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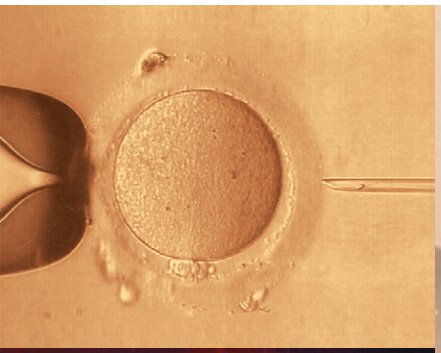

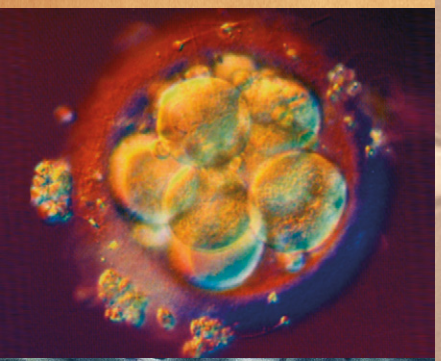

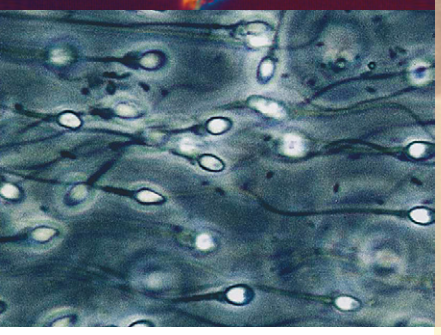

Melatonin

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ENDO FERTI FORUM

ENDOKRINOLOGIE & FERTILITÄT
FÜR KLINIK & PRAXIS

20.-21. März 2026

Universitätsmedizin Mainz

Einladung zu unserer wissenschaftlichen Veranstaltung Endo-Ferti-Forum

Brücke(n) zwischen Unikliniken und Praxen an Rhein und Main(z)

– die aus dem bisherigen Format „Ferti Forum“ ab 2026 hervorgeht –

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Weitere Informationen
& Anmeldung unter

Melatonin

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H. Ahrendt[4], J. Bitzer[5], C. Albring[6], C. Egarter[7], B. Kleine-Gunk[8], K. König[9], G. Merki-Feld[10]

Chemistry: Melatonin is an indolamine which accrues via serotonin from the amino acid L tryptophan. *Point of origin:* The main point of origin in humans is the epiphysis. *Physiological relevance:* – In animals: Due to lighting condition influenced chronobiological processes, melatonin has impact on reproduction and growth. In consequence of its anti-oxidative efficacy, melatonin has protective effects from environmental influences. – In humans: Melatonin can be found in a variety of cells like in lymphocytes and bone marrow cells, the thymus gland and in the gastrointestinal tract as well as in the skin and in the eyes. There, it exerts numerous paracrine functions. The effects of melatonin in humans are divers and not fully understood yet. Melatonin results in down-regulation of several biological and oxidative processes. It plays a role in the endogenous rhythm formation, is a potent anti-oxidant and has immunomodulatory effects. Of clinical relevance is a potential correlation with the development of breast cancer.

Pharmacotherapy: The field of research and the clinical relevance of chronobiology and the possible indications for the use of melatonin is broad. However, there are not sufficient data on the efficacy and safety of melatonin from clinical trials.

Melatonin is used in retarded formulation and is approved for the treatment of sleep disorders in people > 55 years of age with disorders in the sleep architecture. In contrast to benzodiazepines, which are commonly used for the treatment of insomnia, it appears that melatonin does not result in an impairment of psycho-motorics on the following day. The subjective perception of the quality of sleep and the mental performance are improved on the next morning. However, the difference in the response rate compared to placebo is low and therefore melatonin can be considered a weak hypnotic agent only. The rate of recurrent insomnia can not be estimated from the current studies available due to the low numbers of patients.

Melatonin is a weak hypnotic which is approved for the treatment of sleep disorders in people > 55 years of age with disorders in the sleep architecture. It is also used for the treatment of sleep disorders in children as well as in adults with neurological diseases like abnormal development of the CNS and impaired vision, cerebral palsy, attention deficit disorder and autism. A melatonin receptor antagonist is also approved for the treatment of depression. There are inconclusive data regarding the efficacy of melatonin in the treatment of subjective afflictions from jetlag symptoms.

Compounds: – Oral agents: Melatonin is sold over the counter as food supplement in Canada and the U.S. According to the German Drug Act, melatonin is available on prescription only. This is also the case for any melatonin-containing drugs, independent of the concentrations contained. Circadin®: In 2007 Circadin® received approval from the European Commission for the treatment of sleep disorders in people > 55 years of age. It received marketing approval in Switzerland in 2009 and is traded since 2010. Circadin® contains 2 mg melatonin in retarded formulation. The recommended dosage is 2 mg melatonin, taken 1–2 hours before going to bed after the last meal for at least 3 weeks. Capsules containing up to 5 mg melatonin with varying additives are available from different manufacturers on the European market for supplemental diets. Agomelatin®: is a substance with a chemical structure comparable to melatonin. In contrast to melatonin, which has affinity to melatonin receptors types MT1 and MT2, Agomelatin® has antagonistic characteristics on the serotonin receptor 5-HT2c. Agomelatin® has marketing approval for the treatment of depression. – Topical agents: Melatonin is used as hair restorer: Trichosense®

Drug safety: Short term melatonin intake (< 3 months) in low doses should not have any deleterious effects in adults. A final conclusion on the safety of long term intake of melatonin cannot be drawn due to lack of data. **J Reproduktionsmed Endokrinol_Online 2015; 12 (4): 342–52.**

Key words: Melatonin, circadian rhythm, sleep, CNS, jetlag, sleep disorders, antioxidant, chronobiology

History

In 1917, McCord and Allen discovered that tadpoles changed their colour after feeding an extract from the pineal gland [1, 2]. In 1958, Lerner, a professor of dermatology, and colleagues isolated melatonin from the pineal gland of cattle and named the hormone accordingly [3]. In the middle of the 1970's, the circadian rhythm in the human pineal gland was discovered [4].

Chemistry and Biosynthesis

Melatonin (N-acetyl-5-methoxytryptamine) is a biogenic amine (Fig. 1). It is synthesized in the human pineal gland (Epiphysis cerebri). The biosynthesis occurs in two steps (Fig. 2).

