modulators has given way to trying to purvey antidepressants, and particularly old style tricyclics such as doxepin and amitriptyline that have been discontinued for depression. This has raised serious concerns in several quarters internationally and underscores the unsatisfactory state of medical treatment of insomnia in New Zealand of which the financial and legislative restrictions on melatonin use are a significant symptom.

1. Melatonin as a Circadian Stabilizer

There is clear evidence that cyclic melatonin production declines with age and that chronic insomnia of one sort or another is universally accepted as concomitant with the life of the elderly. While it is not clear that the decline in melatonin levels is a primary cause of elderly insomnia, the case for circadian arrhythmias being an important factor in the plight of elderly insomniacs is compelling. It is also known that the human circadian rhythm drifts towards 25 hours in experiments underground lacking light priming, so many people who are night owls are tending towards arrhythmia unless their cycle is well-primed. Melatonin thus has a potential key role in social welfare as a natural substance.

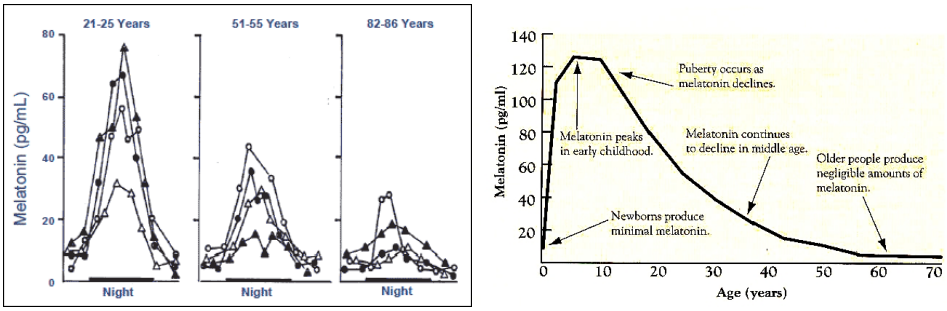


Fig 4: Evidence of the decline in melatonin production with age from two experimental studies.

A study by Richard Wurtman, who first patented melatonin as a sleep supplement (Zhdanova et al. 2001) has shown that doses of melatonin in the range from 0.3 – 3 mg do improve sleep quality in elderly people with insomnia characterized by early waking, with the lower dose being at least as effective as the higher one and involving less hypothermia and residual plasma melatonin into the waking hours. This suggests that a dose in the range of 0.3 – 1 mg is effective for maintaining the circadian rhythm. A further meta-analysis by Wurtman, and colleagues (Brzezinski et al. 2005) confirms that melatonin is an effective sleep aid. The scientists analyzed 17 peer-reviewed scientific papers. To be included the experiments reported in each paper had to be placebo-controlled and include objective measurements on at least six adult subjects. The melatonin meta-analysis delivered a definitive confirmation. Melatonin treatment in doses ranging from 0.3 mg to 10 mg significantly reduced sleep onset latency by 4.0 min; increased sleep efficiency by 2.2%, and increased total sleep duration by 12.8 min.

A the same time this paper gave rise to a special issues of Sleep Medicine Reviews in which the issue of melatonin as a hypnotic (Zhdanova 2005 a,b vs van den Heuvel 2005 a,b) as a chronobiotic (Arendt & Skene 2005) and its physiology and pathophysiology (Claustrat, Brun, & Chazot 2005) and its circadian rhythms (Scheer et al. (eds) 2005) were widely discussed and debated. A & S noted that chronobiological shifts induced by melatonin treatment are sufficient to synchronise to 24 h most blind subjects suffering from non-24 h sleep–wake disorder, with consequent benefits for sleep and that successful use of melatonin's chronobiotic properties has been reported in other sleep disorders associated with abnormal timing of the circadian system: jetlag, shiftwork, delayed sleep phase syndrome, some sleep problems of the elderly. C, B & C noted that, since the regulating system of melatonin secretion is complex, following central and autonomic pathways, there are many pathophysiological situations where the melatonin secretion can be disturbed. The resulting alteration could increase predisposition to disease, add to the severity of symptoms or modify the course and outcome of the disorder.

2. The Sedative Epoch

Originally the available agents were chloral hydrate, which is metabolized to trichlor-ethanol and acts like alcohol as a GABA modulator. Then came barbiturates, which are positive allosteric modulators of GABA but also block AMPA and kainate ionotropic glutamate receptors, meaning that they enhance GABA sedation while also blocking glutamate activation – a perfect storm situation for overdose and suicide. Then came a new wave of selective GABA modulators,

in the form of benzodiazepines. Valium (diazepam) and Serax (oxazepam) were marketed in medical advertisements as a “mother’s little helper” for women with children experiencing problems of handling their stressful domestic situations. The theme then was ‘anxiety’. Benzodiazepines were prescribed in massive quantities both for anxiety and sleep disorders. 2.3 billion pills were sold by Roche at Valium’s 1978 peak. They were freely prescribed for 10 years, before their dependency potential became a concern. Despite elderly people being consigned to chronic sedation in rest homes and ten years went by without major incident even given massive overprescribing, partly as a result of ‘benzos’ becoming a favorite of recreational drug users, there was eventually a recognition, probably, as a result of excessive use by some of these parties, that tolerance can develop over a couple of weeks and in situations of sustained abuse, rebound insomnia and epileptic fits can occur through over activation of the glutamate pathways.

