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Systematic review of drugs that modify the circadian system's phase-shifting responses to light exposure

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We searched PubMed for primary research quantifying drug modification of light-induced circadian phase-shifting in rodents. This search, conducted for work published between 1960 and 2018, yielded a total of 146 papers reporting results from 901 studies. Relevant articles were those with any extractable data on phase resetting in wildtype (non-trait selected) rodents administered a drug, alongside a vehicle/control group, near or at the time of exposure. Most circadian pharmacology experiments were done using drugs thought to act directly on either the brain's central pacemaker, the suprachiasmatic nucleus (SCN), the SCN's primary relay, the retinohypothalamic tract, secondary pathways originating from the medial/dorsal raphe nuclei and intergeniculate leaflet, or the brain's sleep-arousal centers. While the neurotransmitter systems underlying these circuits were of particular interest, including those involving glutamate, gamma-aminobutyric acid, serotonin, and acetylcholine, other signaling modalities have also been assessed, including agonists and antagonists of receptors linked to dopamine, histamine, endocannabinoids, adenosine, opioids, and second-messenger pathways downstream of glutamate receptor activation. In an effort to identify drugs that unduly influence circadian responses to light, we quantified the net effects of each drug class by ratioing the size of the phase-shift observed after administration to that observed with vehicle in a given experiment. This allowed us to organize data across the literature, compare the relative efficacy of one mechanism versus another, and clarify which drugs might best suppress or potentiate phase resetting. Aggregation of the available data in this manner suggested that several candidates might be clinically relevant as auxiliary treatments to suppress ectopic light responses during shiftwork or amplify the circadian effects of timed bright light therapy. Future empirical research will be necessary to validate these possibilities.

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INTRODUCTION

The suprachiasmatic nucleus (SCN), the central circadian pacemaker in mammals, integrates the stimulus information it receives from daily patterns of light exposure to align the phase-positioning of every organ and tissue collective in the body [1]. Over the past 50 years, the underlying pharmacology that shapes the magnitude and direction of these phase-shifting responses has been investigated almost exclusively in rodents and almost exclusively in piecemeal fashion, probing the isolated effects of one receptor manipulation in any one experiment. Efforts to synthesize this literature are lacking by comparison. Here, we report results from a systematic review of the complete rodent circadian-pharmacology literature up to 2017–2018. The objective was to quantify the relative contributions of different neurotransmitter systems to the circadian pacemaker's photic resetting and identify clinically meaningful drug targets that might be tested in humans as countermeasures for situations such as shiftwork. With rotating or fixed-night schedules, shiftworkers are exposed to many competing light signals in the morning and throughout the day in their time off [2, 3]. These signals can interfere with the SCN's interpretation of day versus night, with downstream effects that include: (1) disrupting the robustness of the sleep-wake cycle [4, 5], (2) suppressing melatonin synthesis [6], and (3) possibly seeding conditions linked to the immune-weakening effects of chronic melatonin suppression such as cancer [7, 8]. Identifying drugs that can augment light responses at night and minimize light responses during the day has the potential to strengthen the sleep-wake rhythms of night workers (e.g., nurses, public safety personnel [9]), with beneficial effects extending to many areas of mental and physical health [10–12].

MATERIALS AND METHODS

Literature search

We used a two-stage search strategy to collate published research related to the combinatory effects of light exposure and drug administration on phase shifts of the rodent circadian activity rhythm. The first stage was done by querying PubMed with the following terms connected by the Boolean operators AND/OR: "circadian," "phase shift," "light," "photic," "rodent," "mouse," "hamster," and "rat." This survey resulted in the identification of 232 unique publication hits. For the second step of the search, the "related articles" feature on PubMed was consulted to conduct secondary reviews of all papers associated with the hits. Each publication prompted 120 cross references (on average), producing a candidate pool of approximately 28,000 additional articles. All the abstracts from this pool were scanned for content related to light-induced phase shifting, with further consideration given to articles describing any pharmacology work.

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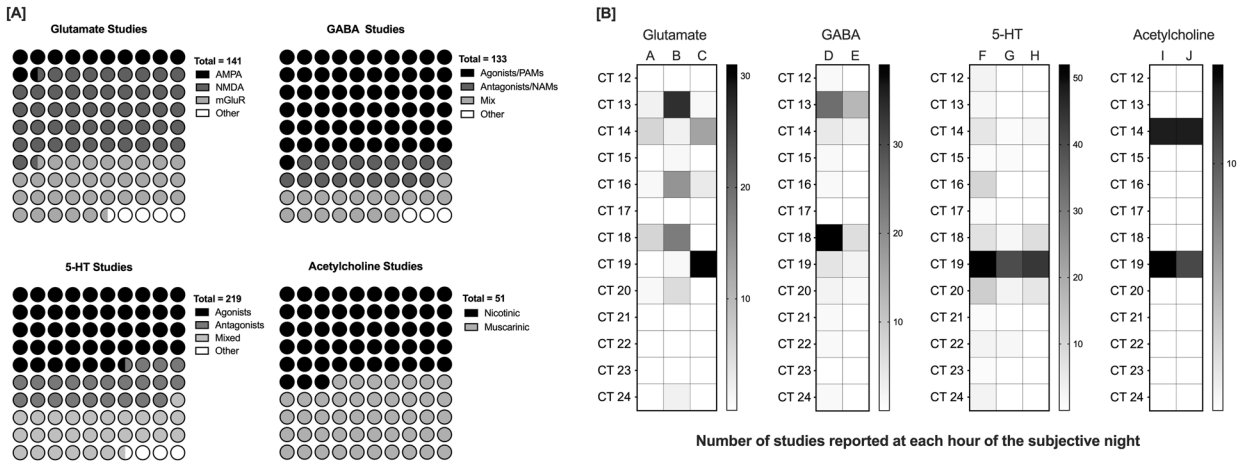


Fig. 1 Drug modulation of light-induced circadian phase shifting. A Percentage of studies conducted over the past half-century targeting different receptor classes operating within the glutamate, GABA, 5-HT, or acetylcholine transmitter systems. The total number of studies canvassed is indicated to the right of each dot plot. **B** Number of studies in the phase-shifting literature broken down by the hour of the subjective night when combined drug and light exposure were tested. Drugs grouped by those targeting or exerting effects as: A = AMPA/kainate receptors; B = NMDA receptors; C = mGluRs; D = GABA agonists; E = GABA antagonists; F = 5-HT agonists; G = 5-HT antagonists; H = 5-HT mixed agonist/antagonists; I = nicotinic receptors; and J = muscarinic receptors.