Serotonin, which is formed from the amino-acid tryptophan, is N-acetylated by acetyl-coenzyme A. Serotonin-N-acetyl transferase (AANAT) serves as catalyst. The product N-acetyl-serotonin is then methylated with S-adenosylmethionine by the acetylserotonine-O-methyltransferase. The first step is rate determining by the activity of the AANAT.

Molecular Biology

The biosynthesis of melatonin occurs after activation of pinealocytes by sympathetic fibres. During the night, pinealocytes release noradrenaline, which mainly binds to beta-1, but also to alpha-1 and alpha-2 receptors. Membrane bound adenylate cyclase is activated by intermediary, regulatory G(s) proteins after stimulation of beta-receptors. The intra-cellular cAMP-concentration increases.

Relevance of the Receptors

Alpha-1 receptors occur in equal concentrations as beta-1 receptors in the pineal compartment but their stimulation solely does not result in increased concentrations of cAMP, NAT or melatonin. Simultaneous activation of beta-1 and alpha-1 receptors leads to a 100-fold potentiation of the effect on the beta-1 receptor in the presence of free calcium [5].

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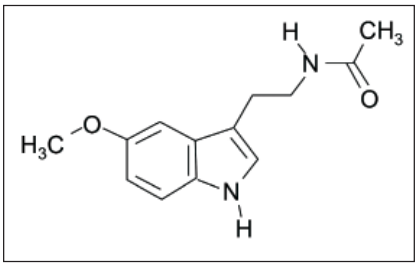

Figure 1. Melatonin.

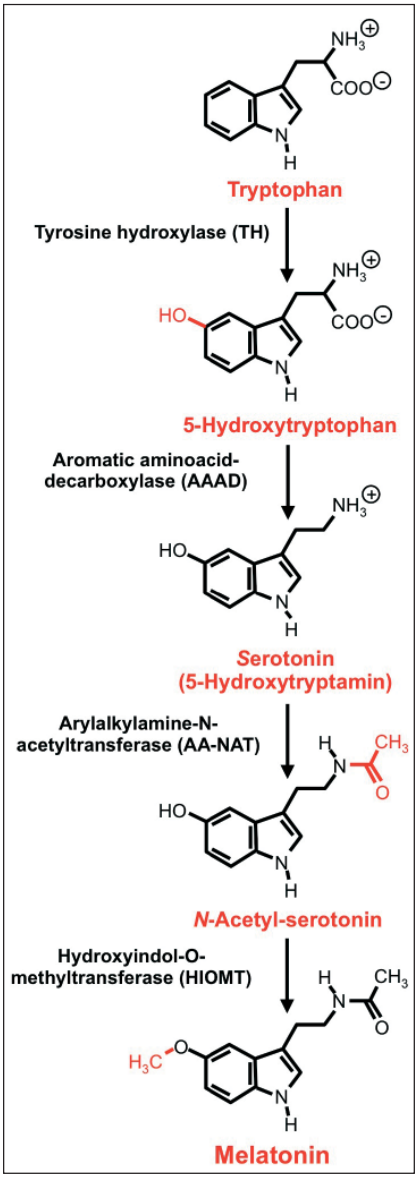

Figure 2. Synthesis of Melatonin.

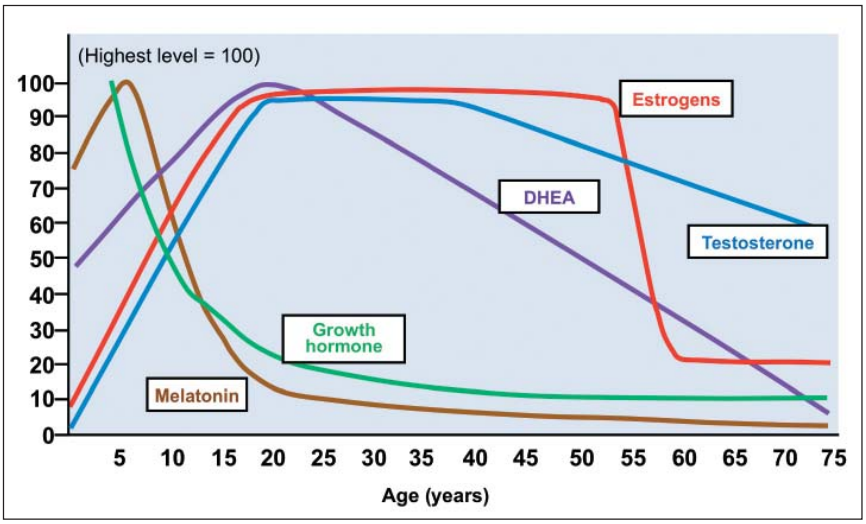

Figure 3. Estradiol, DHEA, Testosterone, Melatonin and growth hormone dependent on the age.
Mod. according to: [Römmler A. Die Adrenopause: Individuelle Substitution mit DHEA (Dehydroepiandrosteron). In: Rabe T, Strowitzki T. Lifestyle & Anti-Aging Medizin. Rendezvous Verlag, Baden-Baden, 2002; 127–6]. © T. Rabe.

A negative feedback for noradrenaline release is mediated by alpha-2 receptors [6]. Alpha-2 agonists like clonidine and caffeine inhibit the formation of melatonin. Particularly during the night, caffeine has a strong inhibitory effect on the secretion of melatonin [7]. During aging melatonin secretion and blood levels decrease (Fig. 3). Elderly people, in which lower circadian fluctuations in the melatonin secretion can be observed, also show a decrease in beta-receptor levels with increasing age [8].

After synthesis, melatonin is secreted in the blood and probably also to liquor fluid since the melatonin concentrations in liquor are higher compared to those in blood.

Physiological Control of Melatonin-Synthesis

Light-dependency: Human melatonin blood-levels are dependent on the individual light exposition: high levels are measured during darkness periods with peak levels between 02:00 and 04:00 a. m. There is barely no melatonin synthesis during the daylight period. The melatonin secretion decreases with approximately 200–400 Lux (e. g. light of a common bulb) and is maximally supressed at approximately 600 Lux. Normal daylight reaches levels up to 10,000 Lux. Blue light (at 509 nm wavelength) seems most efficient in the suppression of melatonin plasma-levels in humans [9].

