Clocking in: chronobiology in rheumatoid arthritis

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Abstract | Circadian rhythms are of crucial importance for cellular and physiological functions of the brain and body. Chronobiology has a prominent role in rheumatoid arthritis (RA), with major symptoms such as joint pain and stiffness being most pronounced in the morning, possibly mediated by circadian rhythms of cytokine and hormone levels. Chronobiological principles imply that tailoring the timing of treatments to the circadian rhythm of individual patients (chronotherapy) could optimize results. Trials of NSAID or methotrexate chronotherapy for patients with RA suggest such an approach can improve outcomes and reduce adverse effects. The most compelling evidence for RA chronotherapy, however, is that coordinating the timing of glucocorticoid therapy to coincide with the nocturnal increase in blood IL-6 levels results in reduced morning stiffness and pain compared with the same glucocorticoid dose taken in the morning. Aside from optimizing relief of the core symptoms of RA, chronotherapy might also relieve important comorbid conditions such as depression and sleep disturbances. Surprisingly, chronobiology is not mentioned in official guidelines for conducting RA drug registration trials. Given the imperative to achieve the best value with approved drugs and health budgets, the time is ripe to translate the 'circadian concept' in rheumatology from bench to bedside.

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Introduction

An intrinsic, ~24 h (circadian), rhythm is a fundamental aspect of cellular and physiological function in the brain and body. Circadian rhythms are genetically encoded and are evident at the behavioural level as well as the metabolomic, proteomic, transcriptomic, acetylomic and methylomic levels.[1] The main function of this intrinsic timekeeping system is to impose a temporal 'architecture' on behaviour, physiology and metabolism in the absence of external cues. This architecture ensures temporal segregation of behavioural and physiological processes for an optimally timed interaction with the environment. The latest developments in neuroscience and molecular biology emphasize the importance of daily circadian oscillation for good health, longevity and amelioration of a range of conditions, including cardiovascular disease, immune dysregulation, cancer and mental illness.[2] However, the 'circadian concept' is not yet part of mainstream medical education or practice. In this Review, we summarize the current understanding of circadian biology, successful application of chronotherapy and the potential for routine chronotherapeutic assessment in RA clinical drug trials.

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The circadian clock

Intrinsic temporal organization of human biology is achieved through the integration of hierarchically organized, multi-oscillator systems via the interaction of central oscillators and their feedback from peripheral rhythms as well as from systemic, behavioural and environmental cues. At the top of this hierarchy is the 'central clock' located in the suprachiasmatic nuclei (SCN), which generate circadian rhythms in neuronal activity and peptide release,[3] which, in turn, are important synchronizing cues to other brain and body regions. The SCN are thought to act as a master clock that synchronizes peripheral clocks and conveys time-of-day information to peripheral organs (Figure 1). Disturbances in this coupling of central and peripheral clocks can lead to metabolic dysfunction and cardiovascular problems (reviewed elsewhere[4]).

Aside from internal synchronization, circadian rhythms are also synchronized by external periodic signals resulting from the rotation of the earth, in other words from the 24 h oscillation of light and dark (Figure 1). This synchronization with the environmental cycle under natural light–dark conditions, known as entrainment, is a result of daily adjustments of the phase and period of the circadian oscillator.[5] The SCN receives photic input directly by retinal projection from a population of intrinsically photosensitive retinal ganglion cells that express the photopigment melanopsin.[6] Light acts as a *Zeitgeber* (a German word meaning 'time-giver' or 'synchronizer') to evoke time-dependent circadian responses in the SCN, such as the release of glutamate and pituitary adenylate-cyclase-activating peptide, to

Key points

- Circadian rhythms of biological processes are genetically encoded and of crucial importance for cellular and physiological functions of the brain and body
- Chronobiology has a prominent function in rheumatoid arthritis (RA), with major symptoms such as joint pain and stiffness usually being most pronounced in the morning
- Therapy that recognizes the underlying chronobiology of RA might improve the benefit-to-risk balance
- Timing the administration of NSAIDs or methotrexate according to biological rhythm determinants might help to optimize treatment outcomes in RA
- New data on successful chronotherapy with glucocorticoids show that coordination of glucocorticoid administration with the nocturnal increase in IL-6 levels improves morning symptoms of RA
- Chronotherapy might have the additional benefit of increasing sleep quality or quantity and relieving depressive and other affective symptoms that are comorbid with RA

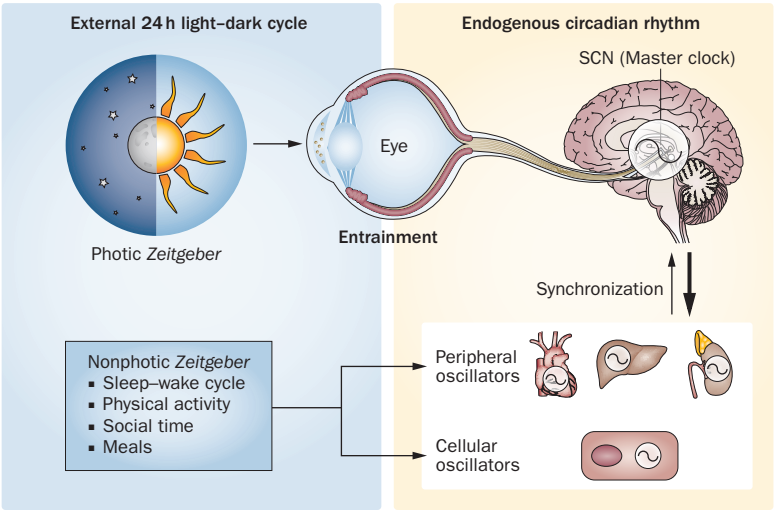

Figure 1 | Internal circadian clocks and external *Zeitgebers*. Intrinsic circadian oscillations in the brain (SCN) and the periphery (organs) are synchronized via humoral signals and the autonomic nervous system. The circadian system actively synchronizes the temporal sequence of biological functions with the environment. The light–dark cycle is the most important *Zeitgeber* (synchronizer). Other potential environmental entrainment cues stem from sleep–wake and activity cycles, meal timing and societal rhythms such as work and leisure times. Abbreviation: SCN, suprachiasmatic nuclei.

