Antidepressants and Circadian Rhythm

Subjects: Neurosciences

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Circadian oscillations alter drug absorption, distribution, metabolism, and excretion (ADME) as well as intracellular signaling systems, target molecules (e.g., receptors, transporters, and enzymes), and gene transcription. There is a positive influence of drug dosing-time on the efficacy of depression therapy. On the other hand, antidepressants have also demonstrated to modulate circadian rhythmicity and sleep–wake cycles.

antidepressant circadian rhythm chronopharmacokinetics chrono-pharmacodynamics

1. Introduction

All organisms display biological processes with rhythmic oscillations of 24 h periodicity defined as circadian rhythms. Among them is the sleep–wake cycle associated with the sleep hormone melatonin, which has a 24 h-variation [1]. In a process regulated by noradrenergic and neuropeptidergic signaling, the pineal gland converts serotonin (5-hydroxytryptamine; 5-HT) to melatonin, which is then released into the systemic circulation [2]. Melatonin secretion is enhanced by darkness and inhibited by light, achieving plasma peak levels between 2h00 and 4h00 in the morning [2]. Other biological processes are repeated throughout the 24 h (i.e., ultradian rhythms) such as blood circulation, respiration, heart rate, and thermoregulation [3]. If repeated for periods longer than 24 h, rhythms are known as infradian, such as the menstrual cycle or seasonal rhythms [4].

At a molecular level, circadian rhythms are controlled by positive and negative feedback loops that dictate the transcription and translation of clock-genes [5]. The transcription factors, brain and muscle ARNT-like 1 (BMAL1) and circadian locomotor output cycles kaput (CLOCK), dimerize and bind to E-box or E-box-like elements of the promotor region of clock-genes, inducing the transcription of rhythmic clock genes Period 1 and 2 (PER1 and PER2) and cryptochrome (CRY) [6]. In the nucleus, the corresponding expressed proteins PER and CRY inhibit BMAL1:CLOCK heterodimerization in a negative feedback loop. The PER and CRY display peak levels at the end of the day and decrease during the night, in opposition to BMAL1:CLOCK activity [6]. Simultaneously, a secondary mechanism mediated by retinoid-related orphan receptors (RORs) and reverse erythroblastosis virus α (REV-ERBα) induce and inhibit BMAL1 transcription, respectively [5][7].

In mammals, the central clock is found in the suprachiasmatic nucleus (SCN) located in the medio-frontal hypothalamus. The SCN is responsible for maintaining all body cells synchronized by directly or indirectly adjusting peripheral clocks through the synthesis of hormones, such as melatonin or cortisol [5][8]. For instance, neuronal and hormonal clock outputs regulate cell growth, renal filtration, cognition, nutrient metabolism, and immune function [9]. Sunlight, temperature, or food intake are known time-givers (zeitgebers in German), i.e., external factors that

modulate circadian rhythms [10]. Light signals are received by visual photoreceptors and retinal photosensitive ganglion cells, and the nerve impulse is then transmitted to the SCN by demyelinated axons via retinohypothalamic tract [5].

A deficient stimulation of post-synaptic neurons by norepinephrine (NE) and 5-HT is one of the principal factors underlying the physiopathology of depression [11]. The mechanism of action of most antidepressant drugs relies on slowing the reuptake and thus raising the concentration of those neurotransmitters in the synaptic cleft, increasing neurotransmission and the relief of depressive symptoms [12]. The classification of antidepressant drugs is associated with their respective mechanism of action: selective 5-HT reuptake inhibitors (SSRIs), 5-HT and NE reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants [13]. New classifications have been proposed by regional and international organizations, including European, Asian, American, and International Colleges of Neuropsychopharmacology and International Union of Basic and Clinical Pharmacology. These classifications rely on a pharmacologically-driven nomenclature focusing on approved indications, efficacy, side effects, and neurobiology, but until today, none have been unanimously accepted [14][15]. Antidepressants are usually applied in chronic treatments for long periods of time, despite revealing several side effects. In particular, TCAs exhibit poor tolerability and adverse effects, such as dry mouth, tremors, blurred vision, body weight gain, memory disorders, postural hypotension, and gastrointestinal disturbances and sedation, which ultimately undermine adherence to treatment [16][17]. Since depression is usually worse in the morning, antidepressants can be administered in this period, although their side effects may shift dosing to bedtime [18]. Even so, less than 50% of depressed patients achieve remission following several pharmacological interventions.

Based on the aforementioned bidirectional interactions between circadian rhythms and depression, interest in chronotherapy with antidepressants has increased exponentially [19]. Pharmacokinetic processes, specifically, absorption, distribution, metabolism, and excretion (ADME), present time-dependent oscillations that can lead to different concentrations in the plasma and tissues and, therefore, distinct therapeutic effects [20]. Complementarily, pharmacodynamic studies describe the association between drug concentrations and their effects [21]. The role of clock genes on antidepressant targets seem to influence antidepressant efficacy and side effects during the day [22][23].

Chronopharmacokinetics, chrono-pharmacodynamics, and chronotoxicology are hence defined by differences in pharmacokinetics and pharmacodynamics due to biological rhythms in ADME or in therapeutic and toxic effects, respectively [24][25]. Variations with clinical impact must be considered to adjust the dosing-time of an antidepressant, in order to improve its benefits [26].

2. Pharmacokinetics of Antidepressants

2.1. Circadian Rhythm Effect on Pharmacokinetic Stages

2.1.1. Absorption

Chronopharmacological studies with antidepressants are often performed in vivo. Light is a strong zeitgeber in rodents, which display an active phase during the night. For this reason, studies are usually performed under a 12h00 light–12h00 dark cycle, during which drugs are administered at different zeitgeber times (ZT). The ZT0 corresponds to the moment that lights are turned on and ZT12 when lights are turned off [27]. In contrast, chronotherapy in humans needs to consider zeitgeber factors other than light, namely mealtime, oxygen levels, temperature, and exercise [27]. Pharmacokinetic alterations at different drug dosing times are associated with intrinsic circadian rhythms in several tissues that are also involved in physiological ADME (**Figure 1**).

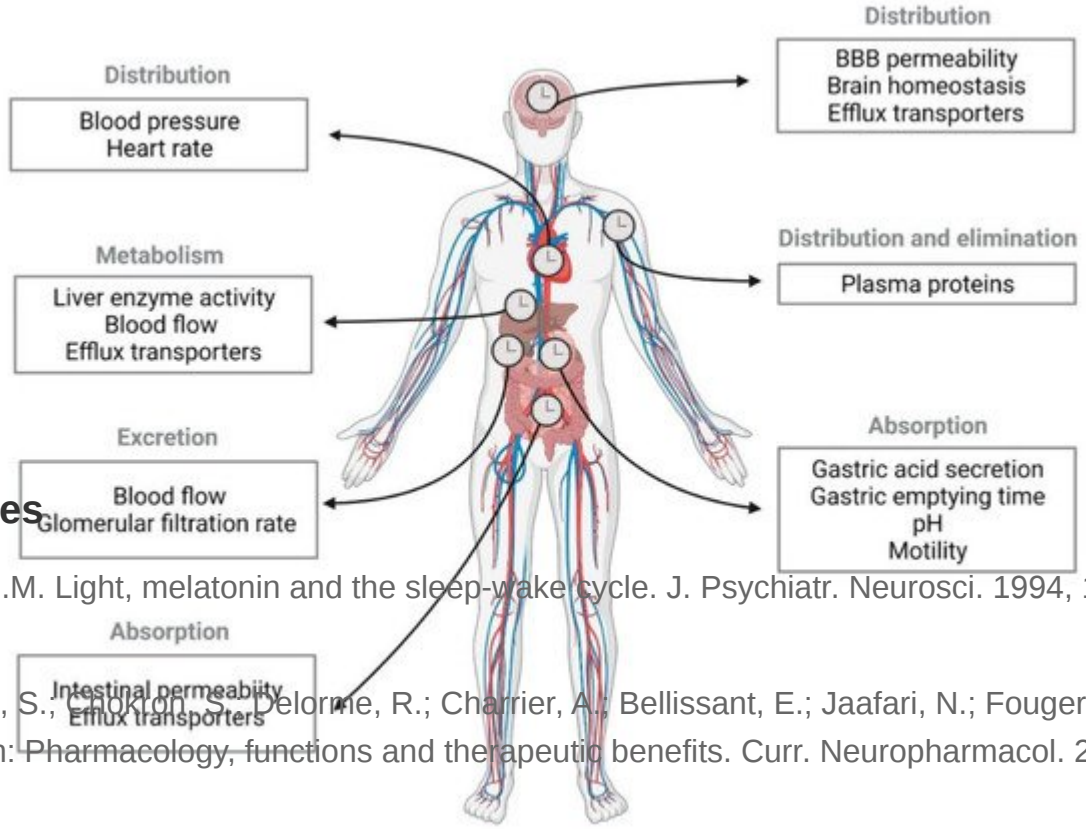

Figure 1. Physiological processes regulated by circadian rhythms with strong effect on the pharmacokinetics of antidepressants. BBB, blood–brain barrier.