Epiphyseal-retinal regulatory circuit: Synthesis and secretion of melatonin is controlled by the circadian pacemaker Nucleus suprachiasmaticus (SCN) which is connected by synaptic fibres with the pineal gland to provide information on the current light intensity (Fig. 4). The SCN receives efferents from the retina through the hypothalamic tract.

During bright daylight, photosensitive receptor cells in the retina, which account for up to 2% of retinal ganglion cells in humans, are in a hyperpolarized condition. As a result, the retino-hypothalamic tract is not able to activate neurons in the SCN. The photosensitive cells release melanopsin, a 7-transmembrane opsin with vitamin A similar cis-retinal co-factor, which has a peak in adsorption at 484 nm [10, 11] (Fig. 5). Due to different light conditions during the seasons, there is a seasonal rhythm beside the circadian rhythm thus, by regulating the fertility in several animal species, there occur more births during the summer period [12].

Detection

The detection of melatonin is performed in the serum or saliva by RIA or ELSA. SI-units will be used whenever feasible. The reported data were obtained under standard conditions if not otherwise indicated.

Typical melatonin concentrations in humans

Children: up to approximately 300 pg/ml during night time. The melatonin levels of new-borns are unsteady. They become more steady with the 3rd month of life with peak-levels between midnight and 08:00 a. m. [13].

Adults (younger): 10–40 pg/ml during day time period and approximately 60–120 pg/ml during the night.

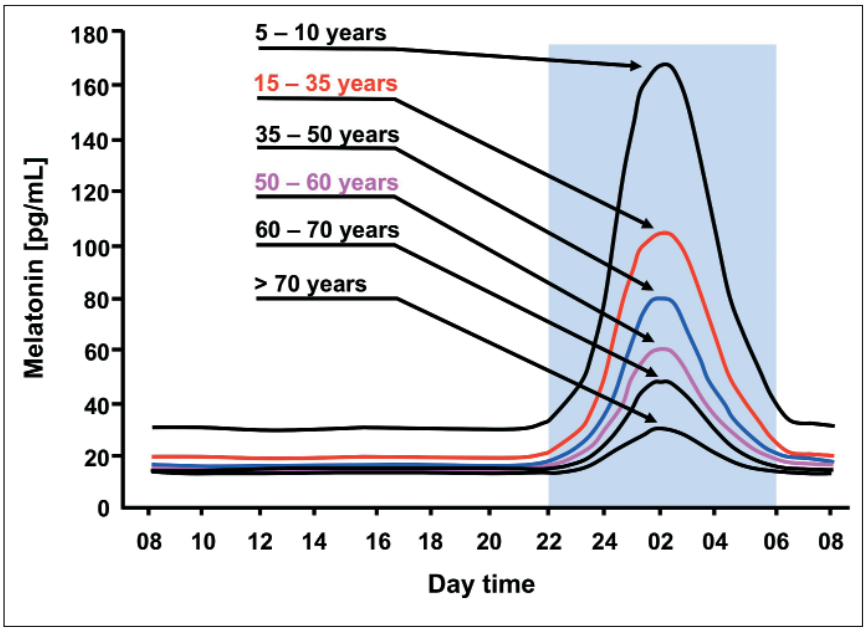

Figure 4. Melatonin – daily rhythm. According to: [https://www.psiram.com/ge/index.php/Datei:Melatonin3.jpg; Open access (http://creativecommons.org/licenses/by-sa/3.0/de/)]

Adults (elderly): 20–50 pg/ml during the night [14].

Alternatively, the metabolite 6-hydroxy-melatonin sulfate can be measured in the urine to conclude on the melatonin secretion during the night [15–18].

Molecular Biological Effects

Melatonin can be found in a variety of cells in humans like in lymphocytes and bone marrow cells, the thymus gland and in the gastrointestinal tract as well as in skin and eyes. It has numerous paracrine functions [19]. Only little is known about the exact mechanism of melatonin-effects. Nevertheless, it can be stated in general that melatonin has preferably inhibitory effects resulting in the down-regulation of a variety of biological and oxidative effects.

Melatonin receptors: Among others, melatonin acts via the activation of specific receptors: membrane-bound-, cytosolic- as well as (controversial) receptors in the nucleus [20]. Three subtypes of melatonin receptors are defined genetically. Two of those were also found in mammals [21]:

– *Mel1a gene:* The human *Mel1a* gene is located on chromosome 4.
– *Mel1b gene:* The human *Mel1b* gene is located on chromosome 11 [22].

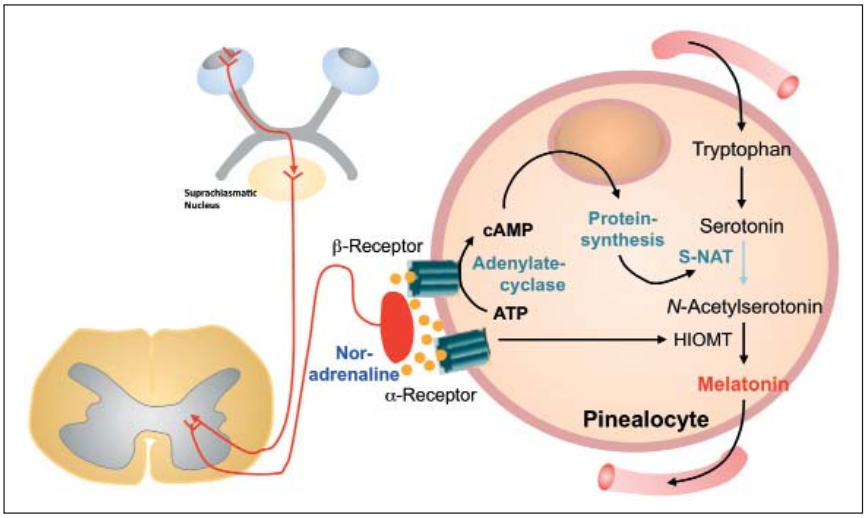

Figure 5. Synthesis of Melatonin. Mod. according to: [Steinhilper D, Natürlicher Schlaf? Melatonin, Melatonin- Rezeptor-Agonisten und Tryptophan als Schlafmittel. Pharm. Unserer Zeit 2007; 6: 213–7)]. © T. Rabe.

Mel1b receptor mRNA was found in the retina, in the hippocampus and throughout the central nervous system in humans. However, there was no expression detected in the SCN.

