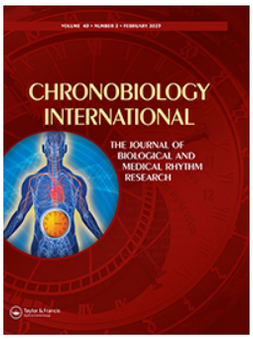

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REVIEW ARTICLE

Chronotherapy in dentistry: A scoping review

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ABSTRACT

The circadian clock modulates almost all vital aspects of our physiology and metabolism, including processes relevant to dentistry, such as healing, inflammation and nociception. Chronotherapy is an emerging field aiming to improve therapeutic efficacy and decrease adverse effects on health outcomes. This scoping review aimed to systematically map the evidence underpinning chronotherapy in dentistry and to identify gaps in knowledge. We conducted a systematic scoping search using four databases (Medline, Scopus, CINAHL and Embase). We identified 3908 target articles screened by two blinded reviewers, and only original animal and human studies investigating the chronotherapeutic use of drugs or interventions in dentistry were included. Of the 24 studies included, 19 were human studies and five were animal studies. Chrono-radiotherapy and chrono-chemotherapy reduced treatment side effects and improved therapeutic response, leading to higher survival rates in cancer patients. Animal studies reported that tooth movement and periodontal tissue response to orthodontic forces follow a diurnal rhythm that might influence bone metabolism. Profound and prolonged local anesthesia could be achieved when injected in the evening. Although the overall quality of the included studies was low, chronotherapy applications in dentistry seem to have favourable outcomes, especially in head and neck cancer treatments.

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Drug chronotherapy; circadian rhythm; oral health; chronobiology; dentistry

Introduction

In humans, circadian rhythms (~24 h) control all major organ systems, thus orchestrating nearly all vital aspects of our physiology and metabolism, including processes very important to dentistry, such as bone healing, the immune response, inflammation and nociception (Chen et al. 2020; Dallmann et al. 2014). These biological rhythms coordinate our brain with other tissues to perform distinct, likely inharmonious, functions pertinent to the day and night cycle, which in turn, strongly influence overall physical and mental health (Reppert and Weaver 2002). Indeed, a healthy robust circadian rhythm is crucial for overall well-being, and circadian clock dysregulation or misalignment has been considered a risk factor for many diseases, such as cancer, diabetes and neurodegeneration (Bass and Lazar 2016; Fu and Lee 2003; Hastings and Goedert 2013; Marcheva et al. 2010; Panda 2016; Parsons et al. 2015; Scheer et al. 2009; Shilts et al. 2018). The circadian rhythm is regulated by molecular pathways comprising several positive and negative transcription-translation feedback loops (TTFLs) that control the expression of clock-controlled genes (CCGs). These feedback loops, in turn, cause clock genes to oscillate for approximately 24 h cycles, consequently influencing behavioural and physiological processes (Battaglin et al. 2021). The core circadian elements involved in the circadian rhythms are circadian locomotor output cycles kaput (CLOCK), neuronal PAS domain protein (NPAS2), brain and muscle ARNT-like protein 1 (BMAL1), PERIOD (PER1, PER2 and PER3), CRYPTOCHROME (CRY1 and CRY2), retinoic acid-related orphan nuclear receptors (ROR) α/β/γ and REV-ERB α/β (Rahman et al. 2020).

The circadian clock controls the devolvement and haemostasis of oral and craniofacial structures (Adeola et al. 2019; Feng et al. 2022). Several circadian clock genes present in craniofacial tissues (e.g. oral mucosa, epithelium, teeth (enamel, dentine and pulp), periodontal ligaments and salivary glands) are involved in maintaining oral health (Adeola et al. 2019; Feng et al. 2022; Janjić and Agis 2019; Papagerakis et al. 2014). For instance, fibroblast cells of the human gingiva and

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periodontal ligaments express circadian core clock genes such as CLOCK, BMAL1, CRY1/2 and PER 1/2/3, suggesting their potential role in periodontal health and disease (Janjić et al. 2017). Furthermore, clock genes and proteins (BMAL1, CLOCK and PER1/2) are expressed in all major salivary glands (serous acini and duct cells) and were found to regulate salivary fluid secretions through the action of the water channel gene aquaporin-5 (Zheng et al. 2012). Moreover, circadian clock alterations (PER2 and BMAL1 knockouts in mice) may be linked to reduced saliva flow in Sjögren syndrome patients. Such key findings provide novel avenues for treating salivary gland disorders (Papagerakis et al. 2014). Clock genes (i.e. CLOCK, BMAL1 and PER1/2) are also expressed in dental tissues (up/down-regulated) at various embryonic stages of tooth development (Zheng et al. 2011) and could be downregulated in pathological dental conditions, such as deep caries (McLachlan et al. 2005).

Moreover, clock genes and their diurnal oscillations have been detected in the healthy oral mucosa (Zieker et al. 2010). For example, PER1, CRY1 and BMAL1 have different circadian expression peaks in the early morning, late afternoon and at night, respectively (Bjarnason et al. 2001). These rhythmic expressions also coincide with cell-cycle phases, that is, PER1 expression aligns with p53 (G1-phase marker), and BMAL1 aligns with cyclin β1 (M-phase marker), thereby suggesting their important role in oncogenesis (Bjarnason et al. 2001).

