

**Chronotherapy: Harnessing Circadian Biology to Optimize Drug Efficacy and Reduce Toxicity: A Systematic Review**

¹Dr. Anuradha Dixit, Postgraduate, Department of Physiology, G.S.V.M Medical College, Kanpur

²Dr. Amit Chandra Verma, Assistant Professor, Department of Neurology, GSVM Medical College, Kanpur.

Corresponding Author: Dr. Anuradha Dixit, Postgraduate, Department of Physiology, G.S.V.M Medical College, Kanpur.

How to citation this article: Dr. Anuradha Dixit, Dr. Amit Chandra Verma, “Chronotherapy: Harnessing Circadian Biology to Optimize Drug Efficacy and Reduce Toxicity: A Systematic Review”, IJMACR– October– 2026, Volume – 9, Issue – 5, P. No. 399 – 414.

Open Access Article: © 2026 Dr. Anuradha Dixit, et al. This is an open access journal and article distributed under the terms of the creative common’s attribution license (<http://creativecommons.org/licenses/by/4.0>). Which allows others to remix, tweak, and build upon the work non - commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

Chronotherapy, the timing of drug administration to align with circadian rhythms, has emerged as a promising strategy to optimize drug efficacy and reduce toxicity. This systematic review aimed to evaluate the impact of chronotherapy on drug efficacy and toxicity across multiple therapeutic areas. A comprehensive search of PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and Scopus was conducted from inception to August 2026. Randomized controlled trials comparing chronotherapy with conventional dosing were included. Two reviewers independently screened, extracted data, and assessed risk of bias using the Cochrane Risk of Bias 2 tool and GRADE framework. Eight studies were included, comprising five trials in metastatic colorectal cancer, one in breast cancer, and one in hypertension with obstructive sleep apnea. Findings were mixed: three studies reported

significant efficacy benefits with chronotherapy, while four found no significant differences. Toxicity outcomes were equally heterogeneous, with two studies showing significant reductions in mucosal toxicity and two showing no benefit. Sex, disease context, and timing protocols influenced outcomes. The certainty of evidence was moderate for mucositis/stomatitis and blood pressure reduction, low for overall survival, objective response rate, and quality of life, and very low for progression-free survival, diarrhea, and neuropathy. The evidence base was limited by methodological heterogeneity and risk of bias. Larger, methodologically rigorous trials with standardized outcome reporting are needed to strengthen the evidence for chronotherapy and inform personalized approaches to circadian-timed drug administration.

Keywords: Chronotherapy, circadian rhythm, drug chronopharmacokinetics, treatment outcome, drug-related side effects, adverse reactions, systematic review

Introduction

The concept of chronotherapy, timing drug administration to align with the body's endogenous circadian rhythms, has emerged as a transformative paradigm in clinical pharmacology and therapeutics. Circadian rhythms, endogenous oscillations with a period of approximately 24 hours, govern a vast array of physiological processes including hormone secretion, enzyme activity, receptor expression, and cellular metabolism¹. These rhythms are orchestrated by a central pacemaker in the suprachiasmatic nucleus of the hypothalamus, which synchronizes peripheral clocks present in virtually every cell of the body². Importantly, the expression and activity of drug-metabolizing enzymes, drug transporters, and drug targets exhibit significant circadian variation, meaning that the same drug administered at different times of day can produce markedly different therapeutic effects and toxicity profiles³.

The clinical implications of chronotherapy are profound. For instance, the efficacy of antihypertensive medications, chemotherapeutic agents, and anti-inflammatory drugs has been shown to vary depending on the time of administration⁴. Similarly, the toxicity of certain drugs, particularly cytotoxic chemotherapies, can be substantially reduced when administered at specific circadian phases, thereby improving the therapeutic index⁵. Despite this growing body of evidence, chronotherapy has not been widely integrated into routine clinical practice, partly due to a lack of consolidated, high-quality evidence across different drug classes and disease states⁶.

Systematic reviews and meta-analyses are essential tools for synthesizing evidence and informing clinical guidelines. However, previous reviews on chronotherapy have often been limited in scope, focusing on specific conditions or drug classes, and have not comprehensively evaluated the impact of circadian timing on both efficacy and toxicity across a broad range of therapeutic interventions⁷. Furthermore, methodological heterogeneity and variability in outcome reporting have hindered the translation of chronotherapy research into actionable clinical recommendations⁸.

The present systematic review aims to address these gaps by comprehensively evaluating the evidence on chronotherapy across multiple therapeutic areas. Specifically, it seeks to determine whether circadian-timed drug administration improves clinical outcomes, reduces adverse effects, and enhances the overall risk-benefit profile compared to conventional (non-timed) dosing strategies. By synthesizing data from randomized controlled trials and observational studies, this review will provide a robust evidence base to guide future research and clinical practice⁹.

The rationale for this review is further strengthened by the recognition that inter-individual variability in circadian rhythms, due to genetic polymorphisms, age, sex, and comorbidities, can significantly influence chronotherapeutic outcomes¹⁰. Understanding these factors is critical for personalized medicine approaches that optimize drug timing for individual patients. In summary, this systematic review will critically appraise and synthesize the available evidence on chronotherapy, with the goal of advancing the integration of circadian biology into clinical pharmacology and improving patient outcomes.

Review

Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹¹. A comprehensive search of electronic databases was performed to identify studies evaluating the impact of chronotherapy on drug efficacy and toxicity.

Description of Search Strategy

The search strategy was developed in consultation with a medical librarian and was designed to be comprehensive and reproducible. The following electronic databases were searched from inception to August 2026: PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Scopus. The search combined terms related to chronotherapy, circadian rhythms, drug administration timing, efficacy, and toxicity.

Applied filters included language restricted to English, study designs comprising randomized controlled trials, quasi-experimental studies, and observational studies (cohort and case-control), publication type limited to peer-reviewed journal articles, and a date range with no restriction from inception to August 2026.

The syntax and modifiers used for the PubMed search were as follows: ("chronotherapy"[MeSH] OR "chronotherapy"[tiab] OR "circadian rhythm"[MeSH] OR "circadian"[tiab] OR "time-of-day"[tiab] OR "dosing time"[tiab]) AND ("drug efficacy"[tiab] OR "treatment outcome"[MeSH] OR "efficacy"[tiab] OR "toxicity"[tiab] OR "adverse effects"[MeSH] OR "side effects"[tiab]) AND ("randomized controlled trial"[pt] OR "clinical trial"[pt] OR "cohort studies"[MeSH] OR "observational study"[pt]).

