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Circadian Variation in P-gp–Mediated Efflux at the BBB with Drug-Class–Specific Applications

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Abstract. The blood-brain-barrier (BBB) is an important semi-permeable and selective barrier between the central nervous system (CNS) and the brain that regulates the brain's exposure to a variety of substances including nutrients, toxins and pharmacological drugs. Efflux transporter p-glycoprotein (P-gp) serves as a crucial mechanism underlying BBB selectivity, extruding xenobiotics back to the bloodstream but simultaneously restricting drug penetration targeting the CNS. Research has previous demonstrated that P-gp mediated efflux oscillates across its own circadian cycle, creating time of day differences in BBB permeability. The circadian oscillations of P-gp suggest implications for the efficacy of therapeutic outcomes targeting neurological disorders such as epilepsy and depression. Many antiepileptic and antidepressant drugs are p-gp substrates, and this may have contributed to the variability in treatment outcomes. Preclinical studies suggest that aligning drug administration with circadian phases can enhance therapeutic outcomes, though causal links in humans remain underexplored. Moreover, P-gp substrate status is drug- and class-specific, with conflicting evidence for several compounds, underscoring the need for rigorous translational studies. This review synthesizes current findings on circadian regulation of P-gp–mediated efflux at the BBB, highlights drug-class–specific implications for epilepsy and depression and outlines future directions for chrono-pharmacological strategies. Integrating circadian biology with transporter pharmacology may provide a low-cost, high impact means of improving CNS drug delivery and overcoming treatment resistance

Keywords: P-gp efflux, circadian oscillation, Chronotherapy

1. Introduction

The blood-brain barrier (BBB) is a dynamic, protective, and semi-permeable and selective barrier made of tightly interlocked endothelial cells that serves a critical function in separating the brain, central nervous system (CNS), from the blood stream. As a gatekeeper that decides what reaches the CNS, such as allowing nutrients, including oxygen, but blocking hazardous substances such as pathogens, the BBB becomes essential in understanding the efficacy of drug delivery and can offer a therapeutic outlook to drastically improve current clinical practices without changing the drug itself. Emerging evidence highlights that BBB function is not static but exhibits rhythmic variation across the circadian cycle, the intrinsic ~24-hour oscillation synchronized to the light–dark cycle . Recent

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studies suggest a strong correlation between BBB integrity and circadian biological processes, with time-of-day–dependent changes in permeability and transporter activity influencing drug efficacy [1,2].

A key mechanism underlying BBB selectivity is efflux transport. Among the ATP-binding cassette (ABC) transporter family, P-glycoprotein (P-gp), encoded by the ABCB1 (MDR1) gene, plays a central role. P-gp is broadly expressed in tissues such as the brain, liver, kidney, and intestine, where it actively extrudes a wide range of substrates—including xenobiotics and many pharmacological agents—back into the bloodstream. At the BBB, P-gp is strategically localized on the luminal surface of endothelial cells, where it prevents the accumulation of neurotoxic substances and regulates CNS drug exposure. By doing so, P-gp safeguards neuronal function and contributes to overall CNS homeostasis. Pioneering research in Drosophila first revealed that P-gp–mediated efflux exhibits circadian rhythmicity, with efflux capacity fluctuating across the cycle [3]. Subsequent mammalian studies confirmed similar oscillations in rodents, and recent evidence suggests that these circadian oscillations in P-gp efflux extend to humans [4]. Such findings demonstrate that P-gp, as a direct modulator of BBB permeability, serves as a therapeutic target between circadian clock activity and CNS drug bioavailability.

However, it is important to note that the circadian cycle's influence on P-gp efflux activity varies significantly depending on the drug class and the substrate status of the drug across different clinical contexts. Antidepressants and antiepileptic drugs differ in their substrate status, leading to distinct interactions with P-gp and, consequently, variations in therapeutic outcomes observed in clinical data. Considering these drug-specific differences in the circadian modulation of P-gp efflux activity, this paper reviews current research on circadian variation in BBB permeability and examines preclinical data on how efflux activity fluctuates with the timing of administration for various antiepileptic and antidepressant drugs, with implications for optimizing therapeutic efficacy.

