Review Article

CDK4/6 inhibitors and SSRIs/SNRIs: A brief review of their safety profiles focusing on potential drug interactions

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Abstract

Currently, the mainstay of treatment for advanced and metastatic hormone receptor positive (HR+), Human Epidermal Receptor -2 (HER-2) negative breast cancer includes the combination of CDK4/6 inhibitors (ribociclib, palbociclib, and abemaciclib) with endocrine therapy. However, interpatient variability has been associated with increased toxicity or questionable therapeutic responses. Indeed, several factors such as concomitant medications and pharmacogenetics may significantly affect the absorption, distribution, metabolism and elimination of CDK4/6 inhibitors, resulting in subtherapeutic or toxic plasma levels. Traditionally, depressive symptoms have been highly associated with cancer patients, and thus antidepressant therapy (typically SSRIs or SNRIs) is frequently co-initiated early in the course of cancer treatment. This brief review aims to compile and present existing data regarding the safety profiles as well as drug-drug interactions that may result from the co-administration of CDK4/6 inhibitors with SSRIs/SNRIs. Increased awareness by medical oncologists warrants a safer and more effective clinical use of CDK4/6 inhibitors.

Keywords: CDK4/6 inhibitors, breast cancer, SSRIs, SNRIs, personalized medicine

Introduction

Breast cancer (BC) is the most frequent cancer in women, representing 12.2% of the newly diagnosed cancers in 2020, while it ranks as the second most common malignancy overall.[1] The most common subtype of breast cancer is Hormone Receptor (estrogen receptor and/or progesterone receptor) positive (HR+), HER2 (human epidermal growth factor receptor 2) negative (HER2-) breast cancer, representing the 72.6% of all diagnosed cases.[2]

The high impact that the alterations of cell cycle regulators have on tumor progression, as well as the various limitations of chemotherapy, led to the development of targeted therapies, which have been proven to be efficacious when added to hormonal therapy.[3-5] Given that cyclin-dependent kinases (CDKs) hold a key role on the cell cycle progression, they constitute a milestone for the development of targeted therapies [3]. This review focuses on CDK4/6 inhibitors, which prevent the cell cycle transition from G1 to S phase and have been recently incorporated into global practice guidelines.[4,6]

Palbociclib was the first representative of this class of targeted therapies that received regulatory approval by the U.S. Food and Drug Administration on 2015 (IBRANCE®, Pfizer Inc.), followed by European's Medicines Agency in 2016.[7-8] Following this, ribociclib (KISQALI®, Novartis Pharmaceuticals Corp.) and abemaciclib (VERZENIO™, Eli Lilly and Company) similarly gained market authorization in 2017 and 2018 respectively.[9-12] A meta-analysis incorporating 8 randomized controlled trials (RCTs) demonstrated that the adjunction of CDK4/6 inhibitors to endocrine therapy significantly improved progression-free survival (PFS) compared to endocrine therapy alone, in patients with metastatic HR+/HER2− breast cancer, irrespectively of their menopausal status and the metastatic site.[13]

Despite the advances in BC treatment, disease diagnosis and treatment are still considered a traumatic experience for the majority of the patients. Multiple studies have demonstrated the increased psychological burden of patients with BC.[14-16] More specifically, women from the very beginning of their diagnosis and during their treatment experience anxiety, depression, fear of death and difficulty in sleeping.[17] Hence, it is common clinical practice to apply psychological interventions, in order to alleviate the burden of these symptoms and improve the quality of life of BC patients.[18] Consequently, antidepressant therapies, mainly selective serotonin reuptake inhibitors (SSRIs)

and serotonin-norepinephrine reuptake inhibitors (SNRIs), are usually prescribed for these cases.[14] However, one major issue emerging from the co-administration of oral drugs, is the increased possibility for drug-drug interactions (DDIs), leading to increased toxicity or sub therapeutic drug levels and thus a negative impact on patient's safety and on the efficacy of the treatment, respectively.[19]

Herein, we try to summarize existing data regarding the possible DDIs between CDK4/6 inhibitors and SSRIs/SNRIs, aiming to serve as a tool for physicians for the optimal therapeutic management of BC patients facing emotional distress.

