Circadian Variation in Efficacy of Medications

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Abstract

Although much has been learned about circadian clocks and rhythms over the past few decades, translation of this foundational science underlying the temporal regulation of physiology and behavior to clinical applications has been slow. Indeed, acceptance of the modern study of circadian rhythms has been blunted because the phenomenology of cyclic changes had to counteract the 20th century dogma of homeostasis in the biological sciences and medicine. We are providing this review of clinical data to highlight the emerging awareness of circadian variation in efficacy of medications for physicians, clinicians, and pharmacists. We are suggesting that gold-standard double-blind clinical studies should be conducted to determine the best time of day for optimal effectiveness of medications; also, we suggest that time of day should be tracked and reported as an important biological variable in ongoing clinical studies hereafter. Furthermore, we emphasize that time of day is, and should be considered, a key biological variable in research design similar to sex. In common with biomedical research data that have been historically strongly skewed towards males, most pharmaceutical data have been skewed towards morning dosing without strong evidence that this is the optimal time of efficacy.

Keywords

chronopharmacology; chronotherapy; circadian rhythms; diel cycles; biological rhythms; chronomodulation; time of day

Introduction

Virtually all animal processes display daily rhythms, termed circadian rhythms, that persist in the absence of external factors. Accordingly, virtually all physiological processes including respiration, metabolism, endocrinological, immunological, cardiovascular, and neuronal, display circadian rhythms in their function. In the presence of environmental light-dark cycles, these self-sustaining endogenous rhythms display 24-hour periods. In the

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absence of environmental light-dark cycles, these rhythms 'free-run' at periods of about 24 hours. Circadian rhythms display both 'bottom-up' and 'top-down' organization (1).

Molecular networks of gene transcription and translation form the basis of circadian rhythms in cells. The molecular clock in the suprachiasmatic nuclei (SCN) of the hypothalamus comprises a set of transcriptional–translational feedback loops that drive rhythmic 24-hour expression of the core clock components (2). In the primary feedback loop, Circadian Locomotor Output Cycles Kaput (CLOCK) and Brain and Muscle ARNT-Like Protein (BMAL1) proteins form heterodimers that activate gene expression of *Period* (*Per*) and *Cryptochrome* (*Cry*). PER and CRY proteins then heterodimerize and translocate into the nucleus, where they suppress their own transcription by acting on the CLOCK/BMAL1 complexes. In an interacting feedback loop, CLOCK/BMAL1 complexes promote expression of retinoic acid-related orphan nuclear receptors, Rev-erbα and RORα. Their protein products feedback to regulate Bmal1 by competitively binding retinoic acid-related orphan receptor response elements in the Bmal1 promoter. Reverse viral erythroblastosis oncogene products repress the transcription of *Bmal1*, whereas RORs activate it. These two loops form the primary basis of the molecular clock, but a complex network of interacting genes and post-translational modifications ensure that the process takes ~24 h to complete (2, 3). Again, this transcriptional–translational feedback loop is the basis of intrinsic daily circadian rhythms.

The top-down organization of circadian rhythms is coordinated in mammals by the SCN (4, 5). Environmental light is detected by specialized photoreceptors, termed intrinsically photosensitive retinal ganglion cells (ipRGCs). Unlike rods and cones, ipRGCs perform non-image-forming functions, sending direct projections to the SCN to synchronize circadian cellular rhythms of clock gene transcription and translation, which in turn transduces this circadian information to a network of peripheral clocks to coordinate bodily functions (Figure 1) (1, 6, 7).

Although much has been learned about circadian clocks and rhythms over the past few decades, translation of this foundational science underlying the temporal regulation of physiology and behavior to clinical applications has been slow. Indeed, the modern study of circadian rhythms as a scientific discipline was initially blunted because the phenomenology of cyclic changes had to counteract the 20th century dogma of homeostasis in the biological sciences and medicine (8–10). Large fluctuations in physiological processes were considered pathological, and many physicians resisted the idea of the programmed changes in physiology and behavior that we now understand to underlie homeostatic processes. Additional barriers to incorporating circadian rhythmicity into the study and treatment of diseases are based on practical considerations, such as patient compliance with dosing times, and additional cost incurred by including multiple dosing times to clinical trials. Despite recent recognition of the field of circadian biology with the awarding of a Nobel Prize to prominent circadian biologists in 2017, translation to clinical practice remains virtually nonexistent.

Although there have been scattered reports of beneficial effects of differential timing of chemotherapy, anesthesia, and effectiveness of specific disease-associated medications, to

our knowledge, there have been few recent systematic reviews of circadian variation in efficacy of pharmaceuticals (e.g., (11)). The goal of this review is twofold: 1) to provide a comprehensive review of medications emphasizing the time of day when benefits are highest and contraindications are at a nadir. Our approach was to use biomedical database search engines (PubMed, Web of Science, EBSCO, etc.) along with key words indicative of assessment of circadian or diel efficacy (circadian, time of day, morning, evening, chrono*) in reported trials and studies for specific conditions or drugs; most of the cited studies are small human clinical studies. There are some publications on dosing time dependent clinical trials on other diseases or types of drugs which may not have been included in this review for brevity. We are are not recommending changing dosing regimens based on the cited studies, but we are suggesting that gold-standard double-blind clinical studies should be conducted to determine the best time of day for optimal effectiveness of various medications. 2) The second goal of this review is to emphasize that time of day should be considered a key biological variable similar to sex. In common with biomedical research data that have been historically strongly skewed towards males (12), most pharmaceutical data have been skewed towards morning dosing without strong evidence that this is the optimal time of efficacy. As Colin Pittendrigh noted, "A rose is not necessarily and unqualifiedly a rose...it is a very different biochemical system at noon and at midnight" (13). The same can be said of humans. Accounting for time-of-day as a biological variable begins with the design of research studies, and should include data collection and analysis of results, as well as reporting of findings. Furthermore, to provide a better mechanistic understanding of chronopharmacology in future clinical trials, it is important to consider time of day in both the pharmacokinetics (14) and pharmacodynamics (15) of the drug and the disease being treated; both factors can interact, or act independently to influence both drug effectiveness and outcomes. Consideration of time-of-day of dosing may be critical to the interpretation, validation, and replication of research results.

Hypertension.

The current clinical practice guidelines for management of hypertension published by the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines (16) neither address nor provide guidance on timing of medications across the day. However, clinical data have been reported suggesting that dosing at specific time-of-day provides benefits in efficacy for various medications used to treat various factors contributing to hypertension; studies reporting these data are reviewed below and listed in Table 1.

Calcium Channel Blockers.

Essentially, calcium channel blockers vary by type for when they are most effective (Table 1). These include amlodipine, nifedipine gastrointestinal therapeutic system (GITS), verapamil, diltiazem, and isradipine (17). For instance, nifedipine GITS administered at bedtime was more effective than morning administration for treating hypertension; nighttime administration was associated with decreased negative side effects (18). Similarly, evening administration of amlodipine has the highest effects on reducing blood pressure (BP) and heart rate (HR) when compared to morning administration (19). In one study verapamil (controlled-onset, extended-release version [COER]) administered at 2200 h reduced BP

values throughout the day in both dippers and non-dippers, with a more pronounced effect on the nocturnal BP decline of non-dippers (20). Another study comparing a 0800 h dose to a 2200 h dose of verapamil-COER found no differences in effects on BP, however, the rate of absorption was slowed with a morning administration (21). Similarly, chronotherapeutic oral drug absorption system (CODAS)-verapamil taken during the evening (2100–2300 h) produced the best anti-hypertensive benefits during the morning (0600–1200 h) (22, 23). Blood pressure in mild to moderate hypertensive patients displayed best 24-hour control of BP when taking CODAS-verapamil at bedtime (22, 23). CODAS-verapamil also best regulated BP throughout the day in patients >65 years of age when taken at night (24). The dihydropyridine derivative nitrendipine was more effective at reducing morning BP surge when taken upon awakening (0600 h) or after dinner (1800 h) than at breakfast (0830 h); 1800 h dosing resulted in the greatest decline in nocturnal BP (25). Compared to morning (0800 h) dosing, non-dipping chronic renal failure patients had better nocturnal BP control when dosed at night (2000 h) with the dihydropyridine derivative isradipine; night dosing also displayed a resetting effect of the misaligned 24-h BP and HR profiles often observed in these patients as a result of their renal failure condition (26). Although graded-release long-acting diltiazem has been approved for once-daily use either at morning or nighttime, evening administration exhibits a pharmacokinetic profile better aligned with the ideal therapeutic time of day (between 1000 – 1200 h) for patients with essential hypertension (27, 28).

NSAIDS (aspirin).

Circadian variation in effectiveness of anti-hypertensive medications has been reported with aspirin. For example, a 100 mg dose of aspirin at bedtime reduced ambulatory BP in mild hypertensive patients, whereas a morning dose increased the 24-h BP mean (29). Furthermore, for patients who were non-dippers at baseline, bedtime administration of aspirin doubled the reduction in nocturnal BP. Bedtime (but not morning) aspirin dosing was best for preventing pregnancy-induced hypertension and preeclampsia (30). Other studies have reported similar results of reduced BP after evening administration of aspirin (reviewed in (31)). Additionally, low dose aspirin administered in the evening is more effective at reducing morning platelet activity than morning dosing (32–34).

Angiotensin-Converting Enzyme (ACE) Inhibitors.

Considered together, the ACE-inhibitors work when administered in the morning or evening, however, they best adjust patients' BP towards the physiological circadian BP rhythm when taken at night. Their effect on decreasing nocturnal BP drives patients towards a more dipper status, effectively reducing the asleep to awake BP ratio (35). The ACE-inhibitors benazepril (36) enalapril (37), perindopril (38), quinapril (39, 40), ramipril (41, 42), spirapril (43, 44), lisinopril (45), zofenopril (46), and trandolapril (47) were most effective at controlling nocturnal and early morning BP and consequently, normalizing the circadian BP profile, when dosed at night. Intake of either ramipril (41), spirapril (43, 44), or perindopril (38) exerted maximum diurnal BP control when administered during the morning, while optimal nighttime BP control, with these drugs, was best achieved when dosed during the evening. Combined dosing of captopril and hydrochlorothiazide (a diuretic) resulted in reduced daytime BP when administered in the morning and reduced evening BP when taken during

the evening (48). Other ACE-inhibitors have been assessed, but possibly due to a small sample size, have not demonstrated a time-of-day-associated difference in effectiveness (reviewed in (35)). Details regarding the studies referenced can be found in Table 1.

α-Adrenoceptor Antagonists.

The effects of α-Adrenoceptor antagonists appear to be circadian-stage dependent, as they have the highest BP-reducing effects in the morning, the time-of-day when BP-spikes typically occur (49, 50). A morning dose of either doxazosin or doxazosin GITS (controlled rate release) only slightly reduced the 24-h systolic BP (SBP) and diastolic BP (DBP) ratio, having no significant effect in asleep BP. Moreover, an evening dose of these drugs had a significant 24-h SBP and DBP-lowering effect throughout the entire day, with the greatest effects on early morning BP (51). Taken together these findings suggest that independent of the drug concentration (pharmacokinetics), the physiological response to it (pharmacodynamics) follows a circadian pattern, which should be taken into consideration when determining optimal timing of dosing.

β-adrenoceptor Antagonists.

Beta blockers generally have greater impact on diurnal BP, yet display little or no effect on circadian BP patterns, or they lean towards a pattern of a non-dipper BP profile (17). This is the case for propranolol (52). Nebivolol, administered during either the morning or evening, had significant BP-lowering effects throughout the day, with more marked effects on the awake BP mean (53). However, morning administration had a greater attenuation of the nocturnal BP decline, which effectively increased the number of non-dipper patients. Hence, according to these data, evening dose might be more beneficial in controlling 24-h BP, as well as the tendency towards the nocturnal BP dip. A more recent study similarly reported that both morning and evening administration of nebivolol control overall 24-h BP, however evening, but not morning, administration significantly reduced prewaking SBP (54). Taken together, the tendency towards a more dipping pattern at night and the increased reduction in prewaking BP suggest that evening administration might have an additional benefit over morning dosing.

Angiotensin II Receptor Blockers.

Angiotensin receptor blockers have been reported to have significant, 24h-reduction in BP when taken either in the morning or night (55), but have a significant increase in the day-night BP ratio, reducing the number of non-dipper patients by 73%, when administered at night. For example, a dose of 160 mg of valsartan taken at night was more effective at reducing nocturnal BP than when taken during the morning (55–57). Furthermore, this increase towards a dipper profile is also seen in non-sleepy (at nighttime) hypertensive patients with obstructive sleep apnea (58) not only supporting the data indicating that hypertensive medications more effectively control BP when administered during the evening, but also suggesting differential BP patterns between day and night. Similarly, olmesartan had an overall greater reduction in nocturnal BP and improved the awake-asleep BP ratio without affecting the overall daily effectiveness (59, 60). Generally, time of administration can be determined according to the dipping status of patients to maximize antihypertensive effects of the drugs, but there may also be other time of day specific

benefits to consider. For example, independent of time of day differences in dosing on controlling BP, evening doses of candesartan were more effective at reducing the risk of microalbuminuria compared to morning dosing (61).