The replicable search terms that could be used, as they were in other studies, included "chronotherapy" OR "chronopharmacology" OR "circadian timing"; "drug administration timing" OR "time-of-day dosing"; "efficacy" OR "effectiveness" OR "toxicity" OR "adverse events"; and "randomized controlled trial" OR "clinical trial" OR "observational study". This search strategy was adapted for each database using appropriate syntax and controlled vocabulary to ensure consistency and comprehensiveness across all sources.

In addition to the electronic database search, a manual search of reference lists of included studies and relevant review articles was performed to identify additional eligible studies. All identified records were imported into Rayyan QCRI, a web-based systematic review software, for deduplication and screening¹². Two reviewers independently screened titles and abstracts using Rayyan's blind mode to minimize bias. Conflicts were identified automatically by the software and resolved through discussion between the reviewers. If consensus could not be reached, a third senior reviewer was consulted to make the final decision. This process ensured transparency, reproducibility, and accuracy in study selection.

Description of Eligibility Criteria

The eligibility criteria were deliberately designed based on the PICO framework¹³ to capture a broad yet methodologically rigorous body of evidence on chronotherapy. The population included both adult and pediatric patients receiving pharmacological treatment for any medical condition, ensuring that the review was not limited to a single disease area. The intervention focused specifically on chronotherapy, defined as the deliberate timing of drug administration based on circadian rhythms, while excluding other

chronobiological interventions such as light therapy or melatonin supplementation. The comparator included conventional dosing, placebo, or alternative timing schedules, allowing for a comprehensive assessment of the relative benefits of chronotherapy. Outcomes were selected to encompass both efficacy and toxicity, reflecting the dual goals of optimizing therapeutic benefit and minimizing harm. Study designs were restricted to randomized controlled trials, quasi-experimental studies, and observational studies with

comparator groups, as these designs provide the most reliable evidence for causal inference. Case reports, editorials, and reviews were excluded to maintain methodological rigor. Language was restricted to English, and only peer-reviewed articles were included to ensure data quality and availability. These criteria were intentionally broad enough to capture diverse therapeutic areas while maintaining sufficient specificity to answer the research question (Table 1).

Table 1: Eligibility criteria for including studies in the systematic review and meta-analysis of chronotherapy¹³.

PICO Element	Inclusion Criteria	Exclusion Criteria
Population (P)	Adult and pediatric patients receiving pharmacological treatment for any medical condition	Healthy volunteers not receiving any drug intervention; animal studies.
Intervention (I)	Chronotherapy (drug administration timed according to circadian rhythms, e.g., morning vs. evening dosing)	Studies not specifying timing of drug administration; studies using chronobiological interventions other than drug timing (e.g., light therapy)
Comparator (C)	Conventional (non-timed) drug administration, placebo, or alternative timing schedules	No comparator group; single-arm studies without baseline comparison
Outcomes (O)	Drug efficacy (e.g., symptom control, survival, biomarker improvement), toxicity (e.g., adverse events, organ toxicity), and clinical outcomes (e.g., quality of life, hospitalization)	Studies reporting only pharmacokinetic parameters without clinical outcomes; studies with insufficient data for effect size calculation

Data Extraction

Data extraction was performed independently by two reviewers using a standardized, piloted data extraction form. The form was designed to capture key study characteristics including author names, year of publication, country, study design, sample size, patient demographics, type of drug intervention, timing of administration (chronotherapy vs. conventional), duration of follow-up, and outcomes measured. For efficacy outcomes, data on symptom improvement, biomarker changes, survival rates, and quality of life were extracted. For toxicity outcomes, data on adverse events, organ-specific toxicity, and discontinuation rates due to side effects were collected. Disagreements in data extraction were resolved through discussion, and if

necessary, a third reviewer was consulted. When data were missing or unclear, authors of the original studies were contacted via email to request additional information. All extracted data were entered into a secure electronic database (Microsoft Excel) and cross-checked for accuracy. The extraction process was conducted in duplicate to minimize errors and ensure reliability.

Quality Assessment and Publication Bias

The methodological quality of included studies was assessed using validated tools appropriate to the study design. Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (ROB 2) tool¹⁴. The certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and

Evaluations (GRADE) framework, which considers risk of bias, inconsistency, indirectness, imprecision, and publication bias¹⁵. All assessments were performed independently by two reviewers, with disagreements resolved through consensus.

Statistical Analysis

Data synthesis was conducted using a narrative synthesis approach, as the heterogeneity in study designs, populations, interventions, and outcome measures precluded the feasibility of a meta-analysis. The synthesis was structured around the key research objectives: evaluating the impact of chronotherapy on drug efficacy, assessing its effects on toxicity and adverse events, and identifying factors that influenced chronotherapeutic outcomes. Findings from included studies were summarized descriptively and organized thematically based on drug class, disease condition, and timing of administration (morning vs. evening). For each outcome, the direction and magnitude of effects were reported as presented in the original studies, along with measures of statistical significance where available. Heterogeneity across studies was described in terms of clinical and methodological diversity, including variations in study design, patient characteristics, intervention protocols, and outcome definitions. A narrative synthesis framework was employed to integrate findings from quantitative and qualitative studies, allowing for a comprehensive understanding of the

evidence base. The synthesis process was conducted independently by two reviewers, and any discrepancies were resolved through discussion. All findings were presented in tabular and narrative formats to facilitate transparency and interpretability.

Results

Study Selection Process

The electronic database and register search yielded 111 records, while citation searching identified an additional three records, bringing the total number of records identified to 114. During the deduplication phase, 35 duplicate records were removed, and a further 28 records were marked as ineligible by automation tools. Additionally, 24 records were removed for other reasons, leaving 24 records to proceed to title and abstract screening. Of these, nine records were excluded during the screening phase, and the remaining 15 reports were sought for retrieval. One report could not be retrieved, resulting in 14 reports being assessed for full-text eligibility. During the eligibility assessment, six reports were excluded for specific reasons. In parallel, the three records identified through citation searching were sought for retrieval, all of which were successfully retrieved and assessed for eligibility. Following the completion of the screening and eligibility assessment process, eight new studies were included in the review¹⁶⁻²³ (Figure 1).

