Supplementary Material for

Dosing time matters

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Supplementary information

Dosing time matters

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Study methodology

We searched published literature for clinical studies, prospective or retrospective, that (1) directly compared at least two different time-of-day treatment schedules, and (2) measured clinical effect or toxicity. We identified 106 clinical studies that met these criteria; references included below. Our assessment of drug half-life utilized public data from DrugBank 5.0 (*107*), FDA-label information, and/or research publications.

Materials

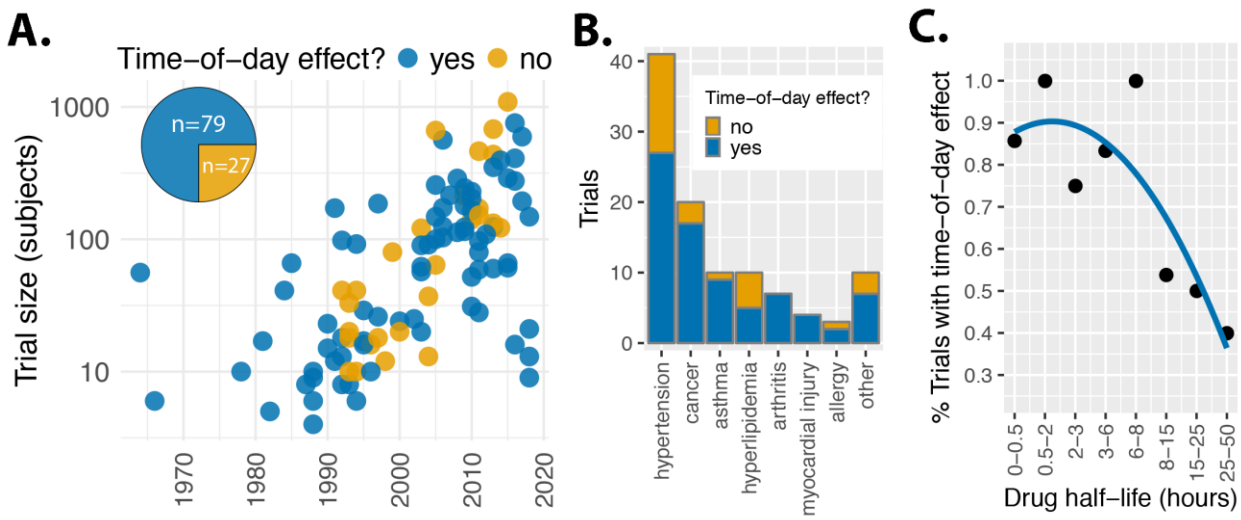

Fig 1. Circadian medicine is accelerating and has a track-record of success in highly prevalent diseases. (A) 75% of clinical trials (79/106) showed dosing-time-dependent efficacy or toxicity, grouped by **(B)** therapeutic area. Individual trials details in Fig. 2 and Table 1. **(C)** Relationship between drug half-life and time-of-day effect. Trials were grouped by drug half-life so that there were approximately equal numbers of trials in each group. For combination therapies, we considered the drug ingredient with the shortest half-life. A total of 88 trials with half-life information were included.

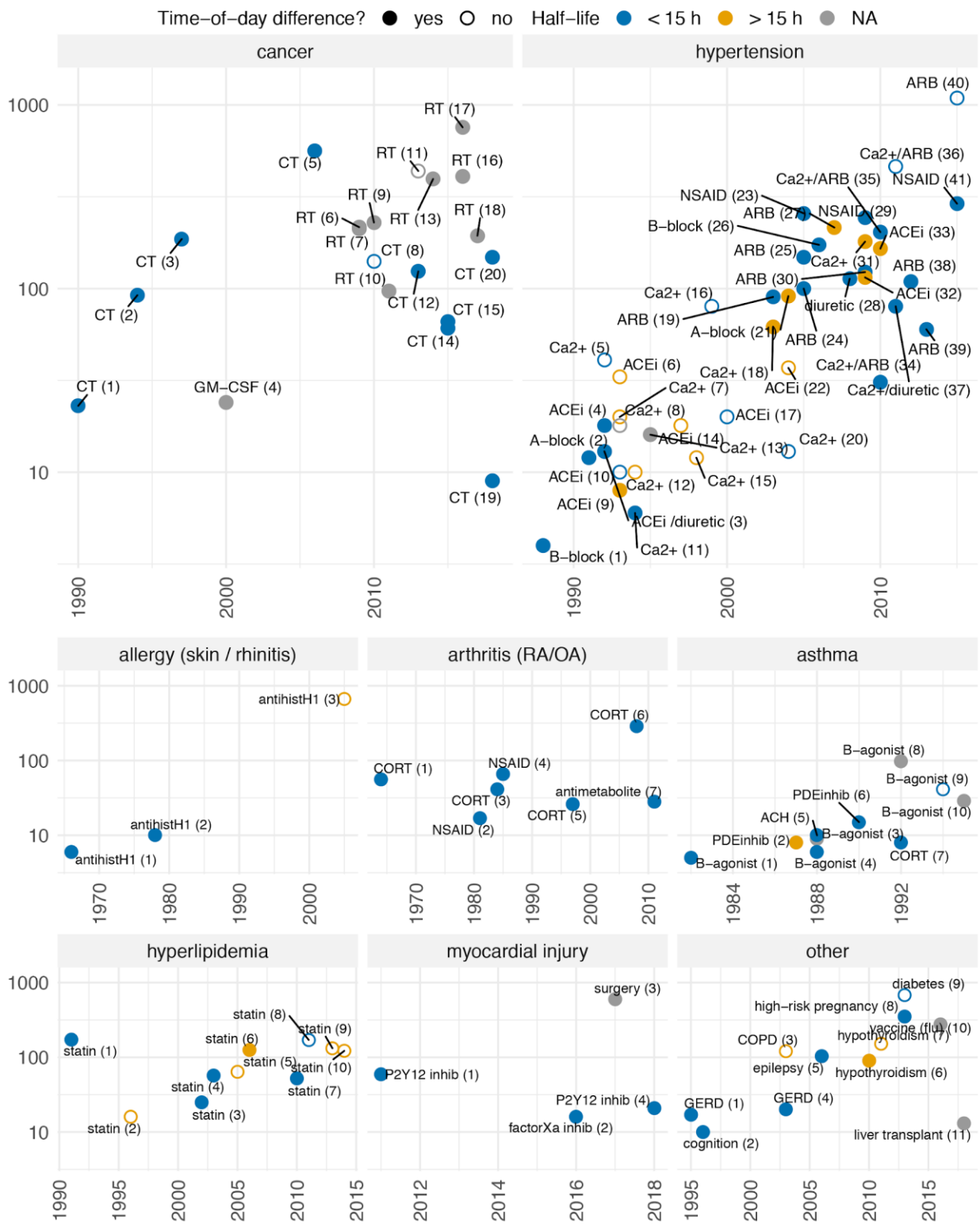

Fig 2. 50 years of clinical studies testing dosing-time-dependence of medical treatment. 105 clinical studies that were: 1) published, 2) directly compared at least two different time-of-day treatment schedules, and 3) measured clinical effect or toxicity. Point color indicates drug

half-life: short (≤15 h), long (>15 h), or unknown (NA). Point fill distinguishes trials that found significant (P-value < 0.05) administration-time-dependent efficacy and/or toxicity (solid) from trials that did not (empty). Trials grouped by therapeutic area and labeled according to drug class. Study citations are indicated by the number in parentheses for each trial (Table 1).