Since antidepressants are orally administered, their bioavailability depends not only on their physicochemical properties, such as lipophilicity, but also on physiological processes of the digestive system modulated by circadian rhythms that may be disrupted in depressed patients [28].

Although the mechanism of action of trimipramine is not fully characterized, it is known to be a TCA that differs from others, particularly because it does not directly inhibit reuptake transporters, namely the 5-HT transporter (SERT) or NE reuptake transporter (NET) [29]. Chronopharmacokinetic studies in humans treated with two oral formulations of the trimipramine (solution and tablet) showed that tablets seem to be less affected by dosing time (**Table 1**) [30]. Importantly, drug absorption remains faster after solution administration than tablets administration.

References

1. Brown, G.M. Light, melatonin and the sleep-wake cycle. J. Psychiatr. Neurosci. 1994, 19, 345–353.
2. Tordjman, S.; Chokron, S.; Delorme, R.; Charrier, A.; Bellissant, E.; Jaafari, N.; Fougerou, C. Melatonin: Pharmacology, functions and therapeutic benefits. Curr. Neuropharmacol. 2017, 15, 434–443.
3. Brodsky, V.Y. Circahoralian (ultradian) metabolic rhythms. Biochemistry 2014, 79, 483–495.
4. Prendergast, B.J.; Nelson, R.J.; Zucker, I. 19—Mammalian seasonal rhythms: Behavior and neuroendocrine substrates. In Hormones, Brain and Behavior; Pfaff, D.W., Arnold, A.P., Fahrbach, S.E., Etgen, A.M., Rubin, R.T., Eds.; Academic Press: Cambridge, MA, USA, 2002; pp. 93–156.
5. Pilorz, V.; Helfrich-Förster, C.; Oster, H. The role of the circadian clock system in physiology. Pflug. Arch. 2018, 470, 227–239.
6. Robinson, I.; Reddy, A.B. Molecular mechanisms of the circadian clockwork in mammals. FEBS Lett. 2014, 588, 2477–2483.
7. Preitner, N.; Damiola, F.; Molina, L.-L.; Zakany, J.; Duboule, D.; Albrecht, U.; Schibler, U. The orphan nuclear receptor REV-ERBα controls circadian transcription within the positive limb of the mammalian circadian oscillator. Cell 2002, 110, 251–260.

Solutions demonstrated significantly higher maximum concentration (Cmax), lower time to reach Cmax (tmax), and lower mean residence time (MRT) in the morning (under fasting conditions) than at night (after a meal).

Table 1. Chronopharmacokinetic parameters of antidepressants in human studies.

Antidepressant or Active Metabolite	Subjects	Study Design	Daily Dose (mg)	Duration (Days)	Formulation	Time of Administration	Plasma Pharmacokinetic Parameters							Ref.
							tmax (h)	Cmax (mg/L)	AUC (mg.h/L)	t1/2β (h)	kel (h^{-1})	ka (h^{-1})	MRT (h)	
Amitriptyline	10 healthy subjects (♂), 22–31 years old.	Crossover	50	21	Injectable solution	9h00	3.2 *	96.1	1270	15.7	-	0.36 *	-	[23]
						21h00	4.4 *	72.8	1224	17.2	-	0.25 *	-	
Nortriptyline	10 healthy subjects (♂), 22–30 years old.	Crossover	100	14	Oral formulation: 25 mg capsules	9h00	6.2	32	730	15.0	-	-	-	[31]
						21h00	8.8	31	730	16.0	-	-	-	
Trimipramine	12 healthy subjects (6 ♀, 6 ♂), 22–37 years old.	Crossover	100	15	Oral formulation: 100 mg tablet	8h00	2.5	37.8	362	10.9	-	-	10.8	[30]
						20h00	2.8	39.2	376	9.9	-	-	11.5	
					Oral formulation: solution	8h00	1.5 *	48.2 *	372	9.9	-	-	9.8 *	
						20h00	2.5 *	28.8 *	322	11.1	-	-	11.8 *	
Sertraline	10 healthy subjects (♂), 18–45 years old.	Crossover	100	1	Oral formulation: 100 mg tablet	Morning	7.0	24.5	0.664	20.0	0.0347	-	-	[32]
						Evening	7.3	24.4	0.705	20.8	0.0333	-	-	

Note: Only average values are presented for pharmacokinetic parameters, and some were converted to uniform units. Abbreviations: AUC, area under the curve; Cmax, maximum concentration; ka, constant absorption rate; kel, constant elimination rate; MRT, mean residence time; t1/2β, elimination half-life time; tmax, time to reach the maximum concentration. * Statistically significant values (* $p < 0.05$).

8. Honma, S. The mammalian circadian system: A hierarchical multi-oscillator structure for generating circadian rhythm. J. Physiol. Sci. 2018, 68, 207–219.

9. Buijs, R.M.; Kalsbeek, A. Hypothalamic integration of central and peripheral clocks. Nat. Rev. Neurosci. 2001, 2, 521–526.

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17. Uher, R.; Farmer, A.; Henigsberg, N.; Rietschel, M.; Mors, O.; Maier, W.; Kozel, D.; Hauser, J.; Souery, D.; Placentino, A.; et al. Adverse reactions to antidepressants. Br. J. Psychiatry 2009, 195, 202–210.

18. Kelly, K.; Posternak, M.; Alpert, J.E. Toward achieving optimal response: Understanding and managing antidepressant side effects. Dialogues Clin. Neurosci. 2008, 10, 409–418.

19. Martiny, K.; Refsgaard, E.; Lund, V.; Lunde, M.; Thougaard, B.; Lindberg, L.; Bech, P. Maintained superiority of chronotherapeutics vs. exercise in a 20-week randomized follow-up trial in major depression. Acta. Psychiatr. Scand. 2015, 131, 446–457.

20. Bicker, J.; Alves, G.; Falcao, A.; Fortuna, A. Timing in drug absorption and disposition: The past, present, and future of chronopharmacokinetics. Br. J. Pharm. 2020, 177, 2215–2239.

21. Keller, F.; Hann, A. Clinical Pharmacodynamics: Principles of drug response and alterations in kidney disease. Clin. J. Am. Soc. Nephrol. 2018, 13, 1413–1420.

Intestinal permeability shows daily rhythmic variations due to expression of tight junction proteins that regulate the epithelial paracellular pathway [33]. In the small intestine, mRNA levels of occludin and claudin-3 were higher during the dark phase than the late light phase and inversely associated with paracellular permeability data [34].

From another point of view, it is important to bear in mind that several antidepressant drugs are known as substrates of efflux transmembrane ATP-binding cassette (ABC) proteins, including P-glycoprotein (P-gp, ABCB1; MDR1) [35][36][37][38][39] and breast cancer resistance protein (BCRP; ABCG2) [40]. These transporters are expressed in several tissues, namely the intestine, kidney, liver, and blood–brain barrier (BBB). They reduce the bioavailability, facilitate the elimination, and hamper the access of compounds to the brain, including antidepressant drugs [41]. The expression of P-gp in the intestine is modulated by proline- and acid-rich basic leucine zipper (PAR bZIP) proteins, particularly hepatic leukemia factor (HLF), whose expression is regulated by core oscillator components [42]. The HLF and E4 promoter binding protein-4 (E4BP4), a putative antagonist of PAR bZIP proteins, respectively, increase and decrease the mRNA levels and expression of P-gp [43]. In the mouse intestine, Mdr1a mRNA levels exhibit a significant 24 h daily variation, increasing during the light phase with a peak at ZT12, when the lights go off [43][44]. Similarly, in the rat jejunum, P-gp mRNA varies 5.4-fold with the circadian time [45]. Consistent with the daily rhythmicity observed in total protein with a peak level at ZT8, the P-gp function in the intestine is significantly higher at ZT12 than ZT0 [44]. Additionally, feeding patterns and gender also influence the expression and activities of the ABC transporters during the day, since circadian amplitudes of mRNA and protein levels of P-gp in the ileum are larger in female mice than in male mice [46].