reset the phase of the SCN clock.[7] The neurohormone melatonin, which is primarily secreted nocturnally from the pineal gland, under the control of the SCN, has been reported to regulate sleep and circadian functions,[8] as well as several different immune functions such as the regulation of proinflammatory cytokine expression or leukocyte functions such as responsiveness to antigens, trafficking and cytotoxicity.[9] Circadian rhythms in the expression of other important hormones, including glucocorticoids, are also SCN-dependent.[10]

The transcription–translation feedback loop

Extensive progress has been made in the identification of mammalian clock genes and their regulation and function.[11] The basis of circadian oscillations involves two interconnected feedback loops in clock gene expression (Figure 2).[12] In the positive limb of this transcription–translation feedback loop (TTL), the transcriptional activators aryl hydrocarbon receptor nuclear translocator-like proteins 1 and 2 (ARNTL and ARNTL2), referred to in this article as brain and muscle ARNT-like 1 and 2 (BMAL1 and BMAL2), dimerize with circadian locomotor output cycles protein kaput (hCLOCK), or possibly with neuronal PAS2 protein in brain tissue.[11,12] This heterodimer binds to the E-box promoter elements in clock genes and clock-controlled genes.[11,12] When activated in this manner, the clock gene isoforms *PER1* and *PER2*, and *CRY1* and *CRY2*, constitute the negative portion of the TTL (Figure 2): the mRNAs of these genes are translated in the cytoplasm, and the resulting proteins (period circadian protein homolog [hPER]1 and hPER2, and cryptochrome 1 and cryptochrome2, respectively) form heterodimers that eventually enter the nucleus to inhibit transcription by binding to hCLOCK–BMAL or neuronal-PAS2–BMAL protein complexes.[11,12]

The positive and negative parts of the TTL are connected by nuclear receptors from the Rev-erbA and retinoic acid receptor (RAR)-related orphan receptor (ROR) families. These receptors are transcriptionally regulated by the positive TTL and activate (ROR proteins) or inhibit (Rev-erbAα, also known as nuclear receptor subfamily 1 group D member 1 [NR1D1]) transcription of *ARNTL*, *NPAS2* and *CLOCK* (Figure 2), thereby modulating their own activators.[12] This process is fine-tuned by hPER2, which interacts with Rev-erbAα to synchronize the negative and positive TTL (Figure 2). A metabolic oscillator is also driven by the TTL, and this oscillator feeds back to the TTL via the clock-controlled-gene products nicotinamide phosphoribosyltransferase and NAD-dependent protein deacetylase sirtuin 1 (hSIRT1), to modulate transcriptional activity of the clock (Figure 2).[12] In addition to these transcriptional mechanisms, many well-coordinated post-translational modifications (such as phosphorylation and acetylation) of core clock proteins are required to keep the clock 'ticking' at appropriate periodicities (reviewed elsewhere[13]).

Circadian regulation of physiology

The molecular clock regulates important physiological processes in a tissue-specific manner, via modulation of the transcriptional landscape in a pervasive and highly complex manner.[14] Circadian patterns exist not only in expression of coding RNAs, but also of noncoding RNAs.[15] The effect of the molecular clock on various physiological process is highlighted by studies showing roles for *NR1D1* (the gene that encodes Rev-erbAα) in the organization of metabolism,[16] regulation of the midbrain dopaminergic system,[17] and in shaping thermoregulatory responses to cold.[18]

Disorders of the human circadian system are often manifested as circadian misalignment between the biological clock, sleep–wake cycles or the external light–dark cycle. This misalignment causes sleep disturbances, reduced attention, impaired daytime alertness, lack of energy, memory problems, negative mood and

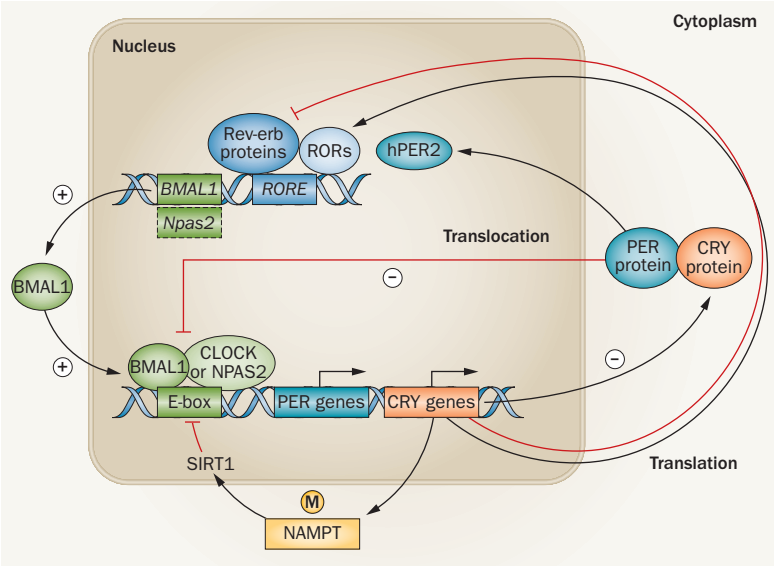

Figure 2 | Molecular circadian clock mechanisms in a mammalian cell. The clock mechanism consists of a TTL consisting of a positive (+) and a negative (–) feedback loop, which are intertwined via clock-protein-driven nuclear receptors and their interactions with hPER2, a component of the negative feedback loop. A metabolic oscillator is driven by the TTL and counter-regulates it via hSIRT1 (M). Abbreviations: CLOCK, circadian locomotor output cycles protein kaput; encircled M, metabolic component of the TTL; hPER2, period circadian protein homolog 2; hSIRT1, NAD-dependent protein deacetylase sirtuin 1; NAMPT, nicotinamide phosphoribosyltransferase; RORE, retinoic acid-related orphan receptor response elements; TTL, transcription–translation feedback loop. Modified with permission from Elsevier © Albrecht, U. *Neuron* **74**, 246–260 (2012).[12]

gastrointestinal disorders. These effects are most evident in shift workers for whom substantial discrepancy exists between endogenous and exogenous time, as they are awake, active and eating during their biological night, and trying to sleep and fast during their biological day.[19]

Interestingly, these neuropsychological symptoms can also occur in people diagnosed with depression, schizophrenia and other psychiatric disorders,[20] with the possibility that internal desynchronization of the constituent pacemakers of the circadian system manifests itself in desynchronization between behavioural and physiological cycles in such conditions.[21] Promising evidence shows that chronotherapeutic interventions that address circadian rhythm abnormalities can produce rapid and long-lasting antidepressant effects in patients with bipolar disorder or seasonal and nonseasonal major depression.[22–25]

Important links between circadian rhythmicity, inflammation and diseases have also been studied.[26,27] Aside from the symptoms already mentioned, shift workers also have an increased risk of developing RA,[28] and shift work is associated with inflammation.[29] An increased inflammatory status might contribute to the increased risk of metabolic disorders, and evidence is accumulating, from large epidemiological studies, that people who work rotating night-shifts have an increased susceptibility (HR 1.03–1.24) to type 2 diabetes mellitus, after adjusting for traditional diabetes risk factors and BMI.[30]

If one considers that circadian and sleep–wake disorders are often prodromal signs of common diseases, and that their treatment has a substantial effect on the development, consequence and treatment of these illnesses, chronobiological intervention might need to be integrated into routine medical practice. This integration could result in shorter duration of hospitalization and, ultimately, a reduced financial burden on healthcare systems.