Records were independently screened by one of the three authors without the assistance of automation tools. From May 23rd to December 6th, 2017, a total of 146 papers were ultimately incorporated into the study database. Citations for these articles are alphabetically organized within Appendix A.

Inclusion-exclusion criteria and data extraction

Relevant articles were those with any extractable data on photic resetting enumerated within the main text or tables or those illustrated within a scatter plot or column graph. For inclusion, papers had to report: 1. Results from wildtype (non-trait selected) mice, hamsters, or rats; 2. Results from a group of vehicle-treated animals alongside a group of drug-treated animals; 3. Delivery of a single light pulse—of defined illuminance and duration—within a four-hour time window during the subjective night (CT12 to CT24); and 4. Use of activity rhythms (e.g., via running wheel or infrared monitoring) as circadian phase markers. Articles were excluded from further consideration if they did not meet all the aforementioned criteria or if phase-shifting data could not be unambiguously extracted from the manuscript's figures. Where available, data were gathered from the Methods sections and from the tables of the Results sections. When data were presented within graphs, the XY Scan program (http://rhig.physics.yale.edu/~ullrich/software/xyscan/) was used to extract the timing of the light pulse and the magnitude of the resulting phase shift. Feedstock data that were introduced into the analysis plan were ultimately derived from studies that measured a phase-shift of the locomotor activity rhythm after light exposure sometime between CT12 and CT24; in nearly all cases, the animals used in these experiments had been housed under constant darkness. To maximize the amount of data available and best visualize trends in drug responses, data were compiled from animals exposed to light during either the first (CT12-CT18) or second-half (CT19-CT24) of the subjective night. At either time, light exposure produces a phase-shift of endogenous and observed rhythms but the directionality of the shift changes: delays are produced in the first-half of the subjective night, while advances are typically produced in the latter half [13] in accordance to the rodent phase-response curve (PRC) to light [14, 15]. Among the caveats with this all-inclusive approach is that neurotransmitter effects on "delays" versus "advances" cannot be distinguished. Another caveat in the current study was that data were drawn/aggregated from animals without regards to the characteristics of the light emission (e.g., intensity, spectrum) that was used to elicit phase resetting. Finally, it is important to note that light or glutamate stimulation can modulate phase-shifts triggered by non-photic, arousal stimuli delivered between CT0 and CT12 [16–19], the daytime window opposite the nighttime one that is considered here. Non-photic phase responses associated with novel wheel running [20], sleep deprivation [21], or NYP injections [22, 23] are all counteracted by bright light exposure during the subjective day or subsequent administration of glutamate to the SCN in vitro [24].

Analysis plan

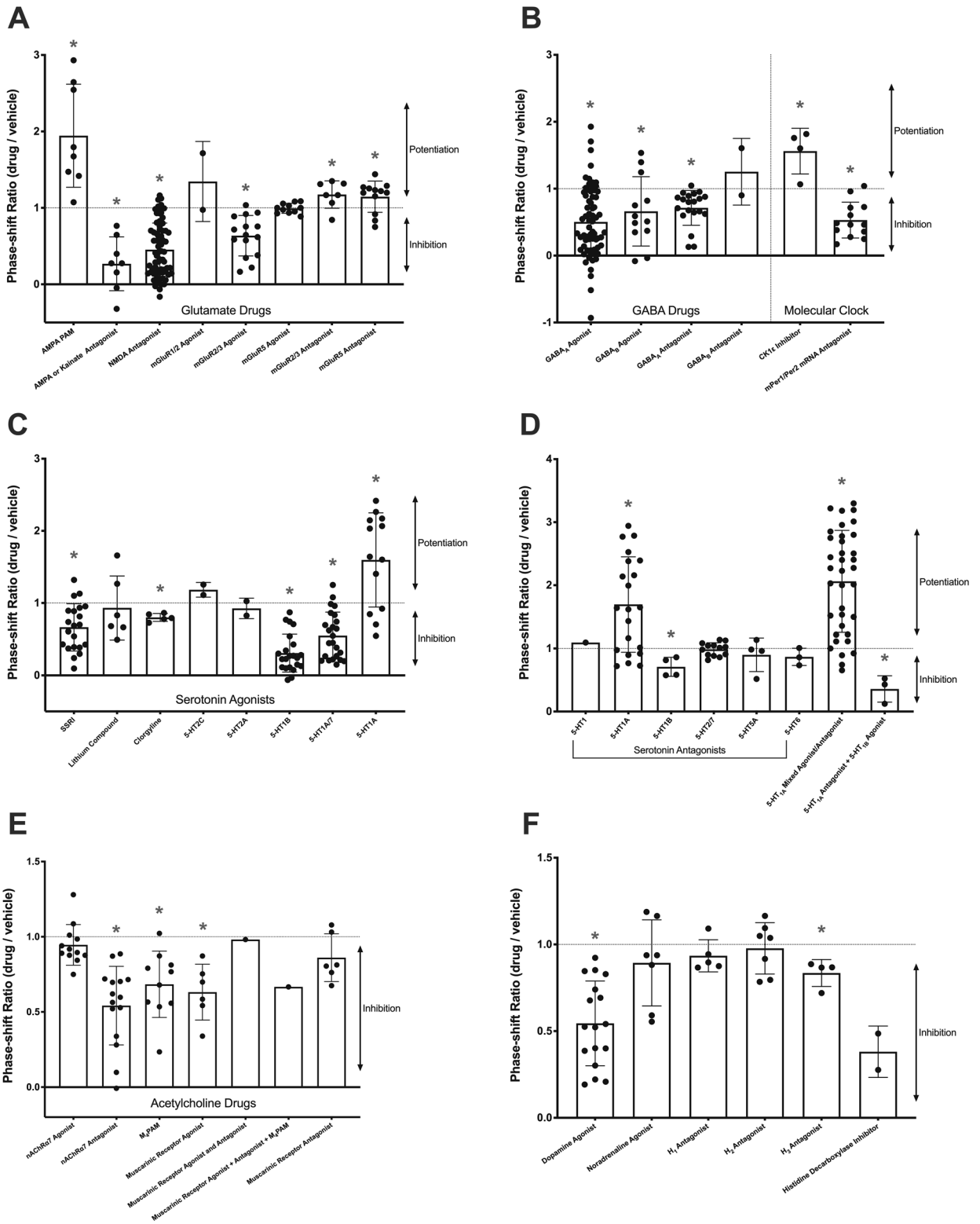
The first part of the review consisted in developing a brief descriptive summary of the 146 papers in the study database. The following parameters were calculated:

(1) percentage breakdown of studies involving drugs targeting one of the four major neurotransmitter systems operating within the SCN, including glutamate, GABA, serotonin, and acetylcholine (a dot plot of these data is available in Fig. 1A), and
(2) breakdown in the hourly intervals across the subjective night from CT12 to CT24 that the effects of light and drug administration were measured in tandem (a heatmap of these data is available in Fig. 1B).

