Physiological Measurement

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From sleep medicine to medicine during sleep—a clinical perspective

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Abstract

Objective. In this perspective paper, we aim to highlight the potential of sleep as an auspicious time for diagnosis, management and therapy of non-sleep-specific pathologies. Approach. Sleep has a profound influence on the physiology of body systems and biological processes. Molecular studies have shown circadian-regulated shifts in protein expression patterns across human tissues, further emphasizing the unique functional, behavioral and pharmacokinetic landscape of sleep. Thus, many pathological processes are also expected to exhibit sleep-specific manifestations. Modern advances in biosensor technologies have enabled remote, non-invasive recording of a growing number of physiologic parameters and biomarkers promoting the detection and study of such processes. Main results. Here, we introduce key clinical studies in selected medical fields, which leveraged novel technologies and the advantageous period of sleep to diagnose, monitor and treat pathologies. Studies demonstrate that sleep is an ideal time frame for the collection of long and clean physiological time series data which can then be analyzed using data-driven algorithms such as deep learning. Significance. This new paradigm proposes opportunities to further harness modern technologies to explore human health and disease during sleep and to advance the development of novel clinical applications—from sleep medicine to medicine during sleep.

1. Introduction

Sleep, a phenomenon observed among all animals, has long been identified as a vital process for general health and wellbeing (Schwartz and Roth 2009). Despite the estimated decrease in average sleep duration in modern society, humans spend approximately one third of their lives sleeping (Bonnet and Arand 1995). Sleep research dates back to at least the 18th century and has developed into the medical subspecialty of ‘sleep medicine’, although it still remains on the fringes of medical training (Stores 2007). To date, this field focuses mainly on the diagnosis and treatment of sleep-related disorders, as classified in the International Classification of Sleep Disorders (ICSD-3) (Sateia 2014), diagnostic and statistical manual of mental disorders (DMS-5) (American Psychiatric Association 2013) or international classification of diseases (ICD-11) (World Health Organization 2020).

1.1. Physiology during sleep

Sleep can be broadly divided into non-rapid eye movement (NREM) and rapid eye movement (REM) phases which are characterized by unique brain activity and muscle tone patterns demonstrated on polysomnography (PSG). Normal adult sleep architecture is comprised of cyclic patterns of NREM followed by REM sleep, with a single cycle lasting 90–120 min. REM percentage and density tend to increase during the night with successive sleep cycles (Ohayon et al 2004). All major body systems are affected by sleep, including the respiratory, cardiovascular and genitourinary systems, in addition to drug detoxification, metabolic, thermoregulatory, immune and cognitive processes. Additionally, many hormones exhibit a relation to the circadian cycle, the most notable being cortisol, growth hormone and prolactin, with levels directly relating to sleep stages, age and...
gender. Alongside alterations in hormone levels, the autonomic nervous system is a major driver of the abrupt changes in physiology observed during sleep. Overall, sleep is characterized by a reduction in peripheral sympathetic activity and increase in parasympathetic activity, with a more complex and fluctuating pattern during REM as compared to NREM sleep (Verrier et al 1996). This shift in neural homeostasis induces the characteristic changes in sleep physiology of various systems, which, in turn, account for the distinctive manifestations of pathologies during sleep.

Sleep modulates the presentation of respiratory disorders due to decreased chemosensitivity to hypoxia and hypercapnia as well as reduced respiratory muscle tone. This ability to tolerate higher levels of CO₂ and lower levels of O₂, which is more pronounced during REM sleep compared to non-REM sleep, may lead to hypoventilation (Xie 2012). As a result, conditions in which ventilation is impaired, such as chronic obstructive pulmonary disease (COPD) and asthma, may be aggravated in the absence of the wakefulness breathing stimulus. This is particularly true in the presence of a concomitant sleep disorder such as obstructive sleep apnea (OSA), which is prevalent in these populations (Kavanagh et al 2018, Malhotra et al 2018). Sleep also impacts several cardiac functions and induces decreased heart rate and systolic blood pressure (BP), an effect termed the ‘dipping phenomenon’ (Di Raimondo et al 2020). This physiologic shift is postulated to enable some rest to the vascular system, endothelial system and heart mechanics. Impairment of this regulatory effect can mirror cardiac or vascular problems and in some cases may be an early manifestation of a cardiac pathology (Verrier et al 1996).