Chronotherapy is a therapeutic modality tailored to the body's circadian rhythms to improve medical intervention outcomes (Dallmann et al. 2016). Mainly, two therapeutic approaches to chronotherapy have been adapted (Cardinali et al. 2021). First, altering sleep/wake cycle rhythms using light therapy or sleep medications, thereby modifying sleep patterns to re-synchronized disrupted circadian rhythms (e.g. affective disorders) (Wirz-Justice and Benedetti 2020). Second, rescheduling interventions or restricting drug administration (Drug Chronotherapy) to the time of day that would be more effective with fewer adverse effects (Kaur et al. 2013). For example, the nighttime administration of anti-hypertensive drugs showed promising results in better controlling blood pressure (Bowles et al. 2018; Thoonkuzhy and Rahman 2020). Also, chronotherapy of commonly prescribed medications for allergic rhinitis and bronchial asthma, at a certain time of the day, yielded better therapeutic outcomes and/or fewer adverse effects (Smolensky et al. 2007). Likewise, chronotherapy shows a potential avenue to improve cancer survival by reducing toxicities of anti-cancer treatments (chemotherapy and radiotherapy), where therapeutic choices and doses are often limited due to the side effect severity (Lévi 2001; Ballesta et al. 2017; Shuboni-Mulligan et al. 2019). In addition, non-steroidal anti-inflammatory drugs (NSAIDs) chronotherapy may improve recovery from bone fracture in mice (Al-Waeli et al. 2020). Finally, it has been recently hypothesized that chronotherapy could be utilized to better manage severe COVID-19 complications, wherein anti-inflammatory drugs are administered in the afternoon targeting detrimental cytokines only (Tamimi et al. 2020).

Based on the above-mentioned observations, this scoping review aimed to systematically map the existing literature on chronotherapy in dentistry and identify gaps in knowledge. This type of review identifies, maps, collates and summarizes the literature to assist researchers in recognizing fundamental ideas, theories, evidence sources and gaps in knowledge in the field of interest (Arksey and O'Malley 2005; Grimshaw 2010). In contrast to systematic reviews, scoping reviews incorporate the "Big Picture" in the underlying literature rather than answering a narrowly defined specific question (Peters et al. 2015). In our case, we chose a scoping review methodology because oral health and dentistry are multidisciplinary fields and evidence thus far supporting chronotherapy is scarce. Also, chronotherapy is a broad field that includes altering sleep/wake cycle rhythms using light therapy or sleep medications and rescheduling interventions or restricting drug administration to a certain time of the day. Therefore, a scoping review is the best choice as it will help to formulate more specific questions than a systematic review can effectively address. Additionally, it will give us an overview of various applications of chronotherapy in a multidisciplinary field such as dentistry.

Methods

This scoping review was reported according to the Systematic Reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews guidelines (Tricco et al. 2018).

Protocol registration

This review protocol was registered (Abusamak et al. 2022) in the Figshare database (https://doi.org/10.6084/m9.figshare.20431683.v1, accessed on August 5th, 2022).

Identifying the research question

This scoping review aimed to systematically map the evidence underpinning chronotherapy in dentistry and

identify knowledge gaps. We formulated the following research question: "What is known from the literature about the application of chronotherapy in dentistry?"

Identifying relevant studies

A medical librarian trained on knowledge synthesis techniques (MM) conducted a systematic scoping search in the literature to identify candidate articles (Morris et al. 2016). A strategy for Ovid Medline was constructed using Medical Subject Headings (MeSH) and keywords and Boolean operators (AND/OR) to combine the concepts of dentistry/oral health, circadian rhythms and chronotherapy. This was then translated to Embase (Ovid), CINAHL and Scopus (Supplemental Table S1). Searches were carried out on June 30th, 2022. The language of articles was limited to English to match our team's expertise, while no restrictions were placed on publication year.

Study selection

A PRISMA extension for Scoping Reviews (Tricco et al. 2018) diagram outlining the article selection process is shown in Figure 1. Duplicates were removed using EndNote X9 citation management software (Philadelphia, PA, US). Candidate articles were then independently screened for title/abstract, and then full