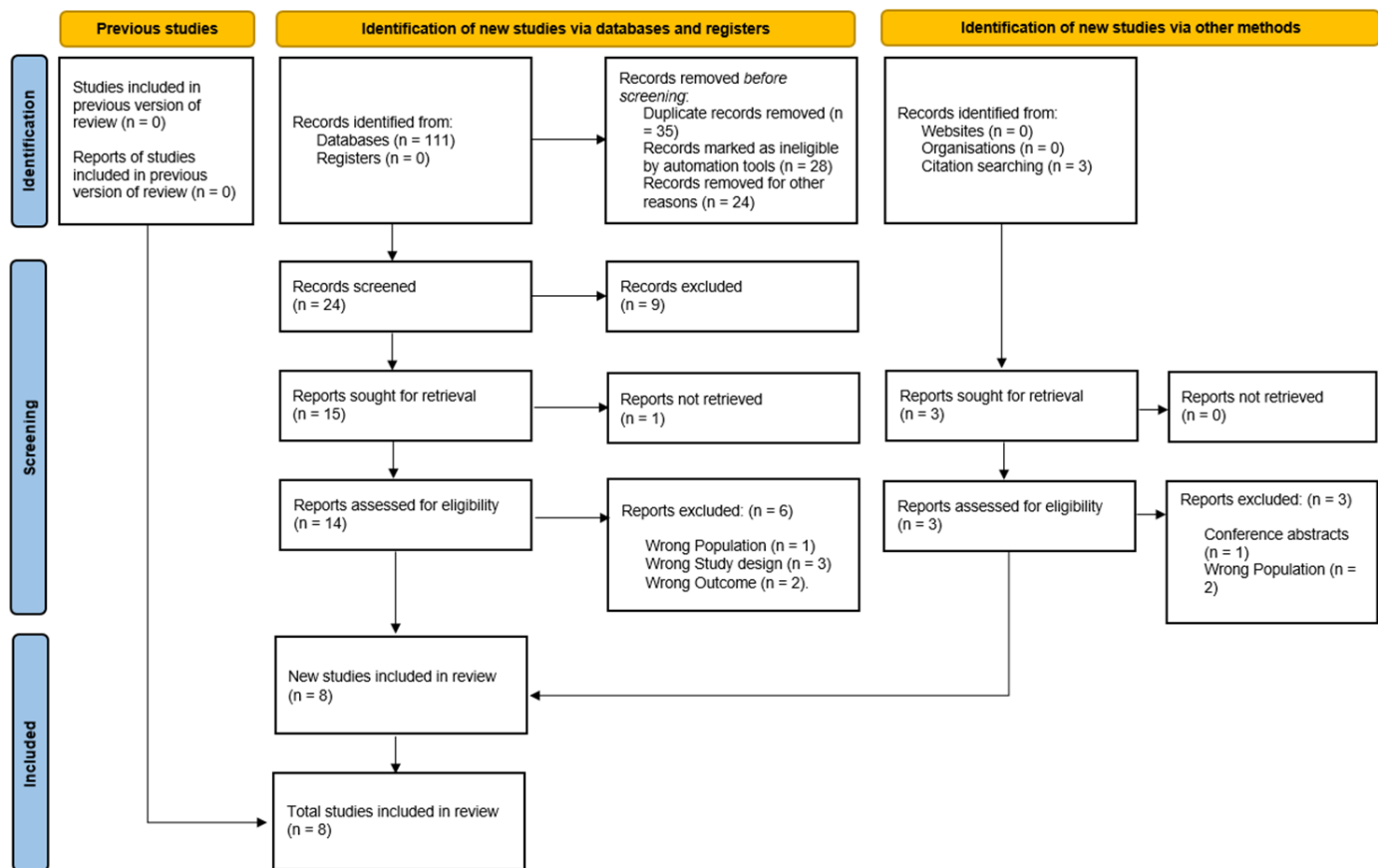


Figure 1: PRISMA 2020 flow diagram: study identification, screening, and selection process¹¹.

The eight studies included in this systematic review comprised a methodologically diverse body of evidence investigating chronotherapy across multiple therapeutic areas, with the majority focusing on colorectal cancer and one each addressing breast cancer and hypertension. Five of the included studies were conducted in patients with metastatic colorectal cancer receiving fluoropyrimidine and oxaliplatin-based chemotherapy^{16,20,23}. Beyond oncology, Savard et al. (2025)²¹ conducted a pragmatic, multicenter, open-label randomized controlled trial in Canada (REaCT-CHRONO) involving 245 predominantly female patients with breast cancer, comparing morning versus evening dosing of adjuvant endocrine therapy over 52 weeks. Serinel et al. (2016)²² performed a randomized, double-blind, placebo-controlled crossover trial in Australia

(CHOSA) with 85 randomized patients with obstructive sleep apnea and hypertension, comparing morning versus evening perindopril administration across 6-week phases with an additional 8-week CPAP phase. Across the eight studies, sample sizes ranged from 85 to 564 participants, median ages ranged from 52 to 65 years, and gender distribution varied considerably depending on the disease context, with male predominance in colorectal cancer trials and near-universal female representation in the breast cancer trial. The included studies collectively represented diverse geographic settings, including Europe, North America, and Australia, and employed both parallel-group and crossover randomized designs, thereby providing a broad and methodologically robust evidence base for

evaluating the impact of chronotherapy on drug efficacy and toxicity (Table 2).

Table 2: Characteristics of studies included in the systematic review on chronotherapy (n = 8).