Circadian rhythms in RA

RA, which affects 0.5–1.0% of adults in developed countries, is a disabling disease that is characterized by persistent synovitis and systemic inflammation.[31,32] Chronobiology has a prominent role in RA, with major symptoms such as joint pain and stiffness usually being most pronounced in the morning.[26,33,34] This temporal factor has been, at least in part, attributed to underlying circadian patterns in cytokines and hormones.[26,35] In patients with RA, increases in nocturnal blood levels of proinflammatory cytokines (for example, IL-6 and TNF) correlate with the severity of morning stiffness, whereas healthy individuals ordinarily have very low levels of these cytokines regardless of the time of day (Figure 3).[36–38] Circadian rhythms in the expression of core clock genes *CRY2* and *RORA* are altered in RA synovial fibroblasts, suggesting a desynchronization of the central clock and the local synovial clock that, in turn, might result in altered responsiveness to inflammatory mediators.[35] Patients with RA also have higher baseline levels (and an altered temporal profile) of melatonin, suggesting a proinflammatory effect of this hormone.[39] Indeed, Hansson *et al.*[40] demonstrated, more than 20 years ago, that melatonin exaggerates the development of collagen-induced arthritis in mice. As melatonin is also an antioxidant with some anti-inflammatory actions, Forrest *et al.*[41] tested this hormone as adjunctive treatment for patients with RA; they did not find statistically significant effects of melatonin treatment on clinical assessments of patient symptoms or on the concentration of IL-1β, IL-6 or TNF, but erythrocyte sedimentation rate, lipid peroxidation, neopterin and kynurenine concentrations were affected and indicate that melatonin can be proinflammatory.[41]

In RA, the temporal variation in cytokine secretion and joint symptoms is directed by the circadian clock, both at a systemic level through temporal regulation of signalling pathways, and at a local level by autonomous clocks present in inflammatory cells and cells exposed to proinflammatory conditions.[26] The functions of some immune cells (for example, macrophages, mast cells and T cells) are tightly regulated by the circadian clock. For example, cryptochrome proteins regulate the expression of proinflammatory cytokines through the NFκB pathway, and *Cry1*$^{-/-}$*Cry2*$^{-/-}$ mice are susceptible to aggressive collagen-induced arthritis.[42] Furthermore, *Cry1*$^{-/-}$*Cry2*$^{-/-}$ mice have higher basal expression of TNF and more severe disease than wild-type controls in a mouse model of inflammatory arthritis.[43] Circadian regulation of other inflammatory responses is shown

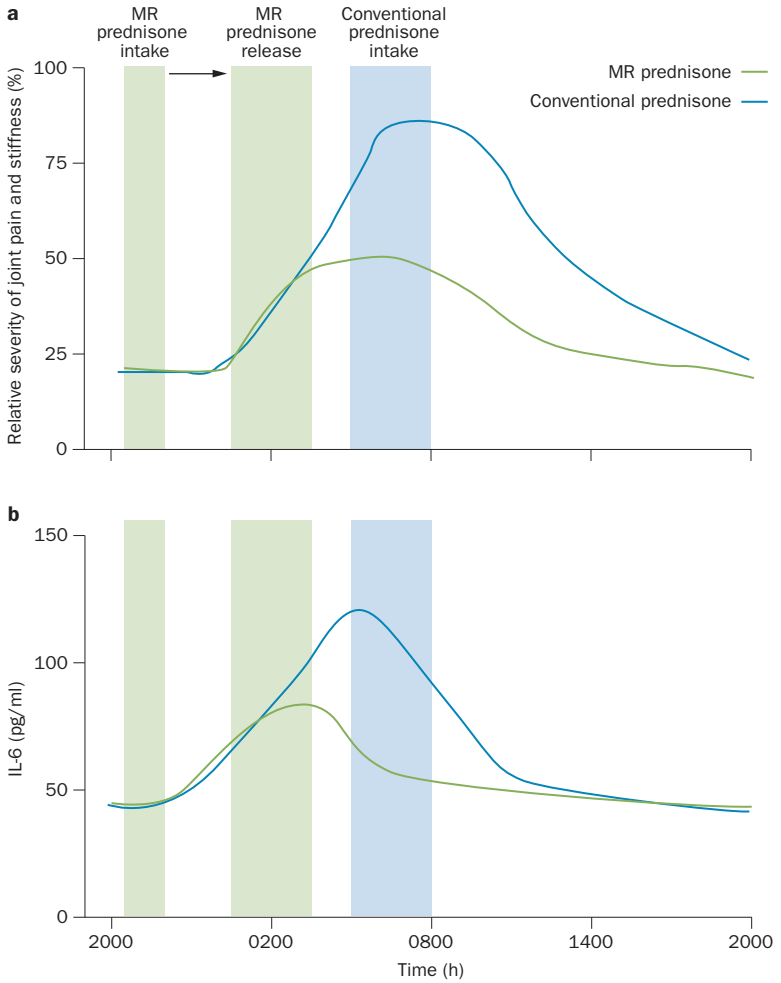

Figure 3 | Responses to conventional prednisone versus chronotherapy for RA. Conventional glucocorticoid administration between 0600 h and 0800 h is usual, but might be too late as night-time pathophysiological processes have already initiated inflammation. MR prednisone enables convenient bedtime administration (~2200 h) with release of glucocorticoids at the optimal time for suppression of proinflammatory cytokines and, consequently, reduction of joint pain and stiffness in the morning. **a** | Patients with active RA have diurnal variation in symptoms. Major symptoms such as joint pain and stiffness are usually most pronounced in the morning. **b** | These symptoms correlate with increased nocturnal levels of circulating proinflammatory cytokines, such as IL-6. Abbreviations: MR, modified release; RA, rheumatoid arthritis.