Methods and Materials

In this brief narrative review, we tried to address the subject of drug interactions between CDK4/6 inhibitors and two commonly prescribed classes of anti-depressants (SSRIs and SNRIs), from two main perspectives. The first one relates to the pharmacokinetic profiles of the medications under discussion. The prediction of DDIs is often based on their pharmacokinetics and predominantly their hepatic metabolism by cytochrome P-450 enzymes. For example, enzymatic inhibition of an isoform i.e. CYP3A4 by drug A, will result in decreased metabolism and thus increased toxicity of drug B, in case that the latest is a substrate for CYP3A4. Similarly, decreased plasma concentrations and thus reduced efficacy of drug B, will result in case of co-administration with an inducer of CYP3A4 (drug A). Moreover, when two co-administered drugs are metabolized by the same isoform, only the one with the highest affinity will be accommodated within the catalytic site of the metabolizing enzyme. Therefore, it will prevent the binding and metabolism of the other drug, leading to increased toxicity. The second perspective relies to the assessment of the hypothesis that the prediction of a pharmacokinetic DDI is clinically significant. This consideration critically driven our conclusions based on current literature, summaries of product characteristics (SPCs) and recent safety data.

CDK4/6 inhibitors: Ribociclib, Palbociclib, Abemaciclib

Mechanism of action. The mechanism of action of CDK4/6 enzyme inhibitors is based on preventing the transition of the cell cycle from G1 to S phase. This can be better comprehended by examining the physiological role of CDK4/6 in cell cycle, as seen *in Figure 1*. Normally, growth signals detected at G1 phase induce the cyclin D expression, which subsequently binds to CDK4/6 enzymes.[3] This CDK-Cyclin D complex leads to the phosphorylation of Retinoblastoma (Rb) protein, and therefore to Rb inactivation. The Rb protein is a negative regulator of the cell cycle, as it attaches to E2F transcription factors, inhibiting, in this way, transition from G phase to S phase. By phosphorylating Rb protein, E2F are released, leading to the expression of genes that are essential for cell cycle progression to S phase. In summary, the role of CDK4/6 inhibitors is the prevention of the Rb protein hyper-phosphorylation, the interruption of the cell cycle and, finally, cancer cell uncontrollable proliferation.[20]

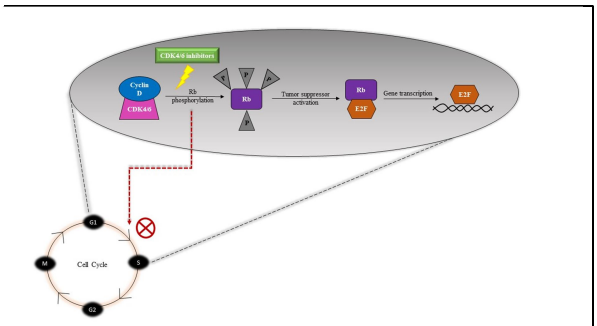

Figure 1. CDK4/6 inhibitors: Main mechanism of action. CDK4/6 inhibitors prevent the transition of the mitotic cell cycle from G1 to S phase. Normally, growth signals at G1 phase induce the cyclin D expression, which subsequently binds to CDK4/6 kinases. This complex leads to the phosphorylation and inactivation of Retinoblastoma (Rb) protein. The latest is a negative regulator of the cell cycle, as it attaches to E2F transcription factors, inhibiting transition from G phase to S phase. By inactivating Rb protein, E2F are released, leading to the expression of genes that are essential for cell cycle progression to S phase. CDK4/6 inhibitors prevent the Rb protein phosphorylation and overall cancer cell uncontrollable proliferation.