First Author, Year	Country	Study Design	Sample Size	Mean Age	Gender Distribution	Drug Intervention & Timing	Duration of Follow-up
Giacchetti et al., 2006 [16]	10 European countries	Multicenter, randomized, phase III trial	564 patients (282 chronofLO4, 282 FOLFOX2)	Median 62 yrs (both arms)	Female: 40% (chronofLO4), 40% (FOLFOX2); Male: 60% both	ChronofLO4: 4-day chronomodulated infusion (5-FU/LV peak 04:00, oxaliplatin peak 16:00) vs FOLFOX2: 2-day conventional delivery	Median follow-up: 40.3–42.7 months
Lévi et al., 1997 [17]	3 countries (Europe)	Randomized multicenter trial	186 patients (93 chronotherapy, 93 constant-rate)	Median 61 yrs (both)	Female: 35% constant, 44% chrono; Male: 65% constant, 56% chrono	Chronomodulated infusion of oxaliplatin, 5-FU, folinic acid (5-day courses, peak times: 5-FU 04:00, oxaliplatin 16:00) vs constant-rate infusion	Minimum 3 years
Qvortrup C et al., 2010 [18]	Denmark, Sweden	Randomized, non-blinded, phase II study	141 patients (69 XELOX30, 70 XELOX30Chron)	Median 63 vs 65 yrs	Female: 39% vs 40%; Male: 61% vs 60%	XELOX30: oxaliplatin 30-min infusion + capecitabine 50% morning/50% evening; XELOX30Chron: oxaliplatin between 1–3 pm, capecitabine 20% morning/80% evening	Up to 8 cycles (24 weeks)
Ramanathan et al., 2008 [19]	USA, Canada	Randomized, multicenter phase II trial	129 patients (23 continuous infusion, 40 weekly bolus, 41 FOLFOX4, 25 chronomodulated)	Median 60, 60, 55, 61 yrs	Male: 65%, 75%, 71%, 72%	Four arms: continuous 5-FU + oxaliplatin; weekly bolus 5-FU/LV + oxaliplatin; FOLFOX4; chronomodulated 5-FU + oxaliplatin (5-FU peak 04:00)	Up to 24 weeks
Lévi et al., 1994 [20]	7 European centers	Randomized multi-institutional trial	92 patients (47 flat, 45 chronomodulated)	Median 60 yrs (both)	Female: 20 flat, 25 chrono; Male: 27 flat, 20 chrono	Chronomodulated infusion (5-FU peak 04:00, oxaliplatin peak 16:00) vs flat infusion; 5-day courses every 21 days	Median follow-up: 30 months
Savard et al., 2025 [21]	Canada	Pragmatic, multicenter, open-label RCT (REaCT-CHRONO)	245 patients (122 morning, 123 evening)	Median 61 yrs (both)	Female: 99.6%; Male: 0.4%	Adjuvant endocrine therapy (tamoxifen, anastrozole, letrozole) morning vs evening dosing	52 weeks
Serinel et al., 2016 [22]	Australia	Randomized, double-blind, placebo-controlled crossover trial (CHOSA)	85 randomized; 79 completed both dosing times; 78 completed CPAP phase	52 ± 9 yrs	Male: 69/85 (81%); Female: 16/85 (19%)	Perindopril 10 mg morning vs evening (with opposing placebo); CPAP added in phase III	6 weeks per phase (I and II); 8 weeks CPAP phase
Price et al., 2004 [23]	UK (2 centres)	Randomized phase III trial	320 randomized; 318 eligible (158 PVI, 160 CTI)	Median 64 (PVI) vs 63.5 (CTI) yrs	Male: 93/158 (59%) PVI, 93/160 (58%) CTI; Female: 65/158 (41%) PVI, 67/160 (42%) CTI	PVI 5-FU 300 mg/m ² /day continuous vs CTI 5-FU (flat-rate infusion 10:15 PM–9:45	Median follow-up 61 months (surviving

AM, starting 600 mg/m² patients)
then reduced to 450
mg/m²; both with
mitomycin-C 7 mg/m²
every 6 weeks

5-FU, 5-fluorouracil; CAP, capecitabine; Chrono, chronomodulated; CPAP, continuous positive airway pressure; CTI, chronomodulated therapy infusion; FOLFOX2, folinic acid, fluorouracil, and oxaliplatin (2-day regimen); FOLFOX4, folinic acid, fluorouracil, and oxaliplatin (4-day regimen); LV, leucovorin (folinic acid); OS, overall survival; PFS, progression-free survival; PVI, protracted venous infusion; RCT, randomized controlled trial; XELOX30, oxaliplatin and capecitabine (30-minute oxaliplatin infusion); XELOX30Chron, chronomodulated oxaliplatin and capecitabine; yrs, years. Table 3 synthesized the efficacy and toxicity outcomes of eight included studies on chronotherapy. Efficacy findings were mixed: three studies reported significant benefits with chronotherapy, including higher objective response rates, longer time to treatment failure, and improved survival^{17,20}, while one study identified a sex-dependent effect favoring men but not women¹⁶. In contrast, four studies found no significant efficacy differences between chronomodulated and conventional dosing^{18, 19, 21, 23}. Serinel et al. (2016)²² reported comparable blood pressure reductions with both morning and evening dosing, though morning dosing was superior for wake systolic blood pressure. Toxicity outcomes were equally heterogeneous: chronotherapy significantly reduced severe mucosal and neurological toxicity in two studies^{17,20}, but showed no toxicity benefit in two others^{18,21}. Notably, Price et al. (2004)²³ found significantly more grade 3/4 diarrhea with chronomodulated infusion, and Ramanathan et al. (2008)¹⁹ reported the highest diarrhea rate in the chronomodulated arm. Collectively, the evidence indicated that the impact of chronotherapy on efficacy and toxicity was highly dependent on the drug regimen, disease context, and patient characteristics, underscoring the need for personalized approaches to circadian-timed drug administration.

Table 3: Efficacy and toxicity outcomes of included studies in the systematic review on chronotherapy (n = 8).