The second part of our investigation analyzed light-induced phase-shifting data by drug class. The average phase-shift (hours) that a cohort of animals exhibited after administration of each drug was ratioed against the average response made by a control batch of animals shown the same light stimulus but given vehicle instead (i.e., [magnitude of light-induced phase-shift after drug administration in a particular study] / [magnitude of light-induced phase-shift after vehicle administration in that same study]). These rationed values were then organized according to the drug's purported mechanism of action (e.g., all the ratios from cohorts receiving an "NMDA receptor antagonist" in the study database were grouped together for subsequent analyses, likewise for those receiving a "$GABA_A$ agonist" or "$5\text{-}HT_{1A}$ antagonist", etc). Ratios settling above a value of 1 indicated that a particular drug class potentiated circadian responses to light. Alternatively, values falling under 1 indicated that it suppressed light responses. The performance of each drug class was evaluated by a one-sample *t* test to determine whether the net shift it produced relative to vehicle was statistically different than one, a score which indicates no changes in phase movements beyond those attributable to light exposure alone. Significance was set at $P = 0.05$ (two-tailed). In the Results section, please note that these ratios are sometimes used to infer percentage changes in the size of a light-induced phase-shift produced by a particular drug class. For example if a phase-shift to light exposure was on average 1.3-fold greater in groups of mice receiving a particular type of drug compared to vehicle, then we refer to that drug as increasing the phase-shift response by 30%.

RESULTS

Together, glutamate and γ aminobutyric acid (GABA) comprise the SCN's most elemental neurotransmitter systems [25–32]. Their positioning atop this signaling hierarchy has motivated 274 circadian pharmacology studies combined over the past several decades (Fig. 1A), most of which were conducted at times during



the subjective night when light exposure generates the largest delay (CT13-14) or advance shifts (CT18-19) of the locomotor activity rhythm in mice, rats, and hamsters (Fig. 1B). While several neural circuits regulate the phase of the SCN, the retinohypothalamic tract (RHT) provides the most direct modulation, originating from retinal ganglion cells co-expressing glutamate and pituitary adenylate cyclase-activating peptide (PACAP) [33–41]. The RHT forms monosynaptic connections onto terminal fields of the SCN located within the ventrolateral core region, translating photic information that the retina receives into changes in glutamatergic transmission from within the SCN [42, 43]. This target area is enriched for vasoactive intestinal peptide (VIP) positive cells expressing NMDA-type and AMPA/kainate type excitatory amino acid receptors [44–56], as well as L-type calcium channels [57].

Fig. 2 The impairing or enhancing effects of major drug classes on light-induced phase-shifting. Data are compiled from individual experiments. Each data point reflects the average phase response made by a group of drug-treated animals rationed against the average response made by a control group of vehicle-treated animals assessed at the same time (with the same light stimulus) within the same experimental series. Asterisks indicate phase movements that were statistically lower or higher than baseline (broken dotted line) when testing the average *phase-shift ratio* observed across studies associated with each drug category against an expected value of 1 (no change). Number of studies for each drug category, (**A**): AMPA PAM, $n = 8$; AMPA/Kainate Antagonist, $n = 8$; NMDA Antagonist, $n = 71$; mGluR1/2 Agonist, $n = 2$; mGluR2/3 Agonist, $n = 15$; mGluR5 agonist, $n = 11$; mGluR2/3 Antagonist, $n = 7$; mGluR5 Antagonist, $n = 12$; (**B**): $GABA_A$ Agonist, $n = 69$; $GABA_B$ Agonist, $n = 12$; $GABA_A$ Antagonist, $n = 20$; $GABA_B$ Antagonist, $n = 2$; CK1epsilon Inhibitor, $n = 4$; mPer1/Per2 Antagonist, $n = 13$; (**C**): SSRI, $n = 21$; Lithium Compound, $n = 6$; Clorgyline, $n = 5$; 5HT2C Agonist, $n = 2$; 5HT2A Agonist, $n = 2$; 5HT1B Agonist, $n = 22$; 5HT1A/7 Agonist, $n = 24$; 5HT1A Agonist, $n = 13$; (**D**): 5HT1 Antagonist, $n = 1$; 5HT1A Antagonist, $n = 21$; 5HT1B Antagonist, $n = 4$; 5HT2/7 Antagonist, $n = 13$; 5HT5A Antagonist, $n = 4$; 5HT6 Antagonist, $n = 3$; $5HT_{1A}$ Mixed Agonist/Antagonist, $n = 36$; $5HT_{1A}$ Antagonist + $5HT_{1B}$ Agonist, $n = 3$; (**E**): nAChRalpha7 Agonist, $n = 12$; nAChRalpha7 Antagonist, $n = 15$; M_4PAM, $n = 10$; Muscarinic Receptor Agonist, $n = 6$; Muscarinic Receptor Agonist and Antagonist, $n = 1$; Muscarinic Agonist + Antagonist + M_4PAM, $n = 1$; Muscarinic Receptor Antagonist, $n = 6$; (**F**): Dopamine Agonist, $n = 17$; Noradrenaline Agonist, $n = 7$; H_1 Antagonist, $n = 5$; H_2 Antagonist, $n = 7$; H_3 Antagonist, $n = 4$; and Histidine Decarboxylase Inhibitor, $n = 2$. $^*P < 0.05$, one sample *t* test.