2.1.2. Distribution

The cardiovascular system is susceptible to circadian rhythmicity since blood pressure, heart rate, and plasma protein levels display daily variations [47][48]. The blood pressure of mammals has a 24 h cycle with a peak during their active phase and a 10–20% slope at rest phase, along with a 17% daily fluctuation of total plasma proteins [49][50]. Particularly for antidepressant drugs that are highly protein-bound, distribution is strongly affected by the presence of plasma proteins, mainly albumin and α1-acid glycoprotein [51][52]. A study performed in rats demonstrated that plasma protein levels are higher in the active phase [50]. Furthermore, in healthy humans, α1-acid glycoprotein plasma levels are also increased during the active phase [53]. Hence, these protein fluctuations may be important to adjust the dosing-time of highly protein-bound antidepressants since differences of unbound fraction and tissue exposure can affect drug efficacy and toxicity [54]. A single intragastric administration of amitriptyline in rats (64 mg/kg) at six different time-points revealed highest bioavailability at the end of the active phase (ZT22) [54]. In fact, the total drug exposure was higher in the beginning of the rest phase, even though the ka after intragastric administration was unaltered during the light–dark cycle [54]. Exposure in liver and lung, given by area under the concentration–time curve (AUC), showed a 24 h oscillation (peak at ZT4). Moreover, multi-dosing for 10 days demonstrated significantly higher AUC values in liver, lung, and kidney tissues in the light than in the dark phase [54]. These results may be linked to the reduction of plasma protein levels during the light phase, since amitriptyline is a highly protein-bound drug (95%) [55].

22. Kawai, H.; Kodaira, N.; Tanaka, C.; Ishibashi, T.; Kudo, N.; Kawashima, Y.; Mitsumoto, A. Time of administration of acute or chronic doses of imipramine affects its antidepressant action in rats. J. Circadian Rhythm. 2018, 16, 5.

23. Nakano, S.; Hollister, L.E. Chronopharmacology of amitriptyline. Clin. Pharm. 1983, 33, 453–459.

24. Erkekoglu, P.; Baydar, T. Chronopharmacodynamics of drugs in toxicological aspects: A short review for clinical pharmacists and pharmacy practitioners. J. Res. Pharm. Pract. 2012, 1, 41–47.

25. Liu, J.; Li, H.; Xu, S.; Xu, Y.; Liu, C. Circadian Clock Gene Expression and Drug/Toxicant Interactions as Novel Targets of Chronopharmacology and Chronotoxicology; InTechOpen: London, UK, 2018.

26. Ruben, M.D.; Smith, D.F.; FitzGerald, G.A.; Hogenesch, J.B. Dosing time matters. Science 2019, 365, 547–549.

27. Gaspar, L.S.; Álvaro, A.R.; Carmo-Silva, S.; Mendes, A.F.; Relógio, A.; Cavadas, C. The importance of determining circadian parameters in pharmacological studies. Br. J. Pharm. 2019, 176, 2827–2847.

28. Dallmann, R.; Brown, S.A.; Gachon, F. Chronopharmacology: New insights and therapeutic implications. Annu. Rev. Pharm. Toxicol. 2014, 54, 339–361.

29. Haenisch, B.; Hiemke, C.; Bonisch, H. Inhibitory potencies of trimipramine and its main metabolites at human monoamine and organic cation transporters. Psychopharmacology 2011, 217, 289–295.

30. Bougerolle, A.M.; Chabard, J.L.; Jbilou, M.; Dordain, G.; Eschalier, A.; Aumaître, O.; Gaillot, J.; Pironi, J.J.; Petit, J.; Berger, J.A. Chronopharmacokinetic and bioequivalence studies of two formulations of trimipramine after oral administration in man. Eur. J. Drug. Metab. Pharm. 1989, 14, 139–144.

31. Nakano, S.; Hollister, L.E. No circadian effect on nortriptyline kinetics in man. Clin. Pharm. 1978, 23, 199–203.

32. Ronfeld, R.A.; Wilner, K.D.; Baris, B.A. Sertraline: Chronopharmacokinetics and the effect of coadministration with food. Clin. Pharm. 1997, 32, 50–55.

33. Oh-oka, K.; Kono, H.; Ishimaru, K.; Miyake, K.; Kubota, T.; Ogawa, H.; Okumura, K.; Shibata, S.; Nakao, A. Expressions of tight junction proteins Occludin and Claudin-1 are under the circadian control in the mouse large intestine: Implications in intestinal permeability and susceptibility to colitis. PLoS ONE 2014, 9, e98016.

34. Tanabe, K.; Kitagawa, E.; Wada, M.; Haraguchi, A.; Orihara, K.; Tahara, Y.; Nakao, A.; Shibata, S. Antigen exposure in the late light period induces severe symptoms of food allergy in an OVA-allergic mouse model. Sci. Rep. 2015, 5, 14424.

35. Uhr, M.; Grauer, M.T. abcb1ab P-glycoprotein is involved in the uptake of citalopram and
trimipramine into the brain of mice. J. Psychiatr. Res. 2003, 37, 179–185.
36. Bundgaard, C.; Eneberg, E.; Sanchez, C. P-glycoprotein differentially affects escitalopram,
levomilnacipran, vilazodone and vortioxetine transport at the mouse blood-brain barrier in vivo.
Neuropharmacology 2016, 103, 104–111.
37. O'Brien, F.E.; O'Connor, R.M.; Clarke, G.; Dinan, T.G.; Griffin, B.T.; Cryan, J.F. P-glycoprotein
inhibition increases the brain distribution and antidepressant-like activity of escitalopram in
rodents. Neuropsychopharmacology 2013, 38, 2209–2219.
38. Uhr, M.; Steckler, T.; Yassouridis, A.; Holsboer, F. Penetration of amitriptyline, but not of fluoxetine,
into brain is enhanced in mice with blood-brain barrier deficiency due to Mdr1a P-glycoprotein
gene disruption. Neuropsychopharmacology 2000, 22, 380–387.
39. Spieler, D.; Namendorf, C.; Namendorf, T.; Uhr, M. abcb1ab p-glycoprotein is involved in the
uptake of the novel antidepressant vortioxetine into the brain of mice. J. Psychiatr. Res. 2019,
109, 48–51.
40. Feng, S.; Zheng, L.; Tang, S.; Gu, J.; Jiang, X.; Wang, L. In-vitro and in situ assessment of the
efflux of five antidepressants by breast cancer resistance protein. J. Pharm. Pharm. 2019, 71,
1133–1141.
41. O'Leary, O.F.; Dinan, T.G.; Cryan, J.F. Faster, better, stronger: Towards new antidepressant
therapeutic strategies. Eur. J. Pharm. 2015, 753, 32–50.
42. Gachon, F.; Olela, F.F.; Schaad, O.; Descombes, P.; Schibler, U. The circadian PAR-domain basic
leucine zipper transcription factors DBP, TEF, and HLF modulate basal and inducible xenobiotic
detoxification. Cell. Metab. 2006, 4, 25–36.
43. Murakami, Y.; Higashi, Y.; Matsunaga, N.; Koyanagi, S.; Ohdo, S. Circadian clock-controlled
intestinal expression of the multidrug-resistance gene mdr1a in mice. Gastroenterology 2008,
135, 1636–1644.

2.1.3. Metabolism and Excretion

44. Ando, H.; Yanagihara, H.; Sugimoto, K.; Hayashi, Y.; Tsuruoka, S.; Takamura, T.; Kaneko, S.;
Fujimura, A. Daily rhythms of P-glycoprotein expression in mice. Chronobiol. Int. 2005, 22, 655–
665.
45. Stearns, A.T.; Balakrishnan, A.; Rhoads, D.B.; Ashley, S.W.; Tavakkoli, A.; Duman, A. Diurnal
rhythmicity in the transcription of jejunal drug transporters. J. Pharm. Sci. 2008, 103, 1444–1453.
46. Okyar, A.; Kumar, S.A.; Filipski, E.; Piccolo, E.; Ozturk, N.; Xandri-Monje, H.; Pala, Z.; Abraham,
K.; Gomes, A.; Orman, M.N.; et al. Sex-, feeding-, and circadian time-dependency of P-
glycoprotein expression and activity—implications for mechanistic pharmacokinetics modeling.
Sci. Rep. 2019, 9, 10505.