Diuretics.

The BP-lowering effects of diuretics in relation to treatment time have not been well studied. The first trial of this kind studied the loop diuretic torsemide. A 5 mg dose of torsemide was most effective at reducing the 24h-SBP to DBP ratio, as well as providing complete 24-h BP coverage when administered at bedtime, but not upon awakening (62). When taken in combination therapy along with the angiotensin receptor blocker valsartan (see previous paragraph), the diuretic hydrochlorothiazide provided the greatest ambulatory BP control when taken in the evening compared to morning dosing (63). Additionally, hydrochlorothiazide in combination therapy with the calcium channel blocker amlodipine similarly provided greater control of BP across the day when taken in the evening compared to the morning (64, 65).

Combination Therapies.

Most of the previously discussed studies focused on monotherapy for treatment of hypertension, however, effective treatment frequently includes combination therapy with multiple classes of antihypertensives along with comorbidities such as diabetes, obstructive sleep apnea, and chronic kidney disease. Meta analyses of extant clinical studies have provided some insight. Analyses of 175 clinical trials concluded that across anti-hypertensive medications, evening dosing evoked the lowest adverse cardiovascular events and BP when compared to morning dosing (66). Meta-analyses of studies in hypertensive patients with chronic kidney disease similarly concluded that evening anti-hypertensive dosing was more effective than morning dosing for controlling nocturnal BP and lowering the percentage of non-dipper BP patterns (67, 68); however, it is important to note no beneficial effects of evening dosing over morning dosing were reported in African Americans (69). A prospective randomized study of 2,012 hypertensive patients (MAPEC study) reported that, compared to morning administration, evening administration of all hypertensive medications provided the greatest reduction in BP, with the added benefit of significantly reducing the risk of developing new-onset type 2 diabetes (T2DM) with evening dosing (70). For treatment of hypertension in T2DM patients, evening administration of antihypertensive agents was similarly reported to be most effective at blood pressure control compared to morning dosing (60, 71, 72). Very few studies have focused on the circadian differences in the effectiveness of antihypertensives in patients with obstructive sleep apnea and/or diabetes (reviewed in (73). However, it is apparent that additional clinical trials are needed to directly test the conclusions of these meta-analyses and to compare circadian patterns of effectiveness of anti-hypertensive medications, alone and in combination, in essential hypertension and across hypertension with comorbidities.

Endocrine Disorders

Adrenal Insufficiency (AI) and Congenital Adrenal Hyperplasia (CAH).—AI and CAH are conditions characterized by deficiencies in adrenal corticosteroid (and androgen)

production. Optimal treatment approaches for CAH and AI must mimic the normal endogenous circadian rhythm of glucocorticoids (74, 75), which is comprised of a sharp rise beginning 2–3 hours before waking that peaks shortly after waking, and then declines gradually across the day reaching nadir in the middle of the night (Figure 2). Daily dosing regimens can mimic the daytime levels of cortisol, but they fail to recapitulate the late nocturnal rise. To recapitulate the late nocturnal rise with current formulations, one must either be on a continuous infusion paradigm or interrupt sleep to dose in the middle of the night, neither of which are practical or lead to compliance. Current clinical practice guidelines for both AI (76) and CAH (77) acknowledge the difficult circadian aspects of replacement therapy, yet current pharmacological approaches still fall far short of this goal. Thus, both guidelines call for more research and robust clinical trials into optimal dosing regimens for replacement therapy. Additionally, physiological glucocorticoid replacement must also fall within a narrow range for each individual; dosing above or below this range can lead to severe adverse effects and poor clinical outcomes (78).

The most common treatment approach for AI and CAH is administration of the glucocorticosteroid hydrocortisone (HC), but there is no consensus on the timing and regimen of dosing, which can range from once daily to over four times daily (76, 77, 79). One underpowered study of two AI and two CAH patients suggests that a 24-hour infusion regimen of HC that mimics circadian rhythms of cortisol levels can restore circulating cortisol rhythms, restore levels of adrenocorticotropic hormone (ACTH), and reduce levels of plasma 17-hydroxyprogesterone (17-OHP) (80). Other small studies supporting these results demonstrated the effectiveness of continuous subcutaneous HC administration on restoring cortisol and ACTH rhythms as well as increasing nocturnal growth hormone and insulin growth factor levels in AI patients (81, 82) (Table 2). In an attempt to more closely mimic normal endogenous circadian rhythms in cortisol, several formulations of modified-release glucocorticoids are currently undergoing clinical trials for approval (reviewed in (83)). Continued research with careful attention paid to circadian parameters will be needed to elucidate optimal treatment approaches for patients with AI and CAH.

Diabetes.—Therapeutic regimens for diabetic patients need to consider both insulin requirements after food ingestion and the diurnal variations in insulin requirements unrelated to meals (84). Chronotherapy for diabetes management has been investigated, but optimal treatment across the day can vary among individuals and should ultimately be based on individual diagnosis, lifestyle, and blood glucose patterns (85, 86) (Table 2). The ideal timing of daily insulin treatments for patients with type 1 diabetes mellitus (T1DM) is variable and may depend on a range of factors. Multiple studies have reported that long-acting insulins, such as glargine or ultratard insulin, are similarly effective at glycemic control when administered at different times throughout the day, albeit with some differences between timing (87–91). For example, split dosing rather than single morning or evening dosing resulted in significant weight gain (1.4 ± 0.5 kg vs. 1.1 ± 0.6 kg and 0.6 ± 0.5 kg) and decreased quality of life (88). However, one study reported that split dosing was effective for patients whose HbA_{1C} and glycemic levels were not controlled by single injections (92). Another study similarly reported that HbA_{1C} levels and 24-hour glycemic control did not differ among groups administering insulin glargine in the morning, evening,

or bedtime in conjunction with prandial insulin lispro; however, morning administration resulted in fewer nocturnal hypoglycemic episodes (90). A randomized crossover study in 23 patients using prandial insulin lispro reported that administration of insulin glargine at lunch, dinner, or bedtime resulted in hypoglycemia at distinct timepoints after each injection; the night-time hyperglycemia after bedtime glargine injections was avoided with lunch or dinner injection schedules (93). Another study in 18 patients with poorly managed T1DM, reported that transitioning from evening to morning administration of insulin glargine, independent of dose, resulted in more favorable glucose control and lipid profile without affecting body weight (94). A study of 13 T1DM patients reported that insulin lispro is more effective at evening and nocturnal glycemic control when the bedtime dose is greater than mealtime doses (95). Insulin detemir, in combination with mealtime insulin aspart, provided equally effective glycemic control when administered as a morning/dinner or a morning/bedtime dose; however both regimens provided better glycemic control with no weight gain when compared to morning/evening NPH insulin regimen (96). For T1DM patients who experience evening hypoglycemia, continuous nocturnal subcutaneous infusions of either insulin or octreotide, compared to multiple injection regimens, better reduced nocturnal and morning hyperglycemia and lowered growth hormone levels (97, 98). Similarly, a pediatric study also demonstrated that continuous subcutaneous injections of insulin glargine reduced HbA$_{1C}$ levels and controlled pre-meal glucose levels better than multiple daily injections (99).

Optimal timing of treatment for type 2 diabetes mellitus (T2DM) is also variable and can depend on drug and treatment schedule based on individual diagnosis, lifestyle, and blood glucose patterns (86) (Table 2). When treating T2DM with morning and evening doses of insulin or insulin analogues, a high morning dose (in ratios between 53:47 and 75:25 morning:evening) was reported by two studies to be more effective for glycemic control (100, 101). When administered as a single daily dose, insulin glargine in conjunction with morning glimepiride was equally effective at glycemic control when given in the morning or evening in a randomized study of 624 patients (102). An additional euglycemic clamp study in 10 patients similarly reported that the timing of single insulin glargine administration did not affect total 24-h insulin activity, although nocturnal administration improved 24-h suppression of both plasma glucagon and markers of lipolysis (103). In T2DM patients who experience inadequate control of glucose levels by metformin, a double-blind placebo-controlled trial in 680 patients reported that morning and evening lixisenatide injections similarly improve glucose control (104). Repaglinide, a fast-acting meglitinide, was also reported to be more effective when administered at mealtimes rather than as split morning/ evening doses in a double-blind randomized parallel-group study of 19 T2DM patients (105). In a randomized double-blind crossover study in 48 T2DM patients morning or evening dosing of vildagliptin, a dipeptidyl peptidase-4 inhibitor, was reported to be equally effective at post-prandial and 24-h glucose control; however only evening dosing was effective at reducing fasting plasma glucose (106). Finally, for treatment of gestational diabetes mellitus, dosing regimens of regular and intermediate insulin that follow a four-times daily administration schedule were reported to provide better glycemic control and maternal/fetal outcomes when compared to twice daily regimens (107, 108).

Hypothyroidism and Hyperparathyroidism.—The primary drug used for treatment of hypothyroidism is levothyroxine, a synthetic thyroid hormone. Despite multiple attempts to elucidate effective circadian timing of administration for disorder control, there is contradicting evidence suggesting when the drug should be administered (Table 2). Some reports suggest that the levothyroxine should be taken in the morning before mealtimes (109). Conversely, other groups report improved thyroid hormone control after administering the drug in the evening compared to morning (110–112), or no variation in efficacy between morning and evening treatment in adults (113) or children (114). A clinical trial is currently underway to compare efficacy of levothyroxine morning dosing to evening dosing in older adults (115). A brief review on the circadian variations of drug efficacy suggests that administration of levothyroxine should be coordinated primarily with timing of meals until further research demonstrates a consistently optimal time of day for drug administration (116). Finally, a randomized cross-over study of 13 patients with hyperparathyroidism providing morning (0800 h) or evening (2000 h) doses of vitamin D3 reported that evening doses were more effective at condition management (117). Due to conflicting reports, no conclusions can be drawn on optimal timing of treatment for thyroid disorders, however it is obvious that further clinical research with a clear consideration of time of day as a biological variable is necessary to optimize efficacy of treatment.

Osteoporosis.—A circadian pattern of markers of bone metabolism in serum, saliva, and urine suggests that chronotherapy should be considered for the treatment of osteoporosis (118–122). Clinical practice guidelines published by various professional organizations do not form a consensus on best approaches (reviewed in (123)), yet one commonality among them is the lack of consideration of circadian rhythms in bone metabolism, likely due to the paucity of clinical studies. Treatments for osteoporosis include nonpharmacological interventions (diet, calcium/vitamin D supplements) and pharmacological interventions (antiresorptive or anabolic medications).

Chronotherapeutic studies of non-pharmacological treatments of osteoporosis have primarily examined the timing of supplemental calcium administration (Table 2). One study of 14 patients with osteoporosis reported that calcium-supplemented meals did not affect the levels of bone resorption or the circadian patterns of resorption in comparison to evening-only supplements (124). Analysis of urinary bone resorption markers in healthy postmenopausal women revealed that a split morning evening dose of 500:1000 mg of calcium suppressed bone resorption across the 24 h period (125), whereas a single evening 1000 mg dose only suppressed bone resorption during the night (126). A randomized trial in 30 healthy adult females reported that altering acute oral calcium load by split, morning, or 4 x daily doses of calcium did not differentially affect bone resorption across the day, however parathyroid hormones were differently affected based on the size and timing of calcium dose, thus the authors concluded that longitudinal studies were needed to determine most effective timing for chronic calcium supplementation on bone health (127).

Chronotherapeutic approaches have also been examined for pharmacological approaches to treating osteoporosis (Table 2). A study in 39 post-menopausal women with osteoporosis treated with raloxifene (an estrogen receptor modulator) reported that morning (0730–0900 h) or evening (1800–2030 h) dosing similarly reduced levels of markers of bone metabolism;

however the authors recommended evening doses due to morning dose-induced upregulation of plasminogen activator inhibitor-1, which is associated with increased venous thromboembolism risk (128). A longitudinal study in osteoporotic patients administered teriparatide, an anabolic drug, reported greater lumbar bone mass density increase with evening administration compared to morning dosing (129). A retrospective longitudinal study examining the timing of etidronate administration determined that dosing was similarly effective when taken as single doses across the day if the patient adhered to a 2 h fast before and after dosing (130). Finally, in a single-blind crossover study examining bone resorption, morning administration of ONO-5334 (a cathepsin K inhibitor) was more effective than evening administration at suppressing C-terminal telopeptide of type I collagen (a marker of bone turnover) across the day (131).

Optimal timing for administration of calcitonin, an antiresorptive hormonal treatment for osteoporosis and Paget's disease, depends on route of administration. For example, 0800 h or 2100 h nasal salmon calcitonin treatment transiently reduced bone resorption but did not effectively alter the circadian pattern of bone resorption (132). However, a randomized, double-blind study in 81 postmenopausal women reported that oral salmon calcitonin (0.8 mg) administered before dinner (1700 h) resulted in the largest 24 h suppression of bone resorption relative to placebo, when compared to morning (0800 h) or evening (2200) dosing (133). Thus, evening dosing of oral salmon calcitonin appears to most effectively blunt the circadian peak in bone resorption (134), however extended calcitonin use has been associated with increased liver cancer risk and has been pulled from several markets (135). To our knowledge, there have been no recent clinical trials on optimal timing of calcitonin injection. Taken together, these studies highlight the need for including time of day as a biological variable in future studies of efficacy of treatments for osteoporosis.