The RHT is obligatory for light-induced phase-shifting [58]. Blocking its activity with AMPA, kainate, or NMDA receptor antagonists significantly reduces the magnitude of circadian responses. On the other hand, amplifying activity with AMPA receptor positive allosteric modulators (e.g., aniracetam) enhances responses beyond those achieved with light exposure alone (Fig. 2A). Drugs that act at Type I-III metabotropic glutamate receptors also impart functional changes in the SCN [59–61]. Agonists and antagonists of the mGluR2/3 receptor decrease and potentiate light-induced phase-resetting, respectively. mGluR5 antagonists also seem to have potentiating effects (Fig. 2A). The literature concerning glutamate and the SCN suggests that one of the most direct ways of modulating light-induced phase-shifting is at the connection point between retinal photoreception and SCN signaling.

Nearly all neurons inside the SCN proper use GABA as their predominant neurotransmitter [32, 62–69]. GABA-elicited post-synaptic currents can be hyperpolarizing (inhibitory) or depolarizing (excitatory) depending on the neuron's baseline intracellular chloride concentration set by the relative expression level of Na-K-2Cl cotransporter 1 (NKCC1) versus K-Cl cotransporter 2 (KCC2) [70–73]. NKCC1 mediates Cl^- uptake and accumulation, establishing a more negative membrane potential upon opening [71, 74]. Conversely, KCC2 opening mediates Cl^- extrusion, thereby depolarizing the membrane potential [75]. The polarity of SCN GABAergic signaling is shaped by an interplay of developmental [76–78], physiological [79], time-of-day [80–85], and seasonal factors [86–88]. In combination, these factors influence the degree to which GABA synchronizes or desynchronizes pacemaker neurons and the amplitude of the SCN's output signal [81, 89–94].

Given the highly dynamic nature of this transmitter gating, it is perhaps not surprising that both agonists and antagonists of the ionotropic $GABA_A$ receptor interfere with light-induced phase-resetting (Fig. 2B). In the case of $GABA_A$ antagonists, opposing effects are also possible based on whether the drugs are given systemically or directly infused within the SCN (Supplementary Fig. 1) [95]. Adding to the complexity still further, the phase-shifting effects of $GABA_A$ receptor activation may also depend on whether these receptors are stimulated acutely or in a sustained fashion [96].

Arguably, $GABA_B$ receptors provide a more parsimonious route for regulating circadian responses by virtue of their localization as presynaptic autoreceptors on RHT terminals [75, 97–102]. Activation of them inhibits voltage-gated Ca^{2+} channels [101, 103], thereby decreasing RHT glutamate release and behavioral shifts to light exposure (Fig. 2B). The scale of glutamate and GABA's effects on SCN light responses (from near total abrogation to threefold enhancement) exceeds the effects observed when manipulating the molecular clock mechanism (Fig. 2B, right side of divided plot). Considered in full, the literature on SCN GABA suggests that GABAergic drugs are particularly effective at modulating circadian light responses. However, owing to changes in the polarity of this transmitter system along with other nuances, the effects of $GABA_A$ agonists or antagonists may not be immediately predictable. $GABA_B$ receptor agonists, by comparison, offer clearer applicability for minimizing circadian light resetting because their activation is directly tied to reductions in RHT activity.

The single largest corpus of work vis-à-vis circadian pharmacology (n = 219 studies) has examined manipulations of serotonin (5-hydroxytryptamine, 5-HT) (Fig. 1A). These assessments have been conducted at times of night consistent with when evaluations have been done on the glutamatergic and GABAergic systems (Fig. 1B). Retinal ganglion cells contributing to the circadian system send bifurcated axons to the SCN as well as other brain regions maintaining *reciprocal connections* with the central pacemaker, including the median and dorsal raphe nuclei [104–110]. Both raphe nuclei innervate the SCN with mixed serotonergic and nonserotonergic projections, although the dorsal raphe likely uses the intergeniculate leaflet (IGL) as a relay [107, 111–114]. The role of serotonin in light-induced phase-shifting has been debated since experimentation began [115]. The bulk of data suggest that 5-HT afferents convey information to the SCN about an animal's behavioral state, particularly as it relates to sleep and arousal [116–119]. Acting through a bevy of presynaptic 5-HT autoreceptors and postsynaptic 5-HT receptors, serotonin conveys an arousal signal to the SCN that minimizes its responses to incoming light signals at the molecular [120, 121], cellular [121–124], and behavioral [125] level. An alternative corpus of work suggests that these non-photic effects might be phase dependent, or reversed, depending on the mix of 5-HT presynaptic and postsynaptic that are stimulated and/or blocked [126–132].

General enhancement of serotonin with serotonin selective reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors (e.g., clorgyline) diminishes light-induced phase resetting (Fig. 2C). Divergent effects can be achieved, however, with drugs preferentially targeting one specific 5-HT receptor pathway or another. Depending on the subtype that is activated and where it is expressed in the SCN, 5-HT drugs either increase or decrease phase-shifting. For example, $5HT_{1B}$ receptor agonists greatly impair circadian responses made to acute light exposure (by an average of 70% across studies; Fig. 2C). The effect is likely mediated by $5HT_{1B}$ receptors expressed presynaptically on RHT terminals; When these autoreceptors are activated, they inhibit glutamate transmission from the RHT to the SCN [133–138].

Further nuances can be found in two separate $5HT_{1A}$ pathways. One is formed by $5HT_{1A}$ receptors expressed postsynaptically on SCN neurons in target areas that are innervated by the median/dorsal raphe nuclei [125, 139, 140]. The other is formed by $5HT_{1A}$ receptors that are expressed somatodendritically as autoreceptors on the raphe neurons themselves [141, 142]. Depending on which 5-HT receptor population an agonist is preferential for, phase shifts to light are either reduced or potentiated (Fig. 2C, last

column of data points). In the case of agonists active at raphe-neuron $5HT_{1A}$ autoreceptors, potentiation occurs at a level similar to that observed with AMPA positive allosteric modulators (i.e., two or threefold enhancement; Fig. 2A).