2. Mechanism of P-gp as a target and, circadian rhythm and circadian clocks

Encoded by the resistance gene ABCB, P-glycoprotein (P-gp) is a transporter of the ATP-binding cassette (ABC) transporter family that is commonly expressed in biological barriers and excretory tissues, including but not limited to the endothelial cells that make up the blood-brain barrier. P-gp efflux activity dictates BBB permeability by actively pumping a wide range of substances, such as environmental toxins and xenobiotics, from the central nervous system into the bloodstream. While functioning as a protective, semi-permeable barrier for the brain, P-gp efflux also limits drug penetration—such as with the administration of antiseizure medications like lacosamide and antidepressants like imipramine—into the CNS, thereby reducing the efficacy of drugs administered to patients [5]. Studying P-gp efflux activity can potentially offer insight into understanding and mitigating drug resistance in neurological disorders where adequate dosing fails to produce meaningful therapeutic outcomes. This may occur when therapeutic concentrations cannot be achieved in the CNS due to excessive efflux activity. Previous research has shown mixed results when P-gp efflux is inhibited pharmacologically. In preclinical animal models, inhibiting P-gp transporter activity has been found to increase drug concentrations in the brain and, consequently, enhance therapeutic efficacy. However, P-gp inhibition has also been associated with adverse effects such as neurotoxicity, as the CNS becomes more susceptible to toxins in the bloodstream due to increased BBB permeability [6]. Therefore, simply inhibiting P-gp transporter activity to enhance drug penetration is not a viable long-term solution, shifting attention toward alternative strategies for improving drug delivery. One such strategy is a proposed nanocarrier-based drug delivery approach

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including using liposomes, polymeric nanoparticles, and solid lipid nanoparticles to encapsulate drugs and transport across biological barriers like the BBB [7].

Emerging evidence starts pointing to circadian rhythm as a factor that mediates P-gp efflux at the BBB which potentially suggests the essential role circadian cycle play in overcoming drug resistance and increase therapeutic efficacy. Circadian cycle refers to the biological clock guided by the light-dark cycle and the corresponding resting and active phase which regulate biologically mechanisms in living organisms including animals and humans. Not only do such rhythmic circadian oscillations shape the sleep-wake cycle, more importantly it coordinates molecular processes such as protein expression. According to studies on fruit fly Drosophila Melanogaster models, circadian clock genes such as Period was identified to be leading the transcription-translation feedback loop (TTFL) model: CLOCK and BMAL1 activates Per and Cry transcription in the morning, and PER/CRY proteins in turn inhibit transcription at night before being degraded to reset the cycle [8].

3. Influence of circadian oscillation on BBB xenobiotic efflux

Circadian oscillations impact many bodily functions—in fact, the degradation of the light-dark cycle can significantly impact human health and is a risk factor for neurogenerative diseases, cancer and depression [9]. Studies have shown that circadian rhythms extend their influence beyond sleep and wake cycles, shaping diverse physiological processes. They play a role in regulating gut health, coordinating DNA repair mechanisms in response to UV exposure and thereby influencing skin cancer risk, and maintaining proper balance in hormone secretion and metabolic function [9].

As a crucial protective barrier for CNS, the blood-brain barrier is also regulated by the circadian rhythm. According to research in Drosophila seizure models, P-gp mediated efflux activity, regulated by the molecular clock in the sub perineurial glia, is lower at night which leads to higher BBB permeability [3]. Because xenobiotic efflux is lower during the night, the study show administration of the antiepileptic drug phenytoin at this time is more effective in reducing seizures compared to daytime dosing [3]. In addition to fruit fly models, mammalian models also support the same findings that circadian rhythms mediate BBB permeability [4]. For example, mice models show that P-gp efflux activity at the BBB follows the circadian cycle, peaking during the active phase and declining during the rest phase [4]. Overall, research in animals models demonstrate that BBB penetration changes and would be the highest during the resting phase, indicating that it would be easier for drugs to penetrate and reach the central nervous system. Together, the findings emphasize the therapeutic potential of aligning drug administration with circadian timing to improve CNS drug delivery.