Calmodulin-Ca^{2+}-complex: Intracellular melatonin binds on the calmodulin-Ca^{2+}-complex which results in an activation of enzymes (adenylate cyclase, phosphodiesterase).

Retinoid-Z-receptors a and b: Melatonin binds on retinoid-Z-receptors a and b in the nucleus [23]

Other Metabolic Pathways

All up to now known melatonin receptors supress the formation of cytosolic cAMP which results in a decrease of Mel1a-receptor mRNA levels [24]. Melatonin results in a decrease of the metabolic activity and protein synthesis in the core areas of the SCN [25]. Melatonin causes a Ca^{2+} dependent inhibition of dopamine-release in the hypothalamus and the retina [26].

Effect of Melatonin in Humans

Brain Function: Rhythm-Formation, Sleep, Cognition and Psyche

Rhythm-Formation

Melatonin influences the seasonal biorhythm, the circadian rhythm and senescence [27]. Melatonin is the hormone of endogenous rhythm-formation. It mediates the circadian rhythm to the body [28]. The melatonin balance can be impaired by shift work and by long distance travels due to time change.

Melatonin and Sleep

Sleep-promotion is a central effect of melatonin. The peak in melatonin levels during darkness has a trigger function. It is speculated that a melatonin peak causes a temperature drop, which exerts the trigger function [29]. The human body produces less melatonin with increasing age and the mean duration of sleep decreases and sleep disorders occur more frequently. The melatonin peak occurs probably more early in elderly people what might explain why the elderly awake more early and suffer from sleep disorders more frequently [30]. In 1990, Waldhauer discovered that melato-

nin shortens the early stages and prolongs the REM-phases of sleep [31].

Winter Depression

Due to the low levels of daylight, the melatonin levels remain increased during the winter period (Fig. 4). In consequence, not only fatigue and sleep disorders but also depressions might occur.

Memory

Relaxing sleep is essential for a functional memory. One of the reasons therefore might be the impact of melatonin on the hippocampus, a region in the brain, which is essential for learning and memory. Due to melatonin, the neuro-physiological basis of learning and memory, which is called the synaptic plasticity, is obviously subjected to the circadian rhythm. Melatonin changes electrophysiological processes like long-term potentiation (LTP) [32]. Some studies indicate a correlation between low levels of melatonin and symptoms of dementia. However, the level of evidence is not sufficient yet [33].

Autism

Some individuals with autistic spectrum disorders (ASD) show decreased melatonin levels compared to healthy volunteers [34]. Healthy parents of patients with ASD show also low levels of melatonin. Autism is also associated with a lower activity of the *ASMT*-gene which codes for the last step of melatonin synthesis [35]. It seems that melatonin improves the sleep in patients with autism spectrum disorderd (ASD) [36]. However, up to date there is no official recommendation by the current guidelines.

Impact of Melatonin on Pituitary-Regulatory Circuits

There is some evidence that melatonin influences the secretion of pituitary hormones. Melatonin stimulates the secretion of the somatropin growth hormone and disorders might result in premature stopping of serotonin release respectively. However, the specific effect of melatonin on the secretion of somatropin is subject of controversial scientific discussions [37].

Melatonin has also impact on the hypothalamic-pituitary-gonadal axis [38]. On the one side, pinealocytes express gonadotropin-, as well as oestrogen-, progesterone- and testosterone-receptors; and on the other side, melatonin receptors are expressed not only in the hypothalamus but also in the pituitary and the gonads [39, 40]. Melatonin stimulates the nucleus arcuatus in the hypothalamus resulting in GnRH secretion [41]. Finnish females from a region with large seasonal differences in daylight showed increased levels of melatonin as well as decreased levels of gonadotropin during the season with low levels of daylight, which indicates a negative feedback loop between melatonin and the hypothalamic-pituitary-gonadal axis [42].

Melatonin lowers the FSH-levels [43]. Exogenous intake of melatonin also seems to influence the pulsatile LH-secretion [44]. A lowered decrease of melatonin levels were found in females at the 12th day of the menstrual cycle [45]. An increase of the endogenous melatonin levels in females might result in changes of the menstrual cycle [46, 47]. During the 1990's, it was attempted to use the anti-gonadotrope effect for an oestrogen-free contraceptive. Supplemental gestagen is required for effective contraception [48].

Contraception Studies in Women

75.0 mg melatonin in combination with 0.3, 0.5, 0.75 and 1.0 mg norethisteron given daily. The combination supressed the ovulation in 36 women [49], whereby the control of the menstrual cycle was dependent on the dose-combination.

75.0 mg melatonin in combination with 0.5 mg norethisteron on days 1–23 resulted in reliable contraception and adequate control of the menstrual cycle [49]. It should be considered that the ovulation-inhibitory dose of norehisteron is 0.4 mg/day [50].

300 mg melatonin/day in combination with or without 0.75 mg norethisteron, either daily or during the days 5–17 of the menstrual cycle, resulted in significantly decreased LH-E2 and progesterone (P4) levels during the night compared to an untreated control group. The peak areas (AUC) of LH and estradiol were significantly decreased in the 4th month of treatment (LH: 30%, estradiol: 20%, both compared to the first month, P-value < 0.005) [49]. These results indicate an additive synergistic effect between melatonin and norethisteron.

Author's comment: The development was stopped since the primary objective of a steroid-free contraception could not be met due to impairment of the menstrual cycle leading to the necessity of progestin treatment.

In males, no classical feedback-loop between the pineal gland and testes seem to exist [51]. Therefore, it deems unlikely that a melatonin therapy might impair the hypothalamic-pituitary-gonadal axis [52]. In contrast, melatonin seems to have an inhibitory effect on Leydig cells in rat and mice [53].

In summary, the effect of melatonin on the reproductive system in humans is not fully understood yet [54].

Anti-Oxidative Effect

Melatonin and its precursor acetyl serotonin have strong anti-oxidative effects [55]. The broad anti-oxidative spectrum of melatonin and its potency as free radical scavenger for oxygen- and nitrogen compounds was discovered in 1993 [56, 57]. Melatonin can easily pass cell membranes [58] and the blood-brain barrier in its function as anti-oxidant [59, 60]. Oxidized melatonin is a terminal anti-oxidant [58, 61]. Compared to other anti-oxidants like vitamin C, melatonin is not subject to a redox cycle and therefore melatonin cannot become an oxidant itself. The primary metabolite is N(1)-acetyl-N(2)-formyl-5-methoxykynuramine (AFMK). A single AFMK molecule can bind 10 ROS/NOS (reactive oxygen-/ reactive nitrogen species) since some of the reaction products are anti-oxidants itself. The capacity of melatonin to absorb free radicals extends at least up to the quaternary structure of its reaction products, which is clearly outstanding compared to simple anti-oxidants [62]. Due to its anti-oxidative effect, melatonin is also considered to have a radiation protective effect since 70% of the damaging potential of ionising radiation is caused by free radicals [62, 63].