Table 1. Details for each trial and reference. For drug combinations, the shortest-acting agent in the combination is reported here and Fig 1.

Group	Specific TA	Trial	Drug	Class	Half-life* (hr)	Ref.
Allergy	skin	1	cyproheptadine	antihistamine H1	8	(*1*)
	skin	2	terfenadine	antihistamine H1	3.5	(*2*)
	rhinitis	3	desloratadine	antihistamine H1	50	(*3*)
Arthritis	RA	1	prednisone	corticosteroid	2.5	(*4*)
	RA	2	flurbiprofen	NSAID	5	(*5*)
	RA	3	prednisone	corticosteroid	2.5	(*6*)
	OA	4	indomethacin	NSAID	4.5	(*7*)
	RA	5	prednisone	corticosteroid	2.5	(*8*)
	RA	6	prednisone	corticosteroid	2.5	(*9*)
	RA	7	methotrexate	antimetabolite	6	(*10*)
Asthma	asthma	1	epinephrine	beta-adrenergic antagonist	0.5	(*11*)
	asthma	2	theophylline sustained release	PDE inhib + adenosineR antagonist	24	(*12*)
	asthma	3	terbutaline-sustained release	beta-adrenergic antagonist	n/a	(*13*)
	asthma	4	orciprenaline	beta-adrenergic antagonist	6	(*14*)
	asthma	5	atropine	anticholinergic	3	(*15*)
	asthma	6	theophylline	PDE inhib + adenosineR antagonist	8	(*16*)
	asthma	7	prednisone	corticosteroid	2.5	(*17*)
	asthma	8	albuterol sustained release	beta-adrenergic antagonist	n/a	(*18*)
	asthma	9	salmeterol	beta-adrenergic antagonist	5.5	(*19*)
	asthma	10	tulobuterol	beta-adrenergic antagonist	n/a	(*20*)
Cancer	breast carcinoma, HCC, bile duct	1	L-OHP	CT	0.5	(*21*)
	colorectal	2	L-OHP + 5-FU + FA	CT	0.5	(*22*)
	colorectal	3	L-OHP + 5-FU + FA	CT	0.5	(*23*)
	soft tissue/bone sarcoma	4	GM-CSF	GM-CSF	n/a	(*24*)
	colorectal	5	L-OHP + 5-FU + FA	CT	0.5	(*25*)
	head and neck	6	radiotherapy	RT	n/a	(*26*)
	head and neck	7	radiotherapy	RT	n/a	(*27*)
	metastatic colorectal	8	L-OHP + capacitabine	CT	0.5	(*28*)
	cervical carcinoma	9	radiotherapy	RT	n/a	(*29*)
	brain metastasis in NSCLC	10	radiotherapy-gamma knife	RT	n/a	(*30*)
	brain metastasis in NSCLC	11	radiotherapy-stereotactic (SRS)	RT	n/a	(*31*)
	advanced NPC	12	5-FU + DDC	CT	0.5	(*32*)
	breast cancer	13	radiotherapy	RT	n/a	(*33*)

	NSCLC	14	DDC	CT	0.5	(*34*)
	locally advanced NPC	15	DOC + DDC + 5-FU	CT	0.5	(*35*)
	prostate adenocarcinoma	16	radiotherapy	RT	n/a	(*36*)
	multiple brain metastases	17	radiotherapy	RT	n/a	(*37*)
	painful bone metastases	18	radiotherapy	RT	n/a	(*38*)
	oral squamous cell carcinoma	19	DOC + DDC + 5-FU	CT	0.5	(*39*)
	locoregionally advanced NPC	20	DDC	CT	0.5	(*40*)
Hyperlipidemia	hyperlipidemia	1	simvastatin	statin	3	(*41*)
	hyperlipidemia	2	atorvastatin	statin	25	(*42*)
	hyperlipidemia	3	simvastatin	statin	3	(*43*)
	hyperlipidemia	4	simvastatin	statin	3	(*44*)
	hyperlipidemia	5	atorvastatin	statin	25	(*45*)
	hyperlipidemia	6	atorvastatin	statin	25	(*46*)
	hyperlipidemia	7	simvastatin	statin	3	(*47*)
	hyperlipidemia	8	simvastatin, ezetimibe	statin, azetidine	3	(*48*)
	hyperlipidemia	9	simvastatin-ER	statin	22	(*49*)
	hyperlipidemia	10	simvastatin-ER	statin	22	(*50*)
Hypertension	hypertension	1	propanalol	beta-adrenergic antagonist	4	(*51*)
	hypertension	2	phenatolamine	alpha-adrenergic antagonist	0.3	(*52*)
	hypertension	3	captopril, hydrochlorothiazide	ACE-inhibitor, diuretic	2	(*53*)
	hypertension	4	quinapril	ACE-inhibitor	3	(*54*)
	hypertension	5	nitrendipine	Ca2+-channel blocker	12	(*55*)
	hypertension	6	ramipril	ACE-inhibitor	24	(*56*)
	hypertension	7	amlodipine	Ca2+-channel blocker	40	(*57*)
	hypertension	8	isradipine-ER	Ca2+-channel blocker	n/a	(*58*)
	hypertension	9	enalapril	ACE-inhibitor	35	(*59*)
	hypertension	10	benazepril	ACE-inhibitor	10.5	(*60*)
	hypertension	11	nitrendipine	Ca2+-channel blocker	12	(*61*)
	hypertension	12	nifedipine-ER	Ca2+-channel blocker	24	(*62*)
	hypertension	13	isradipine-ER	Ca2+-channel blocker	n/a	(*63*)
	hypertension	14	perindopril	ACE-inhibitor	30	(*64*)
	hypertension	15	amlodipine	Ca2+-channel blocker	40	(*65*)
	hypertension	16	nislodipine-ER	Ca2+-channel blocker	14	(*66*)
	hypertension	17	imidapril	ACE-inhibitor	15	(*67*)
	hypertension	18	amlodipine	Ca2+-channel blocker	40	(*68*)
	hypertension	19	valsartan	ARB	7	(*69*)
	hypertension	20	cilnidipine	Ca2+-channel blocker	0.3	(*70*)
	hypertension	21	doxazosin-ER	alpha-adrenergic antagonist	22	(*71*)
	hypertension	22	trandolapril	ACE-inhibitor	24	(*72*)
	hypertension	23	aspirin	NSAID	1	(*73*)