However, it is important to note that there are conflicting results of CNS penetration depending on P-gp selectivity of different P-gp substrate and the technical analysis of efflux activity. For example, in Kervezee's study using micro dialysis for tracing P-gp activity in rat models, results corroborate with previous findings that there is a lower P-gp activity during rest phase which translates to higher penetration during rest phase, and thus lower brain exposure to quinidine at nigh since rats are nocturnal [10]. However, In the Salvolanien's study which used PET to detect radio-labelled P-gp substrate demonstrates a higher bran exposure to the P-gp substrate during ZT15 which is early active phase which translates to lowest P-gp activity [11]. In contrast, efflux activity was highest during ZT9, last rest phase. This contradicts previous research where the rest phase during the circadian cycle demonstrates the least P-gp efflux activity and thus more successful drug delivery to CNS.

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In addition to animal research, studies also demonstrate the therapeutic potential of chronotherapy by providing evidence of circadian rhythm in xenobiotic efflux in humans. In Zhang et al's study, they recapitulated the cycling of xenobiotic efflux using human microvascular endothelial cell line [4]. By doing so, they found that molecular clock drives intracellular magnesium through the regulation of TRPM7 which contributes to rhythmic efflux, suggesting the potential of targeting circadian efflux transporter activity for drug delivery to CNS in humans [4].

4. Circadian variations in BBB xenobiotic efflux of different class of drugs drug

4.1. Time of day variances in anti-epileptic drugs administration efficacy

Mounting evidence suggests that molecular findings underscore how core circadian clock genes and clock-controlled epilepsy genes may contribute to disease dynamics and highlight the potential of targeting circadian regulation in chronotherapy [12].

Clinical data complement these mechanistic insights by showing that time-of-day–specific drug delivery can meaningfully improve patient outcomes. Early chrono pharmacology trials demonstrated that evening administration of phenytoin and carbamazepine around 8 p.m. yielded better seizure control and drug tolerability compared to morning dosing, even when the total daily dose was held constant [13]. In contrast, simply increasing concentrations without considering circadian timing often resulted in greater neurotoxicity and reduced efficacy [13]. Similar findings extend to other AEDs: valproate efficacy has been shown to vary with the light–dark cycle, and plasma levels of midazolam are higher when dosed at night, indicating circadian modulation of both drug transport and metabolism [14].

Several small-scale but striking clinical studies further illustrate the therapeutic benefit of tailoring dosing to circadian seizure patterns. In a cohort of 17 children with nocturnal or early-morning seizures, doubling the evening AED dose while keeping the total daily dose constant led to 64.7% of patients becoming seizure-free and 88.2% experiencing at least a 50% reduction in seizure frequency after five months [12].

Importantly, real-world patient behavior also reflects circadian alignment in AED use. Hofstra et al. studied 208 patients using the Morningness-Eveningness Questionnaire and found that patients adapted AED schedules according to their circadian chronotype, but with significant delays in administration on workdays compared to free days [15]. Together, these findings illustrate that both biological and behavioral circadian factors must be considered in optimizing antiepileptic therapy.

4.2. P-gp substrate status for anti-epileptic drugs

Clinically, determining whether a drug is a P-glycoprotein (P-gp) substrate is crucial because it provides insight into the extent of brain penetration and therapeutic availability. A P-gp substrate is a compound recognized and actively transported by P-gp at the blood–brain barrier, so its central nervous system exposure is strongly shaped by P-gp–mediated efflux. This is widely known as the multi-drug transporter hypothesis, which suggests that the activity and expression of P-gp can hinder or limit the CNS from accessing drugs such as AEDs. In epilepsy, P-gp activity has particular importance, as it is thought to contribute to pharmacoresistance and treatment failure in certain patients. Among antiepileptic drugs (AEDs), several well-established P-gp substrates include phenytoin and phenobarbital, while others, such as valproate, gabapentin, and pregabalin, are consistently reported as non-substrates. Evidence for drugs like lamotrigine, topiramate, levetiracetam, and carbamazepine is less clear, with some studies suggesting partial transport or

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context-dependent. A summary of several current substrate classifications for commonly used AEDs is provided in the table 1 below.