Growth Hormone.—When treating growth hormone (GH) deficiency, early studies indicated that evening administration of GH was more effective at restoration of normal hormone and metabolite circadian patterns (136) (Table 2). A crossover study in 8 adult patients dosed either once at 1900 h or twice-daily at 1900 h (2/3 dose) and 0800 h (1/3 dose) reported that twice daily dosing better matched normal physiological GH profile, increased serum IGF-1, and decreased serum IGFBP-1 while lowering non-esterified fatty acids (137). A study in 34 children undergoing GH therapy either in the morning, afternoon, or evening, reported no differences among groups in growth, IGF-1, or GH-BP after 6 or 12 months of GH treatment (138). Additional circadian considerations for GH treatment were highlighted in a small study examining prednisone administration to 10 healthy children, which reported that evening administration suppressed GH secretion whereas morning administration did not (139). It is also important to note that a common limitation of biomedical studies is a male bias and, as is the case with most physiological processes, there is a significant sex difference in human GH patterns (140). Thus, future studies must consider both time of day and sex as biological variables to optimize GH treatment. One case where sex differences are not an issue is with the treatment of Turner syndrome. A double-blind placebo controlled crossover study in nine girls with Turner syndrome receiving evening GH injections reported that estradiol was more effective at managing

insulin, glucagon, IGF-1 levels when administered in the evening compared to morning (141).

Other Endocrine Treatments.—A randomized crossover study on hormone therapy for the treatment of climacteric symptoms in perimenopausal women reported no difference between morning or evening administration of cycloprogynova (142). In regard to the time of day effects of the estrogen receptor modulator raloxifene on osteoporosis, please see the study in that section by Ando (128). Finally, regulation of ovulatory cycles via once-daily oral contraceptives were reported to be equally effective when administered as a morning or evening dose (143).

Immune System

Glucocorticoids.—The circadian rhythm of glucocorticoids is discussed in detail in the AI/CAH section above. Glucocorticoids are steroidal hormones that function to reduce inflammation, in addition to regulating glucose and metabolism. Glucocorticoids act by binding to glucocorticoid receptors, resulting in dimerization and translocation to the nucleus, repressing inflammatory transcription factors (144). These anti-inflammatory properties make this class of steroids a common treatment for immune disorders and diseases such as asthma, rheumatoid arthritis, and multiple sclerosis. Physiological production and secretion of glucocorticoids occurs in the adrenal glands in a distinct circadian pattern (Figure 2) (145, 146), suggesting that the timing of treatment with glucocorticoids could play an important role in immunotherapeutics, especially for chronic inflammatory diseases (147).

Rheumatoid Arthritis.—Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by joint and tissue damage caused by chronic inflammation of the synovial membrane, resulting in joint pain, stiffness, and swelling of the joint. Symptoms of RA show circadian rhythmicity with a peak occurring in the morning; due in part to blunted levels of rhythmic cortisol secretion that lead to an abnormal elevated morning peak of circulating proinflammatory factors such as tumor necrosis factor (TNF-α) and interleukin-6 (IL-6) (reviewed in (148, 149)).

To determine circadian variations in anti-inflammatory capacity of corticosteroids, 41 RA patients in a crossover study were administered 5.8 mg of prednisolone either in the morning (0600 – 0700 h) or at bedtime (between 2200 – 2300 h); bedtime ingestion of the corticosteroid significantly reduced morning stiffness as compared to patients who took their dose in the morning (0700 h) (150). Another study evaluating timing administration of prednisolone in 85 women reported that mean pain score, based from the disease activity score 28 (DAS28), duration of morning stiffness, and erythrocyte sedimentation rate were decreased when administered at (2200 h) compared to (0800 h) (151); however, this study was neither a crossover study, nor randomized, so it is unclear if the effects were due to timing of the dose or duration of treatment. A randomized, double-blind multicenter trial in 288 patients comparing prednisone delivered in a modified release formulation in the evening, so as to have its peak effects coincide with nocturnal IL-6 upregulation, to prednisone delivered in a rapid release formulation in the morning, reported that morning

pain intensity and duration, DAS28, and plasma IL-6 levels were significantly reduced with the evening modified release dose (152, 153).

In addition to short-term use of corticosteroids, NSAIDS and disease-modifying antirheumatic drugs (DMARDs) are also used to treat RA. Switching methotrexate dosing from morning to bedtime led to significant improvements in both DAS28 and modified health questionnaire (MHAQ) scores in a cohort of RA patients (154). Time-of-day specific effects for other DMARDs used to treat RA, such as baricitinib and tofacitinib, have not been clinically tested to our knowledge. A double-blind crossover study with the NSAID flurbiprofen reported that twice-daily dosing regimens that included an evening dose were more effective in reducing RA symptoms and increasing grip strength (155). Evening administration (2000 h) of the NSAID indomethacin reduced morning pain symptoms in a double-blind crossover study in 66 patients with osteoarthritis; this study further reported that evening dosing resulted in the fewest undesirable effects and that worsening afternoon or evening pain was best relieved by administration in morning (0800 h) or afternoon (1200 h) (156). In an double-blind randomized trial in 117 osteoarthritis patients, evening dosing (2000 h) of ketoprofen was reported to cause longer duration of analgesia with fewer adverse effects when compared to morning dosing (0800 h) (157).

In spite of the clinical evidence (Table 3), the current clinical practice guidelines for RA (158) do not address the circadian aspects of RA nor discuss chronobiological approaches in treatment. However, chronotherapeutic approaches for optimal timing of treatments for RA have been proposed based on this clinical evidence (Figure 3) (159). Future studies should incorporate time of day as a biological variable to optimize efficacy of treatments for RA.

Multiple Sclerosis.—Multiple Sclerosis (MS) is an autoimmune inflammatory disorder characterized by demyelination and neurodegeneration of the central nervous system. This results in varying symptoms depending on the severity and location of nerve damage, but often includes pain, numbness, tremors, unsteady gait, and loss of coordination as the disease progresses. Recent evidence strongly implicates environmental and genetic influences on the circadian system in the development and progression of MS. For example, disruption of circadian rhythms by shift work at an early age is associated with increased risk of developing MS (160). Polymorphisms in the genes for ARNTL and CLOCK, core components of the molecular circadian clock, are associated with MS risk (161). Furthermore, seasonal relapses in MS are associated with changes in melatonin, which is a circadian rhythm-dependent hormone (162). Finally, a study comparing 34 healthy adults with 34 MS patients reported that serum inflammatory markers, and diurnal rhythms in some markers, differ between healthy adults and MS patients, and between MS patients with active and inactive lesions (163).

Pharmacological treatment approaches are trifold: first to modify the disease course, second to treat exacerbations, and third to manage the multitude of symptoms. Interferon-beta (IFN-β) therapy is one of the commonly prescribed disease modifying approaches. A small study in 16 patients with relapsing/remitting MS comparing IFN-β1a injected at 0800 h to 1800 h, reported that on the first day of treatment, morning injection resulted in higher plasma IL-10 whereas evening injection caused an earlier and more robust peak in cortisol, increased

soluble tumor necrosis factor receptor 1 & 2 (sTNF-R), and increased plasma IL-1, which was associated with more intense negative side effects; after 6 months of IFN-β therapy, elevated sTNF-R1 in the morning group was the only difference reported (164). Another clinical study in 105 MS patients reported that switching from evening to morning injections of IFN-β qualitatively improved flu-like symptoms (58%) and sleep quality (48%), common side effects from INF-β delivery (165). Conversely, a recent randomized controlled parallel-group trial in 200 patients with relapsing MS comparing morning and evening dosing of IFN-β1a across 12 weeks of treatment reported that the morning administration group reported more intense flu-like symptoms at weeks 4 and 8, however by week 12 there we no differences in symptoms between groups. Furthermore, there were no reported effects of time of day of dosing on sleep quality, fatigue severity, or circulating leptin, resistin, and adiponectin after 12 weeks of IFN-β1a therapy. (166). Limited and conflicting data make it impossible to determine maximal effectiveness of IFN-β1a therapy based on time of day of dosing (Table 3). To our knowledge, no other disease modifying treatments (such as glatiramer acetate, dimethyl fumarate, teriflunomide, siponimod, mitoxantrone, natalizumab, fingolimod, etc.) have been publicly evaluated in the context of administration time in relation to therapeutic effectiveness.

For managing relapses in MS, immunosuppressive doses of corticosteroids, or adrenocorticotropic hormone (ACTH) to stimulate endogenous corticosteroid release, are generally given during the flare up. Corticosteroid rhythms and time-of-day specific effects of corticosteroid treatments are reviewed above in the context of congenital adrenal hyperplasia and rheumatoid arthritis, however examination of time of day effects of treatment in the context of treating MS are even more limited (Table 3). Methylprednisolone, when administered intravenously at night (2200–0200 h) compared to daytime (1000–1400 h) in 17 MS patients, was reported to reduce serum MMP-9 and adverse events, including symptoms such as insomnia, depression, headaches, restlessness, gastrointestinal symptoms, palpitations (167). Pharmacological approaches to managing the multitude of MS symptoms are greatly varied and are symptom specific. To our knowledge, scant few (if any) studies have directly investigated time-of-day specific effects of symptom modifying drugs in the context of MS. Regardless, taken together it is apparent that treatment of MS should use a chronobiological approach, and the few clinical studies that have investigated time-of-day effects are very limited and grossly underpowered. Finally, the preclinical and clinical studies of remyelination by oligodendrocytes for disease mitigation should take into account circadian rhythms of those cells (168).

Asthma.—Asthma is a chronic inflammatory disease characterized by episodes of shortness of breath, wheezing, and chest tightness due to narrowing or swelling of the airways. Both symptoms and treatments for asthma appear to be affected by circadian rhythms (169, 170), and reported optimal treatment times vary based on drug. The inhaled glucocorticoid triamcinolone was reported to be equally effective when administered as a single 800 μg dose at 1500 h when compared to 200 μg 4 times daily in a study with 30 participants (171). A follow up study in 59 subjects using the same total daily dose similarly reported triamcinolone was equally effective administered as a single dose at 1730 h or four times daily, however a single dose administered at 0800 h was reported less beneficial in

comparison to the other dosing regimens (172). Studies evaluating other steroid inhalants, mometasone furoate (randomized parallel trial in 1537 subjects; (173) and fluticasone furoate (randomized double-blind trial in 28 subjects; (174), reported no difference between morning or evening administration on subjective symptoms. Similarly, no difference in effectiveness based on the time of day of administration was reported when fluticasone furoate was administered in combination with the beta-agonist vilanterol in a randomized, double-blind crossover trial in 26 subjects (175).

Bambuterol, a long-acting β-adrenoreceptor agonist, effectively reduced symptoms of asthma when administered once daily at either 0700 h or 2200 h in a double-blind, randomized, placebo-controlled, crossover study in 29 patients; however, evening administration produced the most improvement in morning forced expiratory volume, suggesting an optimal time of dosing for patients with nocturnal asthma (176). Similarly, a study in 25 adult patients comparing a once-daily administration of sustained release theophylline at 2000 h to twice-daily (0800 and 2000 h) reported that both regimens had similar overall improvements in airflow, however the single evening dose significantly improved peak expiratory flow rate and forced expiratory volume between 0200 h and 0600 h (177). However, a double-blind crossover study in 8 asthmatic children (178) reported that extended release theophylline formulated for once per day administration in the morning, if taken in the afternoon or evening (1500 h or 2100 h), resulted in serum theophylline concentrations greater than 20 μg/mL, which are toxic levels (179). Thus, in common with cortisol replacement therapy described in the adrenal insufficiency section above, theophylline provides another cautionary example of the critical need to account for chronopharmacology and circadian rhythms in clinical research and outcomes.

A third approach for treating asthma has been with leukotriene receptor antagonists such as montelukast (Singulair). Evening dosing is recommended for montelukast; however, there does not appear to be any clinical support for this recommendation. Indeed the both the US FDA and the manufacturer state in the product insert that "There have been no clinical trials in patients with asthma to evaluate the relative efficacy of morning versus evening dosing" (180), thus the evening dosing recommendation may likely represent the time of day for best patient compliance. For exercise induced asthma in children, one study reported no differences in protection from bronchial constriction when comparing in morning to evening dosing of montelukast (181). Similarly, when used for the treatment allergic rhinitis (see below), montelukast is reported to be equally effective when taken once a day in the morning or evening (182).

Allergic rhinitis.—Allergic rhinitis (AR) is an upper airway inflammatory disease characterized by sneezing, congestion of the nasal region, and rhinorrhea in response to allergens present in the environment, including particles such as pollen, dust, and mold. Symptoms of this condition display circadian rhythmicity, with a peak occurring in the early morning (183, 184), in common with what is observed in lower airway inflammation in asthma (185). Current clinical practice guidelines for AR do not discuss or provide guidance on the circadian aspects of this disease, although the guidelines do suggest clinicians should consider sleep-disordered breathing and sleep disturbance in their assessments (186).