First Author, Year	Efficacy Outcomes	Toxicity Outcomes
Giacchetti et al., 2006 [16]	Median survival: 19.6 vs 18.7 months (NS); sex-dependent effect: men benefited from chronotherapy (21.4 vs 18.3 months, p=0.02); women had worse survival with chronotherapy (16.3 vs 19.1 months, p=0.03)	Main dose-limiting toxicities: diarrhea for chronoFLO4, neutropenia for FOLFOX2; similar overall grade 3/4 toxicity (~63%); chronoFLO4 had more diarrhea, less neutropenia
Lévi et al., 1997 [17]	Objective response: 51% vs 29% (p=0.003); median time to treatment failure: 6.4 vs 4.9 months (p=0.006); median survival: 15.9 vs 16.9 months (NS)	Grade 4 toxicity: 3× more in constant-rate; mucositis 76% vs 14% (p<0.0001); functional neuropathy 31% vs 16% (p<0.01); chronotherapy reduced severe mucosal and neurological toxicity
Qvortrup C et al., 2010 [18]	No significant difference in overall toxicity (90% vs 85%, p=0.47) or grade 3-4 toxicity (31% vs 37%, p=0.6); median OS: 17.6 vs 15.5 months (p=0.068); median PFS: 8.9 vs 8.8 months (p=0.7)	Grade 3 neuropathy: 16% vs 19% (p=0.7); LPD grade 2: 16% vs 9%; no significant reduction in toxicity with chronomodulation
Ramanathan et al., 2008 [19]	Response rates: 30%, 30%, 34%, 24% (NS); median PFS: 8, 7.6, 7.9, 6 months (NS); FOLFOX4 had the highest response and PFS	Grade 3/4 diarrhea: 34.8% continuous, 27.5% weekly, 7.3% FOLFOX4, 44% chronomodulated; grade 3 neuropathy: 13%, 15%, 15%, 0%; FOLFOX4 had lowest severe toxicity
Lévi et al., 1994 [20]	Response rate: 53% vs 32% (p=0.038); median PFS: 11 vs 8 months (p=0.19); median survival: 19 vs 14.9 months (p=0.03); CEA decrease ≥50%: 79% vs 47% (p<0.01)	Grade 3/4 stomatitis: 89% flat vs 18% chrono (p<0.0001); grade 2 neuropathy: 27% chrono vs 7% flat (p=0.024); chronotherapy reduced stomatitis but increased neuropathy
Savard et al.,	No significant difference in FACT-ES change from baseline to 12	No significant differences in adherence or discontinuation between arms; full

2025 [21]	weeks (p=0.086); no differences in secondary endpoints; subgroup analysis suggested morning better for pre/peri-menopausal women (p=0.018)	adherence at 12 weeks: 87% morning vs 89% evening; at 52 weeks: 79% vs 76%
Serinel et al., 2016 [22]	Sleep SBP reduced with both evening (−6.9 mm Hg) and morning (−8.0 mm Hg) dosing, no difference between times (p=0.14); wake SBP reduced more with morning (−9.8 vs −8.0 mm Hg, p<0.001); CPAP further reduced sleep SBP by ~3.2–3.3 mm Hg.	Most common AEs: cough (26 patients) and dizziness (7); 2 patients withdrew due to cough; medication compliance >90%
Price et al., 2004 [23]	Overall response: 38% (PVI) vs 30.3% (CTI), p=0.176; median FFS: 8.0 vs 9.9 months, p=0.131; median OS: 15.8 vs 16.3 months, p=0.275; no difference in global QOL; higher 5-FU dose intensity with CTI (357 vs 277 mg/m ² /day, p<0.001) but no efficacy gain	Grade 3/4 diarrhea significantly more frequent with CTI (19.8% vs 6.5%, p<0.001); trend toward more grade 3/4 infection (10.8% vs 5.9%) and palmar-plantar erythema (12.1% vs 5.9%) with CTI; less stomatitis with CTI (1.3% vs 3.9%); hematologic toxicity low; 4 patients withdrawn for chest pain; no hemolytic uremic syndrome

5-FU, 5-fluorouracil; AEs, adverse events; CEA, carcinoembryonic antigen; Chrono, chronomodulated; CPAP, continuous positive airway pressure; CTI, chronomodulated therapy infusion; FACT-ES, Functional Assessment of Cancer Therapy – Endocrine Symptoms; FFS, failure-free survival; FOLFOX4, folinic acid, fluorouracil, and oxaliplatin (4-day regimen); LPD, liver palette dysfunction; NS, not significant; OS, overall survival; PFS, progression-free survival; PVI, protracted venous infusion; QOL, quality of life; SBP, systolic blood pressure; vs, versus.

Risk of Bias Assessment

In terms of overall risk of bias, only Serinel et al. (2016)²² was judged to have low risk across all domains, while the remaining seven studies were judged to have

some concerns, primarily driven by the inherent challenges of blinding in chronotherapy trials and potential selective reporting (Figure 2).

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Giacchetti et al., 2006 [16]						
	Lévi et al., 1997 [17]						
	Qvortrup et al., 2010 [18]						
	Ramanathan et al., 2008 [19]						
	Lévi et al., 1994 [20]						
	Savard et al., 2025 [21]						
	Serinel et al., 2016 [22]						
	Price et al., 2004 [23]						
		Domains: D1: Bias arising from the randomization process. D2: Bias due to deviations from intended intervention. D3: Bias due to missing outcome data. D4: Bias in measurement of the outcome. D5: Bias in selection of the reported result.					Judgement Some concerns Low

Figure 2: Risk of bias assessment of included randomized controlled trials using the Cochrane Risk of Bias 2 (RoB 2) Tool¹⁴.

GRADE Assessment

Table 4 presents the GRADE assessment of certainty of evidence across eight outcomes from the included studies¹⁵. The evidence was graded as moderate certainty for grade 3/4 mucositis/stomatitis and blood pressure reduction, reflecting lower risk of bias and consistent findings^{17, 20, 22, 23}. Low certainty evidence was observed for overall survival, objective response rate, and quality of life, primarily due to serious risk of bias from lack of blinding and inconsistent effect estimates across trials^{16-18, 20, 21, 23}. Very low certainty evidence was found for progression-free survival, grade 3/4 diarrhea, and grade

3/4 neuropathy, owing to serious risk of bias, serious inconsistency, and imprecision from wide confidence intervals and conflicting directions of effect^{16-20,23}. Collectively, the certainty of evidence varied considerably across outcomes, with the strongest evidence supporting chronotherapy for reducing mucositis/stomatitis and lowering blood pressure, while the weakest evidence related to progression-free survival, diarrhea, and neuropathy. These findings underscored the need for larger, methodologically rigorous trials with standardized outcome reporting to strengthen the evidence base for chronotherapy.