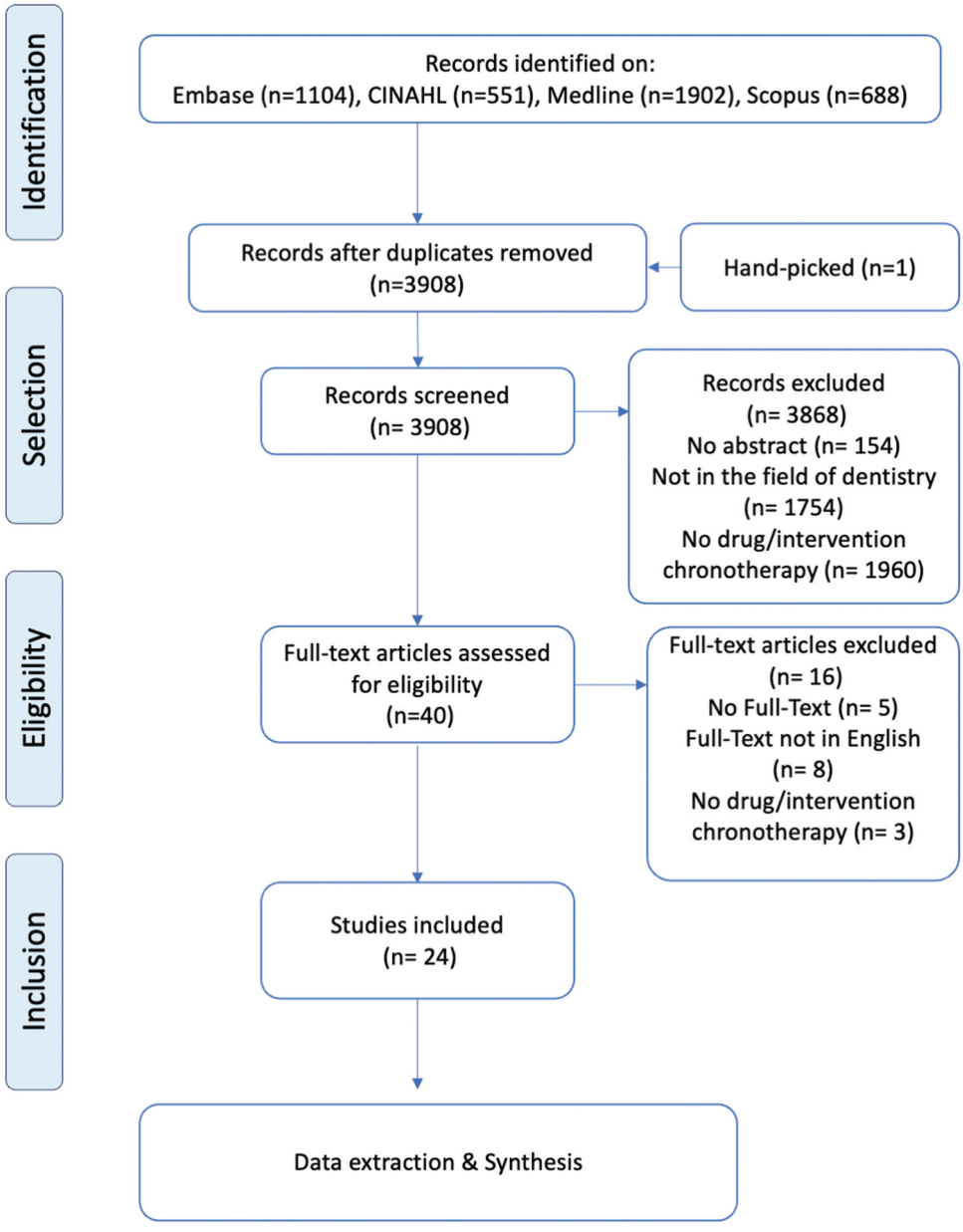

Figure 1. PRISMA flowchart of selected studies.

text, by two independent reviewers (MA, MT); any disagreements were resolved by a third author (WA). Agreement between the reviewers was substantial with a Cohen kappa score of 0.662.

Furthermore, only original animal and human studies investigating the chronotherapeutic use of drugs or interventions in dentistry were included. As for our exclusion criteria, references were excluded if they contained no abstract, were unrelated to dentistry, did not include a timed intervention in their methodology, or did not mention chronotherapy.

Data charting and data synthesis

Two co-authors extracted and charted (MA and MT) the data from the included articles using Excel. Data were then summarized including each study's title, authors, publication year, study design, population, sample size, comparator groups, exposure, outcome and results. Next, MA synthesized the collected data by combining both quantitative and qualitative approaches, which is suitable for amalgamating heterogeneous studies and data (Peters et al. 2015). For the included studies, two blinded co-authors (KT and WC) independently performed quality critical appraisal using the Joanna Briggs Institute (JBI) assessment tool for human studies (Lockwood et al. 2015) and the SYstematic Review Center for Laboratory animal Experimentation's (SYRCLE) a risk of bias assessment tool for animal studies (Hooijmans et al. 2014). These tools were used to assess included studies' internal validity and risk of bias. JBI critical appraisal tools were used in this study because JBI's checklists have the widest applicable range for human studies (e.g. Randomized Controlled Trials (RCTs), non-RCTs, Cohorts and Case reports). In addition, the SYRCLE checklist is considered the most recommended tool to be used for animal studies (Ma et al. 2020).

Results

Following the screening process, 24 articles were retained after applying the inclusion and exclusion criteria. Of the 24 studies assessed and outlined in Table 1, 19 (79%) and 5 (21%) were human and animal studies, respectively. Among those human studies, 11 were clinical trials, 7 were retrospective cohorts and one case report. The number of articles published per year was not evenly distributed. Five general areas of research emerged: Studies on chemotherapy and radiotherapy treatments in head and neck carcinomas ($n = 15$); studies on orthodontic forces and tooth movement ($n = 3$); studies on local anesthesia ($n = 2$); studies on prothodontics and oral medicine ($n = 2$); and studies on post-operative pain management and surgery ($n = 2$). All chemotherapy and radiotherapy included studies ($n = 15$) were within

Table 1. Overview of included studies in the scoping review.