Studies on chronotherapy for AR have generally focused on the most common therapeutic approach, histamine H1 receptor antagonists, however results from these limited studies have been equivocal (Table 3). When compared to breakfast dosing, dinner-time dosing of the H1 antagonist mequitazine was reported to be more effective at controlling both morning peak and 24-h symptoms of AR in a multicenter study (187). The effectiveness of the antihistamine desloratadine (5 mg/day for two weeks) was reported to not differ between morning or evening administration in a randomized study in 663 adult AR patients (188). Similarly, cetirizine was reported to be equally effective at symptom relief in seasonal AR independent of time of day of dosing in two multicenter, randomized, double-blind, parallel-group studies (189). A randomized, double-blind, crossover study in 9 male athletes comparing morning (0700 h) to early evening (1700 h) supra-therapeutic dosing (180 mg) of pseudoephedrine, a common over the counter nasal decongestant used to treat AR, reported that only a morning dose boosted muscle contraction velocity in squat exercises (190). The data are insufficient to draw any recommendations on chronotherapy for AR, however it is apparent that future studies into the effectiveness of treatments should record time of day as a biological variable.

Cystic fibrosis.—Tobramycin is a water-soluble aminoglycoside antibiotic commonly used to treat Cystic Fibrosis (CF) patients. A randomized trial in 18 children comparing dosing at 0800 h to 2000 h reported no differences in pharmacokinetics due to time of day, however urinary KIM-1 (kidney injury molecule) was higher in the 2000 h group, indicating greater potential for kidney damage with evening dosing (191). Consistent with the results in children, a study in 25 adult CF patients reported the same pattern; there were no differences in pharmacokinetics due to time of day, but the evening group (2200 h) had increased serum blood urea nitrogen compared to the morning (0800 h) group (192). Taken together, these studies (Table 3) suggest a chronotherapeutic approach may avoid contraindications caused by time of day of treatment for CF, and as such future studies should consider time of day as a biological variable.

Psoriasis and Eczema.—In common with other organs and physiological processes, the skin also displays circadian rhythms in normal function and disease, such as night time flares of atopic dermatitis (193). Additionally, disruption of circadian rhythms by shift work increases the risk of developing psoriasis (194), suggesting chronobiological approaches should be considered for treatment and prevention of skin disorders. As discussed previously, corticosteroids to treat inflammatory conditions generally have their greatest effect when applied at the nadir of the endogenous circadian cortisol rhythm. This appears to be the case for topical administration of betamethasone, which has its maximal effects on healthy skin with a late afternoon application (195). For acute treatment of psoriasis, evening application of betamethasone was reported to be more effective than morning application (196), however, its effects were attenuated after five nights of application, possibly due to skin saturation with corticosteroids.

Vaccines.—Circadian regulation of the adaptive immune system predicts time of day specific differences in response to antigens in vaccines (197), and thus potential beneficial effects of time of day specific vaccination. Morning vaccinations for influenza and hepatitis

A produce enhanced antibody responses compared to those given in the afternoon (198–200), however some of these enhanced responses can vary by strain (201). Temporally-specific effects of vaccination are still debated as antibody titer is influenced by time of day of sample collection among the elderly (202). However, the aforementioned studies (Table 3) indicate that morning vaccination may enhance efficacy, especially when followed by a quality night of sleep after vaccination (203). Taken together, these few studies indicate that future vaccine trials should incorporate time of day as a biological variable in their design.

Metabolic Disorders

Statins.—Current clinical guidelines for the treatment and management of blood cholesterol (204) neither mention nor provide guidance on circadian aspects of cholesterol biosynthesis and management. However, this has been an active area of clinical investigation for over 30 years, with a clear recognition that time of day must be considered in both dietary and pharmacological approaches to management of blood cholesterol and treatment of atherosclerosis (205, 206). Statins can reduce serum low-density lipoprotein (LDL)-cholesterol ~30% by inhibiting the rate-limiting enzyme in cholesterol biosynthesis, HMG-CoA reductase (207).

Evening administration of an immediate release (IR) formulation of simvastatin (dose of either 2.5 or 5 mg) had a significantly higher percent reduction of plasma LDL-C concentrations when compared to morning administration (208). Similarly, switching adults who were receiving either 10 or 20 mg dose of IR simvastatin in the evening to a morning dose resulted in a 10% increase in LDL-C levels, suggesting that taking IR simvastatin during the evening is most effective (209). Nevertheless, administration of a controlled release (CR) formulation of simvastatin in the morning compared to evening reported no differential effects on reduction of LDL-C (210). When comparing efficacy and safety of morning intake of CR simvastatin to evening intake of IR simvastatin, there were no differences reported between treatment groups (211). In common with CR simvastatin, extended-release fluvastatin is equally effective in reducing LDL when administered in the morning or evening (212). Other clinical statin studies have evaluated lovastatin (213), pravastatin (214), atorvastatin (215, 216), and rosuvastatin (217). These studies had limitations either from confounding factors, failure to reach concrete conclusions, failure to reach statistical significance, or lacking in diversity among the populations studied, which ultimately limits their ability to be extrapolated (reviewed in (218, 219)).

Taken together (Table 4), these results highlight the importance of choosing the optimal time of day for statin administration, dependent upon the circadian pharmacokinetics and pharmacodynamics of each drug and formulation, and in the cases where no differences are observed, time of administration may be chosen that best supports patient compliance. Generally, the effects of statin treatment are improved when drug availability coincides with the time of day of maximum biosynthesis, thus it is likely more effective with bioavailability at night compared to morning. The limitations of previous studies provide insight that time of fday should be considered as a key biological variable in future research design into the effectiveness of statins on hyperlipidemia and atherosclerosis.

Glaucoma.—Production and flow of aqueous humor in the eyes follows a circadian rhythm, with peak during the day and nadir occurring at night (220). Intraocular pressure (IOP) also displays a circadian rhythm, with the peak generally occurring at the end of the nocturnal period and nadir at the end of the day (221, 222); however, these circadian patterns may be shifted in some individuals with glaucoma (223). Thus, although glaucoma treatments may likely benefit from a chronotherapeutic approach, optimal dosing times may need to be tailored to patients' circadian rhythm of IOP and humor flow. Regardless, few studies have evaluated the differential effects of time-of-day specific administration of medications in glaucoma (Table 4). In a randomized crossover study in 30 patients, treatment with travoprost alone either in the morning or evening was equally effective at lowering IOP (224). However, in a prospective randomized crossover comparison study in 32 patients given a fixed combination of travoprost and timolol, evening dosing provided better 24-h pressure control and lower peak IOP when compared to morning dosing (225). Similarly, a recent placebo-controlled crossover trial in 42 patients given preservative-free tafluprost/timolol also reported that evening dosing provided greater reductions in IOP and 24-h IOP fluctuation when compared to morning dosing (226).

Cancer Treatments

Chemotherapy.—Chemotherapy is a mainstay in cancer treatment; the CDC estimates that as many as 600,000 patients will receive chemotherapy treatment in an outpatient setting in this year alone. Chrono-chemotherapy aims to optimally time chemotherapy administration to reduce adverse side effects and increase anti-tumor efficacy. Treatment regimens implementing chrono-chemotherapy time chemotherapy administration at the point in the circadian cycle during which adverse side effects will be the lowest, allowing for an increase in the maximal tolerated dose of chemotherapy to increase anti-tumor efficacy (227). Despite chrono-chemotherapy first being demonstrated to be beneficial more than 40 years ago, (228–230), it remains understudied and underappreciated. Studies examining the beneficial effects of chrono-chemotherapy in humans have primarily focused on treatments for ovarian, renal cell, and colorectal cancers, with few studies examining chronomodulated chemotherapy treatment for breast, lung, and pancreatic cancers (Table 5) (231–233).

One of the first studies examining the effects of chrono-chemotherapy for the treatment of advanced ovarian cancer in 31 patients, administered doxorubicin at either 0600 h or 1800 h followed by cisplatin (CDDP) twelve hours after the completion of doxorubicin treatment, reported that patients with doxorubicin treatment in the morning and cisplatin treatment in the evening had fewer dose reductions, treatment delays, and treatment complications (230). Morning doxorubicin treatment followed with evening cisplatin treatment was also reported to be advantageous in reducing adverse side effects in two other phase III clinical trials for the treatment of ovarian and bladder cancers, with an increase in 5 year survival rate from 11% to 44% in patients with advanced ovarian cancer (231). Similar beneficial effects of morning-timed doxorubicin treatment followed by evening-timed cisplatin treatments have been demonstrated using doxorubicin derivative 4'–0-tetrahydropyranyl doxorubicin (THP) (234). Indeed, in a phase II clinical trial evaluating circadian timing of chemotherapy treatment for advanced ovarian cancer in 31 patients reported that patients receiving a THP intravenous bolus at 0600 h followed 10 hours later by a 4-hour infusion of cisplatin, had

less neutropenia, thrombocytopenia, anemia, and renal toxicity relative to patients beginning THP treatment at 1800 h (234). Furthermore, the favorable effects of evening-timed cisplatin treatments are not limited to ovarian cancer. A study in 41 patients with advanced non-small cell lung cancer reported that patients receiving cisplatin treatment in the evening (1800 h) developed less adverse effects such as leucopenia, neutropenia, and gastrointestinal toxicity relative to the 0600 h treatment group (235). Additionally, studies examining morning-timed (0600 h or 0700 h) etoposide followed with evening-timed cisplatin (1800 h) treatment for advanced lung cancer, mixture of solid tumors, or metastatic cancer demonstrated less adverse hematological toxicities relative to patients receiving etoposide at 1800 h followed by cisplatin at 0600 h (236–238).

Unlike differentially timed chemotherapy boluses described above, most clinical trials evaluating chronomodulated chemotherapy treatment regimens have compared chronomodulated to continuous chemotherapy infusions, primarily in treatment of colorectal and renal cancers. One of the first such studies compared chronomodulated to flat continuous chemotherapy infusions of floxuridine (FUDR) for 14 days in 54 patients with advanced metastatic cancer (239). To achieve the variable rate infusion, the daily dose was broken into 4 segments (6hrs each) of 68%,15%, 2%, and 15% of the total daily dose with the peak dose infusion time from 1500 h to 2100 h (239). Patients receiving chronomodulated variable rate infusions had less frequent and less severe diarrhea, nausea, and vomiting, in addition to a 45% increase in maximally tolerated dose (239). Similar favorable effects of chronomodulated variable rate infusions of FUDR have been reported in multiple clinical trials for patients with renal cancer and colorectal cancers (232).

The antimetabolite, 5-Fluorouracil (5-FU), is likely the most studied chemotherapeutic in the context of chronomodulated chemotherapy treatment regimens (233). To date more than 10 clinical trials have assessed the effects of chronomodulated 5-FU treatments with more than half of the trials evaluating treatment of metastatic colorectal cancer (233). One of the first studies to demonstrate the favorable outcomes of chronomodulated variable rate 5-FU treatment compared to continuous 5-FU infusions involved 92 patients with metastatic colorectal cancer across seven different European cancer centers (240). Patients were randomly assigned to chronomodulated or constant rate treatment regimens and chemotherapeutics were administered consistently for 5 days and repeated every 21 days. Patients in the chronomodulated treatment regimen received oxaliplatin (1-OHP) for 11.5 hours from 1015 h to 2145 h, with a sinusoidally delivery rate and peak delivery at 1600 h; 5-FU and folinic acid were infused from 2215 h to 0945 h, with peak delivery at 0400 h. Patients receiving chronomodulated variable rate infusions of chemotherapeutics demonstrated five times less severe stomatitis, the dose limiting adverse effect of 5-FU, had increased maximal tolerated dose of 5-FU, and increased median survival (19 months vs 14.9) relative to constant rate infusions (240). A follow up randomized multicenter trial involving 93 patients with metastatic colorectal cancer reported that, compared to constant rate infusion, patients receiving chronomodulated variable rate infusions of 5-FU and 1-OHP had a five-fold reduction in mucosal toxicity and half of the peripheral neuropathy, however median survival and three year survival were unchanged by dosing regimen (241). A subsequent multicenter randomized trial utilizing chronomodulated variable rate infusions of 5-FU and cisplatin for the treatment of metastatic pancreatic cancer also reported reduced

adverse effects when compared to constant rate infusions (242). More recent studies however, have failed to demonstrate similar beneficial effects of chronomodulated variable rate infusions of 5-FU for the treatment of metastatic colorectal cancer (243–246), or have only demonstrated favorable effects on males (247–249).

Recent studies in the field of cancer chronotherapy have examined chronomodulated variable rate infusions of docetaxel, cisplatin, or 5-FU with or without radiotherapy for the treatment of advanced nasopharyngeal carcinoma (250–255). Chronomodulated variable rate infusions of chemotherapeutics resulted in less adverse effects (250–253, 255) and improved cellular immune numbers in virtually all clinical trials (250–252, 254, 255).