by mouse studies demonstrating that the temporal variation in response to endotoxin in macrophages is 'gated' (an effect elicited by a constant stimulus, but which is modulated by the circadian phase at which that stimulus is presented) by *Nr1d1*,[44] that mCLOCK upregulates NFκB-mediated transcription,[45] and that knockout of *Arntl* (the gene encoding Bmal1) results in hyperinflammatory responses to aerosolized inhaled endotoxin.[46] Dysregulation of circadian rhythms by behavioural manipulation also leads to exaggeration of the inflammatory response to endotoxin and increased mortality.[47] The dominant cell type driving circadian oscillation of IL-6 secretion and of pathology in RA is not known. $CD4^+$ T cells might be involved, as they possess a circadian oscillator that governs rhythmic cell proliferation and cytokine secretion in response to activating stimuli.[48] Furthermore, macrophages also possess an intrinsic clock, more than 8% of the macrophage transcriptome is under circadian control,[26] and *Bmal1* regulates diurnal oscillations in the $Ly6C^{hi}$ subset of inflammatory monocytes.[49]

Switching the timing of treatment for RA

Progress in circadian medicine has the potential to improve current therapeutic regimens for patients with RA. Treatment for RA aims to achieve remission or low disease activity.[50] Management recommendations suggest that RA is treated initially with synthetic DMARDs such as methotrexate, usually in combination with glucocorticoids.[51] If the treatment target is not reached within 3–6 months, either another synthetic DMARD or a biologic DMARD is used in accordance with risk stratification, with or without concomitant glucocorticoid therapy.[51] Therapy that recognizes the underlying chronobiology of RA might improve the benefit-to-risk balance. Nearly 40 years ago, E.C. Huskisson reported that treatment with indomethacin in the evening (once daily) controlled morning symptoms better than a morning dose.[52] In the 1980s, studies of indomethacin and flurbiprofen confirmed that an evening or bedtime regimen is more effective in controlling morning signs and symptoms of RA than either morning or midday dosing.[53,54] Although bioavailability or the half-life of these drugs might be a factor, these trial results collectively suggest that adjusting the timing of medical interventions according to biological rhythm determinants can serve as a means to optimize treatment outcomes in RA and perhaps also reduce adverse effects.[55] To some extent, this suggestion is also true for DMARD treatment with methotrexate, a drug known for its dose-dependent adverse effects. However methotrexate administration modalities also matter, such that administration of methotrexate once per week as a single dose, or in divided doses over a 24 h period, results in a reduced incidence of adverse effects and improved tolerability. One small study indicated that methotrexate chronotherapy at bedtime, synchronized to the nocturnal increase in blood TNF concentration, is well-tolerated and has superior treatment effects in patients with RA.[56]

Clearly, more research is needed to understand underlying mechanisms of chronotherapy and to derive clinically relevant conclusions to improve patient care. The most compelling evidence for successful RA chronotherapy is with glucocorticoids, with the key observation being that coordination of glucocorticoid administration with the nocturnal rise in blood IL-6 concentrations (0200 h) results in substantially reduced morning stiffness and pain compared with the same dose taken in the morning.[57,58] However, expecting patients to wake during the night to take medication is unreasonable. Modified-release (MR) prednisone enables bedtime administration with release of glucocorticoids at the optimal time for suppression of proinflammatory cytokines (Figure 3). Indeed, the CAPRA-1 (Circadian Administration of

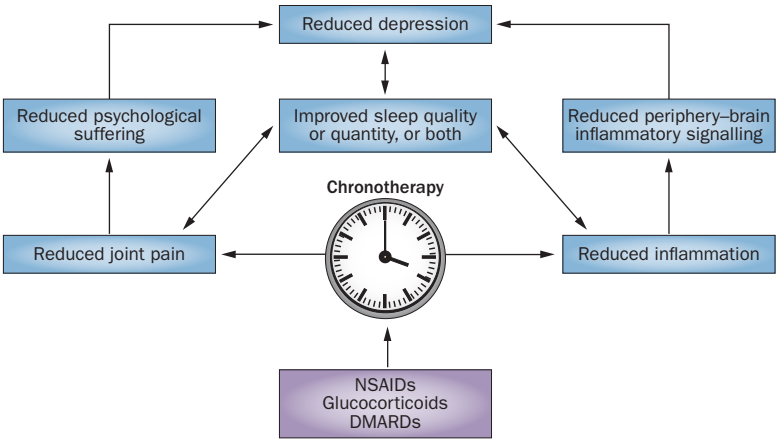

Figure 4 | Effect of RA chronotherapy on associated depression. Several pathways exist via which chronotherapy for RA might result in increased sleep quality or quantity and a reduction of comorbid depressive symptoms. The assessment of sleep and affective outcomes should be included in future trials of chronotherapy for RA. Abbreviation: RA, rheumatoid arthritis.

Prednisone in RA) clinical study found that MR prednisone reduced IL-6 levels and morning stiffness substantially more than conventional glucocorticoids.[59,60] The CAPRA-2 study compared MR prednisone with placebo and showed that the new drug increased treatment response rates and physical function, and reduced morning stiffness, severity of RA and fatigue.[61] These data have now led to the widespread support of this bench-to-bedside development.

RA is a considerable burden on patients, healthcare providers and society, with an estimated cost of €15,000 per patient per year.[62] Indirect costs owing to lost productivity might account for approximately half this expense. When selecting treatments, rheumatologists must consider both economic implications and clinical benefits.[51] Optimizing the timing of administration for currently available conventional drugs incurs no additional costs, but might improve the benefit-to-risk ratio. Although average treatment costs per patient are higher for MR prednisone than conventional prednisone, a health state-transition model generated an incremental QALY (quality-adjusted life years) of 0.044, indicating the cost-effectiveness of MR prednisone.[63] Also, adding MR prednisone to DMARD therapy might allow treatment goals to be reached in an additional 11–13% of patients, without the need for costly biologic therapy.[64] This benefit was demonstrated in a 4 month observational study that showed that switching from conventional prednisone, or 6-methylprednisolone, to MR prednisone improved outcomes, which might reduce the need for biologic treatment.[65]

Mental health

Aside from the classical core symptoms of RA, psychiatric disorders are reported to be comorbid with RA. A systematic review and meta-analysis of depressive disorders in patients with RA reported prevalence rates of major depressive disorder, confirmed by clinical interview, of 16.8% and of dysthymic disorder of 18.7%.[66] Mood disorders present during early RA[67,68] might be underrecognized by attending rheumatologists,[69] and are substantial contributors to impaired quality of life.[70]

Given the evidence that comorbid mood disorders are an issue in RA, how might chronotherapy be used to alleviate them? The first suggestion is that chronotherapy with NSAIDs, DMARDs or glucocorticoids might have the additional benefit of reducing affective symptoms. Increased relief of pain and stiffness, resulting from improved treatment efficacy with chronotherapy, might alleviate the psychological suffering associated with these symptoms and lead to decreased depression and anxiety. However, fundamental biological mechanisms might also exist through which chronotherapy could benefit mental health.