First Author/Year	Design	Population (n)	Outcome Measured
Chrono-chemotherapy			
Yang et al. (2013)	Animal	Mice (n = 75)	Therapeutic response and adverse effects
Chen et al. (2013)	Retrospective	Humans (n = 49)	Therapeutic response and adverse effects
Zhang et al. (2021)	Retrospective	Humans (n = 150)	Therapeutic response and adverse effects
Verma et al. (2014)	RCT	Humans (n = 60)	Therapeutic response and adverse effects
Zhang et al. (2018)	RCT	Humans (n = 148)	Therapeutic response and adverse effects
Lin et al. (2013)	RCT	Humans (n = 125)	Therapeutic response and adverse effects
Tsuchiya et al. (2018)	Crossover	Humans (n = 9)	Adverse effects only
Chrono-radiotherapy			
Zhang et al. (2013)	Animal	Mice (n = 366)	Therapeutic response only
Gu et al. (2020)	Retrospective	Humans (n = 190)	Adverse effects only
Kuriakose et al. (2016)	Retrospective	Humans (n = 142)	Adverse effects only
Brolese et al. (2021)	Retrospective	Humans (n = 617)	Adverse effects only
Elicin et al. (2021)	Retrospective	Humans (n = 655)	Therapeutic response only
Goyal et al. (2009)	RCT	Humans (n = 212)	Therapeutic response and adverse effects
Bjarnason et al. (2009)	RCT	Humans (n = 216)	Therapeutic response and adverse effects
Elzahi et al. (2020)	Non-RCT	Humans (n = 160)	Adverse effects only
Orthodontic Forces and Tooth Movement			
Igarashi et al. (1998)	Animal	Rats (n = 30)	Tooth movement, bone formation and resorption
Miyoshi et al. (2001)	Animal	Rats (n = 100)	Tooth movement, bone formation and resorption
Yamada et al. (2002)	Animal	Rats (n = 37)	Inhibition of condylar growth and differentiation and proliferation of chondrocytes
Local Anesthesia			
Lemmer and Wiemers (1989)	Non-RCT	Humans (n = 83)	Numbness duration
Pöllmann (1982)	Non-RCT	Humans (n = 67)	Numbness duration and pain onset after surgery
Prosthodontics & Oral Medicine			
Latta (1992)	Non-RCT	Humans (n = 30)	Positional changes in centric relation records for edentulous patients
Waghmare and Puthenveetil (2021)	Case Report	Humans (n = 1)	Complete remission
Pain Management & Surgery			
Tamimi et al. (2022)	RCT	Humans (n = 70)	Postoperative pain and healing
Restrepo et al. (2020)	Retrospective	Humans (n = 187)	Postoperative complications (immediate and late)

Abbreviations: RCT: Randomized Controlled Trial.

the scope of dentistry. Furthermore, a detailed overview of the included studies is outlined in Supplemental Table S2. Table 2 presents studies investigating drug chronotherapy and reported targeted pathways.

The risk of bias assessment of the included studies is summarized in Supplemental Table S3. Overall, RCTs did not properly conceal group allocation, and neither patients nor investigators were blinded to treatment assignment, intervention and outcome assessment. On the other hand, non-RCTs displayed low risk of bias. While the included cohort studies generally exhibited low risk of bias, about 70% did not identify confounding variables nor adjusted for them in their analysis. Finally, randomization and sample size calculation were mainly lacking in animal studies attributing to the high risk of bias. Years of publication varied extremely across research areas. For instance, all studies on head and neck cancer were fairly recent and published between 2009 and 2021. In contrast, studies in prosthodontic treatments and local anesthesia were published between 1982 and 1992. Also, orthodontic forces and tooth movement animal studies were conducted between 1998 and 2002. Figure 2 illustrates the best time for different interventions reported in the included studies.

Head and neck cancer

Chrono-chemotherapy

Of the 24 articles included in this review, four RCTs, two retrospective cohort studies and one animal trial assessed chrono-chemotherapy.

Animal studies. In an animal study, Yang et al. (2013) investigated how dosing time influences the efficacy and side effects of oxaliplatin (L-OHP) on oral squamous cell carcinoma in mice. L-OHP injected at 16 and 22 h After Light Onset (HALO) significantly increased survival rate and greatly reduced adverse effects compared to L-OHP injected at 4 and 10 HALO.

Human studies. In the retrospective cohort studies, Chen et al. (2013) compared chronomodulated chemotherapy (i.e. paclitaxel (03:00 h–05:00 h) and carboplatin (16:00 h–20:00 h) on Day 1, while 5-fluorouracil (5-Fu) on Day 1 to 5 at 22:00 h–07:00 h) and conventional (Control) chemotherapy started between 09:00 h and 11:00 h and finished before 17:30 h. They reported that the chronomodulated chemotherapy group had a significantly lower overall incidence of adverse effect with higher tumor response rate and longer patients' survival. Zhang et al. (2021) investigated the efficacy and safety of induction chemotherapy combined with chrono-chemotherapy (i.e. cisplatin 10:00 h–22:00 h with peak delivery of at 16:00 h) or conventional chemotherapy (i.e. intravenous instilling of Cisplatin 10:00 h to 22:00 h) in locally advanced nasopharyngeal carcinoma. Their work showed that chrono-chemotherapy could decrease incidence rates and severity of adverse reactions and improve treatment-induced immunosuppression.

Regarding the RCTs, two RCTs investigated chronomodulated cisplatin administration. Verma et al. (2014) compared cisplatin efficacy and toxicity when prescribed at 06:00 h or 18:00 h, followed by radical external beam radiotherapy in locally advanced head

Table 2. Included studies investigating drug chronotherapy.