Toxicology Profile. CDK4/6 inhibitors (ribociclib, palbociclib and abemaciclib) share common and different pharmacodynamic and pharmacokinetic features. Despite being slight, those differences translate into different types and frequencies of toxicities, that can play a crucial role when selecting the appropriate agent for a patient. In general, CDK4/6 inhibitors demonstrate similar mechanisms of toxicity towards highly proliferative tissues, such as bone marrow suppression and gastrointestinal adverse events.[21-23] However, there are some differences between these three medications regarding the severity and incidence of hematological and gastrointestinal disorders. More specifically, myelosuppression (mainly anemia, leukopenia and neutropenia) is frequently observed with ribociclib and palbociclib, whereas diarrhea, nausea and vomiting are often associated with abemaciclib. The management of the aforementioned hematologic toxicities include dose adjustments or the use of erythropoietin and granulocyte colony-stimulating factors (G-CSFs) in case of symptomatic anemia (Hb<10 g/dl) and neutropenia, respectively.

Gastrointestinal (GI) toxicities, such as nausea, vomiting and diarrhea are easily manageable with conventional methods, including antidiarrheal medication or by dose adjustments.[24-27] Of note, prophylactic use of loperamide is often recommended from the initiation of treatment, in order to avoid abemaciclib-associated diarrhea.[28]

Furthermore, the use of ribociclib has been linked with QT interval prolongation and risk of Torsades de Pointes (TdP). Therefore, co-administration of medications that induce QT prolongation should be avoided. In any case, the recommendations suggest that the patient should be monitored closely by ECG, in order to capture any significant electrophysiological differences from baseline.[23] On the other hand, abemaciclib and palbociclib use has not been linked with QT prolongation; however concomitant use of medications that prolong QT is also discouraged.[21,22] Finally, post-authorization safety data suggest additional monitoring due to the increased risk of thromboembolic events (venous and arterial thromboembolism) with CDK4/6 inhibitors.[29]

SSRIs and SNRIs

Mechanism of action. SSRIs increase serotonin's concentration in the synaptic cleft by blocking its reabsorption by the presynaptic neuron in a highly selective manner. They demonstrate a 20-1500-fold higher selectivity for serotonin than norepinephrine, while no presynaptic release of serotonin or norepinephrine is stimulated.[30] On the other hand, SNRIs inhibit reuptake of both major neurotransmitters of depression, norepinephrine and serotonin. They demonstrate low to no binding affinity for other neurotransmitter receptors, such as adrenergic, muscarinic, dopamine, histamine H1 receptors and postsynaptic serotonin receptors.[31] *(Figure 2)*

Toxicology Profile. Regarding the SSRI and SNRI-induced toxicity, these agents are mainly associated with neuromuscular, autonomic and mental status symptoms.[32] Serotonin receptors are mainly located in the central nervous system (CNS), but they are also detected in platelets and the GI tract.[33] Consequently, GI adverse events, such as nausea, vomiting, and diarrhea are quite common. Risk of GI bleeding, most likely due to the reduction of blood serotonin uptake by platelets, should also be taken under consideration.[33-34] Owed to their anticholinergic activity, SNRI treatment can also cause dry mouth, whereas increased heart rate and increased blood pressure might also occur.[34-35]

On the contrary, SSRIs do not generally affect blood pressure; however, the risk of orthostatic hypotension in high doses and/or in the elderly, has been reported.[34-36] Moreover, even though the exact mechanism is still under discussion, SSRIs tend to reduce basal heart rate, in a dose-dependent manner.[36]