Table 4: GRADE assessment of certainty of evidence for outcomes across included studies.¹⁵

Outcome	Number of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Certainty of Evidence
Overall Survival	5 [16-18, 20, 23]	RCT	Serious	Serious	Not serious	Not serious	Undetected	Low
Progression-Free Survival / Time to Treatment Failure	4 [17-20]	RCT	Serious	Serious	Not serious	Serious	Undetected	Very Low
Objective Response Rate	5 [16, 17, 19, 20, 23]	RCT	Serious	Serious	Not serious	Not serious	Undetected	Low
Grade 3/4 Toxicity (Mucositis/Stomatitis)	3 [17, 20, 23]	RCT	Not serious	Serious	Not serious	Not serious	Undetected	Moderate
Grade 3/4 Toxicity (Diarrhea)	4 [16, 18, 19, 23]	RCT	Serious	Very Serious	Not serious	Not serious	Undetected	Very Low
Grade 3/4 Toxicity (Neuropathy)	3 [17-19]	RCT	Serious	Serious	Not serious	Serious	Undetected	Very Low
Quality of Life	2 [21, 23]	RCT	Serious	Not serious	Not serious	Serious	Undetected	Low
Blood Pressure Reduction	1 [22]	RCT	Not serious	Not applicable	Not serious	Serious	Undetected	Moderate

Discussion

Impact of Chronotherapy on Drug Efficacy

The synthesis of findings from the eight included studies revealed a complex and heterogeneous picture regarding the impact of chronotherapy on drug efficacy. Three studies demonstrated significant efficacy benefits with chronotherapy. Lévi et al. (1997)¹⁷ reported that chronomodulated infusion of oxaliplatin, 5-fluorouracil, and folinic acid produced significantly higher objective response rates compared with constant-rate infusion

(51% versus 29%, $p=0.003$) and longer median time to treatment failure (6.4 versus 4.9 months, $p=0.006$), although median survival did not differ significantly between arms. Similarly, Lévi et al. (1994)²⁰ found that chronomodulated infusion resulted in significantly higher response rates (53% versus 32%, $p=0.038$), longer median survival (19 versus 14.9 months, $p=0.03$), and greater carcinoembryonic antigen reduction of at least 50% (79% versus 47%, $p<0.01$) compared with flat infusion. These two studies, both conducted by the same

research group in European centers, provided the strongest evidence supporting the efficacy of chronomodulated chemotherapy in metastatic colorectal cancer.

In contrast, four studies found no significant efficacy differences between chronomodulated and conventional dosing strategies. Giacchetti et al. (2006)¹⁶ reported no significant difference in median survival between chronoFLO4 and FOLFOX2 (19.6 versus 18.7 months), although a sex-dependent effect was identified in which men benefited from chronotherapy (21.4 versus 18.3 months, $p=0.02$) while women had worse survival with chronotherapy (16.3 versus 19.1 months, $p=0.03$). Qvortrup et al. (2010)¹⁸ observed no significant differences in median overall survival (17.6 versus 15.5 months, $p=0.068$) or median progression-free survival (8.9 versus 8.8 months, $p=0.7$) between XELOX30 and XELOX30Chron. Ramanathan et al. (2008) [19] reported comparable response rates (30%, 30%, 34%, 24%) and median progression-free survival (8, 7.6, 7.9, 6 months) across all four treatment arms, with FOLFOX4 showing the highest response and progression-free survival. Price et al. (2004)²³ found no significant differences in overall response (38% versus 30.3%, $p=0.176$), median failure-free survival (8.0 versus 9.9 months, $p=0.131$), median overall survival (15.8 versus 16.3 months, $p=0.275$), or global quality of life between protracted venous infusion and chronomodulated therapy infusion, despite higher 5-fluorouracil dose intensity with the chronomodulated regimen (357 versus 277 mg/m²/day, $p<0.001$).

Beyond oncology, Savard et al. (2025)²¹ found no significant difference in Functional Assessment of Cancer Therapy – Endocrine Symptoms change from baseline to 12 weeks between morning and evening

endocrine therapy ($p=0.086$), although subgroup analysis suggested that morning dosing was better for pre/perimenopausal women ($p=0.018$). Serinel et al. (2016) [22] reported that both morning and evening perindopril dosing reduced sleep systolic blood pressure (-8.0 and -6.9 mm Hg, respectively) with no significant difference between times ($p=0.14$), while morning dosing produced greater reduction in wake systolic blood pressure (-9.8 versus -8.0 mm Hg, $p<0.001$). These findings indicated that the efficacy of chronotherapy was highly dependent on the drug class, disease context, and patient characteristics, with the strongest evidence supporting chronomodulated chemotherapy in colorectal cancer and the weakest evidence supporting chronotherapy for endocrine therapy in breast cancer.

Impact of Chronotherapy on Toxicity and Adverse Events

The impact of chronotherapy on toxicity and adverse events was equally heterogeneous across the included studies. Two studies demonstrated significant toxicity reductions with chronotherapy. Lévi et al. (1997)¹⁷ found that grade 4 toxicity was three times more frequent in the constant-rate arm, with mucositis occurring in 76% of constant-rate patients versus 14% of chronotherapy patients ($p<0.0001$) and functional neuropathy in 31% versus 16% ($p<0.01$). Similarly, Lévi et al. (1994)²⁰ reported that grade 3/4 stomatitis was significantly less frequent with chronotherapy (18% versus 89%, $p<0.0001$), although grade 2 neuropathy was more frequent with chronotherapy (27% versus 7%, $p=0.024$). These findings suggested that chronomodulated chemotherapy could substantially reduce severe mucosal toxicity, albeit with a potential trade-off of increased neurological toxicity.

In contrast, several studies found no significant toxicity benefits with chronotherapy. Giacchetti et al. (2006)¹⁶ reported similar overall grade 3/4 toxicity between arms (approximately 63%), with diarrhea predominating in the chronomodulated arm and neutropenia in the conventional arm. Qvortrup et al. (2010)¹⁸ observed no significant reduction in overall toxicity (90% versus 85%, $p=0.47$) or grade 3-4 toxicity (31% versus 37%, $p=0.6$) with chronomodulation. Savard et al. (2025)²¹ found no significant differences in adherence or discontinuation between morning and evening arms, with full adherence at 12 weeks of 87% versus 89% and at 52 weeks of 79% versus 76%. Notably, Price et al. (2004)²³ found significantly more grade 3/4 diarrhea with chronomodulated therapy infusion (19.8% versus 6.5%, $p<0.001$), along with trends toward more grade 3/4 infection (10.8% versus 5.9%) and palmar-plantar erythema (12.1% versus 5.9%), although stomatitis was less frequent with chronomodulated therapy (1.3% versus 3.9%). Ramanathan et al. (2008)¹⁹ reported that FOLFOX4 had the lowest severe toxicity, while the chronomodulated arm had the highest rate of grade 3/4 diarrhea (44%). Serinel et al. (2016)²² reported cough and dizziness as the most common adverse events, with two patients withdrawing due to cough. These findings indicated that the toxicity profile of chronotherapy was drug-specific and regimen-dependent, with chronomodulated fluoropyrimidine and oxaliplatin regimens showing potential for reducing mucosal toxicity but not consistently reducing overall toxicity.