1.2. Remote health monitoring and sleep

The emerging role of portable biosensors in clinical practice has been gaining substantial interest (Xu et al 2019). Portable devices and sensors that can record a variety of biosignals are already the subject of hundreds of clinical trials (Dunn et al 2018) and notable publishing houses, such as Nature or the Lancet, have opened new journals in the field of digital medicine with a high focus on portable medicine. Sleep is an ideal time frame for the collection of long and clean physiological time-series data, which can then be analyzed using data-driven algorithms such as deep learning (Bianchi 2018, Perez-Pozuelo et al 2020).

1.3. The knowledge gap

Little is known about how non-sleep-specific diseases manifest during sleep and the contribution of sleep to their pathophysiology. The unique physiological and biomolecular characteristics of sleep imply that pathologic processes, as well as therapeutic interventions, will also exhibit marked differences when applied during sleep as compared to daytime. Nevertheless, despite the potential advantages, sleep is seldom exploited in clinical practice to diagnose, monitor and treat non-sleep-specific conditions—a paradigm we recently coined ‘medicine during sleep’ (Behar 2020). This perspective article motivates this new paradigm by reviewing existing clinical research that focuses on the diagnosis, treatment and management of non-sleep-specific diseases during sleep.

2. Diagnosis and management of non-sleep-specific conditions during sleep

2.1. Ventilation during sleep

Monitoring arterial O₂ saturation and CO₂ levels enables evaluation of pulmonary gas exchange. Both can be non-invasively estimated by continuous measurement of peripheral oxygen saturation (SpO₂) or transcutaneous O₂ (TcO₂) and end tidal CO₂ (ETCO₂) or transcutaneous PCO₂ (TcPCO₂), respectively. Sleep ventilation assessment is being used in a growing number of respiratory-related clinical scenarios ranging from acute infectious episodes in infants to chronic lung or extrapulmonary disorders affecting respiration, in both inpatient and ambulatory settings (Pretto et al 2014).

The importance and high prevalence of sleep desaturation in patients with COPD, including those who do not exhibit significant daytime desaturations, have been noted in several studies (Chauvat et al 1997, Lacasse et al 2011). Due to the variable nature of such desaturations, nocturnal pulse oximetry needs to be implemented for more than one night to detect them at an early stage (Lewis et al 2003). Additional findings suggest that desaturations during NREM sleep contribute to brain impairment in COPD (Alexandre et al 2016). Patients with interstitial lung disease (ILD) also exhibit sleep desaturations and are particularly vulnerable during REM sleep (Mermigkis et al 2017). This may lead to poor sleep quality and interfere with sleep regenerative mechanisms even in the absence of a coexisting sleep disorder. Regular use of nocturnal pulse oximetry to monitor breathing in the management of ILD has been advocated, and the role of TcPCO₂ as well as the impact of additional intermittent hypoxia in these already chronically hypoxic patients is a research priority (Mermigkis et al 2017). A high prevalence of sleep hypoxemia, which aggravates pulmonary arterial hypertension, has been reported in patients with precapillary pulmonary hypertension. As absence of daytime hypoxemia is not a
reliable predictor of sleep hypoxemia (Hildenbrand et al 2012), nocturnal pulse oximetry has been suggested as part of routine evaluation of this patient population (Jilwan et al 2013). To expand the diagnostic potential of sleep ventilation assessment, Levy et al (2020b) developed the first standardized toolbox for continuous oximetry time-series analysis using digital oximetry biomarkers and recently demonstrated the feasibility of COPD diagnosis using nocturnal oximetry (Levy et al 2020a). Thus, sleep respiratory monitoring in chronic respiratory conditions such as COPD and ILD, may be the optimal modality for early detection of disease progression and decompensation, enabling timely, disease-modifying intervention.