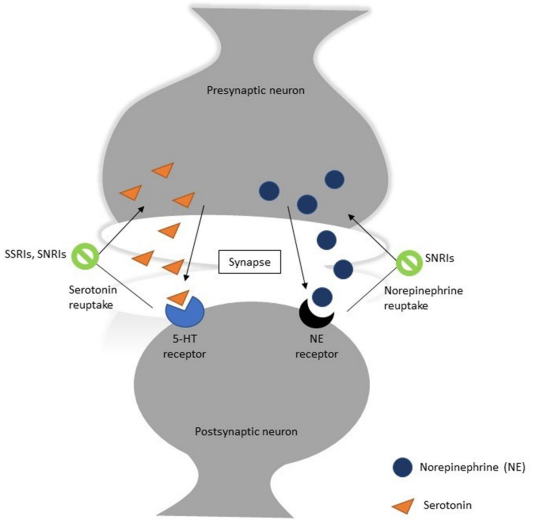

Figure 2. *Mechanism of action of SSRIs and SNRIs.*

Among SSRIs, the QT interval prolongation is demonstrated most significantly by citalopram and escitalopram.[34-35] Another adverse event of these antidepressant classes is sexual dysfunction, often persistent even after treatment discontinuation.[34,38] Finally, serotonin syndrome-caused by excessive stimulation of serotonin receptors- may lead to potentially life-threatening circumstances. This syndrome manifests with a variety of signs and symptoms from tachycardia, fever and agitation at mild and moderate cases to acidosis, hypertension, malignant hyperthermia, rhabdomyolysis, coma and clonus, in severe cases.[33].

Pharmacokinetic and Pharmacodynamic Interactions between CDK4/6 inhibitors and SSRIs/SNRIs

The pharmacokinetic profiles of CDK4/6 inhibitors, SSRIs and SNRIs are summarized in Table 1, 2 and 3 respectively. All three CDK 4/6 inhibitors are subject to hepatic metabolism by the isoform CYP3A4 [39], which represents the dominant biotransformation enzyme for the majority of the drugs. Hence, concomitant medications should be thoroughly monitored for their CYP3A4 inhibitory/induction potential. In addition, drugs that have been identified as CYP3A4 substrates, may require a dose reduction (especially those with a narrow therapeutic index-NTI), since CDK 4/6 inhibitors, mainly ribociclib, display an inhibitory potential on CYP3A4. Previous articles have published extensive lists including

the drugs that are major or sensitive CYP3A4 substrates or have a NTI.[3,39]

***Table 1**. PK parameters of CDK4/6 inhibitors: Palbociclib, Ribociclib and Abemaciclib*

	Palbociclib	Ribociclib	Abemaciclib	References
Indication	HR-positive HER2-negative mBC			[41-43]
	1st line: in combination with AI 2nd line: in combination with Fulvestrat i.m after prior ET → d1, d15, d29	1st line postmenopausal: in combination with AI 1st line premenopausal: in combination with ET 2nd line: in combination with Fulvestrat i.m → d1, d15, d29	Adjuvant (high risk early BC): in combination with AI 1st line: in combination with AI 2nd line: in combination with Fulvestrat i.m→ d1, d15, d29 1st line as monotherapy in adult patients with advanced or metastatic HR+ HER2- BC	
	Pre/perimenopausal women: LHRH-agonist for OFS			
PK parameter				
Bioavailability	46%	66%	45%	[41-45]
Route of Administration	Oral	Oral	Oral	[41-43]
Dosage	125 mg QD 3/1	600 mg QD 3/1	150 mg BID with ET or 200 mg BID as monotherapy	[41-43]
Dose adjustments	100 mg QD 3/1 75 mg QD 3/1	400 mg QD 3/1 200 mg QD 3/1	150 mg BID 100 mg BID 50 mg BID	[41-43]
Dosage form	Caps: 75, 100, 125 mg Tabs: 75, 100, 125 mg	Tabs: 200 mg	Tabs: 50, 100, 150 mg	[41-43]
Human protein binding	85%	70%	96.3%	[41-43]
Plasma distribution volume	2800L	1090L	690-750L	[41-45]
Metabolism	Weak, time dependent CYP3A4 inhibitor SULT2A1	Potent dose-depentent CYP3A4 inhibitor (600mg) moderate CYP3A4 inhibitor (400mg) CYP1A2 CYP2E1	CYP3A4 inhibitor	[41-45]
Active metabolites	M17 (CYP3A4) M22 (UGT) → NCS	M1 (NCS), M4 (major metabolite formed by CYP3A4, NCS pharmacological activity), M13 (NCS)	M2 (CYP3A4) → major M18 (CYP3A4) M20 (CYP3A4)	[41-44, 46]
Major elimination route	Hepatic (sulphonation, oxidation)	Hepatic (oxidation)	Hepatic	[41-43]
Excretion	74% faeces 17% urine	69.1% faeces 22.6% urine	81% faeces 3% urine	[41-45]
Half-life time ($t_{1/2}$)	28.8 h	29.7 to 54.7 h	18.3 h	[3, 41-44]
Substrates (inhibition)	P-gp (BBB) BCRP (BBB)	P-gp (intestine) BCRP (intestine)	P-gp (BBB) BCRP (BBB)	[3, 41-43]
Food effect	Caps with food Tabs with/without food	Tabs with/without food	Tabs with/without food	[41-44]