A well-described, but not fully understood, link exists between peripheral inflammation and affective disorders.[71] In preclinical models, induction of peripheral inflammation can induce long-lasting depression-like behaviour that substantially outlasts the initial sickness–behaviour response.[72,73] The precise mechanisms through which peripheral inflammation leads to such changes are unclear, but might involve neuroimmune processes in the central nervous system (CNS) triggered by signalling from the periphery via a number of routes, including peripheral sensory afferent activation, cytokine transport to the CNS, or leukocyte infiltration of the CNS. This peripheral CNS signalling leads to increased expression of central inflammatory mediators and central neuroinflammation, which is implicated in the pathophysiology of a number of psychiatric disorders, including major depression.[74,75] Similar neuroimmune processes are also postulated as providing a mechanistic link between the well-observed clinical co-occurrence of chronic pain and depression across a number of chronic physical illnesses.[76] Interestingly, in one report, rates of depression and anxiety were lower in patients with RA who were treated with TNF inhibitors than in those treated with other RA medications,[77] suggesting that DMARDs might have a direct biological effect on comorbid psychiatric disorders. Thus, chronotherapeutic tailoring of treatment with NSAIDs, DMARDs or glucocorticoids to optimally suppress proinflammatory peripheral mediators might have the additional benefit of reducing affective symptoms by the reduction of neuroimmune periphery-to-brain signalling (Figure 4). In order to address this important question, future trials of RA chronotherapy should include measures of depression as outcomes. Another possibility is the deployment of chronotherapeutic strategies to directly target affective symptoms in patients with RA. Such approaches have shown substantial promise in the treatment of bipolar disorder and major depression; however, the efficacy of such approaches in affective disorders that are comorbid with chronic physical illnesses, such as RA, has not been trialled, and so opportunities exist for the extrapolation of findings from chronotherapy trials focused on resetting or strengthening circadian rhythms to applications in rheumatology.

Sleep

Like many other chronic inflammatory diseases, sleep is disturbed in patients with RA, and can include sleep fragmentation, increased arousal and waking after sleep onset.[78,79] Sleep has a well-characterized bidirectional relationship with mood,[80] and pain, depression and sleep disturbances seem to be interconnected in RA.[81] Night-pain has been postulated as a factor contributing to increased sleep fragmentation and awakenings after sleep onset in patients with RA.[82] Chronotherapy that targets the nocturnal rise in inflammatory mediators in the blood of patients with RA might, therefore, be an effective countermeasure for reduced sleep consolidation. As experimental sleep restriction has been shown to be proinflammatory,[83] a 'virtuous cycle' might exist in which chronotherapy reduces night pain and increases the quality and duration of sleep, which in turn leads to improved inflammatory status. The CAPRA-1 study showed that MR prednisone modestly increases subjective sleep quality scores on a visual analogue scale, compared with standard glucocorticoid treatment.[59] These possibilities point to the need for a systematic collection of objective and subjective sleep data as outcomes in future trials of chronotherapy for RA.

Time for a change in approach?

A pressing need exists to optimize therapy for RA; chronotherapeutic approaches might help in this respect. Studies with drugs other than glucocorticoids are needed to evaluate the potential of chronotherapy in the treatment of RA and other chronic inflammatory diseases. Although the circadian rhythmicity of proinflammatory cytokines is an important target for chronotherapy, other humoral, immunological, endocrine and oxidative stress parameters need to be similarly evaluated. Assessing circadian regulation of signalling cascades and cellular pathophysiology are also timely, innovative and challenging fields of research. For example, in the CiRA (Circadian Rhythms of Cellular Immunity in RA) pilot study, circadian rhythms of cellular immunity were investigated in postmenopausal women with RA. Peripheral blood from patients with active RA ($n = 5$) and non-RA controls ($n = 5$) was collected every 2 h for 24 h. Circadian rhythms were detected in the relative frequency of peripheral blood cell populations: in non-RA controls but not in patients with active RA; in patients with RA but not in non-RA controls; and in both groups but with differences in peak phase, amplitude, or both amplitude and magnitude. In patients with RA, some immune cell populations lose their normal circadian rhythms, whereas others establish new 'inflammatory' circadian rhythms.[84]

Interestingly, similar reprogramming of the clock has been described in other conditions, such as endotoxaemia-induced lung inflammation[85] and chronic high-fat feeding.[86] More data needs to be collected to sufficiently explore the potential of chronotherapy in RA and other rheumatic diseases. Furthermore, the development of new small-molecule modulators of important molecular components of the circadian clock, such as Rev-erbAα and cryptochrome proteins, might provide new treatment avenues for RA.[87,88] Such developments, however, might be more prospective than the possible immediate clinical benefits offered by chronotherapeutic tailoring of existing approaches.

In this Review, we have provided examples of chronotherapeutic treatment strategies that either directly target the circadian timing system with the therapeutic aim of re-entraining desynchronized rhythms (or even prophylactically attenuating their disruption), or focus on optimal timing of drug administration with the aim of targeting specific circadian profiles of clinical markers in individual patients. Thus, the clearest examples of successful chronotherapy are those with clear time-of-day-dependent disease symptoms (for example, RA and psychiatric disorders). Surprisingly, none of the chronobiological effects of drugs and their pharmacokinetics is considered or even mentioned in official guidelines for conducting drug registration trials in humans. Moreover, entering the search term 'chronotherapy' into the ClinicalTrials.gov website currently yields only 17 hits. Given that approximately half the genome is expressed in a circadian manner when examined across all tissues, and that these circadian gene products are targets for a large percentage of commonly used drugs,[15] this response seems inadequate. One reason for the lack of chronotherapeutic trials might be that industry is not overly interested in expanding the indications for, or improving the applicability of, drugs that were approved many years ago. Thus, trials related to chronotherapy might have to be supported by funds from governments or national and international granting organizations directed at comparative effectiveness research.[89] Whether through healthcare providers or governments, obtaining the best value from approved drugs and healthcare expenditure is in the public interest. Thus, the time is ripe to translate the 'circadian concept' from bench to bedside.