	hypertension	24	valsartan	ARB	7	(*74*)
	hypertension	25	valsartan	ARB	7	(*75*)
	hypertension	26	nebivolol	beta-adrenergic antagonist	10	(*76*)
	hypertension	27	telmisartan	ARB	24	(*77*)
	hypertension	28	torasemide	diuretic	3.5	(*78*)
	hypertension	29	aspirin	NSAID	1	(*79*)
	hypertension	30	olmesartan	ARB	13	(*80*)
	hypertension	31	nifedipine-ER	Ca2+-channel blocker	24	(*81*)
	hypertension	32	ramipril	ACE-inhibitor	24	(*82*)
	hypertension	33	spirapril	ACE-inhibitor	40	(*83*)
	hypertension	34	amlodipine, olmesartan	Ca2+-channel blocker, ARB	13	(*84*)
	hypertension	35	amlodipine, valsartan	Ca2+-channel blocker, ARB	7	(*85*)
	hypertension	36	amlodipine, valsartan	Ca2+-channel blocker, ARB	7	(*86*)
	hypertension	37	amlodipine, hydrochlorothiazide	Ca2+-channel blocker, diuretic	6	(*87*)
	hypertension	38	candesartan	ARB	9	(*88*)
	hypertension	39	valsartan	ARB	7	(*89*)
	hypertension	40	valsartan	ARB	7	(*90*)
	hypertension	41	aspirin	NSAID	1	(*91*)
Myocardial Injury	myocardial injury	1	clopidogrel	P2Y12 inhibitor	8	(*92*)
	cardiovascular thromboembolism	2	rivaroxaban	factorXa inhibitor	7	(*93*)
	myocardial injury	3	aortic valve replacement	surgery	na	(*94*)
	myocardial injury	4	clopidogrel	P2Y12 inhibitor	8	(*95*)
Other	GERD	1	omeprazole	PPI	0.5	(*96*)
	cognition	2	dextromethamphetamine	stimulant	4.5	(*97*)
	COPD	3	tiotropium	anticholinergic	48	(*98*)
	GERD	4	rabeprazole	PPI	1.5	(*99*)
	epilepsy	5	phenytoin, carbamazepine	anticonvulsant	12	(*100*)
	hypothyroidism	6	levothyroxine	hormone	48	(*101*)
	hypothyroidism	7	levothyroxine	hormone	48	(*102*)
	high-risk pregnancy	8	aspirin	NSAID	1	(*103*)
	diabetes	9	lixisenatide	GLP-1 receptor agonist	3	(*104*)
	influenza	10	influenza vaccination	vaccine	na	(*105*)
	viral infection	11	liver transplant	surgery	na	(*106*)

Abbreviations. antihistH1 (antihistamine H1 antagonist); ARB (angiotensin II receptor blocker); PDEinhib (phosphodiesterase inhibitor); CT (chemotherapy); RT (radiotherapy); PPI (proton pump inhibitor); NSAID (nonsteroidal anti-inflammatory drug); L-OHP (oxaliplatin); RA (rheumatoid arthritis); OA (osteoarthritis); 5-FU (5-fluorouracil): FA (folinic acid); DOC (docetaxel); DDP (cisplatin); NSCLC (non small cell lung cancer); GM-CSF (granulocyte macrophage colony stimulating factor); NPC (nasopharyngeal carcinoma); HCC (hepatocellular carcinoma); GERD (gastroesophageal reflux disease); COPD (chronic obstructive pulmonary disease); GLP-1 (glucagon-like peptide 1)

Additional reading (by article section)

INTRODUCTION

1. Whittaker, D.S., Loh, D.H., Wang, H.-B., Tahara, Y., Kuljis, D., Cutler, T., Ghiani, C.A., Shibata, S., Block, G.D., and Colwell, C.S. (2018). Circadian-based Treatment Strategy Effective in the BACHD Mouse Model of Huntington's Disease. J. Biol. Rhythms, 748730418790401.
2. He, B., and Chen, Z. (2016). Molecular Targets for Small-Molecule Modulators of Circadian Clocks. Curr. Drug Metab. *17*, 503–512.
3. Tamai, T.K., Nakane, Y., Ota, W., Kobayashi, A., Ishiguro, M., Kadofusa, N., Ikegami, K., Yagita, K., Shigeyoshi, Y., Sudo, M., *et al.* (2018). Identification of circadian clock modulators from existing drugs. EMBO Mol. Med. *10*.
4. HALBERG, and F (1959). Susceptibility to ouabain and physiologic circadian periodicity. Proc. Natl. Acad. Sci. U. S. A. *27*, 139–143.

STARTS, STOPS, AND SCOPE

1. Shapiro, D.J., and Rodwell, V.W. (1969). Diurnal variation and cholesterol regulation of hepatic HMG-CoA reductase activity. Biochem. Biophys. Res. Commun. *37*, 867–872.
2. Caussanel, J.P., Lévi, F., Brienza, S., Misset, J.L., Itzhaki, M., Adam, R., Milano, G., Hecquet, B., and Mathé, G. (1990). Phase I trial of 5-day continuous venous infusion of oxaliplatin at circadian rhythm-modulated rate compared with constant rate. J. Natl. Cancer Inst. *82*, 1046–1050.
3. Lévi, F., Zidani, R., and Misset, J.-L. (1997). Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. Lancet *350*, 681–686.
4. D'Alonzo, G.E., Smolensky, M.H., Feldman, S., Gianotti, L.A., Emerson, M.B., Staudinger, H., and Steinijans, V.W. (1990). Twenty-four hour lung function in adult patients with asthma. Chronoptimized theophylline therapy once-daily dosing in the evening versus conventional twice-daily dosing. Am. Rev. Respir. Dis. *142*, 84–90.
5. Middeke, M., Klüglich, M., and Holzgreve, H. (1991). Chronopharmacology of captopril plus hydrochlorothiazide in hypertension: morning versus evening dosing. Chronobiol. Int. *8*, 506–510.
6. Palatini, P. (1992). Can an angiotensin-converting enzyme inhibitor with a short half-life effectively lower blood pressure for 24 hours? Am. Heart J. *123*, 1421–1425.
7. Top 200 Prescribed Medicines of 2018 (2018). ClinCalc. Available at: http://clincalc.com/DrugStats/Top200Drugs.aspx [Accessed September 2018].

RENEWED CLINICAL INTEREST

1. Mohawk, J.A., Green, C.B., and Takahashi, J.S. (2012). Central and peripheral circadian clocks in mammals. Annu. Rev. Neurosci. *35*, 445–462.
2. Kaur, G., Phillips, C.L., Wong, K., McLachlan, A.J., and Saini, B. (2016). Timing of Administration: For Commonly-Prescribed Medicines in Australia. Pharmaceutics *8*. Available at: http://dx.doi.org/10.3390/pharmaceutics8020013.
3. Paschos, G.K., Baggs, J.E., Hogenesch, J.B., and FitzGerald, G.A. (2010). The role of clock genes in pharmacology. Annu. Rev. Pharmacol. Toxicol. *50*, 187–214.

HARMONIZING THERAPY AND RHYTHMS

1. Winter, C., Silvestre-Roig, C., Ortega-Gomez, A., Lemnitzer, P., Poelman, H., Schumski, A., Winter, J., Drechsler, M., de Jong, R., Immler, R., *et al.* (2018). Chrono-pharmacological Targeting of the CCL2-CCR2 Axis Ameliorates Atherosclerosis. Cell Metab. *28*, 175–

182.e5.
2. Guan, D., Xiong, Y., Borck, P.C., Jang, C., Doulias, P.-T., Papazyan, R., Fang, B., Jiang, C., Zhang, Y., Briggs, E.R., *et al.* (2018). Diet-Induced Circadian Enhancer Remodeling Synchronizes Opposing Hepatic Lipid Metabolic Processes. Cell. 2018 Aug 9; 174(4): 831-842.e12.