In contrast to $5HT_{1A}$ *agonists* targeting SCN postsynaptic receptors, $5HT_{1A}$ postsynaptic *antagonists* amplify light responses. The amplification is similar to that achieved with $5HT_{1A}$ agonists targeting raphe-neuron autoreceptors (Fig. 2C, D). $5HT_{1A}$ mixed agonist/antagonists, parlaying the complex expression dichotomy for $5HT_{1A}$ receptor subtypes in the SCN circuitry, also enhance light-induced phase-shifting [143–148]. The pattern of all these $5HT_{1A}$-related effects is consistent with the general notion that serotonin signaling from the raphe nuclei normally serves to impair the SCN's light responses. Light-induced phase shifting can thus be enhanced when the serotonin signal is weakened by either: (1) stimulating raphe-neuron $5HT_{1A}$ autoreceptors or (2) blocking $5HT_{1A}$ postsynaptic receptors expressed by SCN neurons (Fig. 2C, D). Conversely, photic resetting can be counteracted by strategies that boost the serotonin signal, such as: (1) blocking raphe-neuron $5HT_{1A}$ autoreceptors or (2) stimulating $5HT_{1A}$ postsynaptic receptors on SCN neurons (Fig. 2C, D).

A smaller corpus of work ($n = 51$ studies) has characterized the role of acetylcholine in the central pacemaker's responses to light across the most sensitive areas of the delay and advance zones (Fig. 1A, B). The SCN is innervated by several brain regions involved with sleep-wake regulation, among them the basal forebrain and the pedunculopontine and lateral dorsal tegmentum nuclei implicated in the maintenance of rapid eye movement (REM) sleep [149–152]. These cholinergic afferents are likely involved with arousal-driven phase shifts of the SCN's rhythm and, as such, a point of entry for crosstalk between the sleep/wake and circadian timekeeping systems. Blockade of α7 nicotinic receptors reduces the magnitude of light-induced phase shifts by about 50%. A similar effect is observed when stimulating muscarinic receptors (including the M4 subtype; Fig. 2E), but the underlying neurophysiology mediating these responses remains ill-defined despite previous detection of both acetylcholine receptor classes within the SCN [153–161]. Given the unknowns in cholinergic signaling [159], drugs targeting nicotinic or muscarinic receptors may not be prime candidates for regulating circadian light responses.

Newer work has highlighted an unexpected role for dopamine (DA) in modulating adult SCN function and photoentrainment beyond a developmental window historically thought to restrict SCN sensitivity to the neurotransmitter [162–165]. DA cells from the ventral tegmental area of adult rodents connect directly to the SCN to set the pace of reentrainment following several-hour displacements of the prevailing LD cycle [166]. A few investigations have also examined the effects of dopaminergic drugs on phase-shifting. They have centered on common drugs of abuse such as cocaine and methamphetamine [167–170], which act by inhibiting the DA transporter in addition to other monoamine transporters for noradrenaline and serotonin [171, 172]. Whilst changes in DA signaling are likely to contribute to the circadian effects of cocaine and methamphetamine, extant data suggest that enhancement of serotonin signaling is likewise involved and may in fact be the primary mechanism by which monoamine transport blockers modulate the SCN [169]. In keeping with this suggestion, DA stimulants decrease the size of light-induced phase shifts (Fig. 2F). Drugs directly modifying other monoamine systems such as noradrenaline or those altering signaling pathways associated with the arousal neurotransmitter, histamine, elicit either little or no tangible effect (Fig. 2F). Interestingly, among the neurotransmitters in the brain's wake-promoting circuitry, it appears that only serotonin, acetylcholine, and dopamine are in a position to influence the SCN's phase-shifting responses to light exposure.

The raphe nuclei are not the only retinorecipient brain regions that send information regarding arousal and physiological state to the SCN so as to modify circadian light responses. Retinal ganglion cells also convey information to the SCN via an auxiliary route running through the IGL of the thalamus and the geniculohypothalamic tract (GHT) [173, 174]. The IGL is comprised of neurons expressing neuropeptide Y (NPY) [175–180]. Analogous to how serotonin operates through the median raphe nucleus, NPY neurons of the IGL provide a check on the resetting effects of light on SCN phase (likely by suppressing SCN responses to retinal input) [23, 181–192]. Accordingly, NPY agonists attenuate light-induced phase shifts (Fig. 3A), while antagonists raise the response ceiling about twofold. The enhancement with NPY antagonists exceeds what is observed with many of the remaining factors previously shown to modulate the SCN's phase-shifting drive (Fig. 3A–E). IGL cells expressing enkephalin are smaller signaling elements of this circuitry [193], yet they likewise discourage light-induced responses when binding δ-opioid receptors located on RHT presynaptic terminals [179, 194, 195]. Drug agonists or antagonists of mu (μ) and kappa (κ) opioid receptors do not appear to influence circadian resetting one way or another (Fig. 3D).

Another transmitter that has been studied in the context of the SCN's light responses is adenosine. It is one of the chemical signals that mediates the homeostatic effects of prolonged wakefulness [196–201]. When energy expenditure in the brain exceeds production after daylong periods of activity, ATP released from astrocytes is degraded by ectonucleotidases, accumulating in the extracellular space as adenosine [198, 202–204]. At threshold concentrations, adenosine then binds to receptors within the basal forebrain and ventrolateral preoptic nucleus to facilitate sleep induction [199, 205, 206]. Within the SCN, adenosine also acts on retinorecipient areas of the ventrolateral core to suppress light-induced RHT activity. Here, stimulation of adenosine A_1 receptors limits intracellular buildup of Ca^{2+}, thereby reducing excitatory synaptic transmission [207–212]. These physiological effects are manifested at the behavioral level, where adenosine A_1 receptor agonists curtail light-induced shifts of the locomotor activity rhythm by ~60%. Stimulation of other adenosine receptor subtypes A_2 and A_3 are without effect (Fig. 3C). The broader context for these data suggests that the adenosine pathway connects sleep homeostatic processes to circadian timekeeping. Through its encoding of sleep-wake history, such signaling is thought to coordinate with the SCN's photic responses in order to optimize an animal's sleep timing relative to the light transitions of the LD schedule [213].