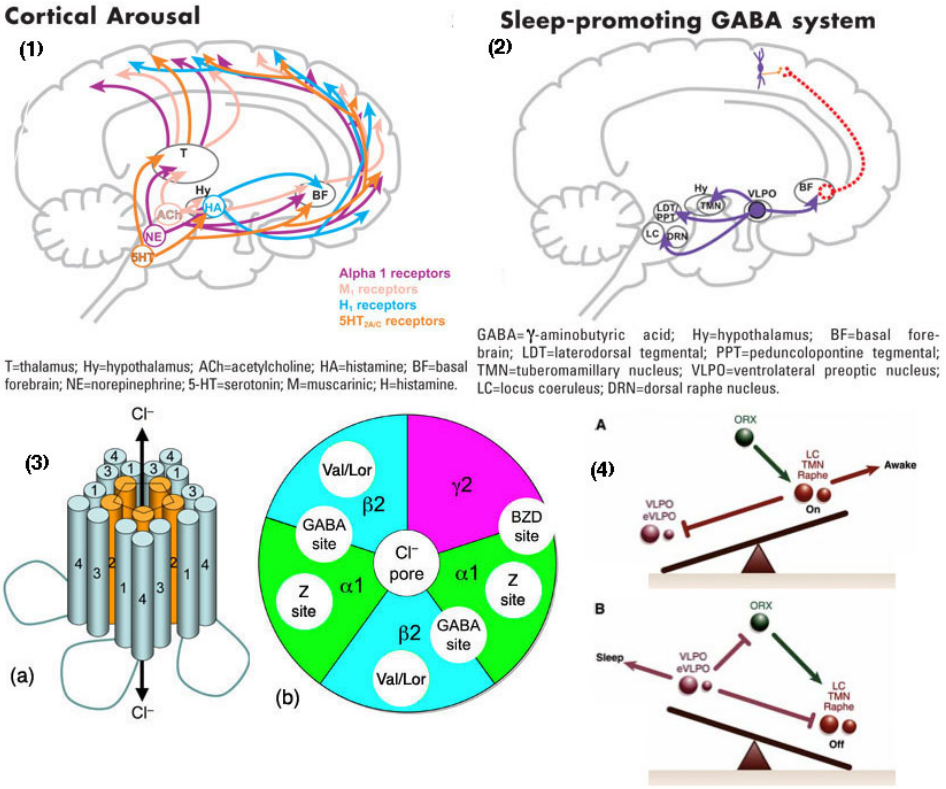


Fig 5: (1) Cortical arousal circuits involve a variety of ascending pathways involving histamine, serotonin and nor-epinephrine, Histamine H1 receptors are activated by neurons in the tuberomammillary nucleus of the hypothalamus, which become active during the 'wake' cycle, firing at approximately 2 Hz. During slow wave sleep, this firing rate drops to approximately 0.5 Hz. Finally, during REM sleep, histaminergic neurons stop firing altogether. It has been reported that histaminergic neurons have the most wake-selective firing pattern of all known neuronal types. The locus coeruleus is the principal site for nor-epinephrine ascending pathways, which maintain vigilance and are almost completely silent in REM sleep. The raphe nuclei send serotonergic projections to wide areas of the cerebral cortex releasing serotonin to the rest of the brain. They also fall silent during REM sleep and are less active during non-REM sleep. They also feedback to the suprachiasmatic nuclei (SCN), providing a responsive basis for circadian rhythms. The SCN transmits to the raphe nuclei via the dorsomedial hypothalamus nucleus altering, serotonin levels for sleep/wake states. The raphe nuclei will then transmit feedback to the SCN about the animal's vigilance and levels of alertness. The onset of REM and PGO spikes is driven by cholinergic neurons in the pons. (2) Complementing these are GABA projections from the venterolateral preoptic nucleus VLPO, which inhibit wakefulness and lead to the onset of sleep (CNS Spectrum 2008;13(12) 1047-55). (3) The GABAa ionotropic receptor is a pentamer of five sub-component proteins facilitating Cl^- flow. (b) Benzodiazepines such as temazepam bind to the same allosteric modulation site between α1 and γ2 components, enhancing the binding of GABA and thus chloride flow. Z-drugs such as zopiclone bind to the α subunit (J. Pharmacol. Exp. Ther. 317 (1): 369–77. doi:10.1124/jpet.105.096701) with short-acting zaleplon binding selectively to α1. Valerenic acid, in the herbal sleep remedy valerian and the synthetic sedative loreclezole, which again are structurally unrelated, are believed to bind to a site on the β2 protein (Neuropharmacology 53 (2007) 178-187, PNAS 91 (1994) 4569-73). This explains why benzodiazepines and Z-drugs show cross-tolerance and both show similar withdrawal effects when used over a period. (4) The sleep system is believed to form a flip-flop (right) in which the VLPO shuts down arousal in one phase while orexin ORX neurons promote arousal in the other. Orexin (hypocretin) is produced by the neuronal cluster in the posterior portion of the lateral hypothalamus. Orexin-1 receptors are found in the locus coeruleus, orexin-2 receptors in the TMN, and both types in the median raphe nuclei and mesopontine reticular formation. (Current Neuropharmacology 2008 6 367-78).