47. Chen, Y.; Yang, C. Recent advances in circadian rhythms in cardiovascular system. Front. Pharmacol. 2015, 6, 71.
48. Lemmer, B.; Soloviev, M. Chronobiology and the implications for safety pharmacology. In Drug Discovery and Evaluation: Safety and Pharmacokinetic Assays; Vogel, H.G., Maas, J., Hock, F.J., Mayer, D., Eds.; Springer: Berlin/Heidelberg, Germany, 2013; Volume 21.
49. Durgan, D.J.; Young, M.E. Cardiomyocyte circadian clock-mediated regulation of blood pressure. Free Radic. Biol. Med. 2018, 119, 108–114.
50. Scheving, L.E.; Pauly, J.E.; Tsai, T.H. Circadian fluctuation of plasma proteins of the rat. Am. J. Physiol. 1968, 215, 1096–1101.
51. Harten, J.v. Clinical pharmacokinetics of selective serotonin reuptake inhibitors. Clin. Pharmacokinet. 1993, 24, 203–220.
52. Borga, O.; Azarnoff, D.L.; Forshell, G.P.; Sjoqvist, F. Plasma protein binding of tricyclic antidepressants in man. Biochem. Pharm. 1969, 18, 2135–2143.
53. Yost, R.L.; DeVane, C.L. Diurnal variation of α1-acid glycoprotein concentration in normal volunteers. J. Pharm. Sci. 1985, 74, 777–779.
54. Rutkowska, A.; Piekoszewski, W.; Brandys, J. Chronopharmacokinetics of Amitriptyline in Rats. Biopharm. Drug Dispos. 1999, 20, 117–124.
55. Wishart, D.S.; Feunang, Y.D.; Guo, A.C.; Lo, E.J.; Marcu, A.; Grant, J.R.; Sajed, T.; Johnson, D.; Li, C.; Sayeeda, Z.; et al. DrugBank 5.0: A major update to the DrugBank database for 2018. Available online: https://go.drugbank.com/drugs/ (accessed on 25 January 2021).
56. Nakazato, R.; Kawabe, K.; Yamada, D.; Ikeno, S.; Mieda, M.; Shimba, S.; Hinoi, E.; Yoneda, Y.; Takarada, T. Disruption of Bmal1 impairs blood-brain barrier integrity via pericyte dysfunction. J. Neurosci. 2017, 37, 10052–10062.
57. Myung, J.; Schmal, C.; Hong, S.; Tsukizawa, Y.; Rose, P.; Zhang, Y.; Holtzman, M.J.; De Schutter, E.; Herzel, H.; Bordyugov, G.; et al. The choroid plexus is an important circadian clock component. Nat. Commun. 2018, 9, 1062.
58. Zhang, S.L.; Lahens, N.F.; Yue, Z.; Arnold, D.M.; Pakstis, P.P.; Schwarz, J.E.; Sehgal, A. A circadian clock regulates efflux by the blood-brain barrier in mice and human cells. Nat. Commun. 2021, 12, 617.
59. Pulido, R.S.; Munji, R.N.; Chan, T.C.; Quirk, C.R.; Weiner, G.A.; Weger, B.D.; Rossi, M.J.; Elmsaouri, S.; Malfavon, M.; Deng, A.; et al. Neuronal activity regulates blood-brain barrier efflux transport through endothelial circadian genes. Neuron 2020, 108, 937–952.
60. Zhang, S.L.; Yue, Z.; Arnold, D.M.; Artiushin, G.; Sehgal, A. A Circadian clock in the blood-brain barrier regulates xenobiotic efflux. Cell 2018, 173, 130–139.

3. Pharmacodynamics of Antidepressants

3.1. Circadian Rhythm Effect on Antidepressant Drug Targets

Different results of chronopharmacodynamic studies with antidepressants can be related with fluctuations of the pharmacokinetic parameters or daily variations of the expression of antidepressant drug targets affected by circadian rhythms (**Figure 2**). Distinct mechanisms of action of antidepressant drugs may lead to different chronopharmacological profiles, and dosing-time can influence both therapeutic and toxic effects.

61. Lemmer, B.; Nold, G. Circadian changes in estimated hepatic blood flow in healthy subjects. Br. J. Clin. Pharm. 1991, 32, 627–629.
62. Hodgson, K.; Tansey, K.E.; Uher, R.; Dernovšek, M.Z.; Mors, O.; Hauser, J.; Souery, D.; Maier, W.; Henigsberg, N.; Rietschel, M.; et al. Exploring the role of drug-metabolising enzymes in antidepressant side effects. Psychopharmacology 2015, 232, 2609–2617.
63. Zhang, T.; Yu, F.; Guo, L.; Chen, M.; Yuan, X.; Wu, B. Small heterodimer partner regulates circadian cytochromes p450 and drug-induced hepatotoxicity. Theranostics 2018, 8, 5246–5258.
64. Zhang, Y.K.; Yeager, R.L.; Klaassen, C.D. Circadian expression profiles of drug-processing genes and transcription factors in mouse liver. Drug Metab. Dispos. 2009, 37, 106–115.
65. Takiguchi, T.; Tomita, M.; Matsunaga, N.; Nakagawa, H.; Koyanagi, S.; Ohdo, S. Molecular basis for rhythmic expression of CYP3A4 in serum-shocked HepG2 cells. Pharm. Genom. 2007, 17, 1047–1056.
66. Matsunaga, N.; Inoue, M.; Kusunose, N.; Kakimoto, K.; Hamamura, K.; Hanada, Y.; Toi, A.; Yoshiyama, Y.; Sato, F.; Fujimoto, K.; et al. Time-dependent interaction between differentiated embryo chondrocyte-2 and CCAAT/enhancer-binding protein alpha underlies the circadian expression of CYP2D6 in serum-shocked HepG2 cells. Mol. Pharm. 2012, 81, 739–747.
67. Mauvoisin, D.; Wang, J.; Jouffe, C.; Martin, E.; Atger, F.; Waridel, P.; Quadroni, M.; Gachon, F.; Naef, F. Circadian clock-dependent and -independent rhythmic proteomes implement distinct diurnal functions in mouse liver. Proc. Natl. Acad. Sci. USA 2014, 111, 167–172.
68. Wyska, E. Pharmacokinetic considerations for current state-of-the-art antidepressants. Expert Opin. Drug Metab. Toxicol. 2019, 15, 831–847.
69. White, C.A.; Pardue, R.; Huang, C.; Warren, J. Chronobiological evaluation of the active biliary and renal secretion of ampicillin. Chronobiol. Int. 1995, 12, 410–418.
70. Oda, M.; Koyanagi, S.; Tsurudome, Y.; Kanemitsu, T.; Matsunaga, N.; Ohdo, S. Renal circadian clock regulates the dosing-time dependency of cisplatin-induced nephrotoxicity in mice. Mol. Pharm. 2014, 85, 715–722.
71. Hara, M.; Minami, Y.; Ohashi, M.; Tsuchiya, Y.; Kusaba, T.; Yamagaki, K.; Koike, N.; Umemura, T.; Inokawa, H.; Yagita, K. Robust circadian clock oscillation and osmotic rhythms in inner medulla reflecting cortico-medullary osmotic gradient rhythm in rodent kidney. Sci. Rep. 2017, 7, 7306.
72. Prins, J.M.; Weverling, G.J.; Ketel, R.J.v.; Speelman, P. Circadian variations in serum levels and the renal toxicity of aminoglycosides in patients. Clin. Pharm. 1997, 62, 106–111.
73. Kawai, H.; Machida, M.; Ishibashi, T.; Kudo, N.; Kawashima, Y.; Mitsumoto, A. Chronopharmacological analysis of antidepressant activity of a dual-action serotonin

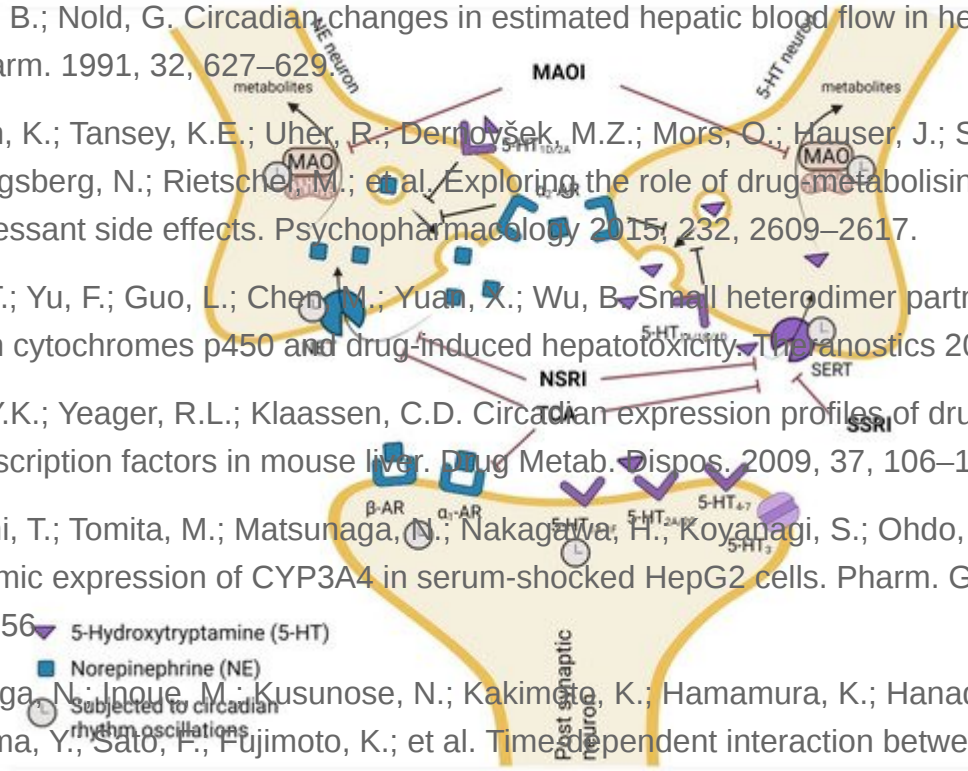

Figure 2. Summary of the mechanism of action of SSRIs, SNRIs, TCAs, and MAOIs at noradrenergic (left) and serotonergic (right) neurons. The influence of circadian rhythms on antidepressant targets is also depicted. SSRIs, SNRIs, and TCAs increase 5-HT neurotransmission through the direct blockade of SERT at presynaptic terminals. NET is inhibited by SNRIs and TCAs in noradrenergic neurons. MAOIs inhibit MAO enzymes present in mitochondria, responsible for breaking down neurotransmitters, such as 5-HT and NE. These processes increase the levels of 5-HT and NE in the synaptic cleft, leading to an antidepressant effect [74]. Circadian rhythms are known to affect the expression or activity of NET and SERT [73][74][75], 5-HT1A receptor [75], adrenergic receptors [76], and MAO [77]. 5-HTX, 5-HT receptor subtypes; α- and β-AR, adrenergic receptors; MAO, monoamine oxidase; MAOI, MAO inhibitors; NET, NE transporter; SERT, 5-HT transporter; SNRI, SERT, and NET inhibitor; SSRI, SERT inhibitor; TCA, tricyclic antidepressant.

