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REVIEW

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Treatment of non-metastatic castration-resistant prostate cancer: facing age-related comorbidities and drug–drug interactions

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ABSTRACT

Introduction: Patients with non-metastatic castration-resistant prostate cancer (nmCRPC) are frequently poly-medicated due to age-related and androgen deprivation therapy (ADT)-derived comorbidities. In high-risk patients, androgen receptor inhibitors (ARIs) have shown to delay disease progression; however, drug–drug interactions (DDIs) with preexisting medications may impact the therapeutic effect and safety of these and of the ARIs themselves.

Areas covered: We review the potential comorbidity burden of nmCRPC patients on the basis of epidemiologic studies on age-related comorbidities, the impact of ADT and specific studies analyzing this topic. Using the DDIs compendia Lexicomp® and Drugs.com®, we provide a scenario of the potential DDIs between common mediations used to treat these comorbidities and the three currently available ARIs: apalutamide, enzalutamide and darolutamide.

Expert opinion: In high-risk nmCRPC patients to be treated with an ARI, careful multidisciplinary evaluation of potential DDIs is a fundamental component in the clinical-decision making. The lower potential for DDIs, the lower need for dose adjustment or change of current comedications and of patient monitoring, and safer introduction of new comedications. To optimize this step, an effort is still needed to determine the clinical relevance of DDIs and to harmonize their definition and classification among the different compendia.

Plain Language Summary

Prostate cancer is one of the most common cancers in men. It is normally diagnosed at age 60 or above, so these men are usually taking medications to treat age-related conditions (e.g. hypertension, diabetes, high cholesterol, etc.).

One of the main treatments for prostate cancer is 'androgen deprivation therapy' (ADT), a hormone treatment that reduces androgens level. This is because the growth of prostate cancer cells is dependent on male sex hormones called androgens. Despite ADT helping keep the cancer controlled for a time, it increases the risk for adverse events that may need new medications. Consequently, men with prostate cancer usually take multiple medications.

After some years, ADT may not be enough to control the prostate cancer. A type of medication called 'androgen receptor inhibitors' (ARIs), which prevent the androgen entering the cell, are helpful at this stage, especially the second-generation ones: apalutamide, enzalutamide, and darolutamide. The problem is that these ARIs usually interact with other medications already taken by patients, an effect called 'drug–drug interaction.' When this happens, the ARI (the interaction 'perpetrator') may modify the effectiveness of other medications (the 'victims') and/or cause unexpected effects. Consequently, the conditions being treated by these medications may not be properly controlled, which may pose a risk to the patient's health. Thus, when starting treatment with a second-generation ARI, it is crucial to consider all possible interactions with the medications taken. The fewer potential interactions the ARI has, the easier it is to properly control other common conditions in prostate cancer patients.

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1. Introduction

Prostate cancer (PC) is the fifth leading cause of cancer-related death among men worldwide, ranking second in 2020 in annual incidence rate (14.8%) in the overall male population and first (18.2%) among men older than 65 years[1]. Ten to 20% of men initially diagnosed with PC will develop castration-resistant PC (CRPC) – an advanced form of PC characterized by disease progression- following first-line treatment with androgen deprivation therapy[2]. It is estimated that ~15%[3]–30%[4] of these will become castration-resistant without any evidence of metastases (non-metastatic castration-resistant prostate cancer, nmCRPC).

Although nmCRPC patients are mostly asymptomatic, ongoing treatment with androgen deprivation therapy (ADT) –

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Article highlights

- Patients with non-metastatic castration-resistant prostate cancer (nmCRPC) are frequently elderly and poly-medicated due to comorbidities related to old age and androgen deprivation therapy (ADT).
- In high-risk nmCPRC patients, the addition of the androgen receptor inhibitors (ARIs) enzalutamide, apalutamide, or darolutamide has shown to delay disease progression. However, drug–drug interactions (DDIs) with common treatments for pre-existing comorbidities may appear.
- Given their harmful consequences, potential DDIs with common treatments for pre-existing comorbidities are a fundamental component in ARI decision-making.
- There is an urgent need to determine the clinical relevance of DDIs and harmonize their definition and classification among the different compendia.
- Of the three currently available ARIs, darolutamide shows the lowest potential for DDIs and, therefore, a lower need for dose adjustment/change of comedications and patient monitoring.