Few studies have examined the effects of chronomodulated oral chemotherapy treatment (256–258). One such retrospective study compared the effects of morning to evening dosing of 6-mercaptopurine and methotrexate for the treatment of childhood acute lymphoblastic leukemia in 118 children and reported that evening dosing increased disease free survival and reduced the risk of relapse by 2.5 times (256). Similarly, when compared to morning dosing, evening dosing of 6-mercaptopurine and methotrexate increased event free survival in a study in 294 children with acute lymphoblastic leukemia (257). However, a phase II clinical trial in patients with advanced colorectal cancer compared the effects of equidose to chronomodulated asymmetrical dose (i.e., 80% of the daily dose consumed at night) of the oral chemotherapeutic capecitabine; the authors concluded that the chronomodulated asymmetrical dose did not significantly reduce toxicity or improve efficacy (258).

Radiotherapy and Other Cancer Treatments.—As evident above, chrono-chemotherapy has beneficial effects relative to conventional chemotherapy in most clinical trials. In contrast, studies examining chrono-radiotherapy are scarce and even fewer studies have evaluated cancer treatments outside of chemotherapy and radiotherapy (Table 5). To date, approximately 13 studies have evaluated chrono-radiotherapy as an improved treatment option compared to conventional radiotherapy, and although somewhat promising, the results lack consistency across studies (259). For example, a retrospective study of 878 breast cancer patients examining adverse effects following radiotherapy concluded that patients receiving radiotherapy in the afternoon (i.e. after 1200) had less adverse reactions (260). However, a prior study had concluded that afternoon (i.e. after 1500 h) timed radiotherapy was associated with higher incidences of adverse skin reactions relative to morning-timed (i.e., before 1000 h) radiotherapy (261). Similarly inconsistent results in adverse effects have been reported in two studies that compared morning to evening timed radiotherapy in the treatment of cervical cancer (262, 263). Additionally, no differences in adverse effects were reported due to time of day of radiotherapy treatment for head and neck carcinoma or squamous cell carcinoma of oral cavity/pharynx/larynx (264, 265). However, afternoon-timed radiotherapy was associated with a higher incidence of complete or moderate pathological response and improved nodal downstaging in advanced rectal cancer (266). Furthermore, studies evaluating chrono-radiotherapy for the treatment of brain metastases have reported either increased overall survival in patients receiving radiotherapy in the morning (i.e., before 1200 h) (267, 268) or reported no difference between morning and afternoon groups (269, 270). Overall, the data examining chrono-radiotherapy as an

improved treatment option is limited and equivocal. Further investigations, primarily randomized clinical trials, are necessary to determine the efficacy of chrono-radiotherapy.

Data on chronomodulated cancer treatments outside of chemotherapy and radiotherapy are extremely scarce. Only a few studies have compared morning to evening consumption of the oral tyrosine kinase inhibitor, Sunitinib, and have reported no differences in adverse events or overall survival (271, 272). However, given the demonstrated circadian timing for tolerability, pharmacokinetics, and antitumor efficacy of antiangiogenic drugs, cell cycle inhibitors, and other cancer treatments in laboratory rodents (273), this is an area desperate for clinical investigation and represents an emerging area of research within the field of chronotherapeutics.

Perspectives and future directions.

In this review we have emphasized what is known and not known about the time of day when benefits are highest and contraindications are at a nadir for medications used in the treatment of multiple conditions. We have also highlighted the lack of consideration of time of day as a biological variable in both clinical research and in current clinical practice guidelines. Taken together, however, it is apparent that time of day is critical in consideration of pharmacokinetics, pharmacodynamics, toxicity, and efficacy of medications. It is also apparent that this factor is woefully understudied and we join our colleagues in highlighting that circadian rhythms must be considered as a key biological variable in both clinical studies and practice (274, 275). As noted, we are are not recommending changing dosing regimens based on the cited studies, but suggest that clinical trials attend to and report on time of day as a key variable for effectiveness.

Acknowledgments

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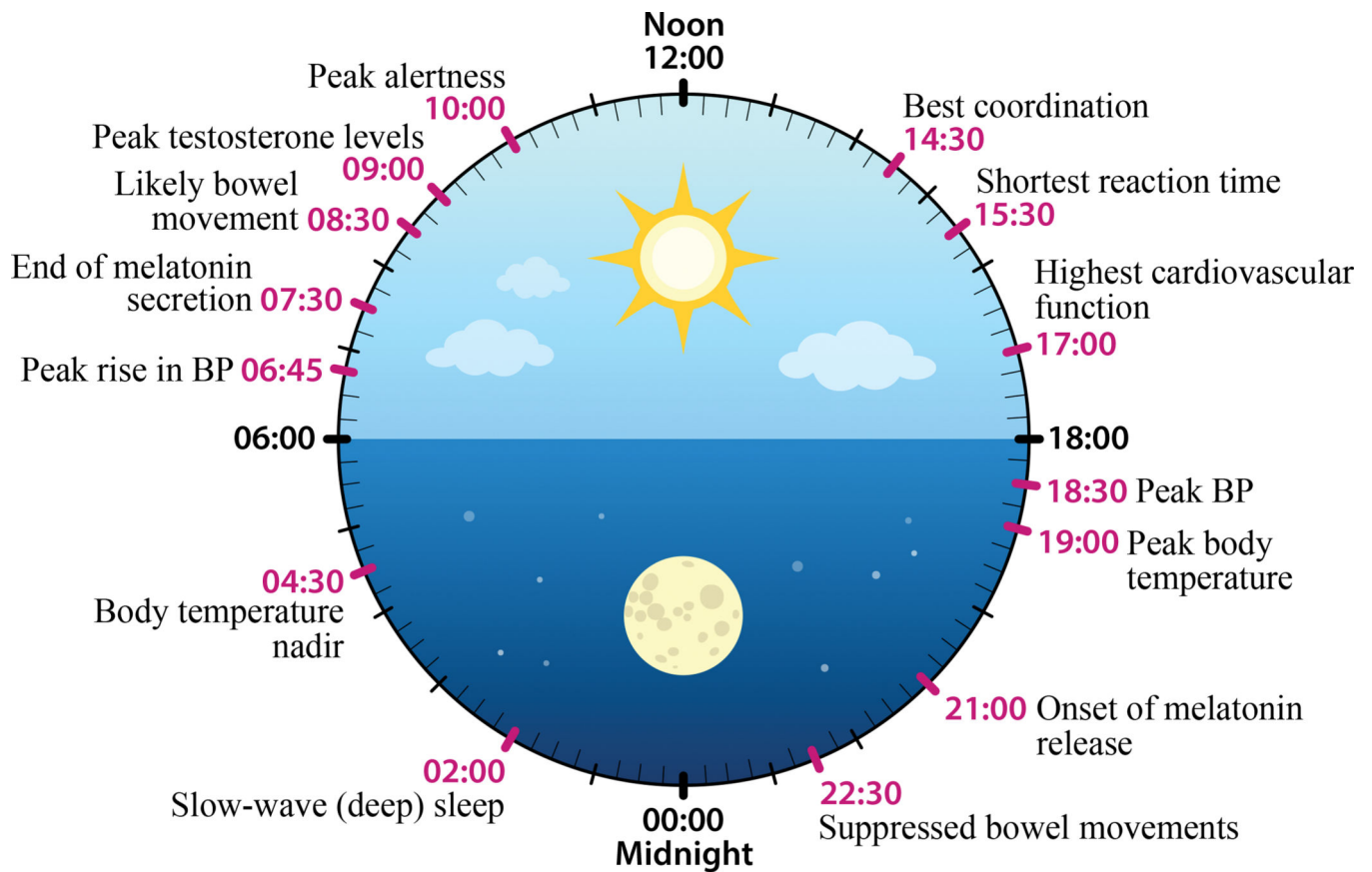
Figure 1. Circadian rhythms in physiology.

In humans, environmental light information is detected by specialized retinal ganglion cells in the eyes that project to the master circadian clock, the suprachiasmatic nuclei in the hypothalamus. In a top-down fashion, the master clock then transduces photic information to drive neural and hormonal signals, such as melatonin and cortisol, which in turn synchronize circadian cellular rhythms in the network of peripheral clocks which control and coordinate physiology and body function. Peak and nadir circadian timing of some of these and other physiological and bodily functions are depicted here (redrawn from [7]).
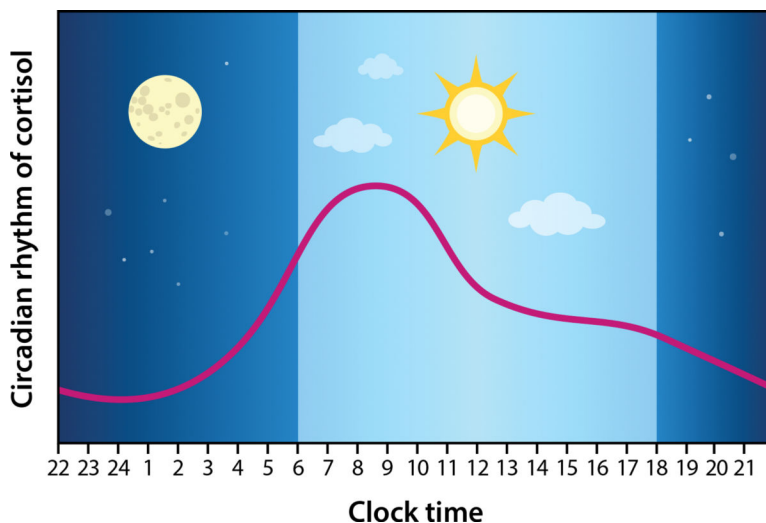
Figure 2. Endogenous circadian rhythm of cortisol.
Cortisol, the primary glucocorticoid in humans, is produced by the adrenal glands and is regulated by one of the major neuroendocrine systems, namely, the hypothalamic-pituitary-adrenal (HPA) axis. Typical physiological cortisol concentrations function to regulate energy mobilization in the body and thus follows a circadian rhythm in which changes in circulating cortisol generally precede daily activity patterns; cortisol values rise sharply just prior to the onset of activity (prewaking) and then gradually decline across the day to reach nadir at the end of the active period (onset of sleep) (based on [74]). The HPA axis also functions to integrate physiological systems (e.g., immune, cardiovascular, reproductive, metabolism, central nervous system) to rapidly adapt to changes in the environment. Strong bidirectional feedback between the HPA axis and these systems place it as the fulcrum of typical physiology; thus, HPA axis dysregulation is implicated in many medical conditions.
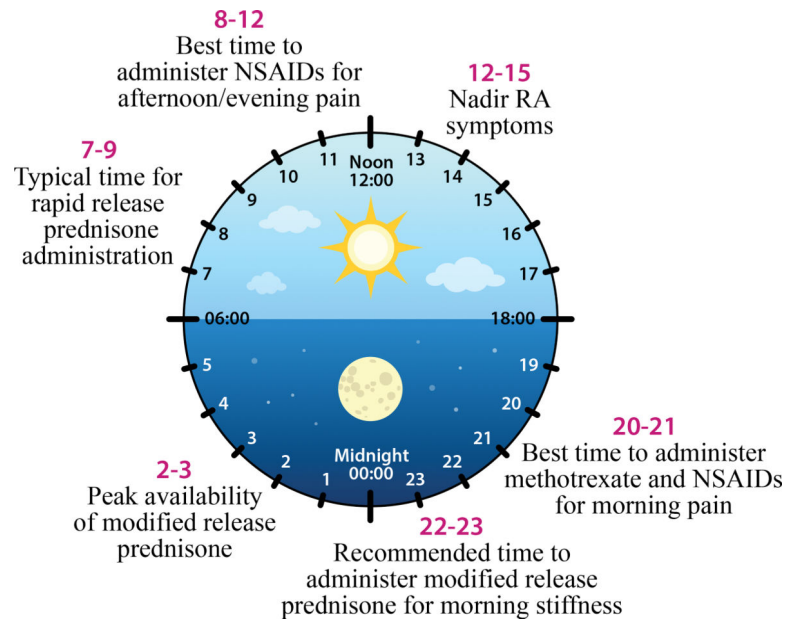
Figure 3. Chronotherapy for rheumatoid arthritis (RA).
Suggested optimal timing of various treatments for circadian RA symptoms (redrawn from [159]).

Table 1.

Clinical trials and studies considering time of day in treatment for hypertension.