Conclusions

Although the role of chronotherapy in cancer and other clinical areas is somewhat controversial,[90] the approaches we have described for chronotherapy of patients with RA are widely accepted among the rheumatology community. Similarly, chronotherapeutic treatment strategies are being established as important adjuvant therapies in other clinical domains, such as psychiatry.[91] Nevertheless, chronotherapy faces dogmatic (in other words, overarching beliefs regarding homeostasis), logistical, technical and financial hurdles. Moreover, the evidence base of chronotherapeutic interventions in RA and other rheumatic diseases is small, but expanding. Finally, it should be noted that the chronotherapy-associated gain in patient-related outcomes is substantial, but smaller than that achieved in recent years by the introduction of new drugs and the treat-to-target strategy. Therefore, we consider that chronotherapy currently has an important complementary role, but with increasing potential for the future.

1. Dallmann, R., Brown, S. A. & Gachon, F. Chronopharmacology: new insights and therapeutic implications. *Annu. Rev. Pharmacol. Toxicol.* **54**, 339–361 (2014).
2. Gillette, M. U. (Ed.) *Chronobiology: Biological Timing in Health and Disease* (Academic, 2013).
3. Hatcher, N. G. *et al.* Mass spectrometry-based discovery of circadian peptides. *Proc. Natl Acad. Sci. USA* **105**, 12527–12532 (2008).
4. Evans, J. A. & Davidson, A. J. Health consequences of circadian disruption in humans and animal models. *Prog. Mol. Biol. Transl. Sci.* **119**, 283–323 (2013).
5. Daan, S. The Colin S. Pittendrigh Lecture. Colin Pittendrigh, Jürgen Aschoff, and the natural entrainment of circadian systems. *J. Biol. Rhythms* **15**, 195–207 (2000).
6. Berson, D. M. Strange vision: ganglion cells as circadian photoreceptors. *Trends Neurosci.* **26**, 314–320 (2003).
7. Meijer, J. H., Michel, S. & Vansteensel, M. J. Processing of daily and seasonal light information in the mammalian circadian clock. *Gen. Comp. Endocrinol.* **152**, 159–164 (2007).
8. Cajochen, C., Kräuchi, K. & Wirz-Justice, A. Role of melatonin in the regulation of human circadian rhythms and sleep. *J. Neuroendocrinol.* **15**, 432–437 (2003).
9. Radogna, F., Diederich, M. & Ghibelli, L. Melatonin: a pleiotropic molecule regulating inflammation. *Biochem. Pharmacol.* **80**, 1844–1852 (2010).
10. Chung, S., Son, G. H. & Kim, K. Circadian rhythm of adrenal glucocorticoid: its regulation and clinical implications. *Biochim. Biophys. Acta* **1812**, 581–591 (2011).
11. Bollinger, T. & Schibler, U. Circadian rhythms —from genes to physiology and disease. *Swiss Med. Wkly* **144**, w13984 (2014).
12. Albrecht, U. Timing to perfection: the biology of central and peripheral circadian clocks. *Neuron* **74**, 246–260 (2012).
13. Buhr, E. D. & Takahashi, J. S. Molecular components of the mammalian circadian clock. *Handb. Exp. Pharmacol.* **2013**, 3–27 (2013).
14. Koike, N. *et al.* Transcriptional architecture and chromatin landscape of the core circadian clock in mammals. *Science* **338**, 349–354 (2012).
15. Zhang, R., Lahens, N. F., Ballance, H. I., Hughes, M. E. & Hogenesch, J. B. A circadian gene expression atlas in mammals: implications for biology and medicine. *Proc. Natl Acad. Sci. USA* **111**, 16219–16224 (2014).
16. Cho, H. *et al.* Regulation of circadian behaviour and metabolism by REV-ERB-α and REV-ERB-β. *Nature* **485**, 123–127 (2012).
17. Chung, S. *et al.* Impact of circadian nuclear receptor REV-ERBα on midbrain dopamine production and mood regulation. *Cell* **157**, 858–868 (2014).
18. Gerhart-Hines, Z. *et al.* The nuclear receptor Reverbα controls circadian thermogenic plasticity. *Nature* **503**, 410–413 (2013).
19. Foster, R. G., & Wulff, K. The rhythm of rest and excess. *Nat. Rev. Neurosci.* **6**, 407–414 (2005).
20. Karatsoreos, I. N. Links between circadian rhythms and psychiatric disease. *Front. Behav. Neurosci.* **8**, 162 (2014).
21. Li, J. Z. *et al.* Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. *Proc. Natl Acad. Sci. USA* **110**, 9950–9955 (2013).
22. Wu, J. C. *et al.* Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. *Biol. Psychiatry* **66**, 298–301 (2009).
23. Benedetti, F. *et al.* Phase advance is an actimetric correlate of antidepressant response to sleep deprivation and light therapy in bipolar depression. *Chronobiol. Int.* **24**, 921–937 (2007).
24. Benedetti, F. *et al.* Rapid treatment response of suicidal symptoms to lithium, sleep deprivation, and light therapy (chronotherapeutics) in drug-resistant bipolar depression. *J. Clin. Psychiatry* **75**, 133–140 (2014).
25. Lewy, A. J., Lefler, B. J., Emens, J. S. & Bauer, V. K. The circadian basis of winter depression. *Proc. Natl Acad. Sci. USA* **103**, 7414–7419 (2006).
26. Gibbs, J. E. & Ray, D. W. The role of the circadian clock in rheumatoid arthritis. *Arthritis Res. Ther.* **15**, 205 (2013).
27. De Cata, A., D'Agruma, L., Tarquini, R. & Mazzoccoli, G. Rheumatoid arthritis and the biological clock. *Expert Rev. Clin. Immunol.* **10**, 687–695 (2014).
28. Puttonen, S. *et al.* Is shift work a risk factor for rheumatoid arthritis? The Finnish Public Sector study. *Ann. Rheum. Dis.* **69**, 779–780 (2010).
29. Puttonen, S., Viitasalo, K. & Härmä, M. Effect of shiftwork on systemic markers of inflammation. *Chronobiol. Int.* **28**, 528–535 (2011).