This box summarizes key points contained in the article.

the standard of care for patients with advanced PC- either with gonadotropin-releasing hormone (GnRH) agonists or GnRH antagonists is associated with adverse events that, along with disease progression, may have a detrimental effect on patients' quality of life (QoL)[5]. These include a severe impact on sexual function (erectile dysfunction), hot flushes, skeletal complications, metabolic syndrome, fatigue, anemia, increased cardiovascular (CV) morbidity, and neurological side effects[5]. Given that ~60% of patients are diagnosed with PC at the age of 65 or older[6], these comorbid conditions are added to common chronic age-related comorbidities, with more than half of patients presenting at least one[7]. Aging and PC treatment lead to nmCRPC patients being treated with one or more long-term pharmacologic treatments, and frequently to polypharmacy[8,9].

In patients with nmCRPC who are at high risk of developing metastatic disease (those with prostate-specific antigen [PSA] doubling time ≤10 months), the addition of the androgen receptor inhibitors (ARIs) enzalutamide, apalutamide, or darolutamide – which also suppresses androgen signaling- have been shown to increase metastasis-free and overall survival [10–16]. However, pharmacokinetic (PK) and pharmacodynamic (PD) drug–drug interactions (DDIs) between these and preexisting treatments may not only intensify their side effects, they can actually contribute to many of these in the case of elderly or poly-medicated patients[17,18]. DDIs also have an impact on the therapeutic effect of preexisting medications, many of which have a narrow therapeutic index, and of the ARIs themselves[19–21]. As a consequence, DDI-related events may lead to an increase in clinical consultations and hospital admissions, thus raising the economic burden of the disease and even putting the patient's life at risk[17,18,22,23]. DDIs may also increase the likelihood of ARI discontinuation [24]. Moreover, DDIs' burden is likely to augment with age and the development of new comorbidities needing pharmacological treatment.

In this narrative review, we provide a scope of the comorbidity burden of nmCRPC, how comorbidities are pharmacologically managed in the European setting, and the potential DDIs between the most common treatments used and currently available ARIs, as identified with the DDI compendia Lexicomp®[25] and Drugs.com®[26].

2. Comorbidity burden in nmCRPC patients

The comorbidity burden of patients with PC does not seem to differ significantly from that of the general population in men of the same age (65 years or older). In a cohort of patients with PC aged 66 or older diagnosed between 1992 and 2005 included in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database in the USA (n = 213,311), the most common comorbidities reported were similar to those found in a random sample of cancer-free Medicare beneficiaries (n = 100,000)[27]. These were mainly diabetes (18.1%) and cardiovascular disease (CVD), followed by respiratory conditions (e.g. chronic obstructive pulmonary disease [COPD]; 9.8%). Using the same database of PC cases diagnosed between 1995 and 2003 (n = 50,147), 8.5% of patients had a diagnosis of depression[28]. However, a study conducted in the General Practice Research database in the UK showed that PC patients had a higher incidence of urinary tract infection (UTI), impotence, and breast disorders after diagnosis compared with men of a similar age without PC[29]. In a regular National Health Survey conducted in Spain, comorbidities reported by 10% of men aged 65–74 years include, in order of prevalence, hypertension, hypercholesterolemia, chronic back pain, arthrosis, diabetes, CVD (myocardial infarction, angina pectoris, coronary disease, stroke, and other heart diseases), and mental disorders (depression, anxiety, and other disorders) (Table 1)[30]. In men with nmCRPC, the negative impact on insulin sensitivity, CV health, cognitive function, and sexual and bone health (including falls and fractures) associated with the use of ADT[5,31–33] is likely to increase their comorbidity burden by adding new comorbidities or aggravating existing ones, all of which has a significant deleterious impact on their QoL. At the same time, drug burden is also increased.