DRUG CLASS	DRUG(S)	STUDY DESIGN; POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
Anti-hypertensives					
Calcium Channel Blockers	Amlodipine	Single center, randomized crossover study; Hypertensive / normotensive subjects.	Highest effect on reducing BP & HR when taken in the morning (0800 h) compared to evening (2000 h).	Morning	Khodadoustan, Nasri Ashrafi et al. 2017
	Nifedipine GITS	Multicenter, double-blind, randomized clinical trial; 180 Hypertensive patients (86 males, 94 females)	Bedtime dose was more effective and was associated with decreased negative side effects.	Bedtime	Hermida, Ayala et al. 2008
	Verapamil - COER	8-wk prospective, multicenter, randomized, double-blind clinical trial; 193 dipper and 64 non-dipper hypertensives	A dose at 2200 h reduced 24h BP on dippers and non-dippers, but had a greater reduction in nocturnal BP on non-dippers.	Night (2200 h)	White, Mehrotra et al. 1997
		Open-label, multiple-dose, four-period, crossover study; 29 healthy men	There were no differences between an 0800 h and a 2200 h dose on BP, however time of administration did affect the rate of absorption (morning dose was slower).	Morning	Gupta, Yih et al. 1995
	CODAS - verapamil	8-week, double-blind, placebo-controlled trial; 257 patients:193 dippers & 64 nondippers	Taken between 2100–2300 h produced best effects in the morning (between 0600 – 12000 h).	Night (2100 – 2300 h)	Smith, Neutel et al. 2001; Prisant 2003
		Open-label, multicenter dose-titration study; Elderly (65 y/o) 628 patients.	200 mg/d at bedtime, dosing was titrated to a maximum of 400 mg/d	Night	Weber, Prisant et al. 2004
	Nitrendipine	6 hospitalized and drug-free patients with essential hypertension.	More effective at awakening (0600 h) or supper compared to breakfast (0830 h) and supper administration brought a deeper asleep BP decline.	Awakening or Supper	Umeda, Naomi et al. 1994,
	Isradipine Sustained Release	Double-blind, randomized, cross-over design; Non-dipping chronic renal failure patients	Both 0800 h and 2000 h effectively reduced 24-h BP, but 2000 h administration showed a more pronounced effect during the night.	Night (2000h)	Portaluppi, Vergnani et al. 1995
	Diltiazem Retard	Open, non-randomized study; 13 dipper, essential hypertension patients	Morning (0800 h, n = 7) dose had the most marked antihypertensive effects during nighttime BP, while evening dose (1900 h, n = 6) dose exerted greatest effects during daytime activity with inhibition of the morning BP rise.	Evening	Kohno, Iwasaki et al. 1997
		Open, non-randomized study; 5 dipper, essential hypertension patients	Dosing 3x a day had the best effect during daytime activity.	3x daily	

DRUG CLASS	DRUG(S)	STUDY DESIGN; POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
	Diltiazem	Open, non-randomized study; 8 non-dipper, essential hypertension patients	Most pronounced antihypertensive effects during nightly rest. Evening dose seems to be more efficacious than the other dosage schedules.	Evening	
	Diltiazem Extended Release (ER)	Open-label, randomized, two-way crossover study; 48 healthy volunteers	Administration in the evening (2200 h) exhibited 17% and 22% greater bioavailability compared to morning (0700 or 0800 h) administration under single-dose and steady-state conditions, respectively. The two times of drug administration were bioinequivalent in both studies. Evening schedule provided more than twofold higher plasma diltiazem levels in the critical morning hours.	Evening	Sista, Lai et al. 2003
NSAIDS	Aspirin	Prospective trial; 328 untreated patients with grade 1 hypertension	100mg at bedtime reduced ambulatory BP, while a dose upon awakening increased the 24h mean BP	Evening	Hermida et al., 2005
		Pregnant women	Bedtime (but not morning) aspirin dosing was best for preventing pregnancy-induced hypertension and preeclampsia.	Bedtime	Smolensky & Haus, 2001
		Randomized control trial	Low dose aspirin administered in the evening is more effective at reducing morning platelet activity than morning dosing.	Evening	Bonten, Snoep et al. 2015, van Diemen, Fuijkschot et al. 2016, Racca, van Diemen et al. 2019
ACE inhibitors	Benazepril		Most effective at controlling nocturnal and early morning BP and consequently, normalizing the circadian BP profile, when dosed at night	Evening	Palatini, Mos et al. 1993
	Enalapril	Randomized, crossover study; 8 hypertensive patients			Witte, Weisser et al. 1993
	Perindopril	20 hypertensive patients	Early morning BP rise is reduced more with night (2100 h) administration. However, it does not reduce BP over 24 h as is achieved with the morning (0900 h) dose.	Night (2100 h)	Morgan, Anderson et al. 1997
	Quinapril	Double-blind clinical trial; 18 hypertensive patients	24-hour BP profiles showed a more sustained antihypertensive action with the evening (2200 h) administration compared with the morning (0800 h) administration.	Evening	Palatini 1992, Palatini, Racioppa et al. 1992
	Ramipril	Open, randomized, crossover trial; 33 patients with mild-to-moderate essential hypertension	A significant decrease from baseline BP was observed with a once-daily dose either at morning (0800 – 1100 h) or evening (2000 – 2300 h), and provided equal or better, BP control when taken in the morning.	Morning (0800 – 1100 h)	Myburgh, Verho et al. 1995
		Prospective, randomized, open-label, parallel-group, blinded end point	Diurnal BP reduction was similar with awakening or bedtime treatment. However, Bedtime administration was significantly	Bedtime	Hermida and Ayala 2009

DRUG CLASS	DRUG(S)	STUDY DESIGN; POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
		multicenter clinical trial; 115 untreated hypertensive patients	more efficient at reducing asleep BP.		
	Spirapril	165 previously untreated subjects	The BP reduction during diurnal activity was similar for both treatment times. However, bedtime administration was more efficient than morning administration in reducing asleep BP. The awake/asleep BP ratio was decreased with the upon-awakening schedule but significantly increased toward a more dipping pattern with the bedtime treatment schedule.	Bedtime	Hermida, Ayala et al. 2010
	Lisinopril	40 subjects with primary mild to moderate hypertension	Greater reduction of systolic BP and diastolic BP from 0600 h to 1100 h after 2100 PM dosing.	Night (2100 h)	Macchiarulo, Pieri et al. 1999
	Zofenopril	33 untreated patients with grade 1 or 2 uncomplicated essential hypertension	Nocturnal BP regulation is better achieved at bedtime administration as compared to at awakening, without any loss in efficacy during diurnal active hours.	Bedtime	Balan, Popescu et al. 2011
	Trandolapril	37 hypertensive patients	The 24-h systolic BP was reduced with both morning and bedtime regimes, but bedtime dosing had a greater decrease in pre-waking and morning systolic BP.	Bedtime	Kuroda, Kario et al. 2004
	Captopril + Hydrochlorothiazide	20 hypertensive patients	Morning dose resulted in reduced daytime BP, and an evening dose reduced evening BP.	Morning intake controls morning BP; Evening intake controls evening BP	Middeke et al., 1991
α-Adrenoceptor Antagonists	Doxazosin	Clinical trial; 111 patients with mild hypertension	Slightly reduced the 24-h systolic BP and diastolic BP ratio, having no significant effect in asleep BP; evening, dose of these drugs had a significant 24-h SBP and DBP-lowering effect throughout the entire day, with the greatest effects on early morning BP.	Evening	Pickering, Levenstein et al. 1994
	Doxazosin GITS	91 subjects: 49 men and 42 women with grade 1–2 essential hypertension	24 h mean BP reduction was larger and statistically significant (6.9 and 5.9 mm for systolic and diastolic BP, respectively, in monotherapy; 5.3 and 4.5 mm Hg in polytherapy) when doxazosin GITS was scheduled at bedtime. This BP-lowering effect was similar during both the day and nighttime hours. Doxazosin GITS ingested daily on awakening failed to provide full 24h therapeutic coverage	Evening	Hermida, Calvo et al. 2004
β-adrenoceptor antagonists	Propranolol	4 subjects	No circadian variation in the maximum decrease in HR, but the time to peak effect dependeded on time intake. Circadian variation in sympathetic tone and vascular reactivity is mainly responsible	No difference	Langner and Lemmer 1988

DRUG CLASS	DRUG(S)	STUDY DESIGN; POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
			for the circadian changes in the effects of propranolol.		
	Nebivolol	Hypertensive patients with a non-dipper BP profile	Either morning or evening administration, had significant BP-lowering effects throughout the day, with more marked effects on the awake BP mean. However, morning administration had a greater attenuation of the nocturnal BP decline, which effectively increased the number of non-dipper patients.	Morning	Hermida, Calvo et al. 2006
		19–76 y/o with mild to moderate hypertension	Morning and evening were equally effective but evening administration had greater anti-hypertensive effects on prewaking BP.	Equally effective; evening had added benefits	Acelejado et al., 2012
Angiotensin II Receptor Blockers	Valsartan	Patients with essential hypertension	1600mg at night was more effective at reducing nocturnal BP than when taken during the morning.	Night	Hermida, Calvo et al. 2003, Hermida, Calvo et al. 2005, Hermida, Calvo et al. 2005
		Non-sleepy (at nighttime) hypertensives w/ obstructive sleep apnea	Evening dose better controls BP; there are differential BP patterns between am and pm	Evening	Kasiakogias, Tsioufis et al. 2015; Reviewed in Bowles, Thosar et al. 2018
	Olmesartan	40 Patients: 23 Females 17 Males	Night-time to create dipper phenotype	Evening	Hermida, Ayala et al. 2009, Tofe Povedano and Garcia De La Villa 2009
	Candesartan		Evening doses were more effective at reducing the risk of microalbuminuria compared to morning dosing.	Evening	Kario, Hoshide et al. 2010
Diuretics	Torsemide	Randomized control study; 113 grade 1 and 2 hypertensive patients, 51.7+/–10.6 yrs of age	A 5 mg dose at bedtime, but not upon awakening, was effective at reducing the 24h-SBP:DBP, and providing complete 24-h BP coverage.	Bedtime	(Hermida et al., 2008)
Combination Therapies	Hydrochlothiazide + Valsartan		Greatest ambulatory BP control when taken in the evening, compared to the morning.	Evening	Hermida, Ayala et al. 2011
	Hydrochlothiazide + Amlodipine		Greater control of BP across the day when taken in the evening compared to the morning.	Evening	Hermida, Ayala et al. 2010, Zeng, Jia et al. 2011
		Hypertensives with chronic kidney disease	Evening anti-hypertensive dosing was more effective than morning dosing for controlling nocturnal BP and lowering the percentage of non-dipper BP patterns.	Evening	Crespo, Pineiro et al. 2013, Wang, Ye et al. 2017
		Hypertensive African Americans	No beneficial effects of evening dosing over morning dosing were reported.	No difference	Rahman, Greene et al. 2013

Table 2.

Clinical trials and studies considering time of day in the treatment of endocrine disorders.

DRUG CLASS	DRUG(S)	POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
Adrenal Insufficiency (AI) and Congenital Adrenal Hyperplasia (CAH)					
Glucocorticosteroid	Hydrocortisone	2 AIH + 2 CAG patients	24-hour infusion regimen of HC that mimics circadian rhythms of cortisol levels can restore circulating cortisol rhythms, restore levels of ACTH, and reduce levels of plasma 17-OHP.	24-h	Merza, Rostami-Hodjegan et al. 2006
		AI patients	24-h sub-cutaneous HC administration on restoring cortisol, ACTH, and 17-OH rhythms as well as increasing nocturnal growth hormone and insulin growth factor levels in AI patients	24-h	Lovas and Husebye 2007; Bjornsdottir, Oksnes et al. 2015
Type I Diabetes Mellitus					
Hormone - Insulin Analogue	Insulin	Open, randomized, cross-over design; 14 patients who experience evening hypoglycemia	Nighttime subcuntaneous continuous injections seem to be more effective at hypoglycemic control.	Continous nighttime	Kanc, Janssen et al. 1998
	Insulin Ultratard	9 Patients	No significant difference in blood glucose levels at any point.	No difference	Edsberg, Dejgaard et al. 1987
		Pediatric patients	Continuous subcutaneous injections of insulin glargine reduced HbA1C levels and controlled pre-meal glucose levels better than multiple daily injections	Continuous	Doyle, Weinzimer et al. 2004
	Insulin Glargine	292 Patients	Similar improvements were seen in morning, evening, or split dose groups. Split dosing results in weight gain.	No difference	Garg, Gottlieb et al. 2004
		Patients whose HbA1C and glycemic levels were not controlled by single injections	Split dosing was effective.	Split dosing	Albright, Desmond et al. 2004
		18 Patients with poorly managed T1DM	Transitioning from evening to morning administration, independent of dose, resulted in more favorable glucose control and lipid profile without affecting body weight.	Morning	Gradiser, Bilic-Curcic et al. 2015
	Insulin Glargine + Lispro		HbA1C levels and 24-hour glycemic control did not differ among groups administring insulin glargine in the morning, evening, or bedtime in conjunction with prandial insulin lispro; morning administration resulted in fewer nocturnal hypoglcemic episodes	No differences; morning had added benefits	Hamann, Matthaei et al. 2003