Nocturnal pulse oximetry has been extensively used in the management of bronchiolitis, although its role in the management of this common infectious condition is a subject of debate. Transient desaturations (even to 70% or less) are commonly observed in infants with bronchiolitis after discharge, but their clinical significance remains unclear (Bajaj and Zorc 2016). The lack of clinically proven benefits of this practice, alongside concerns regarding unnecessary hospital admissions, prolonged length of stay and additional costs, have resulted in guidelines recommending its limited use (Florin et al 2017). Thus, the complexity in interpreting nocturnal oximetry patterns in infants warrants the development of oximetry digital biomarkers and of their association with defined clinical endpoints, such as readmission, enabling leverage of this important tool to detect sleep desaturation patterns which reflect a more severe condition.

2.2. Cardiac monitoring during sleep

Evaluation and monitoring of nocturnal BP is of paramount importance for diagnosis and management of hypertension and its complications. Masked nocturnal hypertension is a well-established phenomenon, referring to patients who only exhibit abnormal hypertensive values overnight (Hoshide et al 2007). Specific patterns of nocturnal BP are associated with several cardiovascular adverse outcomes, including cardiac remodeling and all-cause mortality, and are recognized as better predictors of these outcomes compared to daytime BP (Di Raimondo et al 2020). Furthermore, nocturnal BP monitoring may be important to evaluate before administration of bedtime hypertensive medication in certain patient populations (Di Raimondo et al 2020). BP can be non-invasively recorded by intermittent cuff measurements during nighttime, but this technique is usually disturbing and yields only point measurements. Nowadays, several validated devices for non-invasive continuous BP measurement are available (Ameloot et al 2015). In addition, the pulse-transit-time, a measurement based on the time delay of the pulse wave between two arterial sites, has been shown to accurately reflect dynamics as well as absolute values, to some extent, of BP (Mukkamala et al 2015). Although nocturnal BP is considered a critical tool for diagnosis and risk stratification in hypertensive patients, its current classification is limited to a small number of patterns, based on maximal/minimal values of systolic BP. A more extensive analysis of continuous nocturnal BP measurement could yield more insights into the pathophysiology of this ubiquitous condition.

In clinical practice, there are a few instances where nocturnal ECG is recorded, e.g. Holter ECG, single-lead ECG in PSG and in cases of implanted pacemakers. In a recent research of ours (Chocron et al 2020), we demonstrated that over 22% of individuals with undiagnosed atrial fibrillation could be identified by opportunistic data-driven nocturnal screening of the ECG traces recorded in regular PSG studies. Research has also shown that atrial fibrillation events may be more frequent during sleep than daytime (Yamashita et al 1997), but this may not be the case for other cardiac abnormalities (Portaluppi and Hermida 2007). Clinical ECG trace analysis guidelines do not define cardiac abnormalities as a function of daytime or nighttime (Capes et al 2007). However, cardiac intervals can change during nighttime. For example, changes in body position can result in fluctuation of the ST segment, which represents the interval between ventricular depolarization and repolarization (Adams and Drew 1997). Furthermore, sleep might affect the manifestation of cardiac arrhythmias, such as sinus bradycardia and tachycardia, since the average heart rate during sleep is lower. Thus, there exists a critical gap in our understanding and definitions of the clinical manifestations of sleep versus daytime cardiac abnormalities. In addition, sleep may represent an opportunistic window for clean, continuous ECG recording and for diagnosis. Overall, there is a basis of research suggesting that ECG monitoring during sleep may provide clinical value in certain diagnostic scenarios.