mBC: metastatic breast cancer; AI: Aromatase inhibitor; ET: endocrine therapy; i.m.: intramuscular; LHRH-agonist: luteining hormone-releasing hormone agonist; OFS: Ovarian function suppression; 3/1: 3-weeks-on/1-week-off; BID: twice daily; SULT: sulfotransferase; P-gp: P-glycoprotein; BCRP: breast cancer resistance protein; Caps: capsules; Tabs: tablets; M22: palbociclib glucuronide; M17: lactam palbociclib; M1: secondary glucuronide; M4: LEQ803; N-demethylation; M13: CCI284; N-hydroxylation; M2: N-desethylabemaciclib; M18: hydroxy-N-desethylabemaciclib; M20: hydroxyabemaciclib; GI: gastrointestinal; BBB: blood brain barrier.

In terms of protein binding, abemaciclib displays the highest binding affinity to human plasma proteins, and thus a lower Vd, compared to ribociclib and palbociclib. Since, only the unbound (free) percentage of a drug is pharmacologically active, competitive displacements between co-administered, highly protein-bound drugs, may result in meaningful increases in the free concentration of the displaced drug. Therefore, despite that no such DDI studies exist, one should take into consideration the possibility of altered distribution, in case that abemaciclib is co-administered with another drug that is also highly protein-bound. Furthermore, as shown in *Table 1*, ribociclib, palbociclib and abemaciclib are substrates of the membrane transporters P-gp and

BCRP. There is also evidence that CDK4/6 inhibitors exert an inhibitory effect on drug efflux pumps.[3] Consequently, DDIs may result from a) the competition with other drugs that are also substrates for these transporters and b) the increased plasma concentrations of drugs, due to transporters' inhibition by CDK4/6 inhibitors. However, there are currently no specific guidelines for the management of such DDIs, so appropriate monitoring is suggested.