Drugs	Half-life	Reported Targeted Pathways in Included Studies
Taxanes		
Paclitaxel	8.83 ± 4.10 h Borgå et al. (2019)	Not reported.
Docetaxel	12 h Bruno and Sanderink (1993)	Circadian rhythm of DNA synthesis and cell proliferation were detected in the bone marrow and gastrointestinal mucosa and these biological rhythms could influence docetaxel adverse effects. (Tsuchiya et al. 2018)
Platinum-based antitumor		
Cisplatin	51 ± 22 min (i.v./6 hr) Gouyette et al. (1986)	Glutathione (GSH) is an antioxidant that prevents cell damage, and toxicities caused by Cisplatin are associated with the circadian variation of GSH that peaks at 16:00 h. (Zeng et al. 2005)
Carboplatin	118 ± 15 mins Elferink et al. (1987)	Not reported.
Antimetabolites		
5- Fu	12.9 ± 7.3 min Heggie et al. (1987)	Adapting 5- Fu administration to the daily rhythm of the principal enzyme of degrading 5- Fu, Dihydropyrimidine dehydrogenase (DPD), thus producing less toxicity. (Harris et al. 1990)
Anti-Inflammatory Drugs		
Ibuprofen	2 h Albert and Gernaat (1984)	Postoperative pain, swelling and CRP serum levels peak during the day (Pro-inflammatory phase) (Tamimi et al. 2022)
Prednisolone	2.1–3.5 h Bashar et al. (2018)	Prednisolone administration with peak levels of bodily cortisol (i.e. 08:00 h) showed minimum cumulative cortisol suppression and maximum effects on the action of lymphocytes. (Xu et al. 2008)
Local Anesthesia		
Mepivacaine	1.6 h Malamed (2019)	Circadian variations in distribution, metabolism, elimination processes, nerve cell membrane permeability and access to ion channels. Efflux of K and its cell concertation lowest at 15:00 h. (Chassard et al. 2007)
Articaine	0.5 h Malamed (2019)	

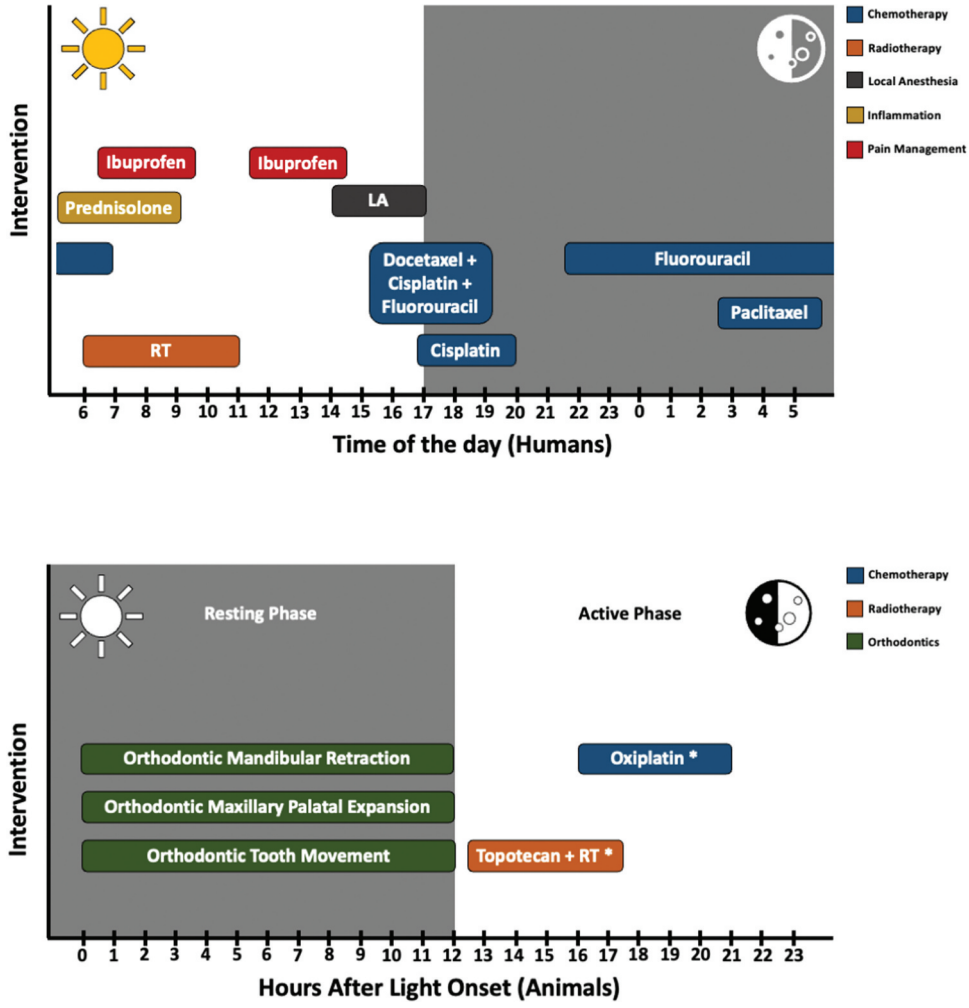

Figure 2. Best time for different interventions reported in the included studies. Abbreviations: RT: Radiotherapy; LA: Local Anesthesia for restorative and surgical procedures; *: Studies conducted on mice. Ibuprofen and Prednisolone were prescribed for pain management after third molar extraction surgery and treating Oral Pemphigus, respectively.

and neck carcinomas. In contrast, Zhang et al. (2018) compared cisplatin chronomodulated infusion (10:00 h –22:00 h with peak delivery at 16:00 h) to flat intermittent cisplatin infusion (10:00 h–14:00 h), combined with intensity-modulated radiotherapy in locoregionally advanced nasopharyngeal carcinoma patients. They assessed adverse effects, immune function impairment and therapeutic efficacy. While both studies concluded that cisplatin chronotherapy received in the evening significantly reduced adverse effects and was better tolerated, there was no significant impact on cancer control or survival (Verma et al. 2014; Zhang et al. 2018).