Melatonin is also considered to slow down neuro-degenerative processes due to its anti-oxidative properties and could therefore potentially be used in the anti-ageing therapy [61, 64].

Immune-Modulatory Effects

The immune-modulatory effects of melatonin are currently subject of controver-

sial scientific discussions. The effects are probably mediated by the MT1 and MT2 melatonin receptors, expressed by immune-competent cells. Melatonin receptors were identified on CD4 and CD8 positive T-cells, influencing the cytokine production and proliferation of such cells [65]. Melatonin increases the cytotoxic capacity of natural killer (NK) cells. It leads to a decreased synthesis of pro-inflammatory cytokines like tumor-necrosis factor alpha (TNF-α) as well as a down-regulation of the inducible NO-synthase (iNOS) gene expression [66]. It was observed that endogenous melatonin led to an increased production of interleukin 1, 2 and 4 in T-helper lymphocytes [67]. It seems that melatonin is also involved in the clonal expansion of antigen stimulated human T-lymphocytes. An increased melatonin production was found in patients with rheumatoid arthritis compared to an age-adjusted control group [68].

There is no proven evidence on whether a therapy with melatonin is contra-indicated in patients with autoimmune-disorders due to its potential stimulation of unspecific immune responses [69]. Some studies investigated the effect of melatonin in the treatment of viral-, bacterial- or parasitic infections like HIV or malaria [70, 71]. Melatonin stimulates the growth and reproduction of *Plasmodium falciparum*, the malaria pathogen, *in vitro*. On the other hand, the anti-oxidative potential of melatonin might be effective in preventing cellular destruction and liver injury due to oxidative processes. Therefore, the therapeutic combination of melatonin and melatonin-antagonists is currently under discussion [72].

Due to melatonin's anti-oxidative, anti-apoptotic and immune-modulatory effects, it is currently objective of several studies, investigating its positive effects in treatment of patients with septic shock or multi-organ failure. However, further results of large randomized studies are required before a routine use can be recommended [73, 74].

Anti-Carcinogenic Effect

The significantly increased rates of people working night-shift is considered the result of a decreased melatonin production [75]. A series of in vivo models in rats, mice and hamsters showed that melatonin is able to prevent DNA damage induced by carcinogenic agents [60].

Breast Cancer

In some older studies, lower melatonin levels were detected in females with primary breast cancer compared to a control collective [76]. The Guernsey III-study, a large cohort study, revealed no evidence for an association between breast cancer and decreased melatonin levels in first void urine in 252 breast cancer patients and 727 matched control cases. However, the authors describe a trend towards an inverse association that should be confirmed in further studies [77].

According to a meta-analysis of data conducted by Cancer Research UK [78], the risk for development of breast cancer is 19–48% higher in females who ever worked night-shift [79–83]. The risk estimation seems higher in older studies.

Nurses working night-shift and flight attendants are night-workers which were most often subject to investigations [80, 82, 84]. Light exposition during the night leads to increased levels of sexual hormones due to the lack of the inhibitory effect of melatonin on the peripheral estrogen level during the night [85, 86]. However, also other influencing variables like life-style factors, tobacco consumption, BMI and physical activity might play a role [79, 81]

Author's comment: The increased radiation exposition during long-distance flights, especially in flight-attendants must also be taken into consideration.

It is also considered that melatonin inhibits fibroblasts, which play a role in the development of breast cancer [87, 88]. In animal models it could be shown that melatonin was able to inhibit tumor cell growth and cell proliferation as well as angiogenesis [89].

Mortality: In a systematic review of clinical studies in 634 cancer patients, a decreased mortality rate of patients that received melatonin treatment was noticed. However, the studies were un-blinded [91]. Different tumor entities and outcomes were analysed in numerous reviews. Thus, further systematic reviews are required to proof the evidence of melatonin in the treatment of cancer [91].

Effect on Metabolic System and Gastrointestinal Tract

Diabetes mellitus: Polymorphisms in the human MT2 melatonin receptor gene are associated with an increased risk for type 2 diabetes [92]. Females with low melatonin levels might also have an increased risk for the development of type 2 diabetes [93, 94]. A constant diet supplemented with melatonin results in weight-reduction in animal models [95]. A potential mechanism is the recruitment of brown adipose tissue (BAT) [96].

Gall bladder: Melatonin has several protective effects in the gall bladder, like the conversion of cholesterol, the regulation of cholesterol passage through the bowel wall and protection from oxidative stress. Throughout the day, the concentration of melatonin in the gall bladder is 2–3-fold higher compared to serum in humans [97].

Gastrointestinal diseases: Some studies also investigated the effect of melatonin in the treatment of gastro-oesophageal reflux disease and in patients with irritable colon [98, 99].

Effect on Skin and Hair

Hair growth: The effect of melatonin on hair growth appears to be a new pharmacological point of application. Melatonin treatment resulted in improved hair growth and increase diameters of hair shafts in rodents [100]. To which extent these results can be transferred in humans is not elaborated yet.

UV induced erythema: Topical applied melatonin has a suppressive effect on the formation on UV induced erythema.

Other skin diseases: The effect of melatonin is under investigation in several indications in dermatology, like atopic eczema, psoriasis and malignant melanoma [100].

Melatonin as Food Supplement

Melatonin is produced by all mammals during the night. Thus, melatonin can also be found in milk. Different levels of melatonin can be found in milk, depending on the time and food basis of the animals. In particular, dairy farming under controlled light conditions as well as grass and herbal based feeding lead to high melatonin levels during the night.

The milk then contains up to 0.04 mg melatonin per litre [101]. The sleep promoting effect of crystals derived from such milk is scientifically not proven [102]. Melatonin can also be found in cherries at concentrations of 0.17–13.46 ng/g as well as in bananas, grapes, rice, cereals, olives, oil, wine and beer [103, 104].