Table 2 *Legend: PK parameters of SSRIs*

SSRIs							
PK parameter	**Escitalopram**	**Citalopram**	**Fluoxetine**	**Sertraline**	**Paroxetine**	**Fluvoxamine**	**Vortioxetine**
Main indication	OCD, MDD, PD, SAD, GAD	MDD	MDD, OCD, bulimia nervosa	OCD, MDD, PD, PTSD, SAD, PMDD	OCD, PD, GAD, PTSD, MDD	OCD, MDD	MDD
Most common adverse event	Nausea, Gastrointestinal disorders, Headache, Sleep abnormalities, Sexual dysfunction						
PK parameter							
Bioavailability	80%	80%	90%	44%	30-60%	53% (2-fold higher in men)	75%
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral	Oral
Dose for MDD	10 mg QD (initial) 20 mg QD (maximum)	40 mg QD	20-60 mg QD	50 mg QD (initial) 200 mg QD (maximum)	20mg QD (initial) 50mg QD (maximum)	50-100 mg QD (initial) 100 mg QD (recommended) 300 mg QD (maximum)	10 mg QD (initial) 20 mg QD (maximum)
Dosage Form	Tabs: 10, 15, 20 mg	Tabs: 10, 20, 40 mg, Oral sol: 2mg/mL	Caps: 20 mg, Oral sol: 20mg/5mL	Tabs: 25,50,100 mg, Oral sol: 20mg/mL	Tabs: 10, 20, 30, 40 mg, Oral suspension: 10mg/5mL	Tabs: 25, 50, 100 mg Extended-release caps: 100, 150 mg	Tabs: 5, 10, 15, 20 mg
Human protein binding	56%	80%	95%	98%	93%	80%	98-99%
Plasma distribution volume	12-26 L/kg	12 L/kg	20-40 L / kg	25 L / kg	3.06 L/kg	25 L/kg	2,600 L/kg
Metabolism (inhibition)	CYP2C19 CYP3A4 CYP2D6 (moderate)	CYP2C19 CYP3A4 CYP2D6 (moderate)	CYP2D6 (potent) CYP2C19 (moderate) CYP3A4 (weak)	CYP3A4 CYP2C19 CYP2D6	CYP2D6 (moderate) CYP3A4 (weak)	CYP1A2 (potent) CYP3A4 (moderate) CYP2C9 (moderate) CYP2C19 (moderate)	CYP2D6 (potent) CYP3A4/5 (weak) CYP2C9 (weak)
Major elimination route	Hepatic	Renal	Renal	Hepatic	Hepatic	Hepatic	Hepatic
Excretion	Urine	Urine	Urine	Faeces	Urine 64% Faeces 36%	Urine 85%	Urine 2/3 Faeces 1/3
Half-life time ($t_{1/2}$)	27-33 h	35 h	4-6 d	26 h	21 h	15.6 h	66 h
Substrates	P-gp	ABCB1	P-gp	P-gp	P-gp	P-gp	P-gp (poor)
References	[47-49]	[49,50]	[49,52]	[51,53,54]	[51,55,56]	[51,57, 58]	[59]

MDD: Major depressive disorder; OCD: Obsessive-compulsive disorder; PD: Panic disorder; PTSD: Post-traumatic stress disorder; SAD: Social anxiety disorder; PMDD: Premenstrual dysphoric disorder; GAD: Generalized anxiety disorder; PE: Premature ejaculation; h: hours; d: days;

Among SSRIs, fluoxetine, sertraline and paroxetine are the ones that are weak inhibitors of CYP3A4. *(Table 2)* Therefore, in terms of metabolism, they are considered relatively safe candidates, compared to other SSRIs that are moderate or potent CYP3A4 inhibitors. However, all three of them are highly bound to plasma proteins, and therefore, as stated above, caution is recommended when co-administered with abemaciclib (in the latest case, paroxetine, may offer a safer option due to the lowest affinity with plasma proteins, compared to sertaline and fluoxetine). Moreover, all of them are substrates for drug efflux proteins, and thus co-administration with drugs that

inhibit P-gp activity, like CDK4/6 inhibitors, may lead to increased bioavailability and therefore risk of toxicity. Another interesting point that could influence the SSRI selection, relates to their half-lives. More specifically, fluoxetine has a long half-life, prolonging the time to reach steady-state plasma concentrations. This should be taken under consideration in cases that require a more rapid therapeutic outcome. To sum up, fluoxetine, sertraline and paroxetine seem to be a good combination with CDK4/6 inhibitors, with paroxetine offering the safest option in case of abemaciclib. On the other hand, duloxetine is the only SNRI that is not metabolized by CYP3A4, being a reasonable candidate for co-administration with CDK4/6 inhibitors. As mentioned above, although there is insufficient data regarding the significance of such interactions, co-administration with abemaciclib should be monitored, due to high binding of duloxetine with human plasma proteins and potential need for dose titrations. Similarly, the effect on P-gp cannot be predicted, since both CDK4/6 inhibitors and duloxetine exhibit inhibitory potential on this transporter.