The other two RCTs evaluated cisplatin chronotherapy combined with other chemotherapeutic medications. For example, Lin et al. (2013) examined the therapeutic and toxic effects of cisplatin and 5-Fu chronomodulated infusion (cisplatin 10:00 h–22:00 h with peak delivery of at 16:00 h and 5-Fu 22:00 h –10:00 h with a peak delivery at 04:00 h) as opposed to the same 12-h time period (for both medications) but with flat intermittent constant infusion rate, followed by radical radiotherapy in advance nasopharyngeal carcinoma patients. Patients prescribed cisplatin and 5-Fu chronotherapy experienced significantly less stomatitis but with similar therapeutic and toxic effects to the flat infusion (Lin et al. 2013). Finally, a crossover RCT design tested the chemotherapeutic regimen trifecta (docetaxel, cisplatin and 5-Fu) in two periods (10:30 h versus 18:30 h) in oral squamous cell carcinoma patients (Tsuchiya et al. 2018). The author observed a reduction in nausea (66.7% versus 22.2% $p < 0.05$) and other adverse effects (e.g. vomiting [33.3% versus 22.2%, $p > 0.05$] and neutropenia [22.2% versus 11.1%, $p > 0.05$]) in the evening-dosing (Tsuchiya et al. 2018). Because this RCT had a crossover design, the therapeutic response could not be assessed.

Chrono-radiotherapy

Animal studies. In the animal study, Zhang et al. (2013) evaluated the chronomodulated effect of topotecan (TPT), a radiosensitizing agent, in a human nasopharyngeal carcinoma mouse model. Their work revealed that TPT's radiosensitivity effect is time dependent, and TPT combined with radiotherapy achieved a superior therapeutic effect on delaying tumor regrowth when administered at 15 HALO (active period).

Human studies. Two retrospective studies included in this review investigated whether radiotherapy timing could influence oral mucositis severity in managing head and neck cancer. Indeed, both studies demonstrated that radiation-induced oral mucositis was significantly lower when patients were exposed to radiotherapy in the morning (Gu et al. 2020; Kuriakose et al. 2016). In contrast, Brolese et al. (2021) reported that seasonality, not daytime (morning/evening), was a predictor for radiation-induced oral mucositis severity. Patients who underwent radiotherapy between September and March (winter) suffered an increased incidence of acute toxicities. Furthermore, while investigating the same cohort, Elicin et al. (2021) found that patients who underwent radiotherapy in the winter had superior loco-regional control and progression-free survival.

Moreover, three clinical trials (two RCTs and one non-RCT) studied the effect of radiotherapy in the morning versus afternoon on radiation-induced oral mucositis severity in head and neck carcinoma patients. Goyal et al. (2009) and Bjarnason et al. (2009) randomly assigned head and neck carcinoma patients to morning and afternoon groups (08:00 h–11:00 h versus 15:00 h–18:00 h and 08:00 h–10:00 h versus 14:00 h–16:00 h, respectively). Both studies stated that the morning radiotherapy group exhibited reduced oral mucositis severity grades (Bjarnason et al. 2009; Goyal et al. 2009). In the third clinical trial, although non-randomized, investigators were blinded to group allocation (06:00 h–08:00 h versus 13:00 h–15:00 h), and participants were matched according to age, sex and tumor site (Elzahi et al. 2020). Nevertheless, similar results were reported regarding the association between radiotherapy time of the day and oral mucositis severity grades (i.e. the morning radiotherapy group had less severe form of mucositis) (Elzahi et al. 2020).

Orthodontic forces and tooth movement

Two studies investigated orthodontic forces (Igarashi et al. 1998) (i.e. maxillary expansion) and tooth movement (Miyoshi et al. 2001) as a function of time, while a third study examined mandibular retractive forces during the resting period (Yamada et al. 2002). Findings from these three studies conducted on rats and in the same Japanese laboratory demonstrated that restricting orthodontic forces to a certain time of day would achieve better outcome (Igarashi et al. 1998; Miyoshi et al. 2001; Yamada et al. 2002). For instance, maxillary expansion and tooth movement were faster in the light-period group (07:00 h–19:00 h) with increased new bone formation on the tension side (Igarashi et al. 1998; Miyoshi et al. 2001). On the other hand, the orthodontic forces were far less effective during the dark period (19:00 h–07:00 h) (Igarashi et al. 1998; Miyoshi et al. 2001). Although all-day force applications achieved similar tooth movement to the light-period group, the light-period group had less extensive periodontal ligament hyalinization (Miyoshi et al. 2001). Also, mandibular retractive forces were more effective when applied during the light period (08:00 h-20:00 h) (Yamada et al. 2002).

Local anesthesia

This review included two studies that investigating local anesthesia injected at different times of the day in humans. Lemmer and Wiemers (1989) used an electronic pulp tester to measure the stimulus threshold of anterior teeth. They quantified the total local anesthesia effect by time to reach peak effect, duration at peak effect and time to return to baseline threshold. On the other hand, Pöllmann (1982) measured numbness duration and pain onset after oral surgery. In addition to reporting circadian behavior of local anesthesia (Lemmer and Wiemers 1989; Pöllmann 1982), both studies showed that maximal drug effect was achieved when local anesthesia was injected at 14:00 h and 17:00 h (Lemmer and Wiemers 1989). Moreover, the longest duration of local anesthesia was achieved when injected at 15:00 h, while the shortest duration was at night and early morning (Pöllmann 1982).

Prosthodontics and oral medicine

(Latta 1992) found that centric relation records for complete denture fabrication showed a circadian variation (Latta 1992). For instance, if centric relation records are taken in the morning, fabricated complete dentures thereafter would better fit the patient's mouth in the morning and vice versa. So, it was suggested that treating edentulous patients in the middle of the day would dilute such circadian changes (Latta 1992).

In the included case report treating oral pemphigus vulgaris, Waghmare and Puthenveetil (2021) showed

that a single dose of prednisolone at 06:00 h achieved complete remission of the oral lesion as opposed to conventional regimen (twice daily), which 50% reduction only.