Then, as we know, a new wave of GABA modulators, the Z-drugs such as zolpidem and zopiclone came on the market. At first these were marketed as panaceas that had few of the side effects of benzodiazepenes, but over time a recognition arose that these too were capable of tolerance and habit formation. In fact it is clear that the problem is universal to GABA modulators probably because it is a characteristic of the feedback processes in the receptor itself.

Benzodiazepines and Z-drugs have major detriments to public health and life expectancy. Both benzodiazepenes and Z-drugs have been associated with increases in dementia in people over 65 (Billioti de Gage et al. 2014). Both Z-drugs and benzodiazepenes also reduce immunity and increase cancer risks around threefold (doi:10.1136/bmjopen-2012-000850, doi:10.1007/s40268-017-0207-7), possibly due to CNS depression during sleep raising lung and throat infection rates. They are known to distort sleep patterns away from deep sleep to stage 2 and to inhibit REM sleep as well (Sleep 2003 26/3 313-7), although many people find Z-drugs in particular give a refreshing sleep, particularly at the beginning of treatment. The half-life of zopiclone of around 4.5 hours is much closer to the correct therapeutic window for maintaining sleep by comparison with temazepam with a half life of 10-20 hours, leading to potential for re-dosing before the previous dose has fully dissipated, and to accidents during the day. My experience is that GABA modulators are essential medication for acute sleep onset insomnia without any substitute and rightly supplied and subsidized by Pharmac as an essential medicine, but their sleep quality is low, resulting in a phase of glassy amnesia from bedtime until awakening that doesn't feel like real sleep at all.

3. Enter the Antidepressants

As a result, of the unstable trends of medical fear and fashion, the pendulum has now swung spasmodically in the opposite direction, in phase with the shift in sentiment about psychotherapeutic drugs from tranquilizers to antidepressants, so that both benzodiazepines and Z-drugs drug are now broadly regarded with trepidation by GPs, who veer in the direction of Spartan refusal to properly treat people with acute insomnia. Patients thus have to struggle to get appropriate treatment. The pharmacological realities are somewhat in between. All GABA modulators have a degree of tolerance that varies with the individual. An estimate of tolerance for zolpidem is that a seven-hour sleep at the onset of treatment will decline to a five-hour effect over a two week course. Thus it is possible to use GABA modulators, as long as it is on an intermittent basis, ideally no more than three times a week, thus allowing for relaxation of tolerance in between. On the other hand many anti-depressants have insidious and alarming forms of dependence and withdrawal symptoms that tend to be ignored or underestimated.