PHARMACOKINETICS MATTER

1. Saito, Y., Yoshida, S., Nakaya, N., Hata, Y., and Goto, Y. (1991). Comparison between morning and evening doses of simvastatin in hyperlipidemic subjects. A double-blind comparative study. Arterioscler. Thromb. 11, 816–826.
2. Lund, T.M., Torsvik, H., Falch, D., Christophersen, B., Skårdal, R., and Gullestad, L. (2002). Effect of morning versus evening intake of simvastatin on the serum cholesterol level in patients with coronary artery disease. Am. J. Cardiol. 90, 784–786.
3. Wallace, A., Chinn, D., and Rubin, G. (2003). Taking simvastatin in the morning compared with in the evening: randomised controlled trial. BMJ 327, 788.
4. Tharavanij, T., Wongtanakarn, S., Lerdvuthisopon, N., Teeraaunkul, S., Youngsriphithak, P., and Sritipsukho, P. (2010). Lipid lowering efficacy between morning and evening simvastatin treatment: a randomized double-blind study. J. Med. Assoc. Thai. 93 Suppl 7, S109–13.
5. Cilla, D.D., Jr, Gibson, D.M., Whitfield, L.R., and Sedman, A.J. (1996). Pharmacodynamic effects and pharmacokinetics of atorvastatin after administration to normocholesterolemic subjects in the morning and evening. J. Clin. Pharmacol. 36, 604–609.
6. Plakogiannis, R., Cohen, H., and Taft, D. (2005). Effects of morning versus evening administration of atorvastatin in patients with hyperlipidemia. Am. J. Health. Syst. Pharm. 62, 2491–2494.
7. Kim, S.-H., Kim, M.-K., Seo, H.-S., Hyun, M.-S., Han, K.-R., Cho, S.-W., Kim, Y.-K., and Hoon Park, S. (2013). Efficacy and safety of morning versus evening dose of controlled-release simvastatin tablets in patients with hyperlipidemia: a randomized, double-blind, multicenter phase III trial. Clin. Ther. 35, 1350–60.e1.
8. Yi, Y.J., Kim, H.J., Jo, S.K., Kim, S.G., Song, Y.R., Chung, W., Han, K.H., Lee, C.H., Hwang, Y.-H., and Oh, K.-H. (2014). Comparison of the efficacy and safety profile of morning administration of controlled-release simvastatin versus evening administration of immediate-release simvastatin in chronic kidney disease patients with dyslipidemia. Clin. Ther. 36, 1182–1190.
9. Mengden, T., Binswanger, B., Spühler, T., Weisser, B., and Vetter, W. (1993). The use of self-measured blood pressure determinations in assessing dynamics of drug compliance in a study with amlodipine once a day, morning versus evening. J. Hypertens. *11*, 1403–1411.
10. Nold, G., Strobel, G., and Lemmer, B. (1998). Morning versus evening amlodipine treatment: effect on circadian blood pressure profile in essential hypertensive patients. Blood Press. Monit. *3*, 17–25.
11. Hoshino, A., Nakamura, T., and Matsubara, H. (2010). The bedtime administration ameliorates blood pressure variability and reduces urinary albumin excretion in amlodipine-olmesartan combination therapy. Clin. Exp. Hypertens. *32*, 416–422.
12. Hermida, R.C., Ayala, D.E., Fontao, M.J., Mojón, A., and Fernández, J.R. (2010). Chronotherapy with valsartan/amlodipine fixed combination: improved blood pressure control of essential hypertension with bedtime dosing. Chronobiol. Int. *27*, 1287–1303.
13. Zeng, J., Jia, M., Ran, H., Tang, H., Zhang, Y., Zhang, J., Wang, X., Wang, H., Yang, C., and Zeng, C. (2011). Fixed-combination of amlodipine and diuretic chronotherapy in the treatment of essential hypertension: improved blood pressure control with bedtime dosing-a multicenter, open-label randomized study. Hypertens. Res. *34*, 767–772.

SMALL TRIALS WITH FEW TIME POINTS

1. Sander, G.E., Fernandez, C., and Giles, T.D. (2016). Fixed-dose combination therapy of nebivolol and valsartan for the treatment of hypertension. Expert Rev. Cardiovasc. Ther. *14*, 563–572.
2. Hermida, R.C., Calvo, C., Ayala, D.E., Domínguez, M.J., Covelo, M., Fernández, J.R., Mojón, A., and López, J.E. (2003). Administration time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. Hypertension *42*, 283–290.
3. Hermida, R.C., Calvo, C., Ayala, D.E., Fernández, J.R., Covelo, M., Mojón, A., and López, J.E. (2005). Treatment of non-dipper hypertension with bedtime administration of valsartan. J. Hypertens. *23*, 1913–1922.
4. Wang, C., Zhang, J., Liu, X., Li, C.-C., Ye, Z.C., Peng, H., Chen, Z., and Lou, T. (2013). Effect of valsartan with bedtime dosing on chronic kidney disease patients with nondipping blood pressure pattern. J. Clin. Hypertens. *15*, 48–54.

MECHANISM-DRIVEN CIRCADIAN MEDICINE

1. Mauvoisin, D., Wang, J., Jouffe, C., Martin, E., Atger, F., Waridel, P., Quadroni, M., Gachon, F., and Naef, F. (2014). Circadian clock-dependent and -independent rhythmic proteomes implement distinct diurnal functions in mouse liver. Proc. Natl. Acad. Sci. U. S. A. *111*, 167–172.
2. Feng, D., and Lazar, M.A. (2012). Clocks, metabolism, and the epigenome. Mol. Cell *47*, 158–167.
3. Krishnaiah, S.Y., Wu, G., Altman, B.J., Growe, J., Rhoades, S.D., Coldren, F., Venkataraman, A., Olarerin-George, A.O., Francey, L.J., Mukherjee, S., *et al.* (2017). Clock Regulation of Metabolites Reveals Coupling between Transcription and Metabolism. Cell Metab. *25*, 961–974.e4.
4. Arnardottir, E.S., Nikonova, E.V., Shockley, K.R., Podtelezhnikov, A.A., Anafi, R.C., Tanis, K.Q., Maislin, G., Stone, D.J., Renger, J.J., Winrow, C.J., *et al.* (2014). Blood-gene expression reveals reduced circadian rhythmicity in individuals resistant to sleep deprivation. Sleep *37*, 1589–1600.
5. Archer, S.N., Laing, E.E., Möller-Levet, C.S., van der Veen, D.R., Bucca, G., Lazar, A.S., Santhi, N., Slak, A., Kabiljo, R., von Schantz, M., *et al.* (2014). Mistimed sleep disrupts circadian regulation of the human transcriptome. Proc. Natl. Acad. Sci. U. S. A. *111*, E682–91.
6. Möller-Levet, C.S., Archer, S.N., Bucca, G., Laing, E.E., Slak, A., Kabiljo, R., Lo, J.C.Y., Santhi, N., von Schantz, M., Smith, C.P., *et al.* (2013). Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome. Proc. Natl. Acad. Sci. U. S. A. *110*, E1132–41.
7. Akashi, M., Soma, H., Yamamoto, T., Tsugitomi, A., Yamashita, S., Yamamoto, T., Nishida, E., Yasuda, A., Liao, J.K., and Node, K. (2010). Noninvasive method for assessing the human circadian clock using hair follicle cells. Proc. Natl. Acad. Sci. U. S. A. *107*, 15643–15648.
8. Wu, G., Ruben, M.D., Schmidt, R.E., Francey, L.J., Smith, D.F., Anafi, R.C., Hughey, J.J., Tasseff, R., Sherrill, J.D., Oblong, J.E., *et al.* (2018). Population-level rhythms in human skin with implications for circadian medicine. Proc. Natl. Acad. Sci. U. S. A. *115*, 12313–12318.
9. Laverty, H., Benson, C., Cartwright, E., Cross, M., Garland, C., Hammond, T., Holloway, C., McMahon, N., Milligan, J., Park, B., *et al.* (2011). How can we improve our understanding of cardiovascular safety liabilities to develop safer medicines? Br. J. Pharmacol. *163*, 675–693.
10. Shryock, J.C., and Belardinelli, L. (1997). Adenosine and adenosine receptors in the