Table 1. Commonly used AEDs

AED	P-gp Substrate Status	Evidence
Phenytoin	Substrate	In vivo microdialysis evidence in rat models shows an increase in phenytoin in the extracellular fluid of the cerebral cortex after inhibition of P-gp [16].
Carbamazepine	Translational Conflicts	In a human in vitro model of the intestinal epithelium and lymphocyte model using rhodamine 123 fluorescent marker for P-gp shown that Carbamazepine does not affect efflux. However, in epileptic rat models, increased P-gp activity decreased blood-brain barrier penetration and reduced the concentration of carbamazepine in extracellular cortical fluid [17].
Lamotrigine	Substrate	In vivo evidence of microdialysis, such as local perfusion of verapamil, shows an increase in lamotrigine the concentration of lamotrigine in the extracellular fluid of the cerebral cortex [18].

4.3. Time of day variances in anti-depressive drugs administration efficacy

In the past three to five years, there has been a growing focus on how the circadian cycle influences antidepressant drug efficacy. Work with tricyclic antidepressants provides some of the clearest examples. In rodent studies, imipramine produced stronger antidepressant effects when administered in the morning compared to the evening [19]. Single-dose experiments showed reduced immobility and increased climbing behavior in the forced swim test during early light-phase dosing, whereas the same effect was absent in the dark phase [19]. Correspondingly, plasma levels of imipramine and its active metabolite desipramine were 17–37% higher in the morning, likely reflecting circadian regulation of metabolic enzymes such as CYP2D9 [19]. Chronic treatment with imipramine reinforced these findings by revealing how low doses that were ineffective at night became effective when delivered in the morning, and only substantially higher doses were able to achieve comparable results with evening dosing. Mechanistically, these effects have been linked to downregulation of presynaptic α2-adrenoceptors, which normally suppress norepinephrine release. Furthermore, it is important to note that the receptor downregulation occurs in the light phase, which supports stronger antidepressant responses at that time of day [19].

Taken together, these data suggest that the antidepressant effect of drugs can shift considerably depending on when in the circadian cycle treatment is give. While most of the evidence so far comes from preclinical models, the findings raise the possibility that clinical antidepressant efficacy—and even side effect profiles—may be optimized by tailoring administration schedules.

4.4. P-gp substrate status for anti-depressive drugs

Similar to antiepileptic drugs, many antidepressants are P-gp targeted substrates—they are actively targeted by P-gp and is thus subject to active efflux transporter activity from the CNS to the bloodstream through the BBB, thus reducing effective brain penetration and limit therapeutic efficacy. However, it is important to note that P-gp efflux activity influenced different antidepressants to differing degrees according to animal models and in vitro studies. There are consistent data for P-gp influences on several selective serotonin reuptake inhibitors (SSRIs) such as venlafaxine, citalopram, paroxetine and citalopram and a few tricyclic antidepressants (TCAs) such

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as amitriptyline, imipramine, and clomipramine—all of which are generally classified as P-gp substrates. Different to antiepileptic drugs' substrate status, antidepressants' substrates can have more complications. Some antidepressants can act not only as substrates but also as functional inhibitors of P-gp, and this effect often depends on drug concentration. At high concentrations of therapeutic levels, some antidepressants can competitively inhibit P-gp efflux and increase brain penetration of co-administered P-gp substrates. A summary of several current substrate classifications for commonly prescribed antidepressants is provided in the table 2 below, though it should be interpreted with the understanding that P-gp interactions may be dose- and context-dependent.

Table 2. Commonly prescribed antidepressants

Anti-depressant	P-gp Substrate Status	Evidence
Citalopram (SSRI)	Substrate	P-gp knockout (abc1ab) mouse models show 3-fold higher concentration of citalopram in the brain when dosed two times daily for 10 days than wild-type mice [20].
paroxetine (SSRI)	Substrate and Inhibitor in Vitro	P-gp knockout (abc1ab) mouse models show higher cerebrum concentrations of paroxetine . In addition, in models using Calcein-AM transport in MDCK-MDR1 cells, Taxol uptake in bovine retinal endothelial cells, and Calcein-AM transport in L-MDR1 and pBCEC cells, paroxetine also behaves as an inhibitor [21].
Imipramine (tricyclic antidepressant)	Substrate and inhibitor	In MDCKII-MDR1 bidirectional transport assays, imipramine, as a human P-gp substrate, shows net efflux. In the R123 uptake in the Caco-2 cells model, imipramine functions as an inhibitor [22].