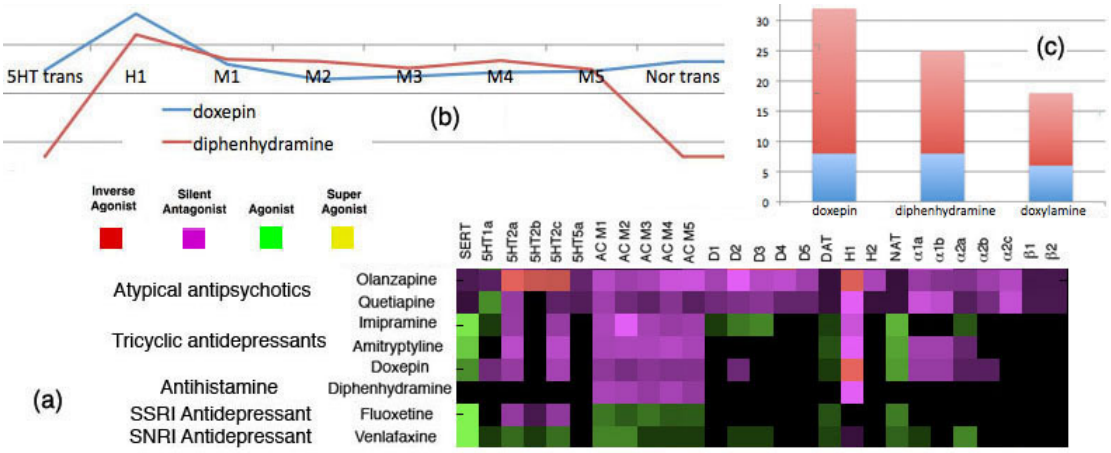


Fig 6: (a) Plot of receptor binding in pKi of major classes of non-GABA binding drugs used in insomnia, from antipsychotics to antidepressants and antihistamines generated using the PDSP database (http://pdsp.med.unc.edu/dataMining/pdspConfigGraph.php and PLoS ONE 5/2 e9019 1-17). Binding may vary from inverse agonist through neutral (silent) antagonist to super-agonist, either by binding to the neurotransmitter cleft or by allosteric modulation at other sites on the receptor. For example antipsychotics such as chlorpromazine are antagonists inhibiting signaling in a broad spectrum of receptors spanning serotonin, dopamine, adrenergic, histamine and muscarinic acetyl-choline subtypes leading to quenching of subjective affect. By contrast psychedelics act as super-agonists in specific serotonin 5HT2a and 5HT2c receptor types leading in turn to coupled glutamate activation. Antidepressants operate on serotonin and nor-epinephrine transporters reducing uptake or acting as releasing agents. Notably the antidepressant doxepin, which is also used as a sleep aid, is believed to act as an inverse agonist of the histamine H1 receptor (https://www.silenor.com/why-silenor). In (b) doxepin's quantitative binding profile scaled by dosage is compared with the antihistamine diphenhydramine showing similar sedative and anti-cholinergic activity while doxepin is also altering the activity of serotonin and nor-epinephrine transporters causing additional side effects. (c) Longer half-life of doxepin by comparison with doxylamine.

This has resulted in a new trend, which is potentially even more pernicious because the agents are much less likeable and dependence is more insidious – the use of anti-depressants to treat insomnia. One marketed extensively is

Doxepin, an old style tricyclic, marketed as Silenor. Although it lacks the debilitating activity of anti-psychotic tricyclics such as thorazine, doxepin is nevertheless a 'dirty' anti-depressant, affecting many unrelated neurotransmitter pathways that has been discontinued for on-label use for depression for this reason. Doxepin basically acts as an H1 histamine inhibitor like the over-the-counter sleep aids doxylamine succinate and diphenhydramine. It affects acetyl choline receptors somewhat less significantly than these two but also affects a swathe of serotonin and nor-adrenaline receptors, while affecting serotonin reuptake in the same manner as SSRIs, as shown in the figure above.

None of these H1 inhibitors are effective at initiating sleep onset but do tend to improve sleep duration towards the morning by suppressing H1 activation, but the tricyclics come at extensive costs in terms of collateral side effects that seem to be ignored by GPs who are more concerned about not being seen to have prescribed a habit forming drug of abuse than giving a patient something moderately toxic they won't like to take otherwise. Doxylamine and Diphenhydramine also come with significant unpleasant side effects, due to their collateral affect on acetyl choline receptors including dry mouth and urinary retention, glaucoma and hangover drowsiness. Both the tricyclics and antihistamines used for insomnia have been cited as leading to significantly increased incidence of dementia (Gray et al. 2015). Doxepin was never designed to be a short-acting drug with overnight effects as an anti-depressant, so its long half-life of around 17 hours, leaves people sedated in the day time, leading to similar risks to temazepam.

My experience of this phenomenon was being immediately offered doxepin at a first GP visit for acute insomnia due to a family crisis to which I demurred as an assault on my mental integrity. A few months later I watched my 95 year old mother-in-law struggle in misery, having taken temazepam regularly without noticeable side-effects for several years, after being forced onto a regime of sertraline, by a new doctor concerned about benzodiazepine dependence, when she moved into a retirement village. Sertraline tends to be associated with a higher rate of anxiety, agitation, and insomnia than other SSRIs so it was thoroughly unsuited to the task. After months of misery, she finally ditched her then GP and found another who would allow her to continue using half an oxazepam as needed and get back to an acceptable quality of life, demonstrating the invidious state of insomnia treatment today.

Patient doxepin reviews span reports form some help with sleep to complete inefficacy, awake all night and tired all day, through massive weight gains: *"I went from 155lbs to 185lbs in only 2 weeks. " " tried this for two weeks and yet I never got to sleep on it. I had to try it for two weeks because otherwise my doctor wouldn't give me anything else." "Helped me a lot with my insomnia. But gained over 50 pounds in the last 4 months. I will not take this anymore." "The bad thing about this medicine is that you feel very sedated throughout the day. You know you slept because of the vivid dreams and you don't wake up the whole night. Nevertheless, you feel extremely tired the whole day." "Silenor was a nightmare for me. I stuck with it for about 3 weeks and thought I was going out of my mind. I did not sleep at all for the first 4 days and then the hallucinations began. If I did sleep it was in for about 30 minutes at a time and then the terrible nightmares kept me awake for the rest of the night." "First night on 10mg didn't fall asleep until 5:15 am after 4 am popcorn binge. Woke up about 7:30 am. Same on next 3 nights with middle-of-the night coffee-cake, chocolates and even a couple of frozen dinners. Dr. upped to 20mg. Same result. Hardly any sleep, night snacking, and started eating more during the day. People have commented about rapid weight gain. They're right. I gained 8 lbs. the first week! My weight has been pretty consistent by 2-3 lbs. for years. Going back to Ambien!"*