Relative to other transmitter systems, the brain's cannabinoid system has been understudied owing to historical roadblocks set in place by U.S. drug agencies. However, the SCN expresses receptors for endogenous cannabinoids along the axons of its resident population of GABAergic neurons. Activation of the major subtype, cannabinoid receptor 1, decreases GABA release from presynaptic terminals, thus freeing target neurons from tonic inhibition and elevating postsynaptic activity in circuits intrinsic to the SCN [214–218]. Cannabinoids may impart other changes to SCN excitability by coordinating astrocytic release and extracellular accumulation of adenosine [219]. In keeping with the predicted functional consequences of elevated adenosine, cannabinoid receptor agonists greatly reduce the magnitude of phase-shifts made to acute light exposure by 80% on average (Fig. 3B). No other pharmacological manipulation appears to be as effective at inhibiting circadian light responses. As such, exogenous cannabinoids and synthetic cannabinoid antagonists are worthy of further study as possible drug regulators of circadian light responses.

Transmitter systems with a more ambiguous role in SCN signaling have also been evaluated for their effects on light-

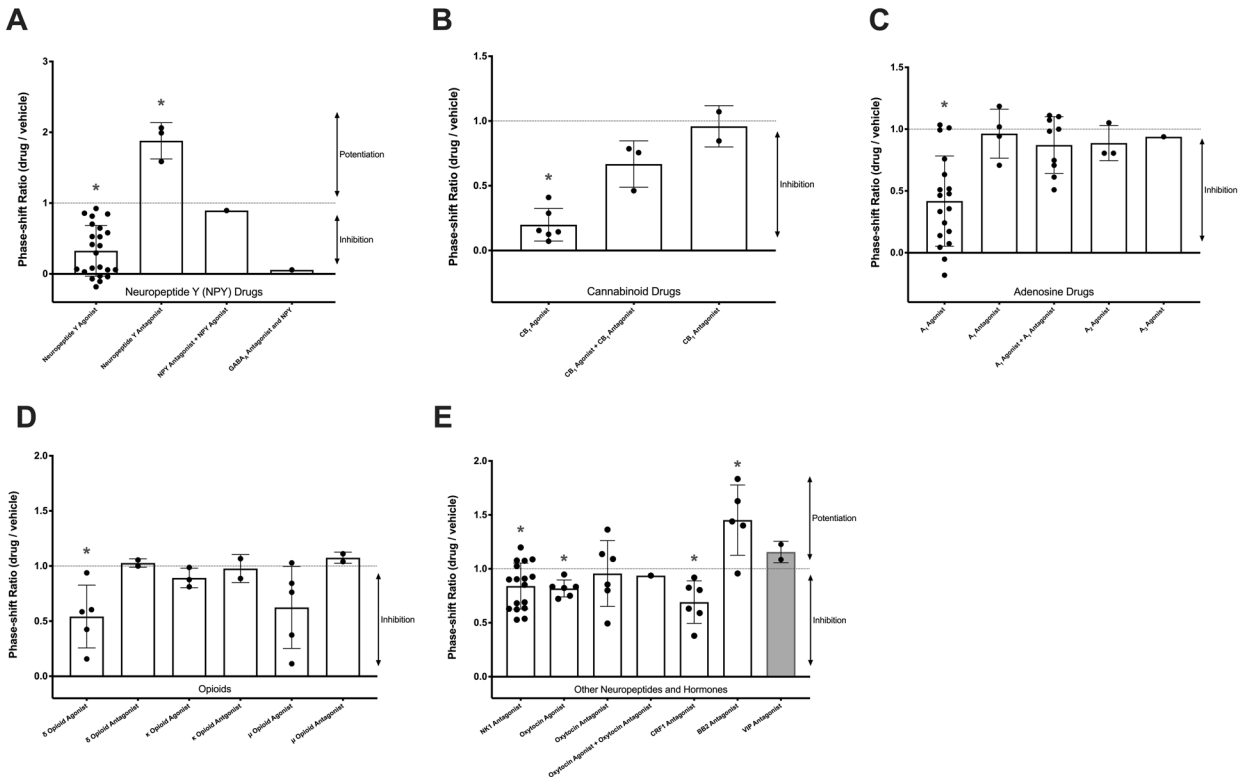


Fig. 3 Other Drug Classes. A–E The impairing or enhancing effects of other drug classes on light-induced phase-shifting. Data are compiled from individual experiments. Each data point reflects the average phase response made by a group of drug-treated animals rationed against the average response made by a control group of vehicle-treated animals assessed at the same time (with the same light stimulus) within the same experimental series. Asterisks indicate phase movements that were statistically lower or higher than baseline (broken dotted line) when testing the average phase-shift ratio observed across studies associated with each drug category against an expected value of 1 (no change). *$P < 0.05$, one sample t test.

induced phase-shifting. The SCN evinces a distinct margin of cells expressing neurokinin 1 (NK1) receptor just inside and extending to just outside its dorsolateral border [220]. This receptor binds Substance P. Unlike PACAP, Substance P's incorporation within the RHT has been difficult to resolve in studies looking to generalize the peptide's optic-tract anatomy and function across mammalian species [220–222]. In any circumstance, Substance P binding to NK1 receptor is likely a redundant mechanism that conveys photic input to the SCN. Commensurate with this notion, NK1 antagonists elicit small, but significant reductions in light-induced phase-shifting (Fig. 3E). The marginal effect of Substance P on SCN light responses stands in contrast to the more substantial effects that have been characterized with other neuropeptides and hormones, including corticotropin-releasing factor (CRF) and oxytocin.

The SCN maintains reciprocal connections with the paraventricular nucleus of the hypothalamus (PVH) [223, 224]. These nuclei coordinate the SCN's output signal to maintain daily rhythms in melatonin secretion and glucocorticoid production via timed daily release of CRF [225–227]. Oxytocin, a hormone known for its contributions to reproduction and social bonding, also bridges each nucleus [228–230]. Magnocellular neurosecretory cells of the PVH are one of the principal sites of oxytocin synthesis in the brain and both the SCN and PVH express oxytocin receptors [228, 231–233]. Interference with either CRF or oxytocin transmission dampens the magnitude of pacemaker shifts mobilized by light (Fig. 3E). These effects may comprise part of a negative feedback mechanism related to stress and/or a zeitgeber input related to social interaction that modulates the SCN's photic responses [234]. Without further research, however, these possibilities remain speculative.