Pharmacotherapy with Melatonin

Melatonin is sold over the counter as food supplement in Canada and in the U.S. According to the German Drug Act, melatonin is available on prescription only. This is also the case for any melatonin-containing drugs, independent of the concentrations contained [AMVV §1, No.1]. Marketing of melatonin as food supplement is prohibited. Nevertheless, the use of melatonin in dietary food is permitted according to the common list by the European Commission in line with article 13 of act 1924/2006 (Health claims) if the health related statements "Melatonin contributes to the relief of subjective feelings of Jetlag" and "Melatonin contributes to the reduction of time taken to fall asleep" are made. The permitted doses and the wording for package information leaflets are predefined [EU Register on nutrition and health claims]. These defaults refer to a scientific evaluation by the European Food Safety Authority (EFSA) which were published in 2010 and 2011 [105, 106]. The inclusion in the common list permits distinct statements on melatonin but does not imply a classical marketing authorization for melatonin containing food. The so-called "Health Claims" are exclusively designated for foods and not for medicines.

The first patent for melatonin as a low dose sleep-inducing agent was granted to Richard Wurtmann in 1995 [107]. The drug Circadin® received marketing approval in April 2008 for the treatment of sleep disorders in people older 55 years of age with disorders in the sleep architecture [108]. Melatonin-containing hair tonic (Karrer Trichosense Solution® [30 × 3 ml]) is commercially available in Switzerland. However, sufficient data on the efficacy in humans are not available.

Pharmacokinetics

Resorption

Melatonin is resorbed after oral intake. However, an issue for the efficacy of systemic substitution is the strong first-pass metabolism [109].

Degradation

90% of melatonin are bio-transformed by cytochrome-P450-mono-oxygenase to 6-OH-melatonin during the hepatic passage. 60–70% are secreted with the urine in sulphated or glucuronide derivate (20–30%). A small amount is directly renal secreted and can be detected in salvia [108]. The half life is approximately 30 minutes.

Side Effects

A short-term (< 3 months) intake of melatonin in low doses should not have any deleterious effects [110, 111]. The side effects are generally low. The following adverse events were observed:

Dizziness or fatigue, irritability, tension, restlessness (with increased activity), nightmares, migraine, vertigo, abdominal pain, constipation, dry mouth, hyperbilirubinaemia, sweating, weakness, orthostatic dysregulation and gain in weight (SmPC Circadin®) [112–114]. The addictive potential of retarded melatonin cannot be estimated due to the small sample size of the available studies [115]. Application of melatonin in children might result in growth retardation and a delayed onset of adolescence [116]. Up to date it is not finally clarified whether melatonin leads to deterioration of symptoms of autoimmune diseases due to its immune-modulatory characteristics (www.drugs.com/melatonin.html) [117].

Drug Interactions

The liver enzymes CYP1A1, CYP1A2 and CYP2C19 are involved in the metabolism of melatonin. Furthermore, melatonin induces CYP3A4. Drug interactions were observed for fluvoxamine, methoxypsoralen, cimetidine, estrogens, carbamazepine, rifampicine, alcohol, tobacco smoke and central nervous system depressants. Light is an effective melatonin antagonist.

Fluvoxamine, ciprofloxacin and other chinolines can significantly increase the melatonin level. Other hypnotics and sedatives like benzodiazepine can increase the sedative effect of melatonin. It is also quite likely that melatonin increases the efficacy of anticoagulants. The INR can be increased if melatonin is taken with warfarin. Melatonin can also increase the blood pressure and heart rate if it is taken with nifedipine.

The effects of botanicals anticoagulants like ginko biloba and ginseng or the sedative effects of valerian and amber can be increased by melatonin. Melatonin might interfere with immunosuppressive therapies due to its immune-modulatory effect.

Clinical Use

Indications

The field of research and the clinical relevance of chronobiology and the possible indications for the use of melatonin is broad. However, there are not sufficient data on the efficacy and safety of melatonin from clinical trials.

Sleep Disorders

2 mg melatonin in retarded formulation is approved for the treatment of sleep disorders in people > 55 years of age with disorders in the sleep architecture. In contrast to benzodiazepines, which are commonly used for the treatment of insomnia, it appears that melatonin does not result in an impairment of psychomotorics on the following day. The subjective perception of the quality of sleep and the mental performance are improved next morning. However, the difference in response rate compared to placebo is low and therefore melatonin can be considered a weak hypnotic agent only. The rate of recurrent insomnia cannot be estimated from the current studies available due to the low numbers of patients [108, 115].

Melatonin is also used for the treatment of sleep disorders in children as well as in adults with neurological diseases like abnormal development of the CNS and impaired vision, cerebral palsy, attention deficit disorder and autism; in rare cases, melatonin is applied before EEG investigations (see Hospital guideline 2014: http://www.southstaffsandshropshealthcareft.nhs.uk/Services/Medicines-Management-and-Pharmacy/Default/Essential-Share-Care-Agreements/docs/Guide-lines/Prescribing-Guidelines-Melatonin-Version-2.aspx

Smaller studies demonstrated that 2–10 mg melatonin is effective in treatment of children having problems to fall

Table 1. Melatonin (Preparations in Germany). © T. Rabe.

Formulation	Trade name	Formulation	Dosage
Short-term	Melatonin (different trade names) (Internet)	Capsules à 0,5, 1, 1,5 2,5, 3 and 5 mg **)	in the evening 1 capsule
	Priorin LF (formerly Asatex)** Trichosense (Kharrer)	topical application for hair loss	topical application for hair loss
Retard forms	Circadin 2 mg Retard tablets*)	Retard tablets à 2 mg available only on prescription	1x 2 mg in the evening

*) http://www.apotheken-umschau.de/do/extern/medfinder/medikament-arzneimittel-information-Circadin-2mg-Retardtabletten-RB2083.html; http://www.pharmawiki.ch/wiki/index.php?wiki=Melatonin
**) http://ads.docmorris.de/index.php?cc=sea_lp&phrase=melatonin&type=medicine&zanpid=1776316187421402112; 2.6.2013
***) http://www.priorinlf.ch/

asleep or to sleep throughout the night [118]) if:
- they have behavioural syndromes or neurological issues like ADHD or autism,
- measures to improve the sleep hygiene were not efficient,
- severe sleep disorders,
- persistence of the symptoms for more than 6 months (https://www.whatdotheyknow.com/request/118302/response/292960/attach/3/attachment.pdf). However, up to date there is no official recommendation by the current guidelines (http://www.awmf.org/uploads/tx_szleitlinien/028-012l_S1_Nichtorganische_Schlafstörungen_2013-09.pdf)