3. The most common comorbidities in nmCRPC patients

3.1. Metabolic disorders

As shown in Table 1, hypertension, hypercholesterolemia, and diabetes are highly prevalent in men over 65 years of age[30]. These are part of the so-called 'metabolic syndrome,' a condition that requires at least three of five criteria including the above-mentioned conditions (defined in men as systolic blood pressure (BP) ≥ 130 mmHg or diastolic BP ≥ 80 or the use of medication for hypertension, a high-density lipoprotein (HDL) cholesterol < 1 mmol/L or < 40 mg/dL or the use of medication for reduced HDL-cholesterol, and fasting glucose ≥ 100 mg/L or the use of medication for hyperglycemia, respectively), waist circumference > 102 cm (abdominal obesity), and serum triglycerides > 1.7 mmol/L or ≥ 150 mg/L or the use of medication for elevated triglycerides[34]. Several studies have demonstrated the detrimental effect of ADT on traditional CV risk factors, including serum lipoprotein levels, insulin

Table 1. Comorbidities requiring pharmacologic treatment during the last 12 months (as diagnosed by a physician) at any age in at least 10% of men aged 65 years or older.

	Age		
Comorbidity	65–74 years	75–84 years	>85 years
Hypertension	49.8%	53.0%	44.5%
Hypercholesterolemia	41.4%	39.2%	24.1%
Chronic back pain	39.1%	43.3%	50.6%
Cervical	15.5%	18.4%	23.0%
Lumbar	23.6%	24.9%	27.6%
Arthrosis (excluding arthritis)	26.8%	38.7%	49.1%
Diabetes	25.0%	25.9%	22.7%
CV disease	18.8%	26.8%	35.1%
Myocardial infarction	1.6%	2.5%	3.0%
Angina pectoris/Coronary disease	2.4%	4.1%	6.3%
Stroke*	2.6%	1.7%	3.6%
Other†	12.2%	18.5%	22.2%
Prostate problems†	18.4%	28.2%	30.9%
Mental disorders	12.6%	16.9%	17.0%
Depression	6.5%	7.2%	6.1%
Anxiety (chronic)	4.3%	4.9%	3.5%
Other†	1.8%	4.8%	7.4%
Chronic allergy‡	10.0%	7.7%	7.7%
Chronic bronchitis, emphysema, COPD	8.7%	12.3%	16.4%
Urinary incontinence#	7.3%	17.9%	27.6%
Kidney disorders†	4.9%	7.9%	11.3%
Chronic constipation	3.4%	5.0%	14.2%

Adapted from the National Health Survey 2017. Ministerio de Sanidad, Consumo y Bienestar Social. Gobierno de España[30]. This survey was carried out using a closed questionnaire. The answers were reported by participants and no confirmed diagnosis is available.
*Includes embolism, cerebral infarction, brain hemorrhage.
†Not specified in the original document.
‡Includes rhinitis, conjunctivitis, food allergies, and other allergies except allergic asthma.
#Includes urine control problems.
COPD, chronic obstructive pulmonary disease.

sensitivity, and obesity[35]. The prevalence of metabolic syndrome has been shown to be higher in men undergoing long-term ADT (≥ 12 months) compared to their non-metastatic counterparts receiving local treatment and age-matched controls, predisposing them to a higher CV risk[36]. Of the criteria defining metabolic syndrome, elevated abdominal obesity and hyperglycemia accounted for this higher prevalence[36]. Moreover, clinical evidence suggests that metabolic changes such as insulin resistance (without causing hyperglycemia) are observed as early as 3 months after starting ADT[37].