Within the SCN, synchronization is effected by neuropeptides such as Gastrin-releasing peptide (GRP; a homolog of bombesin). GRP localizes to the SCN ventral retinorecipient zone and may operate as a photic resetting signal within and between SCN subdivisions [235–243]. GRP binds bombesin 2 (BB2) receptors [244–246], which exhibit a complex pharmacology amenable to drugs acting as antagonists as well as partial agonists [247–249]. Administration of BB2 drugs with partial agonist activity, a maneuver that likely facilitates GRP signaling, leads to corresponding increases in light-induced phase-shifting (Fig. 3E). The enhancement is similar to that observed after more direct manipulations of the molecular clock mechanism (Fig. 2B). In contrast to GRP, pharmacologic manipulations of other synchronization agents in the SCN, such as vasoactive intestinal peptide (VIP), show little effect (Fig. 3E). As previously suggested [249], VIP's ability to phase-shift the central pacemaker when applied to the SCN without light administration [250] might be overshadowed when light is directly used to change the SCN's phase. Changing circadian light responses by augmenting/reducing VIP activity alone might also be futile if there are any signaling redundancies between GRP and VIP [249].

More reductionistic work has examined molecular pathways in SCN neurons that tie glutamate receptor activation to changes in clock gene expression. Dose-dependent activation of AMPA and NMDA receptors via drug agonists, broad-spectrum light, or site-specific electrical stimulation of the RHT mobilizes intracellular Ca^{2+} entry [57, 251, 252]. Calcium accumulation then triggers phosphorylation of cAMP response element binding protein (CREB) [253–257] and induction of immediate-early genes such as c-fos and jun-B [258–261]. CREB transcriptional activity is driven through several convergent second-messenger pathways, including those anchored by protein kinase A (PKA) [262], calcium/calmodulin dependent kinase II (CaMKII) [263, 264], and mitogen-

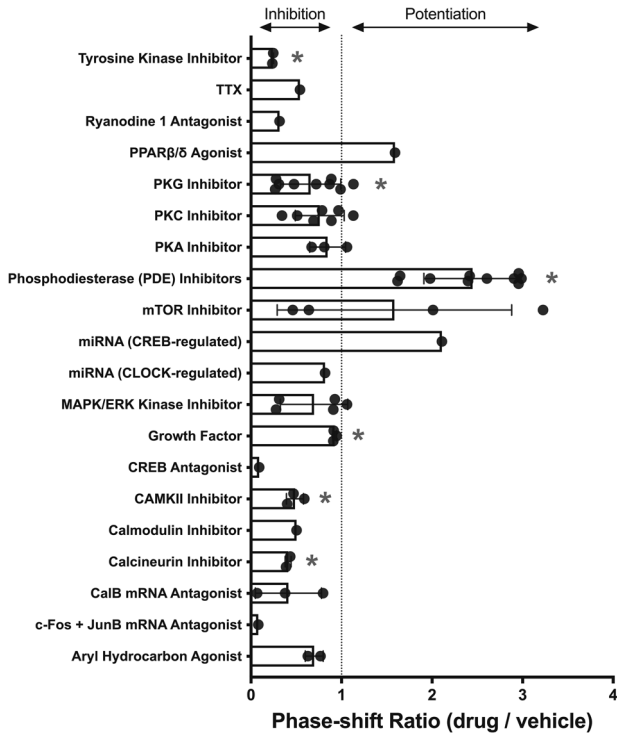


Fig. 4 The impairing or enhancing effects of drugs targeting second-messenger pathways on light-induced phase-shifting. Data are compiled from individual experiments. Each data point reflects the average phase response made by a group of drug-treated animals rationed against the average response made by a control group of vehicle-treated animals assessed at the same time (with the same light stimulus) within the same experimental series. Asterisks indicate phase movements that were statistically lower or higher than baseline (broken dotted line) when testing the average phase-shift ratio observed across studies associated with each drug class (e.g., Tyrosine Kinase Inhibitors, TTX, etc) against an expected value of 1 (no change). *$P < 0.05$, one sample *t* test.

activated protein kinase (MAPK) [265–267]. Upstream, Ca^{2+} entry also triggers nitric oxide (NO) production from nitric-oxide synthase [268–270], stimulating cGMP production [271–273] and protein kinase G (PKG) activity [274, 275].

Photic stimulation couples to SCN entrainment by way of all these signaling dynamics [276, 277]. Interruption of any one step can attenuate transcriptional activation of clock genes (i.e., Per1 and Per2) and phase-shifts made in response to light exposure (Fig. 4). On the other hand, driving these signaling pathways can produce more robust circadian responses to light, as exemplified by experiments with clinically relevant phosphodiesterase 5 inhibitors preventing the degradation of cGMP (Fig. 4). Drugs regulating the accumulation of cAMP or cGMP in SCN neurons post light treatment might represent a subtle way by which to titrate the SCN's phase-shifting response to light exposure.

A final pocket of limited work has evaluated how energy metabolism may factor into the SCN's photic resetting [181, 278–280]. Outside of direct considerations of food entrainment or timing/mistiming of food intake, available data suggest that administration of agents signaling low energy status, such as agonists of the "appetite" hormone ghrelin or glycolysis inhibitors, can reduce phase-shifts made to light exposure. By contrast, those signaling high energy status, as achieved through direct infusion of glucose or the "satiety" hormone leptin, boost light-induced phase-shifting (Fig. 5). Whether such a low-versus-high metabolic dichotomy operates endogenously to calibrate the SCN's photic responses (e.g., by way of

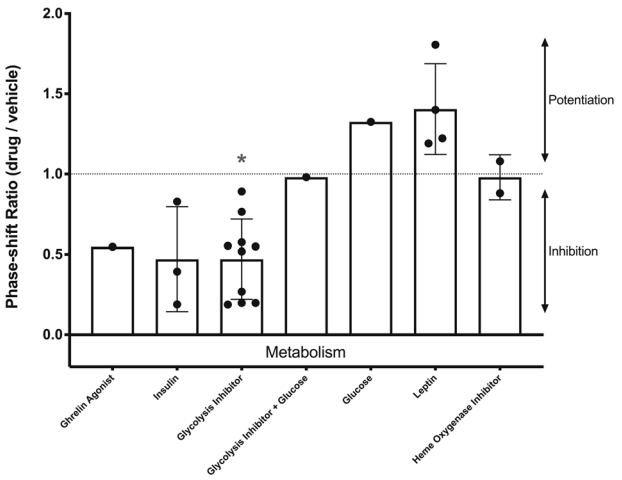


Fig. 5 The impairing or enhancing effects of metabolic drugs on light-induced phase-shifting. Data are compiled from a limited number of individual experiments. Each data point reflects the average phase response made by a group of drug-treated animals rationed against the average response made by a control group of vehicle-treated animals assessed at the same time (with the same light stimulus) within the same experimental series. Asterisks indicate phase movements that were statistically lower or higher than baseline (broken dotted line) when testing the average *phase-shift ratio* observed across studies associated with each drug class (e.g., Ghrelin agonists, Insulin, etc) against an expected value of 1 (no change). *$P < 0.05$, one sample *t* test.

acute dietary fasting or food overconsumption) is currently unknown and requires empirical study.