Redistribution of body fluids during the recumbent position from the legs to the chest and neck, termed rostral fluid shift, has been pointed out as a factor influencing cardiac and respiratory disorders during sleep. Patients who suffer from fluid retention disorders, such as heart failure, are particularly vulnerable to rostral fluid shift which may aggravate both their primary condition and concomitant sleep disorders (White and Bradley 2013). Currently, rostral fluid shift is usually estimated by leg and neck circumference measurement. More robust methods to measure and analyze this phenomenon may enable incorporation of this sleep-specific assessment tool into clinical evaluation. Monitoring of rostral fluid shift may support early diagnosis of exacerbations and identification of their underlying etiology in patients with heart failure and respiratory conditions.
2.2.1. Fetal monitoring during sleep

The fetal heart rate trace is used as a nonstress test to assess fetal wellbeing. Clinicians and engineers have been researching ways to remotely monitor fetal wellbeing to better manage complicated pregnancies. Continuous monitoring with cardiotocography (min to 1 h) may be needed to assess the fetal health in the Dawes Redman analysis (National Health Service 2020). The non-invasive fetal ECG is an alternative recording technique that involves placement of ECG electrodes on the maternal belly to measure both maternal and fetal electrical activity of the heart. From the mixture of signals, the fetal ECG and heart rate may be estimated. Yet, although this technique has been around for decades, with incremental improvement over time, it still faces important challenges, including its high sensitivity to noise, which impairs its clinical implementation. In a recent work, Huhn et al (2017) showed that the success rate of obtaining the fetal heart rate trace from a non-invasive fetal ECG was twice higher in nighttime than daytime recordings. This is because of the reduced movement-induced noise during sleep in comparison to daytime. This example highlights how monitoring during sleep may offer a cleaner window for robust continuous physiological measurement of important vital signs and enhance care.

2.2.2. Intracranial pressure (ICP) during sleep

ICP measurement is considered essential in the diagnosis and management of various neurologic conditions, with a growing corpus of scoring systems and signal analysis methods introduced into clinical decision-making in recent years (Evensen and Eide 2020). ICP values are heavily influenced by posture, with higher values obtained in the horizontal position. Since long and consistent measurements are required for optimal analysis, ICP recording during sleep is considered the ‘gold standard’ (Czosnyka and Pickard 2004). Although primarily utilized in acute settings, such as traumatic brain injury and intracranial hemorrhage or infection, ICP has been implied as a diagnostic tool in chronic conditions including hydrocephalus, idiopathic intracranial hypertension and headaches. In patients with chronic headaches who were examined for suspected isolated cerebrospinal fluid hypertension, abnormal ICP pulsations were associated with nocturnal and postural headaches (Bono et al 2018). Yet, continuous non-invasive ICP measurement technologies still suffer from substantial drawbacks, limiting their clinical implementation and the ability to evaluate their diagnostic potential in chronic conditions (Evensen and Eide 2020). Machine learning algorithms facilitating in-depth analyses, as opposed to the commonly reported mean ICP, are becoming increasingly popular in the analysis of ICP patterns. One prominent example in which machine learning is being adapted into clinical practice is that of B waves, short ICP elevations which are associated with brain dysfunction, with active research studying their significance (Martinez-Tejada et al 2019). Thus, advancements in measurement and analysis technologies may enable leverage of ICP measurements performed during sleep for diagnosis and characterization of chronic neurologic conditions.

2.2.3. Electroencephalography during sleep

Nocturnal electroencephalography (EEG) can be used for early detection of certain neurologic and neuro-psychiatric conditions. It has been shown that early signs of dementia and Parkinson’s disease may be apparent on PSG years before other clinical manifestations and potentially enable therapeutic interventions (Weil and Morris 2019). Other studies have identified characteristic EEG patterns in specific headache types (Engstrom et al 2014) and in various mental disorders (Baglioni et al 2016), emphasizing the importance and relevance of EEG readings collected during sleep to the diagnosis of other neurologic conditions.