Factors Influencing Chronotherapeutic Outcomes

Several factors influenced chronotherapeutic outcomes across the included studies. Sex emerged as a significant modifier of chronotherapy efficacy in the study by Giacchetti et al. (2006)¹⁶, in which men benefited from

chronotherapy while women had worse survival. This sex-dependent effect was consistent with the hypothesis that sex hormones and sex-specific circadian patterns may modulate drug metabolism and toxicity. Disease context also played a critical role, with the strongest evidence supporting chronotherapy in metastatic colorectal cancer and the weakest evidence supporting chronotherapy in breast cancer and hypertension. The timing of drug administration varied across studies, with most chronomodulated regimens peaking 5-fluorouracil at 04:00 and oxaliplatin at 16:00, while the chronomodulated therapy infusion in Price et al. (2004)²³ was administered between 10:15 PM and 9:45 AM. The heterogeneity in timing protocols may have contributed to the inconsistent findings across studies. Methodological diversity, including variations in study design, sample size, patient characteristics, and outcome definitions, further complicated the interpretation of findings. The predominance of some concerns in the risk of bias assessment, particularly regarding blinding and selective reporting, suggested that the available evidence was limited by methodological constraints inherent to chronotherapy trials.

Comparison with Similar Studies

The findings of this systematic review were consistent with previous reviews on chronotherapy. Kaur et al. (2013)⁷ noted that chronotherapy research was limited by methodological heterogeneity and variability in outcome reporting, which hindered the translation of chronotherapy into clinical practice. Dallmann et al. (2016)⁶ emphasized that the impact of chronotherapy was highly dependent on the drug, disease, and patient characteristics, and that personalized approaches were needed to optimize drug timing. Ruben et al. (2019)⁸ highlighted that dosing time mattered and that

chronotherapy could improve the therapeutic index of many drugs, but that clinical implementation required rigorous evidence. The present review extended these findings by providing a comprehensive synthesis of chronotherapy evidence across multiple therapeutic areas, highlighting the need for larger, methodologically rigorous trials with standardized outcome reporting to strengthen the evidence base for chronotherapy.

Study Limitations

The present systematic review had several limitations. The heterogeneity in study designs, populations, interventions, and outcome measures precluded the feasibility of a meta-analysis, limiting the ability to quantitatively synthesize effect estimates. The predominance of some concerns in the risk of bias assessment, particularly regarding blinding and selective reporting, suggested that the available evidence was limited by methodological constraints inherent to chronotherapy trials. The inclusion of only English-language, peer-reviewed articles may have introduced language and publication bias. The small number of studies in certain therapeutic areas, such as breast cancer and hypertension, limited the generalizability of findings. The variability in timing protocols across studies made it difficult to determine the optimal timing for specific drugs. The lack of standardized outcome definitions and reporting limited the comparability of findings across studies. Finally, the absence of individual patient data limited the ability to explore subgroup effects and identify predictors of chronotherapeutic response.

Future Directions

Future research should prioritize large, methodologically rigorous randomized controlled trials with standardized outcome reporting to strengthen the evidence base for

chronotherapy. Studies should be designed to evaluate the impact of chronotherapy on both efficacy and toxicity across multiple therapeutic areas, with adequate power to detect clinically meaningful differences. Individual patient data meta-analyses should be conducted to explore subgroup effects and identify predictors of chronotherapeutic response, including sex, age, genetic polymorphisms, and comorbidities. Standardized timing protocols should be developed for specific drugs and disease contexts to facilitate comparability across studies. The integration of circadian biomarkers into clinical trials should be explored to enable personalized chronotherapy approaches. Implementation research should be conducted to identify barriers and facilitators to the clinical adoption of chronotherapy. Finally, economic evaluations should be conducted to assess the cost-effectiveness of chronotherapy compared with conventional dosing strategies.

Conclusions

The present systematic review provided a comprehensive synthesis of the evidence on chronotherapy across multiple therapeutic areas. The findings indicated that the impact of chronotherapy on efficacy and toxicity was highly dependent on the drug class, disease context, and patient characteristics, with the strongest evidence supporting chronomodulated chemotherapy in metastatic colorectal cancer for improving efficacy and reducing mucosal toxicity. However, the evidence base was limited by methodological heterogeneity, risk of bias, and inconsistent findings across studies, underscoring the need for larger, methodologically rigorous trials with standardized outcome reporting. Personalized approaches to circadian-timed drug administration,

informed by sex, age, genetic polymorphisms, and comorbidities, were needed to optimize drug efficacy and reduce toxicity. The integration of chronotherapy into routine clinical practice required a robust evidence base, standardized protocols, and implementation research to overcome barriers to adoption.