DISCUSSION

In the current systematic review, we have summarized the role of different neurotransmitter systems in the SCN's phase-shifting responses to light. Pulling together rodent studies employing different drug classes up to 2017–2018, we found that most investigation focused on neurotransmitters expressed within the SCN proper (e.g., GABA) or those used by SCN afferents with defined points of origin in the eye or brain, including glutamate, serotonin, acetylcholine, and NPY. The remaining experiments characterized a mix of newer and older factors that may modulate SCN light responses, such as endogenous cannabinoids, the sleep-homeostatic signal adenosine, as well as signal transduction pathways that pair RHT activity to changes in clock gene expression within SCN neurons. Extant data suggest there are many avenues by which to amplify or diminish the central pacemaker's light responses. These avenues are equally visible in traditional laboratory rodents as well as less commonly used diurnal rodents such as grass rats. In African grass rats, just as in mice or hamsters, $GABA_A$ and $GABA_B$ agonists reduce the size of phase shifts made to nighttime light exposure [84, 281], while adenosine antagonists potentiate phase-shifting [282].

For human application, the selection of one particular drug class or another may depend on the strategies that are implemented to optimize sleep-wake rhythms. For example, different strategies might be called on to optimize circadian function in workers with fixed-night schedules versus shiftworkers exposed to rapidly changing photic cycles, such as airline pilots and flight attendants. In the case of night workers, one pattern of use is conceivable. To maximize the zeitgeber strength of nighttime light exposure, individuals could use drug classes that potentiate circadian light responses during their shifts, including 5HT1A autoreceptor agonists or phosphodiesterase 5 (PDE5) inhibitors. To assure that alertness is maintained during working hours, particular emphasis

might be placed on taking PDE5 inhibitors such as Sildenafil [283], which is already approved by the U.S. Food and Drug Administration (FDA) for acute treatment of erectile dysfunction [284]. Other investigational PDE5 inhibitors are being developed for the treatment of cognitive disorders [285]. Advancements in medicinal chemistry might thus lead to other structural variations of PDE5 inhibitors that are tailored to keep night workers at peak cognitive performance while potentiating the zeitgeber strength of the prevailing light environment.

Upon ending their shifts in the morning, night workers might then transition to drugs that will prevent unwanted phase shifts to light, including $GABA_B$, $5HT_{1B}$, and cannabinoid receptor agonists. For individuals that sleep during the day, a secondary consideration might also involve whether the drug facilitates sleep. With that added criterion, $GABA_B$ and cannabinoid receptor agonists would be better candidates than $5HT_{1B}$ agonists [216]. $GABA_B$ receptor agonists cause sedation and promote sleep [286]. Humans have historically used external cannabinoids like THC (tetrahydrocannabinol) from marijuana and cannabidiol oil from hemp as recreational drugs. Though research on sleep and cannabinoids is still in its infancy, preliminary data suggest that THC can reduce sleep latency, reduce nightmares, and improve sleep quality in the presence of chronic pain [287]. Future experiments might test whether different dose schedules, and prioritizing oral intake versus inhalation, can separate cannabinoids' effects on sleep-wake rhythms versus their better-known psychogenic properties.

In the case of airline workers, travel itineraries often involve rapid transit through several time zones before returning home. Under this scenario, it may be advisable to keep the SCN of airline personnel in phase with the home time zone so that they can readjust quickly after their trip. It may also be advisable that they are as alert as possible while taking drugs that will neutralize light-induced phase shifts. With this in mind, $5HT_{1B}$ agonists such as triptans (e.g., sumatriptan and zolmitriptan) might be realistic candidates [288]. Triptans are widely prescribed compounds approved by the FDA for the treatment of cluster headaches, migraines, and migraine-associated photophobia [289, 290]. Given their relatively long half-life of ~ 24 h and favorable adverse-effect profile, triptans could limit the deleterious circadian effects of jet travel when U.S. pilots are asked to fly to western Europe and back in the span of a few days.

All of the strategies conceptualized for night workers and airline personnel are borne out of the present review and the primary work preceding it. They require empirical clinical investigation to establish their efficacy. While these strategies remain speculative, they illustrate some of the secondary and tertiary considerations that factor into the use cases for taking one drug class or another to manage circadian light responses. Undoubtedly, other considerations could also be made regarding gender, age, as well as neurodevelopmental background.

While the present study is the first to tabulate the circadian pharmacology literature, it comes with a few caveats. First, data were aggregated from experiments employing different drug doses and different sites of administration. Thus, drug effects on light-induced phase-shifting may not be perfectly representative of what would be observed when dosages are optimized. Second, to achieve some semblance of statistical power and better visualize overall trends, data were aggregated from experiments conducted in the delay (first half) as well as advance zone (second half) of the subjective night. Circadian photic responses at the beginning of the night phase might be regulated differently than those occurring in the later hours before dawn. In all cases where applicable, we failed to note any general differences in drugs effects that could be attributable to the time of night when the experiments were conducted. Finally, data were aggregated from animals without regards to the characteristics of the light emission that was used to elicit phase resetting. It is possible that circadian photic responses are regulated differently based on the properties of the light exposure, including the emission's spectrum, intensity, and duration.

The world faces unprecedented challenges to sleep and circadian health that are often met with single modality interventions rooted in either light exposure or drug treatment. The present systematic review establishes the range of neurotransmitter systems that influence the SCN's photic responses and emphasizes that this light *versus* drug distinction might be a false dichotomy when thinking about potential treatments for shift-work and the circadian disruptions associated with normative aging and chronic disease. More integrated therapies that look to synergize the effects of light exposure with FDA-approved drugs (or substances generally recognized as safe) might offer better performing treatment alternatives.

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AUTHOR CONTRIBUTIONS

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