2.2.4. Intraocular pressure (IOP) during sleep

Nowadays, IOP, considered the major risk factor of glaucoma progression, can be measured outside office hours in a continuous, invasive or non-invasive fashion (Ittoop et al 2016). Studies of 24 h IOP curves reveal significant variations in nocturnal IOP patterns between different glaucoma patient subtypes, where both peak pressure, as well as more complex parameters, such as fluctuations, are of value in prediction of disease progression. Furthermore, a differential effect of existing treatment modalities on nocturnal IOP was demonstrated (Konstas et al 2016). In normal-tension glaucoma and in treated patients with disease progression despite normal office IOP readings, nocturnal IOP measurements may represent the only window to measure elevated IOP patterns, thus facilitating their diagnosis and supporting management decisions. Yet, the contribution of elevated IOP during sleep to glaucoma pathophysiology remains poorly understood and ongoing research is revealing its extent as well as the characteristics of patient subgroups warranting nocturnal monitoring (Konstas et al 2018).

2.2.5. Imaging during sleep

Despite its potential, imaging during natural sleep has not yet been researched extensively in the clinical context. From a research point of view, sleep imaging could enhance our understanding of sleep-associated pathologies. For example, a study aiming to investigate children with primary nocturnal enuresis (PNE), performed MRI during natural sleep using T2-Relaxation-Under-Spin-Tagging (TRUST), a technique used to estimate brain
example, nocturnal NIV in hypercapnic COPD patients is the mainstay therapy (Yu et al 2017). Imaging during sleep may have a future role in several clinical scenarios. In a recent study, Ayoub et al (2020) demonstrated the feasibility of visualizing upper airway dynamics continuously and non-invasively during natural sleep by electrical impedance tomography (EIT). This technique could potentially replace the more invasive approach of drug induced sleep endoscopy. Some sleep-related systemic pathologies still require nocturnal invasive monitoring for their diagnosis, such as gastroesophageal reflux disease which requires esophageal pH monitoring (Lim et al 2018). Other physiological abnormalities such as intermittent cardiac shunting may have clinical implications (Lynch et al 1984) and can be potentially diagnosed by continuous imaging during sleep. Future development of imaging modalities that can be applied during sleep, particularly modalities which capture physiological processes by continuous recording such as EIT or wearable ultrasound devices, could theoretically replace more invasive techniques used for diagnosis of such pathologies.

### 3. Treatment during sleep

#### 3.1. Non-invasive ventilation (NIV) during sleep

Nocturnal respiratory therapeutic interventions are being studied in a number of clinical scenarios and indications. Early nocturnal intervention can possibly delay or alter the progression of respiratory failure. For example, nocturnal NIV in hypercapnic COPD patients is the mainstay therapy (Macrea et al 2020), and home-initiation of such therapy is becoming practical and safe (Duverman et al 2020). In neuromuscular disease, early initiation of nocturnal NIV has been advocated in patients with sleep hypercapnia and daytime normocapnia (Ward et al 2005). Studies suggest that some patients with cystic fibrosis might also benefit from nocturnal NIV (Moran et al 2017). OSA is a recognized risk factor and modulator of several systemic conditions, and therefore its treatment also exerts broad systemic effects. For example, the 2020 European Society of Cardiology recommends optimizing diagnosis and treatment of OSA as a means to reduce AF recurrences and improve AF treatment results (Hindricks et al 2021). Nocturnal continuous positive airway pressure (CPAP), a therapeutic modality applied primarily in OSA patients, has been shown to induce systemic physiological changes, including a proven blood-pressure-lowering effect on distinct patient subsets with hypertension (Navarro-Soriano et al 2019). Clinical trials have demonstrated additional beneficial effects of nocturnal CPAP in OSA patients, such as improved glycemic control (Mokhlesi et al 2016). Other sentinel clinical trials are evaluating nocturnal CPAP in conditions including asthma (Holbrook et al 2016), stroke rehabilitation (Khot et al 2016) and cluster headache (Tronvik 2018), emphasizing its yet undetermined impact on many systemic conditions. Nocturnal oxygen therapy has also been proposed as home treatment for patients with early-stage COVID-19, potentially diminishing need for subsequent hospitalization (Shen et al 2020). Altogether, interventions to support respiration during sleep are being increasingly considered in a variety of pathologic conditions and recognized as having a broad systemic effect on disease process.