Post-operative pain management and surgery

Tamimi et al. (2022) conducted an RCT evaluating the effect of chronotherapy of NSAIDs on post-operative recovery in a third molar extraction model. They concluded that restricting ibuprofen administration to daytime (morning and afternoon) might be as sufficient as conventional administration regimens (morning, afternoon and evening) in controlling post-operative pain after third molar extraction (Tamimi et al. 2022).

Restrepo et al. (2020) evaluated cleft lip and palate surgeries and their early and late complications. Among other parameters, they investigated the correlation between time of surgery (morning versus afternoon) and post-operative complications. They reported no correlation between incident of complications and surgery time (Restrepo et al. 2020).

Discussion

Chronotherapy (interventional or drug) is a promising and unique therapeutic approach aimed at improving medical outcomes, ultimately leading to better overall health and well-being. Re-scheduling medical interventions and medications to a certain time of the day aligned with the body's biological rhythms are sought to provide a simple and cost-effective way to maximize treatment benefits while minimizing adverse effects. Oral health and dentistry are multidimensional fields, and health-care professionals in such disciplines could greatly benefit from applying chronotherapy to improve patients' quality of life. In this scoping review, we broadly mapped existing literature underpinning chronotherapy applications in dentistry and identified gaps in knowledge. We categorized the available literature into chronotherapy of head and neck cancer treatment, orthodontics, prosthodontics, oral medicine, local anesthesia, post-operative pain management and surgery. Identifying knowledge gaps was attained by an in-depth review of included studies' quality (i.e. risk of bias assessment tools), number, population and design in each research area.

Our findings showed that restricting chemotherapy and/or radiotherapy to specific time of the day might generally reduce treatment adverse events and relatively increases therapeutic response and survival rates in head and neck cancer patients (Bjarnason et al. 2009; Brolese et al. 2021; Chen et al. 2013; Elicin et al. 2021; Elzahi et al. 2020; Goyal et al. 2009; Gu et al. 2020; Kuriakose et al. 2016; Lin et al. 2013; Tsuchiya et al. 2018; Verma et al. 2014; Yang et al. 2013; Zhang et al. 2013, 2018, 2021). However, these studies' findings and clinical implications should be interpreted with caution due to methodological limitations. First, specifically, in RCTs, blinding patients and investigators to treatment allocation, intervention and outcome assessment was absent by design. In other words, study participants and investigators were aware of treatment assigned (e.g. morning versus evening) that might prompt them to behave differently, thus rendering these studies at higher risk of bias and compromising their internal validity. While this limitation could be attributed to the lack of feasibility to blindly conduct time-dependent interventions and using a placebo, the risk of bias should not be underestimated. Second, multiple medications (e.g. paclitaxel, carboplatin, 5-FU, cisplatin and docetaxel) are frequently prescribed when treating head and neck carcinomas with chemotherapy. This presents yet another challenge to developing a research protocol following a rigorous study design that minimize inconsistencies and the risk of bias. In addition, almost all studies investigating chrono-chemotherapy had other cycles of non-time-stipulated induction chemotherapy and/or concurrent radiotherapy. This overlaps between chemotherapy and radiotherapy will influence, for instance, the severity of adverse events, thus diluting the treatment effect. Finally, current studies are insufficient to amend ongoing guidelines. However, conducting systematic reviews and meta-analyses is feasible, which would provide the bases for optimized multicentre RCT designs.

Moreover, dental health-care professionals could take advantage of prolonged and profound local anesthesia when injected in the afternoon (Lemmer and Wiemers 1989; Pöllmann 1982). This is potentially useful for patients undergoing lengthy procedures such as root canal treatments and oral surgeries. This prolonged and profound anesthesia could be achieved because circadian rhythms influence the pharmacological sensitivity of many medications by regulating physiological functions and parameters essential to pharmacokinetics and pharmacodynamics (Bélanger et al. 1997; Chassard and Bruguerolle 2004). Similar to many US Food and Drug Administration (FDA) approved drugs showing diurnal variation, local anesthesia efficacy and toxicity are time dependent (Chassard and Bruguerolle 2004; Ruben et al. 2019). However, chronotherapy of local anesthesia should be further investigated as the included studies were non-randomized, had a high risk of bias and were conducted

more than 30 years ago. Furthermore, NSAIDs chronotherapy (i.e. morning and afternoon administration only) was reported to be of potential therapeutic benefit for post-operative recovery after wisdom tooth extraction (Tamimi et al. 2022). This finding was also in accordance with a recent study, published after our search was conducted, investigating the same outcomes but in a cross-over design (Pérez-González et al. 2022). However, these RCTs had relatively small sample size which could influence their reported findings. Accordingly, multicentred RCTs with larger sample sizes would be essential in changing the current standard of care regimen (3-doses per day) for pain control after surgery. Figure 3 demonstrates proposed dental procedures that would benefit from the chronotherapy of NSAIDs and local anesthesia.

In addition, our review showed that orthodontic forces applied at different times during the day would result in considerable variation in teeth movement in rats (Igarashi et al. 1998; Miyoshi et al. 2001; Yamada et al. 2002). Various studies have shown that bone physiology, including metabolic markers and bone formation and resorption, exhibits diurnal variations (Petrovic et al. 1981; Stutzmann 1984). Given these circadian fluctuations in bone physiology, mechanically induced bone remoulding by orthodontic forces might be time dependent and vary throughout the day and night. However, it is important to mention that rats are nocturnal animals, and the light-period is their resting phase. Thus, when translating these findings to humans, restricting orthodontic treatments to nighttime (intermittent force application for 12 h) would be comparable to continuous all-day orthodontic treatment and would cause less damage to periodontal tissues (i.e. PDL hyalinization). Nevertheless, chronotherapy of orthodontic treatments should be further tested in humans to evaluate its feasibility and whether it could realistically reduce treatment duration.