The monoaminergic hypothesis, established in 1969, postulates that depression is linked with noradrenergic and serotoninergic dysfunction in the CNS [78]. Hence, the development of antidepressants aimed towards the direct inhibition of SERT occurs, a member of the Na^+/Cl^--dependent transporter family, or the blockade of both SERT and NET. The first is mediated by SSRIs, SNRIs, and TCAs and the second by SNRIs and TCAs. Notwithstanding, antidepressants exhibit different inhibitory potencies on reuptake transporters. The fact that inhibition is not equal among all drugs that prevent SERT and NET activity leads to different pharmacodynamic results in the same antidepressant classes [79].

Serotonergic and noradrenergic systems from the prefrontal cortex and hippocampus are very important to reduce depressive symptoms. Both systems have a 30% amplitude of mean content levels in the rat brain during a light–dark cycle [73]. The SERT transcription levels and activity revealed significant time-dependent changes in the

mouse forebrain, with peak levels during the active phase [74]. The 5-HT peak levels in the synaptic cleft occur at the end of the dark phase and are higher throughout the light phase than the dark phase. In the rat hippocampus, 5-HT turnover shows a peak during the ZT18–ZT22 and a trough at ZT10-14, while the NE turnover peaks between ZT22 and ZT2. Base levels were detected at ZT14-ZT18 [73]. Discrepancies of peak activity times in serotonergic and noradrenergic systems may be responsible for differences in the chronopharmacological profiles of antidepressants. In humans, positron emission tomography was applied to examine changes of the 5-HT1A receptor and SERT in the brain of 40–56 healthy volunteers [75]. This study showed an increase and decrease of the 5-HT1A receptor and SERT, respectively, in the midbrain during the day [75]. The increase of the 5-HT1A receptor is directly correlated with the duration of daylight, leading to seasonal differences [75]. Indeed, potential binding values to SERT in the brain were significantly higher in the fall and winter, compared to the spring and summer, revealing a negative correlation with the daily amount of sunshine [80].

The TCAs are potent inhibitors of 5-HT and NE reuptake by binding to sodium-dependent transporters. They also block histamine H1 receptors, α1-adrenergic receptors, and muscarinic receptors causing sedative, hypotensive, and anticholinergic effects (e.g., blurred vision, dry mouth, constipation, urinary retention), respectively [81]. These receptors have been described to be modulated by circadian rhythm in rodents with higher expression during the day [76][82].

Overall, several antidepressant targets are known to be regulated by circadian rhythms, which may have important implications regarding their efficacy at different dosing times. Nevertheless, much is yet unknown about this relationship. Further research in this field would benefit the design of future therapeutic approaches and improve the efficacy of currently available options.

3.1.1. Animal Studies

Before chronopharmacological studies, it is important to ensure the entrainment of circadian rhythms in healthy mice to a standard light/dark cycle. Phenotyping circadian rhythms in mice requires measurements of their activity in free running conditions [83], quantifying circadian clock or clock-related genes [84], or monitoring sleep behavior [85].

The most common behavioral tests in rodents to evaluate antidepressant effects are the forced swimming test (FST) and the tail suspension test (TST). Both present high predictive reliability and validity but different sensitivity [86][87].

Specifically, NET inhibition increases climbing, whereas inhibition of SERT selectively increases swimming [88]. However, for a reliable comparison with clinical data, it is advisable to investigate therapeutic effects following chronic treatment in rodents [89]. It is important to refer that reduction of immobility is interpreted as an antidepressant effect if it does not increase general locomotor activity, which could be interpreted as a false positive result [86]. This is related with the fact that antidepressants and psychostimulants, respectively, reduce and increase the locomotor activity of rodents in new environments [86]. Moreover, behavioral experiments at different

noradrenaline reuptake inhibitor (SNRI), milnacipran, in rats. Biol. Pharm. Bull. 2018, 41, 213–219.

74. Ushijima, K.; Sakaguchi, H.; Sato, Y.; To, H.; Koyanagi, S.; Higuchi, S.; Ohdo, S. Chronopharmacological study of antidepressants in forced swimming test of mice. J. Pharm. Exp. Ther. 2005, 315, 764–770.

75. Matheson, G.J.; Schain, M.; Almeida, R.; Lundberg, J.; Cselenyi, Z.; Borg, J.; Varrone, A.; Farde, L.; Cervenka, S. Diurnal and seasonal variation of the brain serotonin system in healthy male subjects. Neuroimage 2015, 112, 225–231.

76. Pangerl, B.; Pangerl, A.; Reiter, R.J. Circadian variations of adrenergic receptors in the mammalian pineal gland: A review. J. Neural Transm. 1990, 81, 17–29.

77. Hampp, G.; Ripperger, J.A.; Houben, T.; Schmutz, I.; Blex, C.; Perreau-Lenz, S.; Brunk, I.; Spanagel, R.; Ahnert-Hilger, G.; Meijer, J.H.; et al. Regulation of monoamine oxidase A by circadian-clock components implies clock influence on mood. Curr. Biol. 2008, 18, 678–683.

78. Perez-Caballero, L.; Torres-Sanchez, S.; Bravo, L.; Mico, J.A.; Berrocoso, E. Fluoxetine: A case history of its discovery and preclinical development. Expert Opin. Drug Discov. 2014, 9, 567–578.

79. Tatsumi, M.; Groshan, K.; Blakely, R.D.; Richelson, E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur. J. Pharm. 1997, 340, 249–258.

80. Praschak-Rieder, N.; Willeit, M.; Wilson, A.A.; Houle, S.; Meyer, J.H. Seasonal variation in human brain serotonin transporter binding. Arch. Gen. Psychiatry 2008, 65, 1072–1078.

81. Gillman, P.K. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. Br. J. Pharm. 2007, 151, 737–748.

82. Marquez, E.; Pavia, J.; Laukonnen, S.; Martos, F.; Gomez, A.; Rius, F.; Cuesta, F.S.d.l. Circadian rhythm in muscarinic receptor subtypes in rat forebrain. Chronobiol. Int. 1990, 7, 277–282.

83. Eckel-Mahan, K.; Sassone-Corsi, P. Phenotyping circadian rhythms in mice. Curr. Protoc. Mouse Biol. 2015, 5, 271–281.

84. Ripperger, J.A.; Jud, C.; Albrecht, U. The daily rhythm of mice. FEBS Lett. 2011, 585, 1384–1392.

85. Fisher, S.P.; Godinho, S.I.; Pothecary, C.A.; Hankins, M.W.; Foster, R.G.; Peirson, S.N. Rapid assessment of sleep-wake behavior in mice. J. Biol. Rhythms 2012, 27, 48–58.

86. Slattery, D.A.; Cryan, J.F. Using the rat forced swim test to assess antidepressant-like activity in rodents. Nat. Protoc. 2012, 7, 1009–1014.

87. Cryan, J.F.; Mombereau, C.; Vassout, A. The tail suspension test as a model for assessing antidepressant activity: Review of pharmacological and genetic studies in mice. Neurosci. Biobehav. Rev. 2005, 29, 571–625.

times of the day strongly affect the total results [90]. The FST experiments displayed different results if performed during the dark or light phase since rodents are more active during the dark phase [91]. Kelliher et al. also noticed that rats were more agitated or worsened when taken from the swim apparatus during light phase [91].

Seasonal variations seem to influence the efficacy of antidepressants. In rats, FST revealed significant seasonal fluctuations of the antidepressant effect for TCAs, namely amineptine, amitriptyline, desipramine, imipramine, and maprotiline [92]. Maximal reduction of immobility in FST was observed in March for all aforementioned antidepressants. The desipramine and maprotiline anti-immobility effect was also evaluated in a light–dark cycle and was not circadian-dependent (**Table 2**) [92]. Nomifensine, a NE-dopamine reuptake inhibitor, was equally effective throughout the year with no seasonal variations, but it revealed a circadian-dependent effect, more pronounced during the light phase (peak at ZT7) (**Table 2**) [92]. The interpretation of these results is complicated by the low number of experimental replicates (n = 1 or 2). Furthermore, the controlled conditions of rats excluded the influence off the light–dark cycle, humidity and temperature variations that occur during the seasons. Therefore, the observed seasonal effect may be linked with internal mechanisms, namely the daily amplitude of subtype receptor 5-HT1A binding in the rat brain, which is higher in March than December [93].