#### 3.1.1. Hemodialysis during sleep

Dialysis treatments pose a clear burden on patients, which has promoted the development of home-treatment modalities. Both home hemodialysis and peritoneal dialysis were introduced over 50 years ago, but current worldwide trends have shifted towards hemodialysis in a medical center setting in the vast majority of patients (Himmelfarb et al 2020). However, interest in home therapies, particularly home hemodialysis, is rising, partly due to its potential nocturnal implementation (Cherukuri et al 2018). Nocturnal dialysis regimens have been shown to be safe and possibly superior to conventional therapy in various outcomes, including left ventricular mass, BP medication utilization and quality of life (Culleton et al 2007). Although nocturnal regimens are still recommended for select patients only, the Renal Association clinical practice guideline on hemodialysis (Ashby et al 2019) underscores the benefit of wider home hemodialysis implementation owing to its flexibility, economic benefits and the non-inferiority of nocturnal regimens (Tennankore et al 2018). Thus, hemodialysis during sleep is expected to become more common as further evidence accumulates.

#### 3.1.2. Circadian medicine and chronotherapy

The circadian clock, the driver of physiological and biological processes that occur in relation to the day/night rhythm, is an important regulator of the sleep–wake cycle. Novel molecular research techniques and data analysis tools have advanced the characterization of the differential transcriptomes, metabolomes and proteomes of human tissues with relation to their circadian cycle (Dyar et al 2018, Anafi et al 2017). Data indicate that >80% of protein-encoding genes, including known molecular targets of existing drugs, show diurnal variation in their expression (Panda 2019). These findings suggest that timing of drug delivery, termed chronotherapy, could have a substantial impact on their efficacy. Additionally, it has been shown that several
types of cancer cells exhibit dysregulation of their circadian cycle, implying that synchronization of interventions with circadian regulatory components could offer a novel approach to cancer therapy (Fu and Kettnner 2013). These recent advancements highlight the importance of the circadian mechanism in health and disease, promoting a ‘circadian medicine’ approach. The discovery and delineation of transcription-translation feedback loops that control circadian oscillations, the subject of a Nobel Prize granted in 2017, has drawn additional attention to this field (Hardin et al 1990).

3.1.3. Pharmacological chronotherapy during sleep
Several drugs demonstrate improved activity and/or a safety profile when administered within a chronotherapeutic schedule that considers timed physiological processes and pharmacokinetics. For instance, nighttime-release of prednisone, a corticosteroid used to treat inflammatory conditions, was identified as beneficial in patients with rheumatoid arthritis, achieving better outcomes by targeting the circadian rhythms of inflammation (Buttgereit et al 2010). In the case of hypertension, nighttime ingestion of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, was associated with improved efficiency of BP control while reducing dose requirements and adverse effects (Hermida et al 2014). Oxitropium bromide, an anticholinergic drug used to treat asthma, showed increased activity when inhaled at night time (Coe and Barnes 1986). Pharmacological intervention during sleep requires a programmable drug administration system that does not affect patient sleep and does not require human intervention. Several solutions have been developed, such as pulsatile drug delivery systems (PDDS) (Maroni et al 2005), film-coated tablets (Maroni et al 2005), implantable pump systems and aerosol drug delivery systems (Amirav et al 2014). PDDS can administer drugs into the blood circulation, the gastro-intestinal tract and onto the skin. Thus, sleep-related chronopharmaceuticals are becoming increasingly applied in clinical practice, achieving better outcomes through both increased efficacy and safety profiles. As knowledge regarding the circadian nature of pathologic processes and corresponding drug targets is gleaned, their use is expected to expand further.