Table 3. *PK parameters of SNRIs*

SNRIs					
PK parameter	**Venlafaxine (prolonged release)**	**Venlafaxine (immediate release)**	**Desvenlafaxine (ODV)**	**Duloxetine**	**Levomilnacipran**
Main indication	MDD, GAD, SAD, PD, agoraphobia		MDD	MDD, GAD, diabetic peripheral neuropathy	MDD
Most common adverse events	Nausea, Dry mouth, Headache, Hyperhidrosis, Gastrointestinal disorders			Nausea, Headache, Dry mouth, Somnolence, Dizziness	Suicidal thoughts, Nausea, constipation, hyperhidrosis, insomnia
PK parameter					
Bioavailability	40-45%	40-45% (slower absorption rate)	~80%	~50% (range 32-80%)	92%
Route of Administration	Oral		Oral	Oral	Oral
Dosage form	Caps: 37.5, 75, 150 mg	Tabs: 37.5, 50, 75 mg	Caps: 25, 37.5, 50, 75, 150 mg	Caps: 30, 60 mg	Caps: 20, 40, 80, 120 mg
Dose for MDD	37.5 mg QD (initial) 75 mg QD (recommended) 225 mg QD (maximum)	75 mg QD (recommended) 375 mg QD (maximum)	50 mg QD (recommended) 200 mg (maximum)	60 mg QD (recommended) 120 mg (maximum)	20 mg QD (initial) 40 mg (recommended) 120 mg QD (maximum)
Human protein binding	27%		30%	96%	22%
Plasma distribution volume	4.4±1.6 L/kg		200-300 L/kg	1620–1800 L/kg	387-473 L/kg
Metabolism	CYP2D6 (potent) CYP3A4 (weak)		CYP3A4 (weak) CYP2D6 (weak) CYP2C9	CYP1A2 CYP2D6	CYP3A4 (potent) CYP2C8 CYP2C19 CYP2D6 CYP2J2
Major elimination route	Hepatic		Hepatic	Hepatic	Renal
Excretion	Urine 87%		Urine 69%	Urine 72%	Urine 58%
Half-life time ($t_{1/2}$)		5±2 h	9-11 h	~12 h (8-17 h)	~12h
Substrates	P-gp BCRP		Not P-gp substrate *in vitro*	Dose-dependent P-gp inhibition	P-gp
Food effect	With food	With/without food	With/without food	Without food (delays absorption)	With/without food
References	[60, 61]			[31,62,63]	[64]

ODV: O-desmethylvenlafaxin; BCRP: breast-cancer resistance protein

Another major concern is associated with the pharmacodynamic interactions between the drug classes under discussion and mainly their effect on QTc interval. Among all SSRIs and SNRIs citalopram and escitalopram present a known risk of TdP.[40] Additionally, co-administration of CDK4/6 inhibitors (especially ribociclib) with other drugs that prolong QTc is discouraged and/or there are clear recommendations for close monitoring in case that the concomitant medication cannot be discontinued or replaced. Consequently, citalopram and escitalopram may not provide a safe option, especially with ribociclib. Moreover, it should be noted that a thorough medication history should be obtained throughout the course of treatment with CDK4/6 inhibitors, for the identification of other drugs that may have an additive effect in QTc prolongation.

Conclusions

DDIs and their potential impact on drug safety and/or efficacy should be a matter of great significance, especially when treating cancer patients. Despite that our knowledge on clinically meaningful drug interactions is limited, due to the lack of dedicated clinical trials, we tried to summarize and elucidate current evidence on the safe co-administration and potential DDIs between CDK4/6 inhibitors and two major classes of anti-depressants (SSRIs and SNRIs). Sertraline and paroxetine (SSRIs) and duloxetine (SNRI) seem to display relatively safer profiles compared to other SSRIs and SNRIs, when co-administered with CDK4/6 inhibitors.

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