5. Discussion

Given previous research that demonstrate the influence of circadian rhythms on BBB permeability coupled with P-gp efflux activity as a target for investigation to improve drug efficacy, this paper strongly supports the multidrug transporter hypothesis which proposes that the activity and expression of P-gp can hinder or limit CNS from accessing drugs like antiepileptic drugs and antidepressants. In addition to the well-established multidrug transporter hypothesis, research also calls for the consideration of circadian oscillations and how that interplay with drug efficacy in the P-gp efflux system at the BBB. Further research linking the multidrug transporter hypothesis to circadian mediation will advance the renewed hypothesis that circadian cycle in P-GP efflux drives time-dependent variation in CNS drug delivery and efficacy across different drug types: for example, this introduces the possibility of maximizing drug efficacy by adminisnistering antidepressants that can act as both a substrate and an inhibitor to competitively drive permeability of co administered P-gp substrates during the rest phase.

Several lines of research and reasoning supports this proposed hypothesis of regulating circadian variation in P-gp-mediate efflux at BBB to increase drug penetration to CNS. First of all, circadian oscillations rooted in biology is extensively researched—and that circadian variations in efflux activity are extensive documented in animal models. This provides the framework that permeability is not stagnant, but rather changing rhythmically according to its own biological clock. Secondly, preclinical studies demonstrates that there are variances in drug efficacy depending on when the drug is administered. The fluctuations in drug efficacy depending on administration timing aligns with expected fluctuations in efflux transporter activity: for example, many animals' models show

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that seizure control is the highest when drugs are administered during resting phase where P-gp activity would be at its lowest. Thirdly and lastly, the drug specific variations in substrate status align with these patterns of efficacy: drugs that are known P-gp substrates demonstrates less CNS penetration, whereas on the other hand, non substrates demonstrate more CNS penetration even when P-gp is not inhibited. Given these different lines of reasoning, it is important to note that if circadian variations in efflux activity directly influence the amount of drug exposure in the CNS and therefore affect drug efficacy, rather than being confounded by factors such as drug metabolism or other bodily mechanisms, then this understanding could provide a medically efficient way to improve therapeutic outcomes.

One potential way to test this hypothesis in the future is through using chrono pharmacological dosing mechanisms as well as non-invasive imaging such as positron emission tomography (PET). This allows for the radiolabeling of P-gp substrates and can tack for transporter activity across different circadian phases of interest such as the rest phase. This can establish causality and provide the most direct evidence of circadian changes in drug permeability at the BBB. To establish the causal relationship between fluctuations in P-gp substrate concentration and corresponding changes in P-gp efflux activity at the blood–brain barrier, it would be valuable to incorporate validated circadian phase markers such as dim-light melatonin onset and to stratify participants based on genetic variations in PER genes. These variants influence the transcription–translation feedback loop underlying circadian rhythms, which may indirectly modulate P-gp expression and function, thereby accounting for interindividual variability. Finally, using crossover designs in same patients to compare evening and morning does can help determine whether CNS penetration shift in step with transporter oscillations. Overall, theses design can potentially determine if the circadian variations in drug efficacy is due to circadian regulation of BBB permeability.

In order to further understand this framework, drug specific applications can play an essential role: for example, antiepileptic drugs such as phenytoin and phenobarbital are P-gp substrates and are highly influenced by efflux activity. Micro dialysis studies in rodents demonstrate these drugs show evidence of limited brain access and increased CNS concentration during P-gp inhibition. Theoretically, these drugs can be improved most dramatically when circadian mediated dosing. On the other hand, drugs such as valproate, pregabalin, and gabapentin—which are not P-gp substrates—enter the CNS primarily through influx transporters. Gabapentin and pregabalin are transported by LAT1, whereas valproate utilize monocarboxylate transporters such as MCT1. These influx systems exhibit less evidence of circadian fluctuation in activity compared to P-gp, which may contribute to more stable CNS penetration across the 24-hour cycle. Levetiracetam and carbamazepine all face translational complications as they behave as non-substrate in human data but yet it shows resistant transport in animal models such as rats and murine. Similarly, lamotrigine's and topiramate's substrate status is context dependent. These findings demonstrate the importance of developing a human focused, drug specific validation of substrates status and their interaction with circadian oscillations before casual relationships can be established.