Jetlag

Several studies investigated the efficacy of melatonin in the treatment of Jetlag symptoms. The data are very different between the studies. A large meta-analysis published in a Cochrane review indicates significant efficacy of melatonin in doses from 0.5 up to 5 mg [119, 120]. Doses > 5 mg did not further increase the efficacy. The relative ineffectiveness of 2 mg slow-release melatonin compounds indicate that a shorter duration of effectiveness and higher peak levels of melatonin are more effective. The efficacy is higher the more time zones are crossed and in eastbound compared to westbound flights. Subjective parameters of sleep were investigated in these studies but also other symptoms like fatigue during the daytime and well-being. Another meta-analysis failed to show a significant advantage of melatonin in the treatment of jetlag symptoms [110]. None of the studies considered age-related adjustment of objectives and analyses. The efficacy of melatonin might potentially improve in people aged 55 years or above. The selection of studies was criticised for the different endpoints, the short duration of melatonin treatment and short observation periods.

Treatment of Depression

Agomelatin®, a long-term melatonin receptor agonist with serotonin-antagonistic characteristics, is approved for the treatment of depression (major depression disorder) [121]. Some studies also showed that supplemental melatonin is effective in the prevention of migraine and cluster headache [122, 123]. Other clinical studies demonstrated a benefit of melatonin in the treatment of tinnitus in adults [95–97, 124]. Due to its anti-oxidative characteristics, melatonin is considered to have a potential benefit in delay of neuro-degenerative processes and therefore it is considered to be used in anti-ageing therapies [63, 64].

Summary

Chemistry

Melatonin is an indolamine that accrues via serotonin from the amino-acid L-tryptophan.

Point of Origin

The main point of origin in humans is the epiphysis.

Physiological Relevance

In Animals

Due to lighting condition influenced chronobiological processes, melatonin has impact on reproduction and growth. In consequence of its anti-oxidative efficacy, melatonin has protective effects from environmental influences.

In Humans

Melatonin can be found in a variety of cells in humans like in lymphocytes and bone marrow cells, the thymus gland and in the gastrointestinal tract as well as in skin and eyes. There, it exerts numerous paracrine functions. The effects of melatonin in humans are divers and not fully understood yet. Melatonin results in down-regulation of several biological and oxidative processes. It plays a role in the endogenous rhythm formation, is a potent anti-oxidant and has immune-modulatory effects. Of clinical relevance is a potential correlation with the development of breast cancer.

Pharmacotherapy

The field of research, the clinical relevance of chronobiology and the possible indications for the use of melatonin is broad. However, there are no sufficient data on the efficacy and safety of melatonin from clinical trials.

Melatonin is a weak hypnotic, which is approved for the treatment of sleep disorders in people older 55 years of age with disorders in the sleep architecture. It is also used for the treatment of sleep disorders in children as well as in adults with neurological diseases like abnormal development of the CNS and impaired vision, cerebral palsy, attention deficit disorder and autism. A melatonin receptor antagonist is also approved for the treatment of depression. There are inconclusive data regarding the efficacy of melatonin in the treatment of subjective afflictions from jetlag symptoms.

Compounds

Oral agents (Tab. 1)

Melatonin is sold over the counter as food supplement in Canada and in the U.S. According to the German Drug Act, melatonin is available on prescription only (AMWV §1, No. 1). **Circadin®:** In 2007 Circadin® received approval from the European Commission for the treat-

ment of sleep disorders in people > 55 years of age. It received marketing approval in Switzerland in 2009 and is traded since 2010. Circadin® contains 2 mg melatonin in retarded formulation. The recommended dosage is 2 mg melatonin, taken 1–2 hours before going to bed after the last meal for at least 3 weeks [125]. Capsules containing up to 5 mg melatonin with varying additives are available from different manufacturers on the European market for supplemental diets.

Agomelatin® is a substance with a chemical structure comparable to melatonin. In contrast to melatonin, which has affinity to melatonin receptors types MT1 and MT2, Agomelatin® has antagonistic characteristics on the serotonin receptor 5-HT2c. Agomelatin® has marketing approval for the treatment of depression.

Topical agents:
Melatonin is used as hair-restorer: Trichosense®

Drug Safety

Short-term melatonin intake (< 3 months) in low doses should not have any deleterious effects in adults.

A conclusion on the safety of long-term intake of melatonin cannot be drawn due to lack of data.

Weblinks
South Staffordshire and Shropshire Healthcare NHS: http://www.southstaffsandshropshealthcareft.nhs.uk/Services/Medicines-Managementand-Pharmacy/Default/Essential-Share-Care-Agreements/docs/Guidelines/Prescribing-Guidelines-Melatonin-Version-2.asp

Royal Cornwell Hospitals: http://www.rcht.nhs.uk/DocumentsLibrary/RoyalCornwallHospitalsTrust/Clinical/Pharmacy/Melatonin.pdf

NHS Foundation Trust: http://www.tewv.nhs.uk/Global/Policies%20and%20Procedures/Pharmacy/PHARM-0025-v2%20Guidelines%20for%20Safe%20Prescribing%20of%20Melatonin%20in%20Children%20and%20Adults.pdf

Worcestershire Area Prescribing Committee: https://www.whatdotheyknow.com/request/118302/response/292960/attach/3/attachment.pdf

Wikipedia: http://en.wikipedia.org/wiki/Melatonin; http://de.wikibooks.org/wiki/Melatonin; http://www.infomed.ch/infomed_search.php?zoom_sort=0&zoom_xml=0&zoom_query=-melatonin&zoom_per_page=10&zoom_and=1&zoom_cat%5B%5D=-1

EMA: http://www.ema.europa.eu/ema/index.jsp?curl=search.jsp&q=melatonin&btnG=Search&mid=WC0b00ac058001d125v

Cochrane: http://www.cochrane.org/search/site/melatonin

Wikipedia: Psiram.com: http://www.psiram.com/ge/index.php/Melatonin

Guidelines

S3-Leitlinie der DGSM: nicht erholsamerSchlaf/Schlafstörungen. Deutsche Gesellschaft für Schlaffforschung und Schlafmedizin (DGSM) in Somnologie 2009; http://www.awmf.org/leitlinien/detail/ll/063-001.html