Table 2. Chronopharmacodynamic studies of antidepressant drugs in rodents.

Antidepressant	Species (Gender)	Dose (mg/Kg)	Initial of Experiment after Administration (h)	Route	Zeitgeber Time (ZT) Administrations	Pharmacodynamic			Drug Concentration	Ref.
						Test	24 h Rhythm Variation	Observations		
Amitriptyline	ICR mice (male)	15	0.5	Intraperitoneal	ZT2, ZT6, ZT10, ZT14, ZT18, ZT22	FST	Yes	Lowest immobility at ZT14.	-	[74]
Bupropion	C57BL/6 mice (male)	20	1	Intraperitoneal	ZT1, ZT7, ZT13, ZT19	TST	No, but significantly different between ZT	Lowest immobility at ZT1.	No significant differences between dosing times in plasma and brain.	[94]
						Locomotor activity	No	Increased		
Desipramine	CD-COBS rats (male)	20	24, 5 and 1	Intraperitoneal	ZT3, ZT7, ZT11, ZT15, ZT19, ZT23	FST	No	-	-	[92]
Fluoxetine	C57BL/6 mice (male)	30	1	Intraperitoneal	ZT1, ZT7, ZT13, ZT19	TST	Yes	Lowest immobility at ZT1.	No significant differences between dosing times in plasma and brain.	[94]
						Locomotor activity	Yes	Lowest locomotion		

88. Detke, M.J.; Rickels, M.; Lucki, I. Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. Psychopharmacology 1995, 121, 66–72.

89. Cryan, J.F.; Markou, A.; Lucki, I. Assessing antidepressant activity in rodents: Recent developments and future needs. Trends Pharm. Sci. 2002, 23, 238–245.

90. Richetto, J.; Polesel, M.; Weber-Stadlbauer, U. Effects of light and dark phase testing on the investigation of behavioural paradigms in mice: Relevance for behavioural neuroscience. Pharm. Biochem. Behav. 2019, 178, 19–29.

91. Kelliher, P.; Connor, T.J.; Harkin, A.; Sanchez, C.; Kelly, J.P.; Leonard, B.E. Varying responses to the rat forced-swim test under diurnal and nocturnal conditions. Physiol. Behav. 2000, 69, 531–539.

92. Borsini, F.; Lecci, A.; Stasi, M.A.; Pessia, M.; Meli, A. Seasonal and circadian variations of behavioural response to antidepressants in the forced swimming test in rats. Behav. Pharmacol. 1990, 1, 395–401.

93. Weiner, N.; Clement, H.-W.; Gemsa, D.; Wesemann, W. Circadian and seasonal rhythms of 5-HT receptor subtypes, membrane anisotropy and 5-HT release in hippocampus and cortex of the rat.

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... enous depression. Pharmacopsychiatry 1978, 11, 235–240.

99. Kripke, D.F.; Nievergelt, C.M.; Joo, E.; Shekhtman, T.; Kelsoe, J.R. Circadian polymorphisms associated with affective disorders. J. Circadian Rhythm. 2009, 7, 2.

100. Takahashi, T.; Sasabayashi, D.; Yucel, M.; Whittle, S.; Lorenzetti, V.; Walterfang, M.; Suzuki, M.; Pantelis, C.; Malhi, G.S.; Allen, N.B. Pineal gland volume in major depressive and bipolar disorders. Front. Psychiatry 2020, 11, 450.

Antidepressant	Species (Gender)	Dose (mg/Kg)	Initial of Experiment after Administration (h)	Route	Pharmacodynamic				Drug Concentration	Ref.
					Zeitgeber Time (ZT) Administrations	Test	24 h Rhythm Variation	Observations		
								activity at ZT1		
Fluvoxamine	ICR mice (male)	30	0.5	Intraperitoneal	ZT2, ZT6, ZT10, ZT14, ZT18, ZT22	FST	Yes	Lowest immobility at ZT14.	ZT2 > ZT14 in plasma, significantly different after 1h of drug injection. No differences in brain.	[74]
					ZT2, ZT14	Locomotor activity	No	No effect		
Imipramine	C57BL/6 mice (male)	30	1	Intraperitoneal	ZT1, ZT7, ZT13, ZT19	TST	Yes	Lowest immobility at ZT13.	No significant differences between dosing times in plasma and brain	[94]
						Locomotor activity	No	Reduced		
	Wistar Hannover rats (male)	30	1	Intraperitoneal	ZT1, ZT13	FST	Yes	Lowest immobility and highest climbing at ZT1.	ZT1 > ZT13 for imipramine and desipramine in plasma but not significantly different	[22]
		10 for 2 weeks	1	Intraperitoneal	ZT1, ZT13	FST	Yes	Lowest immobility and highest climbing at ZT1.	-	
		30 for 2 weeks	1	Intraperitoneal	ZT1, ZT13	FST	No	-	-	
Mianserin	CD-COBS rats (male)	15	24, 5 and 1	Intraperitoneal	ZT3, ZT7, ZT11, ZT15, ZT19, ZT23	FST	No	-	-	[92]
Milnacipran	Wistar Hannover	60	1	Oral	ZT1, ZT13	FST	Yes	Lowest immobility and highest	No significant differences between	[73]

Melatonin and cortisol increase after fluvoxamine. Br. J. Clin. Pharmacol. 1986, 22, 620–622.

110. Demisch, K.; Demisch, L.; Nickelsen, T.; Rieth, R. The influence of acute and subchronic administration of various antidepressants on early morning melatonin plasma levels in healthy subjects: Increases following fluvoxamine. J. Neural Transm. 1987, 68, 257–270.
111. Hao, Y.; Hu, Y.; Wang, H.; Paudel, D.; Xu, Y.; Zhang, B. The effect of fluvoxamine on sleep architecture of depressed patients with insomnia: An 8-week, open-label, baseline-controlled study. Nat. Sci. Sleep 2019, 11, 291–300.
112. Murata, Y.; Kamishioiri, Y.; Tanaka, K.; Sugimoto, H.; Sakamoto, S.; Kobayashi, D.; Mine, K. Severe sleepiness and excess sleep duration induced by paroxetine treatment is a beneficial pharmacological effect, not an adverse reaction. J. Affect. Disord. 2013, 150, 1209–1212.
113. Wilson, S.; Hojer, A.M.; Buchberg, J.; Areberg, J.; Nutt, D.J. Differentiated effects of the multimodal antidepressant vortioxetine on sleep architecture: Part 1, a

Antidepressant	Species (Gender)	Dose (mg/Kg)	Initial of Experiment after Administration (h)	Route	Zeitgeber Time (ZT) Administrations	Pharmacodynamic				
						Test	24 h Rhythm Variation	Observations	Drug Concentration	Ref.
	rats (male)							swimming at ZT1.	dosing times in plasma and brain	
Nomifensine	CD-COBS rats (male)	5	24, 5 and 1	Intraperitoneal	ZT3, ZT7, ZT11, ZT15, ZT19, ZT23	FST	Yes	Lowest immobility at ZT7	-	[92]
Venlafaxine	C57BL/6 mice (male)	30	1	Intraperitoneal	ZT1, ZT7, ZT13, ZT19	TST	Yes	Lowest immobility at ZT7.	No significant differences between dosing times in plasma and brain	[94]
						Locomotor activity	Yes	Lowest locomotion activity at ZT7.		

117. Refinetti, R.; Menaker, M. Effects of imipramine on circadian rhythms in the golden hamster. Pharm. Biochem. Behav. 1993, 45, 27–33.

118. Castanho, A.; Bothorel, B.; Seguin, L.; Mocaer, E.; Pevet, P. Like melatonin, agomelatine (S20098) increases the amplitude of oscillations of two clock outputs: Melatonin and temperature rhythms. Chronobiol. Int. 2014, 31, 371–381.

119. Redman, J.R.; Francis, A.J.P. Entrainment of rat circadian rhythms by the melatonin agonist s-20098 requires intact suprachiasmatic nuclei but not the pineal. J. Biol. Rhythms 1998, 13, 39–51.

120. Redman, J.R.; Guardiola-Lemaitre, B.; Brown, M.; Delagrange, P.; Armstrong, S.M. Dose dependent effects of S.20098, a melatonin agonist, on direction of re-entrainment of rat circadian activity rhythms. Psychopharmacology 1995, 118, 385–390.

121. Kräuchi, K.; Cajochen, C.; Möri, D.; Graw, P.; Wirz-Justice, A. Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. Am. J. Physiol. 1997, 272, R1178–R1188.