cardiovascular system: biochemistry, physiology, and pharmacology. Am. J. Cardiol. *79*, 2–10.
11. Mladěnka, P., Applová, L., Patočka, J., Costa, V.M., Remiao, F., Pourová, J., Mladěnka, A., Karlíčková, J., Jahodář, L., Vopršalová, M., *et al.* (2018). Comprehensive review of cardiovascular toxicity of drugs and related agents. Med. Res. Rev. Available at: http://dx.doi.org/10.1002/med.21476.
12. Goyal, M., Shukla, P., Gupta, D., Bisht, S.S., Dhawan, A., Gupta, S., Pant, M.C., and Verma, N.S. (2009). Oral mucositis in morning vs. evening irradiated patients: a randomised prospective study. Int. J. Radiat. Biol. *85*, 504–509.
13. Fournier, S., Puricel, S., Morawiec, B., Eeckhout, E., Mangiacapra, F., Trana, C., Tapponnier, M., Iglesias, J.F., Michiels, V., Stauffer, J.-C., *et al.* (2014). Relationship between time of day and periprocedural myocardial infarction after elective angioplasty. Chronobiol. Int. *31*, 206–213.

FUTURE DRUG DEVELOPMENT

1. Smolensky, M.H., Hermida, R.C., Ayala, D.E., Tiseo, R., and Portaluppi, F. (2010). Administration-time-dependent effects of blood pressure-lowering medications: basis for the chronotherapy of hypertension. Blood Press. Monit. *15*, 173–180.
2. Hughes, M.E., Abruzzi, K.C., Allada, R., Anafi, R., Arpat, A.B., Asher, G., Baldi, P., de Bekker, C., Bell-Pedersen, D., Blau, J., *et al.* (2017). Guidelines for Genome-Scale Analysis of Biological Rhythms. J. Biol. Rhythms *32*, 380–393.
3. Wu G, Ruben MD, Schmidt, RE, Francey LJ, Smith DF, Anaf RCi, Hughey JJ, Tassef Rf, Sherrill JD, Oblong JE, Mills KJ, Hogenesch JB (2018). Population level rhythms in human skin: implications for circadian medicine. bioRxiv. Available at: http://dx.doi.org/10.1101/301820.
4. Wittenbrink, N., Ananthasubramaniam, B., Münch, M., Koller, B., Maier, B., Weschke, C., Bes, F., de Zeeuw, J., Nowozin, C., Wahnschaffe, A., *et al.* (2018). High-accuracy determination of internal circadian time from a single blood sample. J. Clin. Invest. Available at: http://dx.doi.org/10.1172/JCI120874.
5. Braun, R., Kath, W.L., Iwanaszko, M., Kula-Eversole, E., Abbott, S.M., Reid, K.J., Zee, P.C., and Allada, R. (2018). Universal method for robust detection of circadian state from gene expression. Proc. Natl. Acad. Sci. U. S. A. Available at: http://dx.doi.org/10.1073/pnas.1800314115.
6. Alibhai, F.J., Tsimakouridze, E.V., Chinnappareddy, N., Wright, D.C., Billia, F., O'Sullivan, M.L., Pyle, W.G., Sole, M.J., and Martino, T.A. (2014). Short-term disruption of diurnal rhythms after murine myocardial infarction adversely affects long-term myocardial structure and function. Circ. Res. *114*, 1713–1722.
7. Beauchemin, K.M., and Hays, P. (1998). Dying in the dark: sunshine, gender and outcomes in myocardial infarction. J. R. Soc. Med. *91*, 352–354.
8. Vásquez-Ruiz, S., Maya-Barrios, J.A., Torres-Narváez, P., Vega-Martínez, B.R., Rojas-Granados, A., Escobar, C., and Angeles-Castellanos, M. (2014). A light/dark cycle in the NICU accelerates body weight gain and shortens time to discharge in preterm infants. Early Hum. Dev. *90*, 535–540.
9. McKenna, H., van der Horst, G.T.J., Reiss, I., and Martin, D. (2018). Clinical chronobiology: a timely consideration in critical care medicine. Crit. Care *22*, 124.

CIRCADIAN PRECISION

1. Campian, J.L., Talcott, G., Meyer, M., Slat, E., Avvaru, C., Bhatta, P., and Rubin, J. (2018). Randomized feasibility study of temozolomide chronotherapy for high grade glioma. In (American Society of Clinical Oncology), pp. e14035–e14035.

106 CLINICAL STUDIES SELECTED FOR STUDY

1. A. Reinberg, E. Sidi, Circadian changes in the inhibitory effects of an antihistaminic drug in man. *J. Invest. Dermatol.* **46**, 415–419 (1966).

2. A. Reinberg, F. Levi, P. Guillet, J. T. Burke, A. Nicolai, Chronopharmacological study of antihistamines in man with special references to terfenadine. *Eur. J. Clin. Pharmacol.* **14**, 245–252 (1978).

3. R. Haye, K. Høye, O. Berg, S. Frønes, T. Odegård, Morning versus evening dosing of desloratadine in seasonal allergic rhinitis: a randomized controlled study [ISRCTN23032971]. *Clin. Mol. Allergy*. **3**, 3 (2005).

4. J. R. Deandrade, J. N. Mccormick, A. G. Hill, SMALL DOSES OF PREDNISOLONE IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS. *Ann. Rheum. Dis.* **23**, 158–162 (1964).

5. I. C. Kowanko, R. Pownall, M. S. Knapp, A. J. Swannell, P. G. Mahoney, Circadian variations in the signs and symptoms of rheumatoid arthritis and in the therapeutic effectiveness of flurbiprofen at different times of day. *Br. J. Clin. Pharmacol.* **11**, 477–484 (1981).

6. M. De Silva, A. Binder, B. L. Hazleman, The timing of prednisolone dosage and its effect on morning stiffness in rheumatoid arthritis. *Ann. Rheum. Dis.* **43**, 790–793 (1984).

7. F. Levi, C. Le Louarn, A. Reinberg, Timing optimizes sustained-release indomethacin treatment of osteoarthritis. *Clin. Pharmacol. Ther.* **37**, 77–84 (1985).

8. N. G. Arvidson, B. Gudbjörnsson, A. Larsson, R. Hällgren, The timing of glucocorticoid administration in rheumatoid arthritis. *Ann. Rheum. Dis.* **56**, 27–31 (1997).

9. F. Buttgereit *et al.*, Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. *Lancet*. **371**, 205–214 (2008).

10. H. To *et al.*, Methotrexate chronotherapy is effective against rheumatoid arthritis. *Chronobiol. Int.* **28**, 267–274 (2011).

11. P. J. Barnes, G. A. Fitzgerald, C. T. Dollery, Circadian variation in adrenergic responses in asthmatic subjects. *Clin. Sci.* . **62**, 349–354 (1982).