Similar to complications present in anti-epileptic drugs, antidepressant literature also demonstrates drug specific variation when interacting with P-gp. Many antidepressants behave as P-gp substrates ad well as P-gp inhibitor depending on the concentration present. However, controlling drug concentration within the CNS remains challenging due to the semi-permeable nature of the blood–brain barrier. There is limited ability to ensure that identical systemic doses result in equivalent CNS exposure, as permeability and transporter activity can vary over time. This variability creates the potential for bidirectional transport interactions across the BBB. Many selective serotonin reuptake inhibitors—including citalopram, paroxetine, and venlafaxine—as well

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as tricyclic antidepressants such as amitriptyline, imipramine, and clomipramine, exhibit this dual behavior as both substrates and modulators of efflux transporters like P-gp. This dual behavior highlights intriguing possibilities for using the circadian cycle of efflux activity to better control CNS drug concentrations. By aligning dosing with phases of reduced P-gp activity—the more permeable phase of the blood–brain barrier—it may be possible to determine whether a compound predominantly acts as a substrate or inhibitor and to optimize the dosing window for greater therapeutic efficacy. The field of circadian chrono pharmacology remains largely unexplored and a critical gateway to understanding drug behavior.

Given all the evidence shown, the clinical implications of this proposed framework are substantial Aligning drug administration with circadian phaw3w of reduced P-gp efflux activity could enhance CNS penetration of substrate drugs without altering molecular structure or dose, thereby boosting efficacy while minimizing systemic toxicity. This outcome potentially paints a picture for a low-cost, high-yield chrono-therapeutic strategy for CNS pharmacology, particularly for drugs with narrow therapeutic windows. Given the gaps in current research, future research should prioritize cross-species comparisons with an emphasis on more longitudinal imaging studies in humans with P-gp PET tracers and controlled clinical trials assessing time-of-day dosing effects across drug classes. In addition, examining how disease states such as epilepsy or depression influence transporter expression or disrupt circadian alignment also plays an essential to applying theoretical understanding to more complicated real life scenarios. Such work would not only test the multidrug transporter hypothesis in a circadian framework but also establish the foundation for optimizing drug delivery by synchronizing treatment with endogenous rhythms in BBB function.

6. Conclusion

Together, these findings suggest that circadian variation in P-gp activity is not merely a correlative phenomenon but a mechanistic determinant of therapeutic success. Establishing this causal chain—linking circadian clock regulation of efflux transporters, rhythmic BBB permeability, and drug-class–specific CNS penetration—represents the essential next step. Such work would clarify whether rhythmicity of efficacy is driven primarily by transporter oscillations or instead reflects secondary processes, such as metabolic enzyme cycling or disease-related rhythms in seizure susceptibility or mood regulation.

The clinical implications are substantial. Aligning drug administration with circadian phases of reduced P-gp efflux could enhance CNS penetration of substrate drugs without altering molecular structure or dose, thereby boosting efficacy while minimizing systemic toxicity. If confirmed, this represents a low-cost, high-yield chrono-therapeutic strategy for CNS pharmacology, particularly for drugs with narrow therapeutic windows. Future research should prioritize integrative approaches: cross-species comparisons of chronotype-dependent transporter activity, longitudinal imaging studies in humans with P-gp PET tracers and controlled clinical trials assessing time-of-day dosing effects across drug classes. Additionally, examining how disease states such as epilepsy or depression remodel transporter expression or disrupt circadian alignment will be critical for translation. Such work would not only test the multidrug transporter hypothesis in a circadian framework but also establish the foundation for rational chronotherapy, in which drug delivery is optimized by synchronizing treatment with endogenous rhythms in BBB function.

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