Doxepin and related tricyclics can also cause profound withdrawal effects if used long-term: *"I have been taking a tricyclic (Doxepin or Amitriptyline) for 13 years for migraine headaches [not for depression]. Now the headaches are gone - but I cannot get off these evil drugs and it is very clear the medical professionals don't want me to either. I started at 50mg and had gone down to 30mg over time no problem. I hovered at 30 for years because each time I went to 20mg the headaches would come back. Motivated by the risk of long term side effects, I stayed at the 20mg through the headache which lasted 10 days then went away - but I had a new symptom - surges of dizziness. For 2 weeks I was great - the dizziness was there but I felt my mind start to clear. Then with no warning I went down - I thought I was passing out, but then it turned into a seizure, but I was totally coherent just out of control of my jerking body. Then all hell broke lose in the next few days. I had all the flu like, dizziness, electric shock waves from the back of my scull to front, couldn't eat and if I did it just came right out with the intermittent seizures and now we add anxiety - the kind that grips your very being - makes you grit your teeth and doubt every fiber of your being. In my case I had to go back on the drug and get well and sane again and do it right this time. It has been 4 months since I am back on the 30mgs and I am still not 100% (http://icfda.drugawareness.org/Archives/Survivors/2004/record0040.html)."*

The same concerns apply to other SSRI antidepressants, laying waste to the notion that only GABA modulators have a withdrawal problem. Wikipedia notes: Evidence has shown that paroxetine has among the highest incidence rates and severity of withdrawal syndrome of any medication of its class. Common withdrawal symptoms for paroxetine include nausea, dizziness, lightheadedness and vertigo; insomnia, nightmares and vivid dreams; feelings of electricity in the body, as well as crying and anxiety (https://en.wikipedia.org/wiki/Paroxetine).

There are a great number of concerns that can be raised about GPs summarily prescribing drugs for mental conditions to people suffering sleep disorders that invoke a "Brave New World" scenario. It is true that anxiety can cause insomnia and clinical depression can also result in early awakening, but is it right for a GP to summarily prescribe a psychoactive drug that is designed to affect a person's mood above and beyond their own rational autonomy? This is a serious ethical red line that appears to be now blatantly crossed without due professional care.

In Medscape, Thomas Roth notes: *Despite the availability of BZRAs and the development of safer compounds within the category [Z-drugs], low-dose sedating antidepressants represent an increasingly used modality for the management of insomnia. Specifically trazodone, and secondarily doxepin, mirtazapine, and amitriptyline, are being used for the treatment of insomnia even in the absence of a depressive disorder. There has been much speculation as to the increased use of these medications for the management of insomnia given that their use for their primary indication, treatment of depression, is declining due to safety-toxicity concerns. Although the BZRAs produce their sleep-promoting effects via the GABAa receptor, the mechanism of action of the low-dose sedating antidepressants is not fully understood. For the tricyclic antidepressants, their antihistaminic (H1) activity is critical. The role of their anticholinergic activity in the modulation of sleep has not been made clear. Trazodone is a mild inhibitor of serotonin reuptake, and also has antagonistic action at the α1 and α2 adrenoreceptors. There have been several hypotheses proposed for the use of low-dose sedating antidepressants: Insomnia patients typically also have depression; perceived safety at "lower" doses; availability of cheaper generics; nonschedule status; and the absence of quantity limits. A review of the literature suggests that some of these hypotheses are valid while others are not, but mostly there are inadequate data to judge the relative safety and efficacy of these "low-dose" antidepressants for the management of insomnia. In fact, when prescriptions for low-dose sedating antidepressants are written, they are written for more pills and for more refills compared with drugs indicated for insomnia (http://www.medscape.org/viewarticle/508820).*

The NIH State-of-the-Science Conference Statement on manifestations and management of chronic insomnia in adults 2005 noted the lack of evidence to support the use of antidepressants in long-term insomnia: *Chronic insomnia is a major public health problem affecting millions of individuals, along with their families and communities. Little is known about the mechanisms, causes, clinical course, comorbidities, and consequences of chronic insomnia. Evidence supports the efficacy of cognitive-behavioral therapy and benzodiazepine receptor agonists in the treatment of this disorder, at least in the short term. Very little evidence supports the efficacy of other treatments, despite their widespread use. Moreover, even for those treatments that have been systematically evaluated, the panel is concerned about the mismatch between the potential lifelong nature of this illness and the longest clinical trials, which have lasted 1 year or less. A substantial public and private research effort is warranted, including developing research tools and conducting longitudinal studies of randomized clinical trials. Finally, there is a major need for educational programs directed at physicians, health care providers, and the public (NIH Consens State Sci Statements. 2005 Jun 13-15;22(2):1-30).*

4. Orexin Agents

A fourth avenue, involving orexin-1 and -2 receptor antagonism is in various phases of research development, and one product, suvorexant, has been approved by the FDA and has been the subject of Committee hearings in New Zealand. However the orexin system is potentially sensitive to damage as there are only 10,000 to 20,000 orexin neurons in the brain fanning out to form an ascending pathway similar to those of serotonin and nor-epinephrine. Autoimmune destruction of orexin neurons leads to the disabling failure of sleep regulation narcolepsy. Suvorexant has also been criticized as having only a marginal efficacy over placebo and acts mainly to reduce the activity of histamine neurons, so may have a similar profile to antihistamine sedatives, although it has been claimed that it has little development of tolerance and doesn't appear to cause the acetyl choline related side effects of doxepin and doxylamine.

5. Cognitive Behavioral Therapy

Complementing the use of supplements such as melatonin or herbs like valerian and pharmaceuticals like GABA modulators and antidepressants, is the idea of psychological therapies, either for anxiety underlying insomnia, or to teach people with insomnia better ‘sleep hygiene’. These all have their place, but it would be unwise of the medical profession to try to rely on the idea that cognitive behavioral therapy is any kind of substitute for medical treatment.