12. M. H. Smolensky *et al.*, Administration-time-dependency of the pharmacokinetic behavior and therapeutic effect of a once-a-day theophylline in asthmatic children. *Chronobiol. Int.* **4**, 435–447 (1987).

13. R. Dahl, H. Harving, L. Säwedal, S. Anehus, Terbutaline sustained-release tablets in nocturnal asthma—a placebo-controlled comparison between a high and a low evening dose. *Br. J. Dis. Chest*. **82**, 237–241 (1988).

14. C. Gaultier, A. Reinberg, Y. Motohashi, Circadian rhythm in total pulmonary resistance of asthmatic children. Effects of a beta-agonist agent. *Chronobiol. Int.* **5**, 285–290 (1988).

15. J. F. Morrison, S. B. Pearson, H. G. Dean, Parasympathetic nervous system in nocturnal asthma. *Br. Med. J.* . **296**, 1427–1429 (1988).

16. G. E. D'Alonzo *et al.*, Twenty-four hour lung function in adult patients with asthma. Chronoptimized theophylline therapy once-daily dosing in the evening versus conventional twice-daily dosing. *Am. Rev. Respir. Dis.* **142**, 84–90 (1990).

17. W. R. Beam, D. E. Weiner, R. J. Martin, Timing of prednisone and alterations of airways inflammation in nocturnal asthma. *Am. Rev. Respir. Dis.* **146**, 1524–1530 (1992).

18. W. W. Storms *et al.*, The effect of repeat action albuterol sulfate (Proventil Repetabs) in nocturnal symptoms of asthma. *J. Asthma*. **29**, 209–216 (1992).

19. P. Faurschou, A. M. Engel, O. C. Haanaes, Salmeterol in two different doses in the treatment of nocturnal bronchial asthma poorly controlled by other therapies. *Allergy*. **49**, 827–832 (1994).

20. N. Burioka *et al.*, Alteration of the circadian rhythm in peak expiratory flow of nocturnal asthma following nighttime transdermal beta2-adrenoceptor agonist tulobuterol chronotherapy. *Chronobiol. Int.* **22**, 383–390 (2005).

21. J. P. Caussanel *et al.*, Phase I trial of 5-day continuous venous infusion of oxaliplatin at circadian rhythm-modulated rate compared with constant rate. *J. Natl. Cancer Inst.* **82**, 1046–1050 (1990).

22. F. A. Lévi *et al.*, Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid (leucovorin) in patients with colorectal cancer metastases: a randomized multi-institutional trial. *J. Natl. Cancer Inst.* **86**, 1608–1617 (1994).

23. F. Lévi, R. Zidani, J.-L. Misset, Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. *Lancet*. **350**, 681–686 (1997).

24. D. Dinçol *et al.*, Prospective randomized comparison of morning versus night daily single subcutaneous administration of granulocyte-macrophage-colony stimulating factor in patients with soft tissue or bone sarcoma. *Cancer*. **88**, 2033–2036 (2000).

25. S. Giacchetti *et al.*, Phase III trial comparing 4-day chronomodulated therapy versus 2-day conventional delivery of fluorouracil, leucovorin, and oxaliplatin as first-line chemotherapy of metastatic colorectal cancer: the European Organisation for Research and Treatment of Cancer Chronotherapy Group. *J. Clin. Oncol.* **24**, 3562–3569 (2006).

26. G. A. Bjarnason *et al.*, Comparison of toxicity associated with early morning versus late afternoon radiotherapy in patients with head-and-neck cancer: a prospective randomized trial of the National Cancer Institute of Canada Clinical Trials Group (HN3). *Int. J. Radiat. Oncol. Biol. Phys.* **73**, 166–172 (2009).

27. M. Goyal *et al.*, Oral mucositis in morning vs. evening irradiated patients: a randomised prospective study. *Int. J. Radiat. Biol.* **85**, 504–509 (2009).

28. C. Qvortrup *et al.*, A randomized study comparing short-time infusion of oxaliplatin in combination with capecitabine XELOX(30) and chronomodulated XELOX(30) as first-line therapy in patients with advanced colorectal cancer. *Ann. Oncol.* **21**, 87–91 (2010).

29. P. Shukla *et al.*, Circadian variation in radiation-induced intestinal mucositis in patients with cervical carcinoma. *Cancer*. **116**, 2031–2035 (2010).

30. D. A. Rahn 3rd *et al.*, Gamma knife radiosurgery for brain metastasis of nonsmall cell lung cancer: is there a difference in outcome between morning and afternoon treatment? *Cancer*. **117**, 414–420 (2011).

31. S. N. Badiyan *et al.*, Impact of time of day on outcomes after stereotactic radiosurgery for non-small cell lung cancer brain metastases. *Cancer*. **119**, 3563–3569 (2013).

32. H.-X. Lin *et al.*, Randomized study of sinusoidal chronomodulated versus flat intermittent induction chemotherapy with cisplatin and 5-fluorouracil followed by traditional radiotherapy for locoregionally advanced nasopharyngeal carcinoma. *Chin. J. Cancer*. **32**, 502–511 (2013).

33. J. M. Noh *et al.*, Comparison of acute skin reaction following morning versus late afternoon radiotherapy in patients with breast cancer who have undergone curative surgical resection. *J. Radiat. Res.* **55**, 553–558 (2014).

34. J. Li, R. Chen, M. Ji, S.-L. Zou, L.-N. Zhu, Cisplatin-based chronotherapy for advanced non-small cell lung cancer patients: a randomized controlled study and its pharmacokinetics analysis. *Cancer Chemother. Pharmacol.* **76**, 651–655 (2015).

35. Bi T. *et al.*, [Phase II clinical trial of two different modes of administration of the induction chemotherapy for locally advanced nasopharyngeal carcinoma]. *Zhonghua Zhong Liu Za Zhi*. **37**, 676–681 (2015).

36. F.-M. Hsu *et al.*, Differences in toxicity and outcome associated with circadian variations between patients undergoing daytime and evening radiotherapy for prostate adenocarcinoma. *Chronobiol. Int.* **33**, 210–219 (2016).

37. S. Chan *et al.*, Could time of whole brain radiotherapy delivery impact overall survival in patients with multiple brain metastases? *Ann. Palliat. Med.* **5**, 267–279 (2016).

38. S. Chan *et al.*, Effects of circadian rhythms and treatment times on the response of radiotherapy for painful bone metastases. *Ann. Palliat. Med.* **6**, 14–25 (2017).

39. Y. Tsuchiya *et al.*, Influence of a dosing-time on toxicities induced by docetaxel, cisplatin and 5-fluorouracil in patients with oral squamous cell carcinoma; a cross-over pilot study. *Chronobiol. Int.* **35**, 289–294 (2018).

40. P. X. Zhang *et al.*, A randomized phase II trial of induction chemotherapy followed by cisplatin chronotherapy versus constant rate delivery combined with radiotherapy. *Chronobiol. Int.* **35**, 240–248 (2018).

41. Y. Saito, S. Yoshida, N. Nakaya, Y. Hata, Y. Goto, Comparison between morning and evening doses of simvastatin in hyperlipidemic subjects. A double-blind comparative study. *Arterioscler. Thromb.* **11**, 816–826 (1991).

42. D. D. Cilla Jr, D. M. Gibson, L. R. Whitfield, A. J. Sedman, Pharmacodynamic effects and pharmacokinetics of atorvastatin after administration to normocholesterolemic subjects in the morning and evening. *J. Clin. Pharmacol.* **36**, 604–609 (1996).