DRUG CLASS	DRUG(S)	POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
	Lispro	Randomized, cross-over study. 23 patients	Administration of insulin glargine at lunch, dinner, or bedtime resulted in hypoglycemia at distinct timepoints after each injection; the night-time hyperglycemia after bedtime glargine injections was avoided with lunch or dinner injection schedules		Ashwell, Gebbie et al. 2006
		13 Patients	More effective at evening and nocturnal glycemic control when the bedtime dose is greater than mealtime doses; Lower mealtime and higher bedtime doses might be most effective at evening glycemic control.	Low mealtime, higher bedtime	Ahmed, Mallias et al. 1998
	Detemir + Aspart		Combination therapy at mealtime provided equally effective glycemic control when administered as a morning/dinner or a morning/ bedtime dose; however both regimens provided better glycemic control with no weight gain when compared to NPH morning/evening insulin regimen.		Pieber, Draeger et al. 2005
Octapeptides	Octreotide	8 T1DM patients who experience evening hypoglycemia: 4 Females 4 Males	Continuous subcuntaneous night injection is more effective at reducing hyperglycemia and growth hormone levels than single injections across the night.	Continous nighttime	Lunetta, Di Mauro et al. 1998
Type 2 Diabetes Mellitus					
Hormone	Insulin	100 Patients	Higher morning:evening ratio seems to have greater safety and efficacy.	Higher morning:evening	Jung, Park et al. 2014
		143 Patients	For twice-daily doses of insulin, a higher morning:evening ratio might be more effective at managing glycemic levels.	Higher morning:evening	Lee, Lee et al. 2012,
	Insulin Glargine + Glimepiride	624 patients	Single daily dose was equally effective at glycemic control when given in the morning or evening.	No difference	Standl, Maxeiner et al. 2006
	Insulin Glargine	10 Patients	Total insulin activity is similar between morning/ evening doses. However, evening administration controls nocturnal EGP, lipolysis, and glucagon concentration more consistently, whereas morning administration has greater protection against nocturnal hypoglycemia.	No difference	Porcellati, Lucidi et al. 2015
Incretin Mimetics	Lixisenatide	680 T2DM patients with inadequate control of glucose levels by metformin	Morning and evening injections similarly improve glucose control.	No difference	Ahren, Leguizamo Dimas et al. 2013
Meglitinide - Antidiabetic	Repaglinide	19 T2DM patients	Mealtime dosing is more effective than morning/ evening split dose.	Mealtime	Schmitz, Lund et al. 2002
Dipeptidyl Peptidase-4 Inhibitor	Vildagliptin	48 Patients	Morning and evening dosing were equally effective at post-prandial	No difference, but evening has additional benefits	He, Valencia et al. 2010

DRUG CLASS	DRUG(S)	POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
			and 24-h glucose control; however an evening dose was effective at reducing fasting plasma glucose.		
Gestational Diabetes Mellitus					
Hormone	Insulin	274 Females w/ Gestational Diabetes 118 Females with Pregestational Diabetes	Insulin administered four times daily is more effective at glycemic control than twice daily. 30 mins before each meal and before bedtime.	Four times/day	Nachum, Ben-Shlomo et al. 1999
		480 Females, >30 weeks pregnant.	Four times daily. 30 mins before each meal, and before bed-time.	Four times/day	Saleem, Godman et al. 2016
Hypothyroidism					
Thyroid hormone	Levothyroxine	50 Patients	Morning dose is more effective, but if evening dose is necessary for compliance, evening dose is acceptable.	Morning, before mealtime	Ala, Akha et al. 2015
		12 Females	Bedtime administration seems to improve thyroid hormone levels and reduced TSH levels.	Bedtime	Bolk, Visser et al. 2007, Banerjee, Hossain et al. 2018
		105 Patients	Bedtime administration improved thyroid hormone levels.	Bedtime	Bolk, Visser et al. 2010
		152 Patients	Morning and evening doses are equally effective	No difference	Rajput, Chatterjee et al. 2011
		163 Children: 125 Females 38 Males	No difference between bedtime and morning treatments.	No difference	Akin 2018
		Older adults	Clinical trial currently underway	TBD	Giassi, Piccoli et al. 2019
Fat-soluble vitamin	Vitamin D3	13 Patients: 5 Females, 8 Males with secondary hyperparathyroidism in end-stage renal failure.	Evening dose is more effective at managing hyperparathyroidism in patients with renal osteodystrophy.	Evening	Tsuruoka, Wakaumi et al. 2003
Osteoporosis					
Mineral	Calcium	14 patients	Calcium-supplemented meals did not affect the levels of bone resorption or the circadian patterns of resorption in comparison to evening-only supplements	No difference	Aerssens, Declerck et al. 1999
		26 early-menopausal females	Split morning:evening dose of 500:1000 mg (Tot. 1500mg)	Higher evening:morning	Scopacasa, Need et al. 2002
		19 post-menopausal females	Single evening 1000 mg dose only suppressed bone resorption during the night.	Split morning/ evening	Scopacasa, Horowitz et al. 1998
		19 Females	Split dosing improved daytime bone resorption but not nighttime resorption.	Split morning/ evening	Scopacasa F, Need AG, Horowitz M, Wishart JM, Morris HA and Nordin BE (2000) Inhibition of bone

DRUG CLASS	DRUG(S)	POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
					resorption by divided-dose calcium supplementation in early postmenopausal women. *Calcif Tissue Int* **67**:440–442.
		30 Females 21–34 y	Split, morning, or 4 x daily doses showed no difference on bone resorption across the day, However parathyroid hormones were differently affected based on the size and timing of calcium dose, Need for longitudinal studies.	No difference	Kärkkäinen MU, Lamberg-Allardt CJ, Ahonen S and Välimäki M (2001) Does it make a difference how and when you take your calcium? The acute effects of calcium on calcium and bone metabolism. *Am J Clin Nutr* **74**:335–342.
Estrogen receptor modulator	Raloxifene	39 Post-menopausal females	The only difference between morning/evening dose was the increase of plasminogen activator inhibitor (PAI)-1 with morning administration. Authors recommend evening administration.	Evening	Ando, Otoda et al. 2013
Parathyroid Hormone	Teriparatide	50 Females, post-menopausal	Morning administration resulted in increase in lumbar spine BMD.	Morning	Michalska, Luchavova et al. 2012
	Etidronate	retrospective longitudinal study	Dosing was similarly effective when taken as single doses across the day if the patient adhered to a 2 h fast before and after dosing	No difference	Cook, Blake et al. 2000
Cathepsin K Inhibitor	ONO-5334	14 Females; single-blind crossover study	Morning dose is more effective at reducing bone resorption than evening dose.	Morning	Eastell, Dijk et al. 2016
Hormone	Salmon Calcitonin	9 Females, Post-Menopausal	Both 0800 h and 2100 h administration are effective with no obvious advantage to either. 0800 h versus 2100 h treatment transiently reduced bone resorption but did not effectively alter the circadian pattern of bone resorption.	No difference	Schlemmer, Ravn et al. 1997
		81 Females between 40–70 y/o	Pre-dinner (1700 h) administration resulted in the greatest reduction in bone resorption, when compared to 0800 h or 2200 h administration.	Evening	Karsdal, Byrjalsen et al. 2008
Growth Hormone Deficiency					
Hormones	Growth Hormone		Evening administration of GH was more effective at restoration of normal hormone and metabolite circadian patterns.	Evening	Jorgensen, Moller et al. 1990

DRUG CLASS	DRUG(S)	POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
		8 adult patients	Compared to one dose at 1900 h, split dosing at 1900 h (2/3 dose) and 0800 h (1/3 dose), better matched normal physiological GH profile, increased serum IGF-1, and decreased serum IGFBP-1 while lowering non-esterified fatty acids.	Split dose at 0800 h, 1900 h	Laursen, Jorgensen et al. 1994
		34 children	No differences between morning, afternoon or evening administration, in growth, IGF-1, or GH-BP after 6 or 12 months of GH treatment	No difference	Zadik, Lieberman et al. 1993
Glucocorticoid	Prednisolone	8 Patients: 4 Females 4 Males	Morning administration attenuates nocturnal growth hormone suppression, therefore potentially attenuating stunted growth.	Morning	Wolthers, Ramshanker et al. 2017
Turner Syndrome					
Hormone	Estradiol	9 girls with Turner Syndrome receiving GH injections	Estradiol was more effective at managing insulin, glucagon, IGF-1 levels when administered in the evening compared to morning, but further studies are needed.	Evening	Naeraa, Gravholt et al. 2001
Other Endocrine Treatments					
Hormone Therapy	Cyclo-Progynova Therapy	62 patients	No obvious difference in efficacy of morning/evening treatment.	No difference	Pongsatha, Chainual et al. 2005
Artifical Hormones	Hydrocortisone	6 females	Morning and evening administration is equally effective.	No difference	Kiriwat and Fotherby 1983

Table 3.

Clinical trials and studies considering time of day in the treatment of disorders involving the immune system.

DRUG CLASS	DRUG(S)	STUDY DESIGN; POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
Rheumatoid Arthritis					
Glucocorticoids	Prednisolone	41 patients	Bedtime dose (between 2200 –2300 h) significantly reduced morning stiffness as compared to morning (0700 h) dose.	Bedtime (between 2200 –2300 h)	De Silva, Binder et al. 1984
		85 women	Mean pain score based from the disease activity score 28, duration of morning stiffness, and erythrocyte sedimentation rate were decreased when administered at (2200 h) compared to (0800 h)	Night (2200 h)	Gul H 2017
	Prednisone Modified Release (PMR) v. Prednisone Rapid Release (PRR)	288 patients	PMR significantly reduced morning pain intensity and duration, DAS28, and plasma IL-6 levels, compared to PRR in the morning.	Evening	Buttgereit, Doering et al. 2008, Buttgereit, Doering et al. 2010
DMARDS	Methotrexate	Prospective, single-arm study; 17 patients	Methotrexate dosing from morning to bedtime led to significant improvements in both DAS28 and modified health questionnaire (MHAQ) scores in a cohort of RA patients	Bedtime, 3x/wk	To, Yoshimatsu et al. 2011
Osteoarthritis					
NSAIDs (Aspirin)	Flurbiprofen	Double-blind crossover study; 17 patients	Twice-daily dosing regimens that included an evening dose were more effective in reducing RA symptoms and increasing grip strength.	2x/daily with an evening dose	Kowanko, Pownall et al. 1981
	Indomethacin	Double-blind crossover study in 66 patients with osteoarthritis	Evening administration (2000 h) reduced morning pain and reported the fewest undesirable effects and that worsening afternoon or evening pain was best relieved by administration in morning (0800 h) or afternoon (1200 h).	Evening	Levi, Le Louarn et al. 1985
	Ketoprofen	double-blind randomized trial in 117 osteoarthritis patients	Evening dosing (2000 h) caused longer duration of analgesia with fewer adverse effects when compared to morning dosing (0800 h).	Evening	Perpoint, Mismetti et al. 1994
Multiple Sclerosis					
Cytokines	IFN-β1	16 patients with relapsing/remitting MS	On day 1 of treatment, morning injection resulted in higher plasma IL-10; evening injection caused an earlier and more robust peak in cortisol, increased soluble tumor necrosis factor receptor 1 & 2 (sTNF-R), and increased plasma IL-1, which was associated with more intense negative side effects; after 6 months of IFN-β therapy, elevated sTNF-R1 in the morning	Inconclusive	Kumpfel, Schwan et al. 2007

DRUG CLASS	DRUG(S)	STUDY DESIGN; POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
			group was the only difference reported.		
	IFN-β	105 patients	Switching from evening to morning injections of IFN-β qualitatively improved flu-like symptoms (58%) and sleep quality (48%), common side effects from INF-β delivery	Morning	Nadjar, Coutelas et al. 2011
	IFN-β1a	Randomized controlled parallel-group trial in 200 patients with relapsing MS	Morning administration reported more intense flu-like symptoms at weeks 4 & 8; by week 12 there were no differences in symptoms between groups. No reported effects of time-of-day on dosing, sleep quality, fatigue severity, or circulating leptin, resistin, and adiponectin after 12 weeks of therapy.	No differences	Patti, Zimatore et al. 2020
Glucocorticoid	Methylprednisolone	17 patients	Night (2200 – 0200 h) administration vs. day (1000 – 1400 h) was reported to reduce serum MMP-9 and adverse events, including symptoms such as insomnia, depression, headaches, restlessness, gastrointestinal symptoms, palpitations	Night (2200 – 0200 h)	Glass-Marmor, Paperna et al. 2007
Asthma treatments					
Glucocorticoids	Triamcinolone	30 patients	Equally effective when administered as a single 800 μg dose at 1500 h when compared to 200 μg 4x/day. Authors suggest 1x/d dose should increase compliance of steroid use,	1x/d at 1730 h or 4x/d	Pincus, Szefler et al. 1995
		59 subjects	Equally effective administered as a single dose at 1730 h or 4x/d, but a single dose at 0800 h was less beneficial in comparison to the other dosing regimens.	Afternoon (1500 –1730 h)	Pincus, Humeston et al. 1997
	Mometasone Furoate	Open-label, randomized, parallel-group study; 1537 subjects with mild to moderate asthma	No difference between morning or evening administration on subjective symptoms.	No difference	Zetterstrom, Dahl et al. 2008
	Fluticasone Fluroate	Randomized double-blind clinical trial; 28 patients	No difference between morning or evening administration on subjective symptoms.	No difference	Kempsford, Bal et al. 2016
Glucocorticoids + β-agonist	Fluticasone Furoate + β-agonist Vilanterol	Randomized, double-blind crossover clinical trial; 26 subjects	No difference between morning or evening administration on subjective symptoms.	No difference	Kempsford, Oliver et al. 2013
	Bambuterol	Double-blind, randomized, placebo-controlled, crossover study; 29 patients	Reduced symptoms at either 0700 h or 2200 h; evening administration produced the most improvement in morning forced expiratory volume.	Evening	D'Alonzo, Smolensky et al. 1995
Nonselective phosphodisterase enzyme inhibitor	Sustained release theophylline	25 adult patients	Once (2000 h) or twice (0800 & 2000 h) daily doses had similar improvement in airflow. Single evening dose significantly	Similar improvements; evening dose had	D'Alonzo, Smolensky et al. 1990