3.1.4. Cancer treatment during sleep
Nocturnal administration of chemotherapy was proposed, already in the 1990s, as a means of improving anti-tumor efficacy. However, despite decades of intense research of circadian rhythm in cancer, chronotherapy has had limited impact on the mainstream clinical oncology (Takimoto 2006). This might be explained by its failure to show significant improvement in overall survival in previous large clinical trials (Innominato et al 2010, Bi et al 2015, Zhang et al 2018). However, at the same time, positive effects of nocturnal chemotherapy on toxicity and tolerability have been demonstrated for almost all types of chemotherapeutic drugs, including: 5-fluorouracil, irinotecan, doxorubicin and most platinum-based drugs (To et al 2005, Gholam et al 2006, Giacchetti et al 2006, Sulli et al 2019). This clear clinical benefit of safer chronomodulated chemotherapy warrants further investigations with higher doses or with immunotherapy, one of the most promising treatment modalities of recent times. Major limitations of previous chronotherapy trials were the highly generalized patient selection and lack of personalized medicine and genetic profiling. Today, the application of genetic information in personalized cancer medicine has transformed cancer care and is also being studied in the context of chronotherapy, far beyond chemotherapy. Chronomodulated regimens, including nocturnal regimens, of targeted kinase inhibitors, such as alpelisib, lapatinib, sunitinib and erlotinib, which are used for personalized cancer treatments, have shown substantial benefits in multiple animal models as well as in patients (Szalek et al 2013, 2014, Liu et al 2016). For example, nocturnal administration of alpelisib, a PI3K inhibitor recently approved for breast cancer, was associated with better control of glycaemia and with a better clinical outcome compared to daytime administration ( Schnell et al 2018). Several studies have also explored chronomodulated radiotherapy or nocturnal radiodosing in cancer patients. While no clear conclusions regarding efficacy has been reached, due to mixed results of recent trials, it seems that gender and genetic profiles may be determinants of the toxicities and response rates of chronomodulated dosing schemes (e.g. women seem to benefit more from chronoradiotherapy) (Chan et al 2016, 2017, Harper and Talbot 2019). Consequently, cancer therapy during sleep is a rapidly expanding field, with promising breakthroughs in both tumor response to therapy and adverse effect profiles, and is becoming an important aspect of personalized cancer therapy.

3.1.5. Nocturnal interventions to reduce circadian dyssynchronization
Light pollution at night from external lighting systems in big cities or from smartphone/computer screens, may be responsible for several public health issues as it impairs the circadian clock’s normal resynchronization (Chepesiuk 2009). It has been reported that night exposure to artificial light inhibits the production of melatonin. In addition, a higher risk of obesity, diabetes, cardiovascular disease, depression, sleep disturbances and cancer has been observed in shift workers (Karlsson 2001, Schernhammer et al 2003, Kalmbach et al 2015). Intensive care units (ICU), which, in most cases, are under constant light intensity, represent a particularly stressful environment. This is postulated to contribute to ICU delirium, an acute brain dysfunction associated
with increased mortality, prolonged ICU and hospital length of stay, and development of post-ICU cognitive impairment (Baumgartner et al 2019). Interventions to reduce this risk and improve patient recovery using lighting systems that mimic the day-night cycle, successfully diminished adverse circadian dyssynchronization-related outcomes (Engwall et al 2015). Further investigation of the effect of light exposure (e.g. intensity, light spectrum and rhythms) on human health will support additional circadian-oriented modifications of the healthcare environment.