43. T. M. Lund *et al.*, Effect of morning versus evening intake of simvastatin on the serum cholesterol level in patients with coronary artery disease. *Am. J. Cardiol.* **90**, 784–786 (2002).

44. A. Wallace, D. Chinn, G. Rubin, Taking simvastatin in the morning compared with in the evening: randomised controlled trial. *BMJ*. **327**, 788 (2003).

45. R. Plakogiannis, H. Cohen, D. Taft, Effects of morning versus evening administration of atorvastatin in patients with hyperlipidemia. *Am. J. Health. Syst. Pharm.* **62**, 2491–2494 (2005).

46. M. Ozaydin *et al.*, Effects of morning versus evening intake of atorvastatin on major cardiac event and restenosis rates in patients undergoing first elective percutaneous coronary intervention. *Am. J. Cardiol.* **97**, 44–47 (2006).

47. T. Tharavanij *et al.*, Lipid lowering efficacy between morning and evening simvastatin treatment: a randomized double-blind study. *J. Med. Assoc. Thai.* **93 Suppl 7**, S109–13 (2010).

48. H. S. Yoon *et al.*, Comparison of effects of morning versus evening administration of ezetimibe/simvastatin on serum cholesterol in patients with primary hypercholesterolemia. *Ann. Pharmacother.* **45**, 841–849 (2011).

49. S.-H. Kim *et al.*, Efficacy and safety of morning versus evening dose of controlled-release simvastatin tablets in patients with hyperlipidemia: a randomized, double-blind, multicenter phase III trial. *Clin. Ther.* **35**, 1350–60.e1 (2013).

50. Y. J. Yi *et al.*, Comparison of the efficacy and safety profile of morning administration of controlled-release simvastatin versus evening administration of immediate-release simvastatin in chronic kidney disease patients with dyslipidemia. *Clin. Ther.* **36**, 1182–1190 (2014).

51. B. Langner, B. Lemmer, Circadian changes in the pharmacokinetics and cardiovascular effects of oral propranolol in healthy subjects. *Eur. J. Clin. Pharmacol.* **33**, 619–624 (1988).

52. J. A. Panza, S. E. Epstein, A. A. Quyyumi, Circadian variation in vascular tone and its relation to alpha-sympathetic vasoconstrictor activity. *N. Engl. J. Med.* **325**, 986–990 (1991).

53. M. Middeke, M. Klüglich, H. Holzgreve, Chronopharmacology of captopril plus hydrochlorothiazide in hypertension: morning versus evening dosing. *Chronobiol. Int.* **8**, 506–510 (1991).

54. P. Palatini, Can an angiotensin-converting enzyme inhibitor with a short half-life effectively lower blood pressure for 24 hours? *Am. Heart J.* **123**, 1421–1425 (1992).

55. B. Meilhac *et al.*, [Study of the influence of the time of administration on the antihypertensive effect and nitrendipine tolerance in mild to moderate essential hypertensive patients. Value of ambulatory recording of blood pressure on 24 hours]. *Therapie*. **47**, 205–210 (1992).

56. D. P. Myburgh, M. Verho, J. H. Botes, T. P. Erasmus, H. G. Luus, 24-hour blood pressure

control with ramipril: comparison of once-daily morning and evening administration. *Curr. Ther. Res. Clin. Exp.* **56**, 1298–1306 (1995).

57. T. Mengden, B. Binswanger, T. Spühler, B. Weisser, W. Vetter, The use of self-measured blood pressure determinations in assessing dynamics of drug compliance in a study with amlodipine once a day, morning versus evening. *J. Hypertens.* **11**, 1403–1411 (1993).

58. R. Fogari, E. Malacco, F. Tettamanti, A. E. Gnemmi, M. Milani, Evening vs morning isradipine sustained release in essential hypertension: a double-blind study with 24 h ambulatory monitoring. *Br. J. Clin. Pharmacol.* **35**, 51–54 (1993).

59. K. Witte *et al.*, Cardiovascular effects, pharmacokinetics, and converting enzyme inhibition of enalapril after morning versus evening administration. *Clin. Pharmacol. Ther.* **54**, 177–186 (1993).

60. P. Palatini *et al.*, Effect of evening versus morning benazepril on 24-hour blood pressure: a comparative study with continuous intraarterial monitoring. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **31**, 295–300 (1993).

61. T. Umeda *et al.*, Timing for administration of an antihypertensive drug in the treatment of essential hypertension. *Hypertension*. **23**, I211–4 (1994).

62. P. Greminger, P. M. Suter, D. Holm, R. Kobelt, W. Vetter, Morning versus evening administration of nifedipine gastrointestinal therapeutic system in the management of essential hypertension. *Clin. Investig.* **72**, 864–869 (1994).

63. F. Portaluppi, L. Vergnani, R. Manfredini, E. C. degli Uberti, C. Fersini, Time-dependent effect of isradipine on the nocturnal hypertension in chronic renal failure. *Am. J. Hypertens.* **8**, 719–726 (1995).

64. T. Morgan, A. Anderson, E. Jones, The effect on 24 h blood pressure control of an angiotensin converting enzyme inhibitor (perindopril) administered in the morning or at night. *J. Hypertens.* **15**, 205–211 (1997).

65. G. Nold, G. Strobel, B. Lemmer, Morning versus evening amlodipine treatment: effect on circadian blood pressure profile in essential hypertensive patients. *Blood Press. Monit.* **3**, 17–25 (1998).

66. W. B. White *et al.*, Differential effects of morning and evening dosing of nisoldipine ER on circadian blood pressure and heart rate. *Am. J. Hypertens.* **12**, 806–814 (1999).

67. I. Kohno *et al.*, Effect of imidapril in dipper and nondipper hypertensive patients: comparison between morning and evening administration. *Chronobiol. Int.* **17**, 209–219 (2000).

68. Y.-G. Qiu, J.-Z. Chen, J.-H. Zhu, X.-Y. Yao, Differential effects of morning or evening dosing of amlodipine on circadian blood pressure and heart rate. *Cardiovasc. Drugs Ther.* **17**, 335–341 (2003).

69. R. C. Hermida *et al.*, Administration time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. *Hypertension*. **42**, 283–290 (2003).

70. Y. Kitahara *et al.*, Effect of morning and bedtime dosing with cilnidipine on blood pressure,

heart rate, and sympathetic nervous activity in essential hypertensive patients. *J. Cardiovasc. Pharmacol.* **43**, 68–73 (2004).

71. R. C. Hermida *et al.*, Administration-time-dependent effects of doxazosin GITS on ambulatory blood pressure of hypertensive subjects. *Chronobiol. Int.* **21**, 277–296 (2004).

72. T. Kuroda *et al.*, Effects of bedtime vs. morning administration of the long-acting lipophilic angiotensin-converting enzyme inhibitor trandolapril on morning blood pressure in hypertensive patients. *Hypertens. Res.* **27**, 15–20 (2004).

73. R. C. Hermida *et al.*, Differing administration time-dependent effects of aspirin on blood pressure in dipper and non-dipper hypertensives. *Hypertension*. **46**, 1060–1068 (2005).

74. R. C. Hermida *et al.*, Administration time-dependent effects of valsartan on ambulatory blood pressure in elderly hypertensive subjects. *Chronobiol. Int.* **22**, 755–776 (2005).