Furthermore, there are several factors/modifiers that have been reported to influence\alter one's circadian rhythm such as age, sex, chronotype, diet, sleeping habits, social interactions, exercise, disease status, smoking and drugs (Walton et al. 2022; Yousefzadehfard et al. 2022). Most included human studies did not consider circadian rhythm modifiers in their analyses. Only one study looked in the chronotype of their studied population, and three studies performed secondary subgroup analyses for circadian rhythm modifiers (Supplemental Table S4). Considering such modifiers are important; for example, Bjarnason et al. (2009) observed different trends in the chrono-radiotherapy effect between males and females, which could be attributed to gender-specific genes involved in various pathways including the cell cycle (Bjarnason et al. 2007). While a proper study design with randomization would eliminate the subtle confounding difference in recruited patients, considering circadian rhythm modifiers would increase the internal validity and reliability. However, there are limitations in terms of feasibility and maintaining internal validity of the study (i.e. restricted inclusion/exclusion criteria)

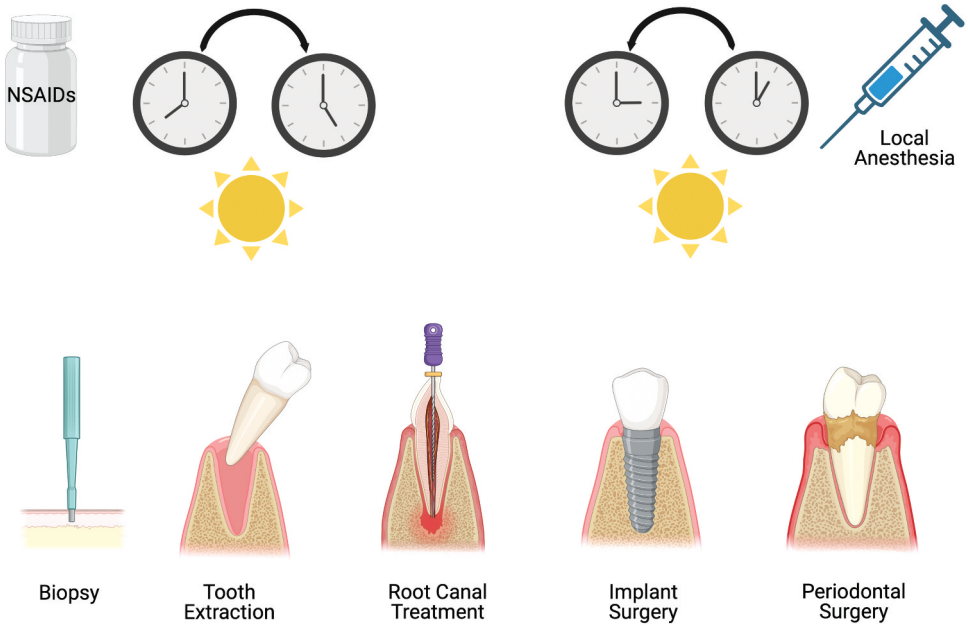

Figure 3. Proposed dental procedures that could benefit from chronotherapy of NSAIDS and Local Anesthesia. Clocks in the figure represent optimized dosing time for interventions. Figure was created with BioRender.Com.

(Yousefzadehfard et al. 2022). Nonetheless, prospective studies should consider incorporating circadian-based protocols into patient recruitment strategies, study design and analyses.

The role of clock-modulating small molecules and their therapeutic potential have recently gained increasing attention in clock-related diseases. These small molecules can act directly (activation/inhibition) on core clock components or with key regulatory mechanisms (non-core clock components) that significantly alter or control the circadian clock (Oshima et al. 2015; Ribeiro et al. 2021; Wallach and Kramer 2015). Compared to traditional chronotherapy (i.e. explicit rescheduling of existing drugs to improve efficacy and/or reduce toxicity), clock-modulating small molecules provide a novel strategy that directly manipulates the circadian clock to improve medical outcomes intrinsic to disease etiology (Chen et al. 2013). Jetlag is a famous example, which is essentially a phase misalignment and thus can be targeted by clock-modulating small molecules with phase-resitting properties (Chen et al. 2013). Thus far, in a recently published thesis, SR9009 (i.e. clock-modulating small molecules demonstrated chemotherapeutic benefits on squamous cell carcinoma cell lines (Shivanantham 2022). However, more preclinical and clinical studies are needed to further our understanding of the potential therapeutic uses and benefits of clock-modulating small molecules.

Conclusions

Overall, chronotherapy applications in dentistry have shown favourable outcomes. Although evidence thus far suggests that chrono-chemotherapy and chrono-radiotherapy could be promising therapeutic regimens for head and neck cancer, standardized study protocols are needed. While chronotherapy of orthodontic treatments in animal trials revealed promising results, human clinical trials are lacking. Prolonged and profound local anesthesia could be achieved when injected in the afternoon. However, chronotherapy of local anesthesia should be further investigated in an optimized study design. In addition, even though NSAIDs chronotherapy could be an effective and simple dosing regimen to better control post-operative pain after surgery, multicenter RCTs should be further conducted. Finally, centric record accuracy for complete denture fabrication showed time-dependency, while time of surgery showed no correlation with post-operative incidence of complications.

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