In my first consultation for acute insomnia, I was both offered doxepin and basically instructed to undergo CBT. This has two fatal flaws. Firstly I am an intelligent individual and the idea that you can take an epidemic social condition and just treat it as one requiring re-education of the victim is as unethical as treating insomnia with mood-altering anti-depressants. Secondly it is an expensive option, suited only to those who have the time and money to throw $250 at a 30 minute or hour long refresher course. It has a valuable complementary role, but my experience of the techniques was that it was only when I discarded them completely that I cured the ongoing fallout from the original acute situation.

6. Personal Testimony

After a bout of acute severely debilitating sleep onset insomnia, punctuated by very short courses of temazepam and 18 months later zopiclone, I have found that I can maintain excellent sleep taking 1.5 mg of melatonin, close to the low range suggested above nightly, I have rapid sleep induction, excellent sleep quality, good daily energy, alertness and health, good deep sleep and active REM sleep. I do not have falls in the night. I do not feel groggy in the morning. I do not have any withdrawal symptoms when I reduce my dose and I have been taking this supplement now for some

three years. At the dosage I am taking it, given a 15% oral uptake my natural melatonin levels are only being marginally complemented enough to preserve circadian stability.

7. Conclusion

Melatonin plays a critical role in the spectrum of remedies for insomnia, in which it has major role in insomnia caused by organic or socially driven circadian arrhythmias. Restricting it to prescription use without a prescription subsidy acts as a filter to its ability to achieve therapeutic benefits and tends to drive patients towards more dangerous drugs, including both the GABA modulators and tricyclics and over the counter preparations doxylamine and diphenhydramine with known serious side effects in dependency, increased rates of dementia, cancer, accidents such as falls and fractures and overall death rate. None of the pharmacological treatments for insomnia are magic bullets and melatonin and potentially suvorexant stand out as significantly safer by comparison. Allowing over the counter purchase of melatonin would provide a cheap safer avenue to first round public health than the existing medications and for this reason has prime status as a non-prescription natural dietary supplement. At the very minimum the legislation should be brought into line with Australia, Canada and countries in the EU by allowing for personal purchase of melatonin by e-mail order from jurisdictions where it is permitted as a dietary supplement.

Costs and Benefits:

The costs all pertain to the current situation:

1. Melatonin is doubly filtered by both financial and legislative barriers. While Medsafe insists it is a prescription drug, Pharmac declines to subsidize it, taking it potentially out of reach of low-income families. Costs become discouraging and around ten times higher than mail order.
2. The restrictions on melatonin use have unsavory effects on public health because the other agents all have serious side effects, with concomitant mortality risks and risks of dementia and major ethical questions associated with their use. By contrast melatonin presents as a natural substance universal to life with no fully verified risks impeded from access by contrived reasoning of past Committee decisions.
3. People in good health who seek to use melatonin to aid a healthy lifestyle under urban intrusions into their circadian cycle cannot do so without seeking treatment for a medical condition they don't necessarily have.
4. Restrictions on melatonin are inconsistent with over-the -counter use of antihistamine sedatives, which do have manifest negative side effects, including dementia.

The benefits lie entirely with releasing melatonin from prescription status and/or allowing mail order importation for personal use as in several other countries.

1. Facilitates individuals with sleep arrhythmias correcting their situation naturally without having to take habit-forming sedatives or mood altering anti-depressants both with serious life expectancy negatives.
2. Provides an easy first line of defence against the physiological impacts of modern civilization without pathologizing the general population.
3. Saves Medsafe a pyrrhic time-wasting cost and personnel battle policing a diverse range of dietary supplements from the US and then having to negotiate with the purchaser to see a doctor to legitimize it, when its services could be much better applied to dealing with real threats to public health.

References:

1. Amstrup A, T. Sikjaer, L. Mosekilde & L. Rejnmark (2013) Melatonin and the skeleton Osteoporos Int (2013) 24:2919–2927 DOI 10.1007/s00198-013-2404-8.
2. Arendt J, Skene D (2005) Melatonin as a chronobiotic Sleep Medicine Reviews (2005) 9, 25–39
3. Hanae Armitage 2015 Melatonin could help treat multiple sclerosis http://www.sciencemag.org/news/2015/09/melatonin-could-help-treat-multiple-sclerosis
4. Narinder Bhalla (2016) Fracture risk associated with melatonin and other hypnotics National Institute for Health and Care Excellence October Cambridge University Hospitals NHS Foundation Trust http://arms.evidence.nhs.uk/resources/hub/1057851/attachment
5. Sophie Billioti de Gage, Yola Moride, Thierry Ducruet, Tobias Kurth, Hélène Verdoux, Marie Tournier, Antoine Pariente, Bernard Bégaud (2014) Benzodiazepine use and risk of Alzheimer's disease:case-control study BMJ 2014;349:g5205 doi:10.1136/bmj.g5205.
6. Amnon Brzezinski, Mark G. Vangel, Richard J. Wurtman, Gillian Norried, Irina Zhdanovae, Abraham Ben-Shushana, Ian Ford, 2005 Effects of exogenous melatonin on sleep: a meta-analysis Sleep Medicine Reviews (2005) 9, 41–50.
7. G.A. Bubenik, S.J. Konturek (2011) Melatonin And Aging: Prospects For Human Treatment Journal of Physiology and Phamacology http://jpp.krakow.pl/journal/archive/02_11/articles/02_article.html

8. Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, Baker G, Klassen TP, Vohra S (2005). "The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis". J Gen Intern Med. 20 (12): 1151–58. doi:10.1111/j.1525-1497.2005.0243.x.
9. Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, Vohra S, Klassen TP, Baker G (2006). "Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis". BMJ. 332 (7538): 385–93. doi:10.1136/bmj.38731.532766.F6.
10. Caroline Cassels (2014) Disturbed Sleep Linked to Increased Dementia Risk https://www.medscape.com/viewarticle/828286#vp_1
11. Pin-Liang Chen et al. (2012) Risk of Dementia in Patients with Insomnia and Longterm Use of Hypnotics: A Population-based Retrospective Cohort Study PLOS ONE 7(11) e49113.
12. Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. (2015) Trends in the use of complementary health approaches among adults: United States, 2002–2012. National health statistics reports; no 79. Hyattsville, MD: National Center for Health Statistics..
13. Bruno Claustrat, Jocelyne Brun, Guy Chazot (2005) The basic physiology and pathophysiology of melatonin Sleep Medicine Reviews (2005) 9, 11–24.
14. Hui-Feng Fang, Nae-Fang Miao, Chi-Dan Chen, Trevor Sithole, Min-Huey Chung (2015) Risk of Cancer in Patients with Insomnia, Parasomnia, and Obstructive Sleep Apnea: A Nationwide Nested Case-Control Study 2015; 6(11): 1140-1147. doi: 10.7150/jca.12490.
15. Martin Frisher, Nicholas Gibbons, James Bashford, Steve Chapman, Scott Weich (2016) Melatonin, hypnotics and their association with fracture: a matched cohort study Age and Ageing; 45: 801–806 doi: 10.1093/ageing/afw123.
16. Daniel J. Gottlieb, MD, et al. (2005) Association of Sleep Time With Diabetes Mellitus and Impaired Glucose Tolerance Arch Intern Med. 165(8):863-867. doi:10.1001/archinte.165.8.863.
17. Shelly L. Gray et al. (2015) Cumulative Use of Strong Anticholinergic Medications and Incident Dementia JAMA Intern Med. 175(3): 401–407. doi:10.1001/jamainternmed.2014.7663.
18. Younho Han, Young-Mi Kim, Hyung Sik Kim & Kwang Youl Lee (2017) Melatonin promotes osteoblast differentiation by regulating Osterix protein stability and expression Scientific RepoRts | 7: 5716 | DOI:10.1038/s41598-017-06304-x.
19. Tina Histing, M.D. et al. (2012) Melatonin Impairs Fracture Healing by Suppressing RANKL-Mediated Bone Remodeling Journal of Surgical Research 173, 83–90 doi:10.1016/j.jss.2010.08.036.
20. Glyn Howatson, Phillip G. Bell, Jamie Tallent, Benita Middleton, Malachy P. McHugh, Jason Ellis (2012) Effect of tart cherry juice (Prunus cerasus) on melatonin levels and enhanced sleep quality Eur J Nutr 51:909–916 DOI 10.1007/s00394-011-0263-7.
21. Hyung Joon Kim, Ha Jin Kim, Moon-Kyoung Bae and Yong-Deok Kim (2017) Suppression of Osteoclastogenesis by Melatonin: A Melatonin Receptor-Independent Action Int. J. Mol. Sci., 18, 1142; doi:10.3390/ijms18061142
22. Koo Kim, Seunghoon Lee, Yunkyung Hong, Minkyung Lee, and Yonggeun Hong (2013) Melatonin promotes fracture healing at pharmacological doses on the early phase in perforating fracture model FASEB Journal 27/1 Apr Sup.
23. Hiroki Koyama, Osamu Nakade, Yukihiro Takada, Tohru Kaku, and K.H. William Lau (2002) Melatonin at Pharmacologic Doses Increases Bone Mass by Suppressing Resorption Through Down-Regulation of the RANKL-Mediated Osteoclast Formation and Activation Journal of Bone And Mineral Research 17/7,
24. Jie Liu, Fang Huang and Hong-Wen He (2013) Melatonin Effects on Hard Tissues: Bone and Tooth Int. J. Mol. Sci., 14, 10063-10074; doi:10.3390/ijms140510063
25. Luboshitzky R, Shen-Orr Z, Nave R, Lavi S, Lavie P. (2002) Melatonin administration alters semen quality in healthy men. J Androl. Jul-Aug;23(4):572-8.
26. Maria P Milagres, Valeria P R Minim, Luis A Minim, Andrea A Simiqueli, Liliane E S Moraes and Hercia S D Martino (2014) Night milking adds value to cow's milk J Sci Food Agric; 94: 1688–1692 DOI 10.1002/jsfa.6480.
27. Ostrowska S et al. (2010) Melatonin, the RANKL/RANK/OPG system, and bone metabolism in girls with anorexia nervosa Endokrynologia Polska/Polish Journal of Endocrinology Tom/Volume 61; 1/2010.
28. Sarah Otmani, Deborah Metzger, Nathalie Guichard, Philippe Danjou, Tali Nir, Nava Zisapel and Amnon Katz (2012) Effects of prolonged-release melatonin and zolpidem on postural stability in older adults Hum. Psychopharmacol Clin Exp, 27 270–276. DOI: 10.1002/hup.2219
29. Sairam Parthasarathy et al. (2014) Persistent Insomnia is Associated with Mortality Risk Am J Med. 128(3): 268–275.e2. doi:10.1016/j.amjmed.2014.10.015.
30. Sirimon Reutrakul, et al. (2017) Short sleep duration and hyperglycemia in pregnancy: Aggregate and individual patient data meta-analysis Sleep Medicine Reviews doi:10.1016/j.smrv.2017.09.003.
31. Klaus Richter, Elmar Peschke and Dorothee Peschke (2000) A neuroendocrine releasing effect of melatonin in the brain of an insect, Periplaneta americana (L.) J. Pineal Res. 28:129–135
32. B. Vivien-Roels and P. Pevet (1993), Melatonin: presence and formation in invertebrates Experientia 49 Birkh/iuser Verlag, CH-4010 Basel/Switzerland 642-7.