4. Discussion

This paper aimed to provide a perspective regarding the clinical benefits of nocturnal diagnostic and therapeutic practices for non-sleep-specific diseases. It pointed out the rationale behind this approach, by reviewing nocturnal characteristics of conditions such as respiratory, cardiovascular and ocular pathologies, as well as circadian-related considerations in drug administration and cancer treatment. It discussed advantages of such practices, such as improved patient convenience due to ambulatory diagnosis and treatment options, early detection of pathologies and complications, avoidance of daytime drug side effects and cost reduction. Finally, it presented non-invasive continuous measurement modalities and highlighted sleep as an optimal time for collection of clean and long, continuous physiological time-series data which can be analyzed using machine learning. Essential components of the presented paradigm are summarized in figure 1. The prominent nocturnal diagnostic and therapeutic modalities along with selected clinical examples covered in this paper are presented in panel I.

The conceptual foundations of this paradigm have been around for a long time. An excellent example is the work by Verrier et al (1996), in which nocturnal cardiovascular physiology and its significance are described in depth. However, clinical applications are still limited. Recent advances in sensor technology and machine
Effective pre-clinical testing of such interventions will require use of a non-nocturnal mammalian model. Rodent models are based on rodents which are nocturnal, with a very different circadian clock than humans. Therefore, animal models are not always the best model for research of circadian interventions. Research of circadian interventions is particularly complicated, since most common pre-clinical measurements can be quickly tested in humans, therapeutic interventions require substantial pre-clinical data in animal models. However, depending on the studied condition, such a large amount of data might not be available. Dogs, in particular, are considered for additional clinical scenarios due to its potential systemic advantages.

During sleep, the metabolism is naturally slowed, and parameters such as heart rate and blood pressure tend to be averaged over the entire sleep cycle. This means that the variability in these parameters during sleep can be greater than during the waking state.

The time has come to include medicine during sleep as a clinical pathway for diagnostic and therapeutic applications, albeit still sporadic. With the ongoing efforts to develop more personalized and remote medicine, the time has come to include medicine during sleep as a clinical pathway for diagnostic and therapeutic applications.

Several challenges must be considered in the clinical implementation of this paradigm. Collection and analysis of raw continuous data from non-invasive sensors is relatively new to many medical fields, more so during sleep. As with any newly introduced modality, vigorous clinical groundwork will be required to establish accurate reference ranges and reliable clinical standards. Measurements collected during sleep may require revision of some diagnostic criteria, definitions of significant pathological findings and management of incidental findings. Finally, the introduction of novel sensor technologies specifically designed for medicine during sleep, may enable the realization of this discipline.

Another significant challenge arises from the interventional aspect of this paradigm. While non-invasive measurements can be quickly tested in humans, therapeutic interventions require substantial pre-clinical data in animal models. Research of circadian interventions is particularly complicated, since most common pre-clinical models are based on rodents which are nocturnal, with a very different circadian clock than humans. Therefore, effective pre-clinical testing of such interventions will require use of a non-nocturnal mammalian model (e.g. dogs) or implementation of genetic tools to explore the human circadian clock in transgenic or knock-in mice that recapitulate human genetics.

Some intriguing future developments of this paradigm can be proposed. Robust measurement and analysis tools will enable studying of the association between simultaneously measured signals, such as IOP, ICP and BP in glaucoma. Additionally, harnessing of machine learning algorithms to support screening strategies in selected populations is a promising route. For example, opportunistic nocturnal screening for hypertension, atrial fibrillation (Chocron et al 2020) or COPD (Levy et al 2020a), may be performed in high-risk patient populations.

Sleep specialists will play a critical role in the advancement and clinical implementation of sleep-centered diagnostic and therapeutic approaches. Exploitation of this paradigm will require thorough knowledge of sleep physiology and circadian medicine, with emphasis on multidisciplinary training which will broaden sleep diagnosis and treatment beyond current practice. As sleep diagnosis and treatment modalities become a central part of personalized medicine, sleep and circadian medicine will receive more attention in general medical training and within various medical specialties.
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Author contributions

All authors have contributed to the writing of this manuscript.

Competing interest statement

All authors have declared no conflict of interest.

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