75. R. C. Hermida *et al.*, Treatment of non-dipper hypertension with bedtime administration of valsartan. *J. Hypertens.* **23**, 1913–1922 (2005).

76. R. C. Hermida *et al.*, in *Journal of Hypertension* (LIPPINCOTT WILLIAMS & WILKINS 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA, 2006), vol. 24, pp. S89–S89.

77. R. C. Hermida, D. E. Ayala, J. R. Fernández, C. Calvo, Comparison of the efficacy of morning versus evening administration of telmisartan in essential hypertension. *Hypertension*. **50**, 715–722 (2007).

78. R. C. Hermida *et al.*, Comparison of the effects on ambulatory blood pressure of awakening versus bedtime administration of torasemide in essential hypertension. *Chronobiol. Int.* **25**, 950–970 (2008).

79. R. C. Hermida, D. E. Ayala, A. Mojón, J. R. Fernández, Ambulatory blood pressure control with bedtime aspirin administration in subjects with prehypertension. *Am. J. Hypertens.* **22**, 896–903 (2009).

80. R. C. Hermida, D. E. Ayala, L. Chayan, A. Mojon, J. R. Fernandez, Administration-time-dependent effects of olmesartan on the ambulatory blood pressure of essential hypertension patients. *Chronobiol. Int.* **26**, 61–79 (2009).

81. R. C. Hermida, D. E. Ayala, A. Mojón, J. R. Fernández, Chronotherapy with nifedipine GITS in hypertensive patients: improved efficacy and safety with bedtime dosing. *Am. J. Hypertens.* **21**, 948–954 (2008).

82. R. C. Hermida, D. E. Ayala, Chronotherapy with the angiotensin-converting enzyme inhibitor ramipril in essential hypertension: improved blood pressure control with bedtime dosing. *Hypertension*. **54**, 40–46 (2009).

83. R. C. Hermida *et al.*, Administration-time-dependent effects of spirapril on ambulatory blood pressure in uncomplicated essential hypertension. *Chronobiol. Int.* **27**, 560–574 (2010).

84. A. Hoshino, T. Nakamura, H. Matsubara, The bedtime administration ameliorates blood pressure variability and reduces urinary albumin excretion in amlodipine-olmesartan combination therapy. *Clin. Exp. Hypertens.* **32**, 416–422 (2010).

85. R. C. Hermida, D. E. Ayala, M. J. Fontao, A. Mojón, J. R. Fernández, Chronotherapy with valsartan/amlodipine fixed combination: improved blood pressure control of essential hypertension with bedtime dosing. *Chronobiol. Int.* **27**, 1287–1303 (2010).

86. R. Asmar, P. Gosse, S. Queré, A. Achouba, Efficacy of morning and evening dosing of amlodipine/valsartan combination in hypertensive patients uncontrolled by 5 mg of amlodipine. *Blood Press. Monit.* **16**, 80–86 (2011).

87. J. Zeng *et al.*, Fixed-combination of amlodipine and diuretic chronotherapy in the treatment of essential hypertension: improved blood pressure control with bedtime dosing-a multicenter, open-label randomized study. *Hypertens. Res.* **34**, 767–772 (2011).

88. K. Eguchi, M. Shimizu, S. Hoshide, K. Shimada, K. Kario, A bedtime dose of ARB was better than a morning dose in improving baroreflex sensitivity and urinary albumin excretion--the J-TOP study. *Clin. Exp. Hypertens.* **34**, 488–492 (2012).

89. C. Wang *et al.*, Effect of valsartan with bedtime dosing on chronic kidney disease patients with nondipping blood pressure pattern. *J. Clin. Hypertens.* . **15**, 48–54 (2013).

90. D. H. Zappe, N. Crikelair, A. Kandra, P. Palatini, Time of administration important? Morning versus evening dosing of valsartan. *J. Hypertens.* **33**, 385–392 (2015).

91. T. N. Bonten *et al.*, Time-dependent effects of aspirin on blood pressure and morning platelet reactivity: a randomized cross-over trial. *Hypertension*. **65**, 743–750 (2015).

92. M. Kozinski *et al.*, Diurnal variation in platelet inhibition by clopidogrel. *Platelets*. **22**, 579–587 (2011).

93. S. Brunner-Ziegler *et al.*, Comparison between the impact of morning and evening doses of rivaroxaban on the circadian endogenous coagulation rhythm in healthy subjects. *J. Thromb. Haemost.* **14**, 316–323 (2016).

94. D. Montaigne *et al.*, Daytime variation of perioperative myocardial injury in cardiac surgery and its prevention by Rev-Erbα antagonism: a single-centre propensity-matched cohort study and a randomised study. *Lancet* (2017), doi:10.1016/S0140-6736(17)32132-3.

95. S. C. Gruber *et al.*, Twenty-four-hour time dependency of clopidogrel effects in patients with acute coronary syndromes: The CiCAD-Study. *Platelets*, 1–7 (2018).

96. J. Hendel, L. Hendel, S. Aggestrup, Morning or evening dosage of omeprazole for gastro-oesophageal reflux disease? *Aliment. Pharmacol. Ther.* **9**, 693–697 (1995).

97. S. A. Shappell, G. L. Kearns, J. L. Valentine, D. F. Neri, C. A. DeJohn, Chronopharmacokinetics and chronopharmacodynamics of dextromethamphetamine in man. *J. Clin. Pharmacol.* **36**, 1051–1063 (1996).

98. P. M. A. Calverley *et al.*, Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. *Thorax*. **58**, 855–860 (2003).

99. N. D. Pehlivanov, M. Olyaee, I. Sarosiek, R. W. McCallum, Comparison of morning and evening administration of rabeprazole for gastro-oesophageal reflux and nocturnal gastric acid breakthrough in patients with reflux disease: a double-blind, cross-over study. *Aliment. Pharmacol. Ther.* **18**, 883–890 (2003).

100. R. Yegnanarayan, S. D. Mahesh, S. Sangle, Chronotherapeutic dose schedule of phenytoin and carbamazepine in epileptic patients. *Chronobiol. Int.* **23**, 1035–1046 (2006).

101. R. Rajput, S. Chatterjee, M. Rajput, Can Levothyroxine Be Taken as Evening Dose? Comparative Evaluation of Morning versus Evening Dose of Levothyroxine in Treatment of Hypothyroidism. *J. Thyroid Res.* **2011**, 505239 (2011).

102. N. Bolk *et al.*, Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. *Arch. Intern. Med.* **170**, 1996–2003 (2010).

103. D. E. Ayala, R. Ucieda, R. C. Hermida, Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. *Chronobiol. Int.* **30**, 260–279 (2013).

104. B. Ahrén, A. Leguizamo Dimas, P. Miossec, S. Saubadu, R. Aronson, Efficacy and safety of lixisenatide once-daily morning or evening injections in type 2 diabetes inadequately controlled on metformin (GetGoal-M). *Diabetes Care*. **36**, 2543–2550 (2013).

105. J. E. Long *et al.*, Morning vaccination enhances antibody response over afternoon vaccination: A cluster-randomised trial. *Vaccine*. **34**, 2679–2685 (2016).

106. X. Zhuang, A. G. Lai, J. A. McKeating, I. Rowe, P. Balfe, Daytime variation in hepatitis C virus replication kinetics following liver transplant. *Wellcome Open Res*. **3**, 96 (2018).

107. D. S. Wishart *et al.*, DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res.* **46**, D1074–D1082 (2017).