AWMF-Leitline Bipolare Störungen: http://www.awmf.org/leitlinien/detail/ll/038-019.html

AWMF-Leitlinie Clusterkopfschmerz und trigeminoautonome Kopfschmerzen: http://www.awmf.org/leitlinien/detail/ll/030-036.html

National Institute for Health and Care Excellence (NICE) Guidelines IFPUO2: Using melatonin to treat sleep disorders in children and young people with ADHD: http://publications.nice.org.uk/ifpuo2-using-melatonin-to-treat-sleep-disorders-in-children-and-young-peoplewith-adhd-ifpuo2/prescribing-melatonin

Further References

McGrane et al [126] investigated the role of melatonin in REM-sleep disorders and demonstrated that melatonin shows a favourable safety profile. In particular, in elderly patients with several concomitant medications, melatonin was better tolerated due to lack of drug-drug interactions compared to clonazepam. However, prospective clinical studies are demanded.

On whether melatonin has any impact on sleep and Alzheimer's disease was investigated by Peter-Derex et al. 2015 [127].

Damiani et al. [128] described melatonin as an optional treatment of sleep disorders in children with autistic disorders.

Costello et al. [129] investigated the efficacy of melatonin in inducing a normal sleeping behaviour. However, recommendations for shift workers or for the improvement of hormonal cycles in healthy subjects can not be made due to the currently available data since long-term RCTs are missing.

Biologic rhythms
Trivedi and Kumar [130] describe the effect of melatonin as internal signal for the daily an annually timing.

Jetlag
Herxheimer [131] investigated the role of melatonin in jetlag in a systematic review. There, 5 studies could have been evaluated.

Reproduction
Cruz et al. [132] addressed the role of melatonin on the production and preservation of gametes and embryos in a short review.

The coincidence of melatonin and female reproduction is subject of a review by Tamura et al [133].

Reiter et al [134] described the role of melatonin and the circadian system in the context of successful female reproduction and found that stable circadian rhythm as well as cyclic melatonin secretion are of importance for optimal ovarian physiology and placental functions. Light exposition during the night should be avoided since exposition to light interferes with nocturnal melatonin secretion.

Fernando and Rombauts [135] addressed the correlation between light and infertility in a review article.

Cebrian-Perez et al [136] and Casao et al [137] investigated the coherence between melatonin and spermatogenesis and sperm function.

Impact on Metabolism
The athero-protective effect of melatonin was described in a review article by Favero et al [138].

A review by Cipolla-Neto et al [139] investigated melatonin in the context of energy metabolism.

Romero et al [140] addressed the protective effects of melatonin on metal-catalysed molecular damages.

Vielma et al [141] addressed the role of melatonin in oxidative stress, in the resistance against bacterial pathogens, parasitic and viral infections and summarized the data available.

Andersen et al [142] conducted a systematic review regarding peri-operative melatonin levels and conclude, that melatonin might decrease oxidative stress and the demand of anaesthetics.

A clear answer on whether melatonin acts as a proteasome-inhibitor could not be made in the review by Vriend and Reiter [143].

Navarro-Alarcon et al [144] addressed the question of melatonin and regulation of metabolism in a review also. Nevertheless, further clinical studies are missing here.

Gurer-Orhan and Suzen [145] investigated the effect of melatonin and its metabolites as anti-oxidants in a review.

The role of melatonin in oxidative stress in patients with type 2 diabetes was analysed by Zephy and Ahmad [146]. They concluded that large-scale studies in several countries with different ethnic populations are lacking.

Breast Cancer

Cos et al [147] addressed the impact of melatonin on the cross talk between malignant epithelial-, endothelial- and fat cells in breast cancer.

Basler et al [148] conducted a meta-analysis and a literature review on urinary excretion of melatonin in the context of breast cancer. Due to the results, melatonin seems to correlate with breast cancer recurrences. Nevertheless, further clinical studies are required due to methodological deficiencies.

Psychiatric and Neuro-Degenerative disease

Polimeni et al [149] addressed melatonin administration in neuro-degenerative diseases.

The importance of melatonin in bipolar diseases and biologic rhythms was analysed by Gonzalez [150].

Escribano et al [151] addressed the role of melatonin in multiple sclerosis, Huntington's disease and cerebral ischemia and analysed the neuro-protective mechanism of melatonin on the central nervous system in a review article.

Joshi et al [152] investigated the use of melatonin as neuro-protective compound in neuro-degenerative diseases. Here, clinical studies proving the efficacy or futility are lacking also.

If melatonin has any impact on sleep and Alzheimer's disease was investigated by Peter-Derex et al [127].

Tinnitus

The therapeutic relevance of melatonin in treatment of tinnitus was investigated by Merrick et al [153]. The authors presume that melatonin might show a favourable neuro-protective effect in patients with tinnitus and recommend taking melatonin in consideration for treatment of patients with tinnitus.

Various

In how far melatonin can be used in the treatment of irritable bowel disease was described by Siah et al [154].

Li et al [155] addressed the role of melatonin in hepatic ischemia/re-perfusion disorders and clinical liver damages. Here, a final evaluation can not be done also.

Olcese and Beesley [156] evaluated the clinical significance of melatonin receptors in human myometrium and observed a significant role of circulating melatonin over the time and the intensity of uterine contractions in late pregnancy. The regulation of melatonin receptors requires further investigations here also.

New aspects

Singh and Jadhav [157] describe the function and ligands of melatonin.

Agomelatine: Guardiola-Lemaitre et al [158] addressed agomelatine and the described modes of action and the pharmacological profile in terms of its anti-depressant effects.

Tasimelteon: Johnsa and Neville [159] investigated tasimelteon, a melatonin receptor agonist, in patients with sleep-wake disorders.

Conflict of Interest

No conflict of interest: H-J. Ahrendt, C. Albring, A. Bachmann, J. Bitzer, C. Egarter, B. Kleine-Gunk, K. König, T. Rabe, N. Sänger

G. Merki-Feld: During the past years G. Merki-Feld had financial relationship (lecturer, member of Advisory Boards and/or consultant) with Bayer-Schering Pharma, MSD and HRA Pharma.

E. Merkle had financial relationship (lecturer, travel costs, member of Advisory Boards) with MSD and Shionogi.

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