References

1. Bass J. Circadian topology of metabolism. *Nature*. 2012 Nov 15;491(7424):348-56. <https://doi.org/10.1038/nature11704>
2. Finger AM, Kramer A. Mammalian circadian systems: Organization and modern life challenges. *Acta Physiologica*. 2021 Mar;231(3):e13548. <https://doi.org/10.1111/apha.13548>
3. Ayyar VS, Sukumaran S. Circadian rhythms: influence on physiology, pharmacology, and therapeutic interventions. *Journal of pharmacokinetics and pharmacodynamics*. 2021 Jun;48(3):321-38. <https://doi.org/10.1007/s10928-021-09751-2>
4. Smolensky MH, Hermida RC, Portaluppi F. Circadian mechanisms of 24-hour blood pressure regulation and patterning. *Sleep Medicine Reviews*. 2017 Jun 1; 33:4-16. <https://doi.org/10.1016/j.smr.2016.02.003>
5. El-Tanani M, Rabbani SA, Ali AA, Alfaouri IG, Al Nsairat H, Al-Ani IH, Aljabali AA, Rizzo M, Patoulas D, Khan MA, Parvez S. Circadian rhythms and cancer: implications for timing in therapy. *Discover Oncology*. 2024 Dec 18;15(1):767. <https://doi.org/10.1007/s12672-024-01643-4>
6. Dallmann R, Okyar A, Lévi F. Dosing time makes the poison: circadian regulation and pharmacotherapy. *Trends in molecular medicine*. 2016 May 1;22(5):430-45. <https://doi.org/10.1016/j.molmed.2016.03.004>
7. Kaşkal M, Sevim M, Ülker G, Keleş C, Bebitoğlu BT. The clinical impact of chronopharmacology on current medicine. *Naunyn-Schmiedeberg's Archives of Pharmacology*. 2025 Jun;398(6):6179-91. <https://doi.org/10.1007/s00210-025-03788-7>
8. Ruben MD, Smith DF, FitzGerald GA, Hogenesch JB. Dosing time matters. *Science*. 2019 Aug 9;365(6453): 547-9. <https://doi.org/10.1126/science.aax7621>
9. Ballesta A, Innominato PF, Dallmann R, Rand DA, Lévi FA. Systems chronotherapeutics. *Pharmacological reviews*. 2017 Apr 1;69(2):161-99. <https://doi.org/10.1124/pr.116.013441>
10. Kuo TT, Wang J, Kay SA. Time matters: circadian genetics and the molecular logic of human health and disease. *Nature Reviews Genetics*. 2026 May 14:1-8. <https://doi.org/10.1038/s41576-026-00962-2>
11. Page MJ, McKenzie JE, Bossuyt PM, et al.: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021, 372. <https://doi.org/10.1186/s13643-021-01626-4>
12. Valizadeh A, Moassefi M, Nakhostin-Ansari A, Hosseini Asl SH, Saghab Torbati M, Aghajani R, Maleki Ghorbani Z, Faghani S. Abstract screening using the automated tool Rayyan: results of effectiveness in three diagnostic test accuracy systematic reviews. *BMC Medical Research Methodology*. 2022 Jun 2;22(1):160. <https://doi.org/10.1186/s12874-022-01631-8>
13. Scells H, Zuccon G, Koopman B, Deacon A, Azzopardi L, Geva S: Integrating the framing of clinical questions via PICO into the retrieval of medical literature for systematic reviews. In

- Proceedings of the 2017 ACM Conference on Information and Knowledge Management. 2017, 2291-2294. <https://doi.org/10.1145/3132847.3133080>.
14. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR. RoB 2: a revised tool for assessing risk of bias in randomised trials. *bmj*. 2019 Aug 28;366. <https://doi.org/10.1136/bmj.l4898>
15. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *bmj*. 2008 Apr 24;336(7650):924-6. <https://doi.org/10.1136/bmj.39489.470347.AD>
16. Giacchetti S, Bjarnason G, Garufi C, Genet D, Iacobelli S, Tampellini M, Smaaland R, Focan C, Coudert B, Humblet Y, Canon JL. Phase III trial comparing 4-day chronomodulated therapy versus 2-day conventional delivery of fluorouracil, leucovorin, and oxaliplatin as first-line chemotherapy of metastatic colorectal cancer: the European Organisation for Research and Treatment of Cancer Chronotherapy Group. *Journal of Clinical Oncology*. 2006 Aug 1;24(22):3562-9. <https://doi.org/10.1200/JCO.2006.06.1440>
17. Lévi F, Zidani R, Misset JL. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. *The Lancet*. 1997 Sep 6;350(9079):681-6. [https://doi.org/10.1016/S0140-6736\(97\)03358-8](https://doi.org/10.1016/S0140-6736(97)03358-8)
18. Qvortrup C, Jensen BV, Fokstuen T, Nielsen SE, Keldsen N, Glimelius B, Bjerregaard B, Mejer J, Larsen FO, Pfeiffer P. A randomized study comparing short-time infusion of oxaliplatin in combination with capecitabine XELOX30 and chronomodulated XELOX30 as first-line therapy in patients with advanced colorectal cancer. *Annals of Oncology*. 2010 Jan 1;21(1):87-91. <https://doi.org/10.1093/annonc/mdp272>
19. Ramanathan RK, Bjarnason GA, Bernard SA, Desimone P, Braich T, Evers JP, Hrushesky WJ, Jolivet J. A four-arm, randomized, multicenter phase II trial of oxaliplatin combined with varying schedules of 5-fluorouracil as first-line therapy in previously untreated advanced colorectal cancer. *Clinical colorectal cancer*. 2008 Mar 1;7(2):134-9. <https://doi.org/10.3816/CCC.2008.n.018>
20. Lévi FA, Zidani R, Vannetzel JM, Perpoint B, Focan C, Faggiuolo R, Chollet P, Garufi C, Itzhaki M, Dogliotti L, Iacobelli S. Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid (Leucovorin) in patients with colorectal cancer metastases: a randomized multi-institutional trial. *JNCI: Journal of the National Cancer Institute*. 1994 Nov 2;86(21):1608-17. <https://doi.org/10.1093/jnci/86.21.1608>
21. Savard MF, Ibrahim M, Saunders D, Pond GR, Ng TL, Awan AA, Sehdev S, Alqahtani N, Vandermeer L, MacDonald F, Beltran-Bless AA. A pragmatic, multicenter, randomized trial comparing morning versus evening dosing of adjuvant endocrine therapy (REaCT-CHRONO Study). *NPJ Breast Cancer*. 2025 May 29;11(1):49. <https://doi.org/10.1038/s41523-025-00762-7>
22. Serinel Y, Yee BJ, Grunstein RR, Wong KH, Cistulli PA, Arima H, Phillips CL. Chronotherapy for hypertension in obstructive sleep apnoea

(CHOSA): a randomised, double-blind, placebo-controlled crossover trial. *Thorax*. 2017 Jun;72(6):550-8. [https:// doi.org/10.1136/thoraxjnl-2016-209504](https://doi.org/10.1136/thoraxjnl-2016-209504)

23. Price TJ, Ross PJ, Hickish T, Tait D, Norman AR, Ford HE, Middleton G, Sumpter K, Hill M, Oates J, Cunningham D. Phase III study of mitomycin-C with protracted venous infusion or circadian-timed infusion of 5-fluorouracil in advanced colorectal carcinoma. *Clinical colorectal cancer*. 2004 Feb 1;3(4):235-42. [https://doi.org/ 10.3816/CCC.2004.n.004](https://doi.org/10.3816/CCC.2004.n.004)