122. Leproult, R.; Van Onderbergen, A.; L'Hermite-Baleriaux, M.; Van Cauter, E.; Copinschi, G. Phase-shifts of 24-h rhythms of hormonal release and body temperature following early evening administration of the melatonin agonist agomelatine in healthy older men. Clin. Endocrinol. 2005, 63, 298–304.

123. Cajochen, C.; Krauchi, K.; Mori, D.; Graw, P.; Wirz-Justice, A. Melatonin and S-20098 increase REM sleep and wake-up propensity without modifying NREM sleep homeostasis. Am. J. Physiol. 1997, 272, R1189–R1196.

124. Descamps, A.; Rousset, C.; Millan, M.J.; Spedding, M.; Delagrange, P.; Cespuglio, R. Influence of the novel antidepressant and melatonin agonist/serotonin2C receptor antagonist, agomelatine, on the rat sleep-wake cycle architecture. Psychopharmacology 2009, 205, 93–106.

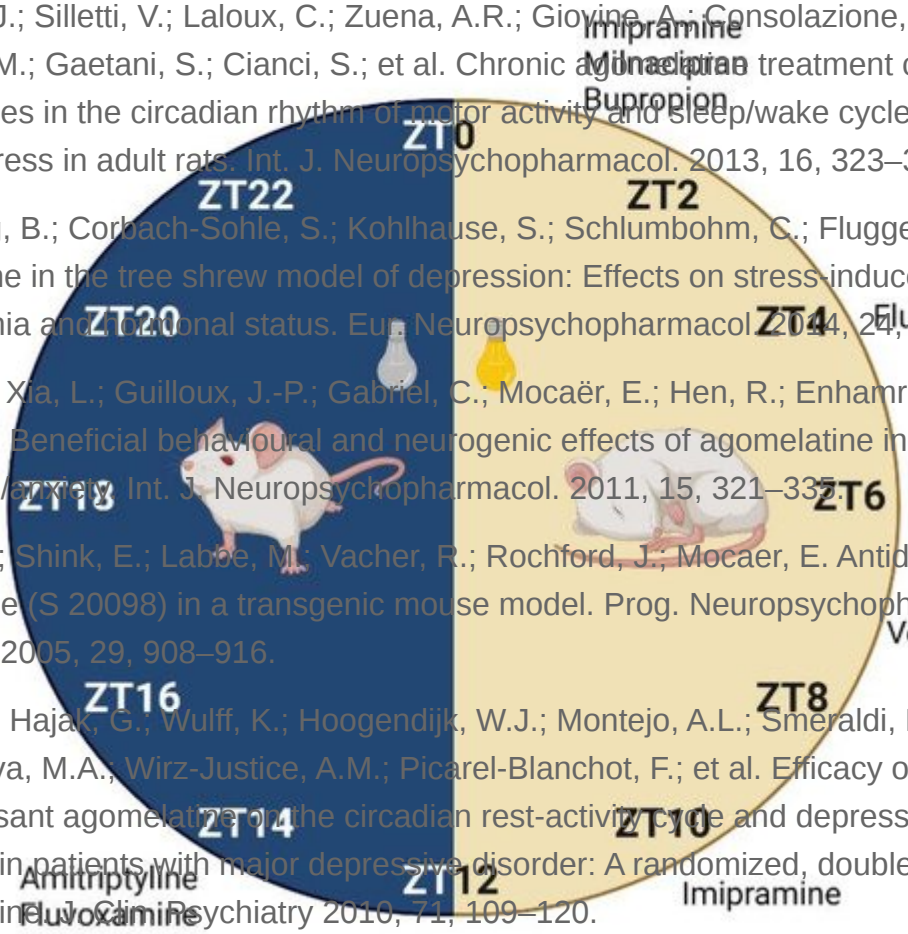

Figure 3. Proposed drug dosing time of antidepressants according to chronopharmacological studies in rodents. This placement was based on studies performed in mice or rats when higher antidepressant effect was observed during forced swimming [22][73][74] or tail suspension [94] tests. ZT0 represents lights on and ZT12 indicates lights off.

In general, data from the animal studies herein discussed demonstrate that antidepressants display distinct chronopharmacodynamic outcomes (**Figure 3**) which should be specifically evaluated. Other behavioral experiments (sucrose preference test or elevated plus maze) could be additionally performed to increase result reliability [95]. Moreover, the use of depressive mice and the monitorization of circadian rhythms could facilitate the implementation of clinical studies in humans. Transferability of data from mice to humans regarding circadian rhythms is challenging. For instance, although mice are nocturnally active and humans are diurnally active, both secrete melatonin during the nighttime [96]. Therefore, the translation of chronopharmacological results of antidepressants from mice to humans needs particular care.

3.1.2. Human Data

Despite having yielded interesting and helpful results, chronopharmacodynamic studies in humans have not been performed in recent years. Side effects of TCAs are the principal focus of these types of studies and experiments showed diverse results for different TCAs (**Figure 4**).

125. Mairesse, J.; Silletti, V.; Laloux, C.; Zuena, A.R.; Giovine, A.; Consolazione, M.; van Camp, G.; Malagodi, M.; Gaetani, S.; Cianci, S.; et al. Chronic agomelatine treatment corrects the abnormalities in the circadian rhythm of motor activity and sleep/wake cycle induced by prenatal restraint stress in adult rats. Int. J. Neuropsychopharmacol. 2013, 16, 323–338.
126. Schmelting, B.; Corbach-Sohle, S.; Kohlhause, S.; Schlumbohm, C.; Flugge, G.; Fuchs, E. Agomelatine in the tree shrew model of depression: Effects on stress-induced nocturnal hyperthermia and behavioral status. Eur. Neuropsychopharmacol. 2004, 14, 437–447.
127. Rainer, Q.; Xia, L.; Guilloux, J.-P.; Gabriel, C.; Mocaër, E.; Hen, R.; Enhamre, E.; Gardier, A.M.; David, D.J. Beneficial behavioural and neurogenic effects of agomelatine in a model of depression/anxiety. Int. J. Neuropsychopharmacol. 2011, 15, 321–335.
128. Barden, N.; Shink, E.; Labbe, M.; Vacher, R.; Rochford, J.; Mocaer, E. Antidepressant action of agomelatine (S 20098) in a transgenic mouse model. Prog. Neuropsychopharmacol. Biol. Psychiatry 2005, 29, 908–916.
129. Kasper, S.; Hajak, G.; Wulff, K.; Hoogendijk, W.J.; Montejo, A.L.; Smeraldi, E.; Rybakowski, J.K.; Quera-Salva, M.A.; Wirz-Justice, A.M.; Picarel-Blanchot, F.; et al. Efficacy of the novel antidepressant agomelatine on the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder: A randomized, double-blind comparison with sertraline. J. Clin. Psychiatry 2010, 71, 109–120.
130. Quera Salva, M.A.; Vanier, B.; Laredo, J.; Hartley, S.; Chapotot, F.; Moulin, C.; Lofaso, F.; Guilleminault, C. Major depressive disorder, sleep EEG and agomelatine: An open-label study. Int. J. Neuropsychopharmacol. 2007, 10, 691–696.
131. Bellet, M.M.; Vawter, M.P.; Bunney, B.G.; Bunney, W.E.; Sassone-Corsi, P. Ketamine influences CLOCK:BMAL1 function leading to altered circadian gene expression. PLoS ONE 2011, 6, e23982.
132. Duncan, W.C., Jr.; Sloshena, E.; Hejazi, N.S.; Brutsche, N.; Yu, K.C.; Park, L.; Ballard, E.D.; Zarate, C.A., Jr. Motor-activity markers of circadian timekeeping are related to ketamine's rapid antidepressant properties. Biol. Psychiatry 2017, 82, 361–369.
133. Schmid, D.A.; Wichniak, A.; Uhr, M.; Ising, M.; Brunner, H.; Held, K.; Weikel, J.C.; Sonntag, A.; Steiger, A. Changes of sleep architecture, spectral composition of sleep EEG, the nocturnal secretion of cortisol, ACTH, GH, prolactin, melatonin, ghrelin, and leptin, and the DEX-CRH test in depressed patients during treatment with mirtazapine. Neuropsychopharmacology 2006, 31, 832–844.