33. Jerome A. Roth, Byung-Gook Kim, Wen-Lang Lin, and Moon-Il Cho (1999) Melatonin Promotes Osteoblast Differentiation and Bone Formation* THE JOURNAL OF BIOLOGICAL CHEMISTRY Vol. 274, No. 31, Issue of July 30, pp. 22041–22047, 1999
34. Sae-Teaw M, Johns J, Johns NP, Subongkot S (2012). "Serum melatonin levels and antioxidant capacities after consumption of pineapple, orange, or banana by healthy male volunteers". J. Pineal Res. 55 (1): 58–64. doi:10.1111/jpi.12025.
35. E. J. Sanchez-Barcelo, M. D. Mediavilla, D. X. Tan, and R. J. Reiter (2010) Scientific Basis for the Potential Use of Melatonin in Bone Diseases: Osteoporosis and Adolescent Idiopathic Scoliosis Journal of Osteoporosis Volume 2010, Article ID 830231, doi:10.4061/2010/830231 .
36. Scheer F et al. (eds) (2005) Melatonin, sleep, and circadian rhythms Sleep Medicine Reviews (2005) 9, 5–9.
37. Haroon Siddique (2017) Viagra will be available over the counter in UK, says medicines regulator Guardian 28 Nov https://www.theguardian.com/business/2017/nov/28/viagra-will-be-available-over-the-counter-in-uk-says-medicines-regulator .
38. Venkatramanujan Srinivasan (ed), Gabriella Gobbi, Samuel D. Shillcutt, Sibel Suzen (2014) Melatonin: Therapeutic Value and Neuroprotection CRC Press Taylor & Francis ISBN 9781482220094.
39. Tan DX, Manchester LC, Terron MP, Flores LJ, Reiter RJ (2007). "One molecule, many derivatives: a never-ending interaction of melatonin with reactive oxygen and nitrogen species?". J. Pineal Res. 42 (1): 28–42. doi:10.1111/j.1600-079X.2006.00407.x
40. Tan DX, Hardeland R, Manchester LC, Korkmaz A, Ma S, Rosales-Corral S, Reiter RJ (2012). "Functional roles of melatonin in plants, and perspectives in nutritional and agricultural science". Journal of Experimental Botany. 63 (2): 577–97. doi:10.1093/jxb/err256. PMID 22016420.
41. van den Heuvel C et al. (2005) Melatonin as a hypnotic: Con Sleep Medicine Reviews (2005) 9, 71–80.
42. van den Heuvel C et al. (2005) Reply to the comment on 'Melatonin as a hypnotic: Con Sleep Medicine Reviews (2005) 9, 83–84.
43. Van Winkle's (2015) The Dark Side of Melatonin https://www.huffingtonpost.com/van-winkles/the-dark-side-of-melatoni_b_8855998.html
44. Alexandros Vgontzas et al. (2009) Insomnia with Objective Short Sleep Duration is Associated with a High Risk for Hypertension SLEEP, 32(4), 491-7.
45. Alexandros N. Vgontzas, et al. (2010) Insomnia with Short Sleep Duration and Mortality: The Penn State Cohort Sleep, 33(9) 1159-64.
46. Irina V. Zhdanova, Richard J. Wurtman, Meredith M. Regan, Judith A. Taylor, Jian Ping Shi, and Ojingwa U. Leclair (2001) Melatonin Treatment for Age-Related Insomnia The Journal of Clinical Endocrinology & Metabolism 86(10): 4727–4730.
47. Zhdanova I (2005) Melatonin as a hypnotic: Pro Sleep Medicine Reviews (2005) 9, 51–65.
48. Zhdanova I (2005) Comment on 'Melatonin as a hypnotic: Con Sleep Medicine Reviews (2005) 9, 81.