DRUG CLASS	DRUG(S)	STUDY DESIGN; POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
			improved peak expiratory flow rate and forced expiratory volume between 0200 h and 0600 h.	additional benefits.	
	Extended release theophilline	Double-blind crossover study; 8 pediatric patients	Treatment irrespective of dosing time resulted in comparable enhancement of the group24-hr mean, minimum and maximum values of airways patency with reference to placebo baselines. However, dosing at 1500 or 2100 h, resulted in the best effect on the airways as assessed by the 24-hr mean forced expiratory volume.	Evening (1500 h) or Night (2100 h)	Smolensky, Scott et al. 1987
Allergic Rhinitis					
H1 Histamine Antagonist	Mequitazine	Multicenter	Dinner-time dosing was more effective at controlling morning peak and 24-h symptoms, as compared to breakfast dosing.	Dinner-time	Reinberg, Gervais et al. 1985
	Desloratadine	randomized study in 663 adult AR patients	No difference in morning vs evening administration.	No difference	Haye, Hoye et al. 2005
	Cetirizine	two multicenter, randomized, double-blind, parallel-group studies	Morning and evening administration was equally effective at symptom relief in seasonal AR.	No difference	Urdaneta, Patel et al. 2018
Nasal Decongestants	Pseudoephedrine	Randomized, double-blind, crossover study in 9 male athletes	Morning (0700 h) but not afternoon (1700 h) supra-therapeutic dose boosted muscle contraction velocity in squat exercises.	Morning (0700 h)	Pallares, Lopez-Samanes et al. 2015
Cystic Fibrosis					
Antibiotic	Tobramycin	Randomized trial in 18 children	Morning (0800 h) compared to evening (2000 h) administration showed no differences in pharmokinetics due to time of day, however urinary KIM-1 (kidney injury molecule) was higher in the 2000 h group, indicating greater potential for kidney damage with evening dosing	Morning due to evening side effects	Prayle, Jain et al. 2016
		25 adult CF patients	No differences in pharmacokinetics due to time of day, but the evening group (2200 h) had increased serum blood urea nitrogen compared to the morning (0800 h) group	Morning due to evening side effects	van Maarseveen, van der Meer et al. 2020
Eczema / Psoriasis					
Corticosteroids	Betamethasone		Maximal therapeutic effects achieved on healthy skin with a late afternoon application.	Late afternoon	Pershing, Corlett et al. 1994
			Evening application was more effective than morning application; however, its effects were attenuated after 5 nights of application.	Evening	Nguyen, Lacour et al. 2017
Vaccines					

DRUG CLASS	DRUG(S)	STUDY DESIGN; POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
Vaccines	Influenza and Hepatitis A		Morning vaccinations produce enhanced antibody responses compared to those given in the afternoon.	Morning	Phillips, Gallagher et al. 2008, Kirby 2016, Long, Drayson et al. 2016

Table 4.

Clinical trials and studies considering time of day in the treatment of metabolic disorders.

DRUG CLASS	DRUG(S)	STUDY DESIGN; POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
Statins: Management of Blood Cholesterol					
Statins	Simvastatin Immediate Release (IR)	Double-blind, placebo-controlled study; 172 patients	Evening administration had a significantly higher reduction of plasma [LDL-C] compared to morning administration.	Evening	Saito, Yoshida et al. 1991
		Adults receiving either 10 or 20 mg of IR Simvastatin	Switching adults from an evening to a morning dose resulted in a 10% increase in LDL-C levels, suggesting that taking IR simvastatin during the evening is most effective.	Evening	Wallace, Chinn et al. 2003
	Simvastatin Continuous Release (CR)	Prospective, randomized, double-blind, multicenter, placebo-controlled Phase III study; 132 patients with hypercholesterolemia	Morning compared to evening reported no differential effects on reduction of LDL-C.	No difference	Kim, Kim et al. 2013
		Prospective, multicenter, double-blind, Phase IV trial with an active comparator. 122 patients with chronic kidney disease and dyslipidemia	There were no differences reported between morning versus evening administration.	No difference	Yi, Kim et al. 2014
	Fluvastatin Extended Release (ER)		Equally effective in reducing LDL when administered in the morning or evening. Authors suggest that morning administration is expected to increase patient compliance.	No difference	Scharnagl, Vogel et al. 2006
	Lovastatin		These studies had limitations either from confounding factors, failure to reach concrete conclusions, failure to reach statistical significance, or lacking in diversity among the populations studied, which ultimately limits their ability to be extrapolated. (Reviewed in (Plakogiannis and Cohen 2007, Awad and Banach 2018)		Illingworth et al., 1986
	Pravastatin				Hunninghake, Mellies et al. 1990
	Atorvastatin				Cilla, Gibson et al. 1996, Plakogiannis, Cohen et al. 2005
	Rosuvastatin				Martin, Mitchell et al. 2002
Glaucoma					
Prostaglandin Analogs	Travapost	Randomized crossover study; 30 patients; age > 18	No difference between morning and evening administration.	No difference	Ford, Gooi et al. 2013
Prostaglandin Analogs + Beta Blocker	Fixed combination of travoprost and timolol	prospective randomized crossover comparison study in 32 patients	Evening dosing provided better 24-h pressure control and lower peak IOP when compared to morning dosing.	Evening	Konstas, Tsironi et al. 2009
Prostaglandin Analogs + Beta Blocker	Preservative-free tafluprost/ timolol	placebo-controlled crossover trial in 42 patients	Evening dosing provided greater reductions in IOP and 24-h IOP fluctuation when compared to morning dosing.	Evening	Konstas, Katsanos et al. 2018

Table 5.

Clinical trials and studies considering time of day in the treatment of cancer.

DRUG(S)	CANCER TYPE	STUDY DESIGN; POPULATION	STUDY CONCLUSIONS	SUGGESTED TIME OF DAY	CITATION
Chemotherapeutics					
Doxorubicin (DOX) + Cisplatin (CDDP)	Ovarian Cancer	31 patients with advanced ovarian cancer	DOX treatment at O600 h followed by CDDP treatment 1800 h, compared to DOX treatment at 1600 h followed by CDDP treatment at 0600 h, had fewer dose reductions, treatment delays, and treatment complications.	DOX at 0600 h + CDDP at 1800 h	Hrushesky 1985
		Patients with advanced ovarian cancer	0600 h DOX treatment with 1600 h CDDP treatment is advantageous in reducing adverse side effects; this study demonstrated that this treatment schedule increased the 5 year survival rate from 11% to 44%.	DOX at 0600 h + CDDP at 1800 h	Hrushesky and Bjarnason 1993
4'–0-tetrahydropyranyl doxorubicin (THP) + Cisplatin (CDDP)		Randomized phase II trial; 31 patients with advanced ovarian cancer	Patients receiving a THP intravenous bolus at 0600 h followed by a 4-hour infusion of CDDP at 1600 h, had less neutropenia, thrombocytopenia, anemia, and renal toxicity relative to patients beginning THP treatment at 1800 h, followed by CDDP at 0400 h.	THP at 0600 h + CDDP at 1600 h	Levi, Benavides et al. 1990
Cisplatin (CDDP)	Advanced non-small cell lung cancer	Patients with advanced non-small cell lung cancer	Evening treatment caused less adverse effects such as leucopenia, neutropenia, and gastrointestinal toxicity relative to a morning treatment group.	Evening	Li, Chen et al. 2015
Etoposide + Cisplatin	Advanced lung cancer, mixture of solid tumors, or metastatic cancer	advanced lung cancer, mixture of solid tumors, or metastatic cancer	Morning (0600 h or 0700 h) etoposide and evening CDDP (1800 h) treatment demonstrated less adverse hematological toxicities relative to patients receiving etoposide at 1800 h and CDDP at 0600 h.	Etopside at 0600 or 0700 h + CDDP at 1800 h	Krakowski, Levi et al. 1988, Krakowski, Levi et al. 1988, Focan 1995
Floxuridine (FUDR)	Advanced Metastatic Cancer	54 patients with advanced metastatic cancer	Patients receiving chronomodulated variable rate infusions had less frequent and less severe diarrhea, nausea, and vomiting. Additionally, patients receiving variable rate infusions increased their maximally tolerated dose by 45%.	Chronomodulated variable rate infusions	von Roemeling and Hrushesky 1989
Oxaliplatin (1-OHP) + 5-Fluorouracil (5-FU) and Folinic Acid	Metastatic Colorectal Cancer	92 patients with metastatic colorectal cancer	Chronomodulated variable rate infusions of chemotherapeutics demonstrated five times less severe stomatitis, the dose limiting adverse effect of 5-FU, an increased in the maximal tolerated dose of 5-FU, and an increase in median survival (19 months vs 14.9)	Chronomodulated variable rate infusions	Levi, Zidani et al. 1994

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			relative to constant rate infusions.		
5-FU and 1-OHP		Randomised multicentre trial; 186 patients with untreated metastases from colorectal cancer	Patients receiving chronomodulated variable rate infusions had five time less severe mucosal toxicity and half as much peripheral neuropathy. However, median survival and three year survival were unchanged relative to constant rate infusion.	Chronomodulated variable rate infusions	Levi, Zidani et al. 1997
5-FU and cisplatin (CDDP)			Less adverse effects with chronomodulated variable rate infusions.	Chronomodulated variable rate infusions	Levi, Tubiana-Mathieu et al. 2004
5-FU			Failed to demonstrate beneficial effects of chronomodulated variable rate infusions.	No differences	Price, Ross et al. 2004, Garufi, Vanni et al. 2006, Ramanathan, Bjarnason et al. 2008, Huang, Yu et al. 2017
5-FU			Chronomodulation only demonstrated favorable effects on males.		Giacchetti, Bjarnason et al. 2006, Levi, Innominato et al. 2009, Giacchetti, Dugue et al. 2012
Docetaxel (DOC)	Advanced Nasopharyngeal Carcinoma		Chronomodulated variable rate infusions of chemotherapeutics resulted in less adverse effects.	Chronomodulated variable rate infusions	Bi, Jin et al. 2015, Mao 2015, Liao 2016, Gou, Jin et al. 2018, Wan 2018, Zhang, Jin et al. 2018
Cisplatin (CDDP)					
5-FU + radiotherapy			Improved cellular immune numbers in virtually all clinical trials.		
5-FU without radiotherapy					
6-Mercaptopurine and Methotrexate	Childhood Acute Lymphoblastic Leukemia		Evening administration of 6-mercaptopurine and methotrexate increased disease-free survival and reduced the risk of relapse by 2.5 times.	Evening	Rivard, Infante-Rivard et al. 1993
		Phase II clinical trial;	Similar effects of increased event free survival from evening consumption.	Evening	Schmiegelow, Glomstein et al. 1997
Capecitabine	Advanced Colorectal cancer		Chronomodulated asymmetrical dose did not significantly reduce toxicity or improve efficacy.		Qvortrup, Jensen et al. 2010
Radiotherapeutics					
Radiotherapy	Breast Cancer	Retrospective study of 878 patients	Examining adverse effects following radiotherapy, the authors conclude that patients receiving radiotherapy in the afternoon (i.e. after 1200) had less adverse reactions.	Afternoon (after 1200 h)	Johnson, Chang-Claude et al. 2019
Radiotherapy			Afternoon (after 1500 h) timed radiotherapy was associated with higher incidences of	Morning	Noh, Choi et al. 2014)

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			adverse skin reactions relative to morning-timed.		
Radiotherapy	Cervical cancer		Inconsistent results in adverse effects.	Inconclusive	Shukla, Gupta et al. 2010, Chang, Li et al. 2016
Radiotherapy	Head and Neck Carcinoma or Squamous Cell Carcinoma of Oral Cavity/Pharynx/Larynx		No significant differences in adverse effects.	No differences	Bjarnason, Mackenzie et al. 2009, Goyal, Shukla et al. 2009
Radiotherapy	Advanced Rectal Cancer		Afternoon-timed radiotherapy was associated with a higher incidence of complete or moderate pathological response and improved nodal downstaging in advanced rectal cancer.	Afternoon	Squire, Buchanan et al. 2017
Radiotherapy	Brain Metastases		Increased overall survival in patients receiving radiotherapy in the morning (before 1200 h).	Morning (before 1200 h)	Rahn, Ray et al. 2011, Badiyan, Ferraro et al. 2013
Radiotherapy			No difference between morning and afternoon groups.	No differences	Kabolizadeh, Wegner et al. 2011, Chan, Rowbottom et al. 2016
Sunitinib			No differences in adverse events or overall survival.	No differences	Escudier, Roigas et al. 2009, George, Blay et al. 2009