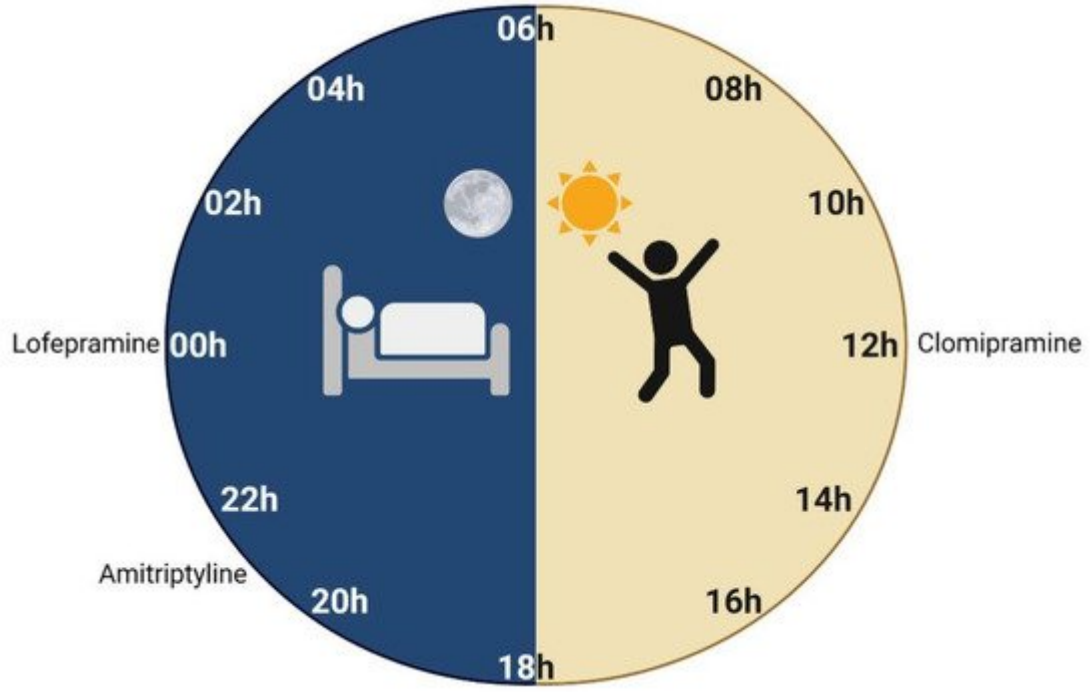

Figure 4. Drug dosing-time of antidepressant drugs according to chronopharmacodynamic studies in humans. This figure includes an optimal time for administration based on lower side effects for amitriptyline [23] and higher antidepressant effects for clomipramine [97] and lofepramine [98].

The side effects of amitriptyline seem to be higher after morning administrations. Its antimuscarinic effect, measured through the mean percent decrease from the pre-drug level in salivary flow, demonstrated to be higher if the drug is administered in the morning than in the evening, at 2 h (78 ± 3% vs 59 ± 7%) and 3 h (76 ± 4% and 65 ± 5%) post-administration [23]. Identically, amitriptyline-induced sedative effects, such as drowsiness, confusion, and mental slowness, measured by self-rating scales, were higher with morning than evening doses (**Table 3**) [23].

Table 3. Chrono-pharmacodynamics of orally administered antidepressant drugs in humans.

Antidepressant	Subjects	Study Design	Daily Dose (mg)	Duration (Days)	Time Administrations	Pharmacodynamic Test	Pharmacodynamic 24 h Rhythm Variation	Pharmacodynamic Observations	Ref.
Amitriptyline	10 healthy (♂) subjects. Range age: 22–31 years old.	Crossover	50	21	9h00 21h00	Antimuscarinic action (saliva flow) and sedation effect by self-rating scales	Yes	Highest salivary flow and lowest sedative effect at 21h00	[23]
Clomipramine	40 patients with	Crossover	150	28	8h20 12h20 20h30	HRSD and BDRS	Yes	Lowest depressive	[97]

Antidepressant	Subjects	Study Design	Daily Dose (mg)	Duration (Days)	Time Administrations	Pharmacodynamic Test	Pharmacodynamic 24 h Rhythm Variation	Pharmacodynamic Observations	Ref.
	MDD (15 ♀, 25 ♂). Range age: 18–65 years old.							symptoms at 12h20	
Lofepramine	30 patients with MDD (22 ♀, 8 ♂). Range age: 25–60 years old.	Parallel	210	21	8h00 16h00 24h00	HRSD and CSRS	Yes	Lowest depressive symptoms at 24h00	[98] [99]

ough the altered and its symptomatology [100]. Therefore, the evaluation of circadian rhythm differences in depressed-like mice before and after antidepressant treatments is of utmost importance. Depressed patients experience a wide range of circadian rhythms and sleep-cycle disruptions, and chronotherapy has proved to reduce their depressive symptoms [101]. Therefore, drugs targeted to normalize circadian rhythms could be of interest for the treatment of depression. The main implications of antidepressants on circadian rhythms in pre-clinical and clinical studies are depicted in **Table 4**.

Beck Depression Rating Scale (BDRS); Clinical Self Rating Scales (CSRS); HRSD, 17-item Hamilton Rating Scale for Depression; MDD, major depressive disorder.

Table 4. Main findings of pre-clinical and clinical studies reporting the influence of different classes of antidepressants on circadian rhythms.

Antidepressant	Pre-Clinical Studies	Clinical Studies	References
SSRI			
Citalopram/escitalopram	- Modulates Per1 oscillation in vitro.	- Restores daily rhythms of PER2 and BMAL1 and baseline levels of serum melatonin; - Increases melatonin suppression and delays the internal clock rhythm.	[102][103][104]
Fluoxetine	- Modulates Per1 oscillation in vitro; - Induces non-photic effects in light–dark cycle in mice;	- Increases 6-sulfatoxymelatonin in urine.	[102][105][106][107][108]

Antidepressant	Pre-Clinical Studies	Clinical Studies	References
		SSRI	
	- Induces light-phase advances of SCN firing; - Normalizes disrupted circadian locomotor activity and clock gene expression in depressive-like mice; - Decreases the response of mice to light-induced phase-delays.		
Fluvoxamine	- Modulates Per1 oscillation in vitro.	- Increases plasma levels of melatonin and cortisol; - Improves sleep parameters and reduces insomnia.	[102][109][110][111]
Paroxetine	- Modulates Per1 oscillation in vitro.	- Delays REM onset and reduces REM time sleep; - Increases the changeover time of wakefulness to sleep; - May induce “hypersomnia”.	[102][112][113]
Sertraline	- Modulates Per1 oscillation in vitro.		[102]
		SNRI	
Duloxetine		- Increases 6-sulfatoxymelatonin in urine.	[105]

Antidepressant	Pre-Clinical Studies	Clinical Studies	References
	SSRI		
	TCA		
Desipramine	- Restores photic entrainment of activity after exposure to glucocorticoids.	- Increases melatonin plasma levels.	[114][115][116]
Imipramine	- Does not restore photic entrainment after light shifting.	- Increases melatonin plasma levels.	[114][115][117]
	Atypical		
Agomelatine	- Modulates daily rhythm of melatonin secretion; - Induces circadian effects on locomotor activity and body temperature; - Restores resynchronization of light–dark cycle advances; - Improves sleep parameters (only if taken at night); - Restores circadian rhythm activity in depressive-like rodents.	- Induces circadian alterations of cortisol and melatonin levels, core body temperature and heart rate; - Improves sleep parameters; - Resynchronizes the circadian rhythms and sleep parameters of depressed patients.	[118][119][120][121][122][123][124][125][126][127][128][129][130]
Ketamine	- Alters the entrainment of clock genes; - Resets main clock in the SNC.	- Increases neuroplasticity; - Improves sleep quality.	[131][132]

Antidepressant	Pre-Clinical Studies	Clinical Studies	References
SSRI			
Mirtazapine	[123]	- Improves sleep continuity; - Increases slow-wave sleep; - Increase melatonin plasma levels; - Reduces cortisol plasma levels.	[105] [123][124][125] [124]
Vortioxetine	[132]	- Delays REM onset and reduces REM time sleep; - Increases the changeover time of wakefulness to sleep	[113] [132]

SCN, suprachiasmatic nucleus; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

In conclusion, commercially available antidepressants have demonstrated to play a critical role on circadian entrainment. Nevertheless, the [illegible] behind the modulation of circadian rhythms by antidepressants still require more investigation. New insights may help the design of better chronopharmacological strategies for the treatment of depression.

4. Conclusions

Chronotherapy is known to improve drug efficacy and reduce toxicity. The choice of an appropriate dosing-time for antidepressants is a possible factor of variation in pharmacokinetics and may promote therapeutic effects, while reducing adverse effects. Several factors that can affect the pharmacokinetics and pharmacodynamics of antidepressants are modulated by circadian rhythms, which undermine the comprehension of in vivo and human findings. In spite of increasing scientific evidence emerging in this field, further studies in animals and humans remain necessary to determine pharmacokinetic and pharmacodynamic parameters and understand the best time of administration for different antidepressants.

Exploring the chronopharmacological profiles of each antidepressant is expected to provide a more effective pharmacotherapy. Depressed patients can require different dosing-times for the same antidepressant, indicating that individual chronopharmacological therapy should be the primary tool for effective treatment. Moreover, the readjustment of circadian rhythms by some antidepressants is partially responsible for their effectiveness. Thus, restoring circadian rhythmicity is a valid mechanism to promote the development of rapid and sustained treatments in MDD, as it has been discovered in the recent years.