30. Pan, A., Schernhammer, E. S., Sun, Q. & Hu, F. B. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. *PLoS Med.* **8**, e1001141 (2011).
31. Scott, D. L., Wolfe, F. & Huizinga, T. W. Rheumatoid arthritis. *Lancet* **376**, 1094–1108 (2010).
32. McInnes, I. B. & Schett, G. The pathogenesis of rheumatoid arthritis. *N. Engl. J. Med.* **365**, 2205–2219 (2011).
33. Buttgereit, F., Burmester, G. R., Straub, R. H., Seibel, M. J. & Zhou, H. Exogenous and endogenous glucocorticoids in rheumatic diseases. *Arthritis Rheum.* **63**, 1–9 (2011).
34. Bellamy, N., Sothern, R. B., Campbell, J. & Buchanan, W. W. Circadian rhythm in pain, stiffness, and manual dexterity in rheumatoid arthritis: relation between discomfort and disability. *Ann. Rheum. Dis.* **50**, 243–248 (1991).
35. Kouri, V. P. *et al.* Circadian timekeeping is disturbed in rheumatoid arthritis at molecular level. *PLoS ONE* **8**, e54049 (2013).
36. Perry, M. G., Kirwan, J. R., Jessop, D. S. & Hunt, L. P. Overnight variations in cortisol, interleukin 6, tumour necrosis factor α and other cytokines in people with rheumatoid arthritis. *Ann. Rheum. Dis.* **68**, 63–68 (2009).
37. Crofford, L. J. *et al.* Circadian relationships between interleukin (IL)6 and hypothalamic–pituitary–adrenal axis hormones: failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. *J. Clin. Endocrinol. Metab.* **82**, 1279–1283 (1997).
38. Arvidson, N. G. *et al.* Circadian rhythm of serum interleukin6 in rheumatoid arthritis. *Ann. Rheum. Dis.* **53**, 521–524 (1994).
39. Sulli, A. *et al.* Melatonin serum levels in rheumatoid arthritis. *Ann. NY Acad. Sci.* **966**, 276–283 (2002).
40. Hansson, I., Holmdahl, R. & Mattsson, R. The pineal hormone melatonin exaggerates development of collagen-induced arthritis in mice. *J. Neuroimmunol.* **39**, 23–30 (1992).
41. Forrest, C. M., Mackay, G. M., Stoy, N., Stone, T. W. & Darlington, L. G. Inflammatory status and kynurenine metabolism in rheumatoid arthritis treated with melatonin. *Br. J. Clin. Pharmacol.* **64**, 517–526 (2007).
42. Narasimamurthy, R. *et al.* Circadian clock protein cryptochrome regulates the expression of proinflammatory cytokines. *Proc. Natl Acad. Sci. USA* **109**, 12662–12667 (2012).
43. Hashiramoto, A. *et al.* Mammalian *clock* gene *cryptochrome* regulates arthritis via proinflammatory cytokine TNF-α. *J. Immunol.* **184**, 1560–1565 (2010).
44. Gibbs, J. E. *et al.* The nuclear receptor REV-ERBα mediates circadian regulation of innate immunity through selective regulation of inflammatory cytokines. *Proc. Natl Acad. Sci. USA* **109**, 582–587 (2012).
45. Spengler, M. L. *et al.* Core circadian protein CLOCK is a positive regulator of NFκB-mediated transcription. *Proc. Natl Acad. Sci. USA* **109**, E2457–E2465 (2012).
46. Gibbs, J. *et al.* An epithelial circadian clock controls pulmonary inflammation and glucocorticoid action. *Nat. Med.* **20**, 919–926 (2014).
47. Castanon-Cervantes, O. *et al.* Dysregulation of inflammatory responses by chronic circadian disruption. *J. Immunol.* **185**, 5796–5805 (2010).
48. Bollinger, T. *et al.* Circadian clocks in mouse and human $CD4^+$ T cells. *PLoS ONE* **6**, e29801 (2011).
49. Nguyen, K. D. *et al.* Circadian gene *Bmal1* regulates diurnal oscillations of $Ly6C^{hi}$ inflammatory monocytes. *Science* **341**, 1483–1488 (2013).
50. Smolen, J. S. *et al.* Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann. Rheum. Dis.* **69**, 631–637 (2010).
51. Smolen, J. S. *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann. Rheum. Dis.* **73**, 492–509 (2014).
52. Huskisson, E. C. in *Inflammatory Arthropathies* (Eds Huskisson, E. C. & Velo, G. P.) 99–105 (Excepta Medica. 1976).
53. Kowanko, I. C., Pownall, R., Knapp, M. S., Swannell, A. J. & Mahoney, P. G. Circadian variations in the signs and symptoms of rheumatoid arthritis and in the therapeutic effectiveness of flurbiprofen at different times of day. *Br. J. Clin. Pharmacol.* **11**, 477–484 (1981).
54. Levi, F., Le Louarn, C. & Reinberg, A. Timing optimizes sustained-release indomethacin treatment of osteoarthritis. *Clin. Pharmacol. Ther.* **37**, 77–84 (1985).
55. Haus, E., Sackett-Lundeen, L. & Smolensky, M. H. Rheumatoid arthritis: circadian rhythms in disease activity, signs and symptoms, and rationale for chronotherapy with corticosteroids and other medications. *Bull. NYU Hosp. Jt Dis.* **70** (Suppl. 1), 3–10 (2012).
56. To, H. *et al.* Methotrexate chronotherapy is effective against rheumatoid arthritis. *Chronobiol. Int.* **28**, 267–274 (2011).
57. Arvidson, N. G., Gudbjornsson, B., Larsson, A. & Hallgren, R. The timing of glucocorticoid administration in rheumatoid arthritis. *Ann. Rheum. Dis.* **56**, 27–31 (1997).
58. Cutolo, M., Straub, R. H. & Buttgereit, F. Circadian rhythms of nocturnal hormones in rheumatoid arthritis: translation from bench to bedside. *Ann. Rheum. Dis.* **67**, 905–908 (2008).
59. Buttgereit, F. *et al.* Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA1): a double-blind, randomised controlled trial. *Lancet* **371**, 205–214 (2008).
60. Buttgereit, F. *et al.* Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. *Ann. Rheum. Dis.* **69**, 1275–1280 (2010).
61. Buttgereit, F. *et al.* Low-dose prednisone chronotherapy for rheumatoid arthritis:

a randomised clinical trial (CAPRA2). *Ann. Rheum. Dis.* **72**, 204–210 (2013).
62. Franke, L. C., Ament, A. J., van de Laar, M. A., Boonen, A. & Severens, J. L. Costofillness of rheumatoid arthritis and ankylosing spondylitis. *Clin. Exp. Rheumatol.* **27**, S118–S123 (2009).
63. Dunlop, W., Iqbal, I., Khan, I., Ouwens, M. & Heron, L. Cost-effectiveness of modified-release prednisone in the treatment of moderate to severe rheumatoid arthritis with morning stiffness based on directly elicited public preference values. *Clinicoecon. Outcomes Res.* **5**, 555–564 (2013).
64. Boers, M. & Buttgereit, F. A simple model that suggests possible cost savings when modified-release prednisone 5 mg/day is added to current treatment in patients with active rheumatoid arthritis. *Rheumatology (Oxford)* **52**, 1435–1437 (2013).
65. Cutolo, M. *et al.* Efficacy of the switch to modified-release prednisone in rheumatoid arthritis patients treated with standard glucocorticoids. *Clin. Exp. Rheumatol.* **31**, 498–505 (2013).
66. Matcham, F., Rayner, L., Steer, S. & Hotopf, M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)* **52**, 2136–2148 (2013).
67. Jyrkkä, J. *et al.* Antidepressant use among persons with recent-onset rheumatoid arthritis: a nationwide register-based study in Finland. *Scand. J. Rheumatol.* **43**, 364–370 (2014).
68. Rathbun, A. M., Reed, G. W. & Harrold, L. R. The temporal relationship between depression and rheumatoid arthritis disease activity, treatment persistence and response: a systematic review. *Rheumatology (Oxford)* **52**, 1785–1794 (2013).
69. Rathbun, A. M., Harrold, L. R. & Reed, G. W. A description of patient- and rheumatologist-reported depression symptoms in an American rheumatoid arthritis registry population. *Clin. Exp. Rheumatol.* **32**, 523–532 (2014).
70. Lempp, H. *et al.* Comparative quality of life in patients with depression and rheumatoid arthritis. *Int. Rev. Psychiatry* **23**, 118–124 (2011).
71. Dantzer, R. Depression and inflammation: an intricate relationship. *Biol. Psychiatry* **71**, 4–5 (2012).
72. Anderson, S. T., Commins, S., Moynagh, P. N. & Coogan, A. N. Lipopolysaccharide-induced sepsis induces long-lasting affective changes in the mouse. *Brain Behav. Immun.* **43**, 98–109 (2014).
73. Maciel, I. S., Silva, R. B., Morrone, F. B., Calixto, J. B. & Campos, M. M. Synergistic effects of celecoxib and bupropion in a model of chronic inflammation-related depression in mice. *PLoS ONE* **8**, e77227 (2013).
74. Fineberg, A. M. & Ellman, L. M. Inflammatory cytokines and neurological and neurocognitive alterations in the course of schizophrenia. *Biol. Psychiatry* **73**, 951–966 (2013).
75. Eyre, H. A., Stuart, M. J. & Baune, B. T. A phase-specific neuroimmune model of clinical depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **54**, 265–274 (2014).
76. Walker, A. K., Kavelaars, A., Heijnen, C. J. & Dantzer, R. Neuroinflammation and comorbidity of pain and depression. *Pharmacol. Rev.* **66**, 80–101 (2014).
77. Uguz, F., Akman, C., Kucuksarac, S. & Tufekci, O. Anti-tumor necrosis factor-α therapy is associated with less frequent mood and anxiety disorders in patients with rheumatoid arthritis. *Psychiatry Clin. Neurosci.* **63**, 50–55 (2009).
78. Abad, V. C., Sarinas, P. S. & Guilleminault, C. Sleep and rheumatologic disorders. *Sleep Med. Rev.* **12**, 211–228 (2008).
79. Westhovens, R., Van der Elst, K., Matthys, A., Tran, M. & Gilloteau, I. Sleep problems in patients with rheumatoid arthritis. *J. Rheumatol.* **41**, 31–40 (2014).
80. Walker, M. P. Sleep, memory and emotion. *Prog. Brain Res.* **185**, 49–68 (2010).
81. Nicassio, P. M. *et al.* The contribution of pain and depression to self-reported sleep disturbance in patients with rheumatoid arthritis. *Pain* **153**, 107–112 (2012).
82. Lavie, P. *et al.* Actigraphic measurements of sleep in rheumatoid arthritis: comparison of patients with low back pain and healthy controls. *J. Rheumatol.* **19**, 362–365 (1992).
83. Faraut, B., Boudjeltia, K. Z., Vanhamme, L. & Kerkhofs, M. Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery. *Sleep Med. Rev.* **16**, 137–149 (2012).
84. Spies, C. M. *et al.* Circadian rhythms of cellular immunity in rheumatoid arthritis: a hypothesis generating study. *Clin. Exp. Rheumatol.* (in press).
85. Haspel, J. A. *et al.* Circadian rhythm reprogramming during lung inflammation. *Nat. Commun.* **5**, 4753 (2014).
86. Eckel-Mahan, K. L. *et al.* Reprogramming of the circadian clock by nutritional challenge. *Cell* **155**, 1464–1478 (2013).
87. Chun, S. K. *et al.* Identification and validation of cryptochrome inhibitors that modulate the molecular circadian clock. *ACS Chem. Biol.* **9**, 703–710 (2014).
88. Solt, L. A. *et al.* Regulation of circadian behaviour and metabolism by synthetic REV-ERB agonists. *Nature* **485**, 62–68 (2012).
89. Sox, H. C. & Greenfield, S. Comparative effectiveness research: a report from the Institute of Medicine. *Ann. Intern. Med.* **151**, 203–205 (2009).
90. Ortiz-Tudela, E., Mteyrek, A., Ballesta, A., Innominato, P. F. & Lévi, F. Cancer chronotherapeutics: experimental, theoretical, and clinical aspects. *Handb. Exp. Pharmacol.* **2013**, 261–288 (2013).
91. Bunney, B. G. *et al.* Circadian dysregulation of clock genes: clues to rapid treatments in major depressive disorder. *Mol. Psychiatry* http://dx.doi.org/10.1038/mp.2014.138.

Author contributions

All authors researched the data for the article, provided a substantial contribution to discussions of the content and contributed to writing the article and to review and/or editing of the manuscript before submission.