In the ARAMIS study, which evaluated the efficacy of darolutamide for delaying metastasis and death in men with nmCRPC[15], most patients (98.4% in both treatment arms) had at least one comorbid condition[8]. The most common comorbidities were metabolic disorders: hypertension (darolutamide arm: 64.6%; placebo arm: 64.6%), obesity (59.5% and 60.1%), hypercholesterolemia (13.0% and 12.6%), and diabetes mellitus (10.6% and 12.3%). Diabetes mellitus was present in 10.6% and 12.3% of patients, respectively, dyslipidemia in 8.9% and 9.2%, type 2 diabetes mellitus in 7.9% and 9.6%, and hyperlipidemia in 7.7% and 8.5%[8]. Unfortunately, no information is available in this regard for nmCRPC patients participating in the SPARTAN (apalutamide)[10] or PROSPER (enzalutamide)[11] studies.

Hypertension is a common adverse event associated with ARIs treatment[10,11,15]. However, differences vs. placebo disappeared after adjustment for exposure for apalutamide and darolutamide[10,15]. This was not investigated for enzalutamide[11], although differences between the studies in the duration of treatment and follow-up could have directly affected the incidence of adverse events. DDIs with antihypertensive treatments should be especially considered in nmCRPC patients receiving ARIs.

The primary goal of clinical management in individuals with metabolic syndrome is to reduce the risk for clinical atherosclerotic disease. First-line therapy is directed at the major CV risk factors: LDL-cholesterol above target, hypertension, and diabetes[34]. Most common treatments for these pathologies are shown in Table 2.

3.2. Cardiovascular diseases

CVD (mainly coronary heart disease [CHD], cerebrovascular disease [CVD], peripheral arterial disease [PAD], and deep vein thrombosis and pulmonary embolism) are the leading causes of death globally. In 2019, they represented 32% of all global deaths and 85% of these were caused by heart attack and stroke[38]. Their prevalence among men aged 65–74 years is 18.8%, a figure that rises rapidly with age (Table 1)[30].

The relationship between ADT (GnRH agonists) and an increased risk of diabetes mellitus, coronary heart disease (CHD), myocardial infarction (MI), and sudden cardiac death was first observed in the above-mentioned SEER-Medicare database[39]. Subsequent observational studies and randomized controlled trials (RCTs) have not been able to find a clear association between ADT and increased CV risk, probably due to several study limitations and biases, although

Table 2. DDIs between ARIs and frequent treatments for common metabolic disorders in men with nmCRPC receiving ADT.

			Effect of ARIs on comedication exposure ('perpetrators')			Effect of comedications on ARI exposure ('victims')		
Condition	Drug class	Common treatments	Apalutamide	Enzalutamide	Darolutamide	Apalutamide	Enzalutamide	Darolutamide
Hypertension	Ca channel blocker	Diltiazem	↓↓/↓↓	↓↓/↓	-/-	-/-	-/-	-/-
		Nifedipine	↓↓/↓↓	↓↓/↓↓	-/-	-/-	-/-	-/-
		Verapamil	↓↓/↓↓	↓↓/-	-/-	-/-	-/↑	-/-
		Amlodipine	↓/↓↓	↓/↓↓	-/-	-/-	-/-	-/-
	ARB	Losartan	↓/↓	↓/↓	-/-	-/-	-/-	-/-
		Valsartan	-/↓	-/-	-/↑	-/-	-/-	-/-
	Beta-blocker	Atenolol	-/-	-/-	-/-	-/-	-/-	-/-
		Propranolol	-/↓	-/↓	-/-	-/-	-/-	-/-
		Bisoprolol	↓/-	↓/-	-/-	-/-	-/-	-/-
	ACE inhibitor	Enalapril	-/-	-/-	-/-	-/-	-/-	-/-
		Captopril	-/-	-/-	-/-	-/-	-/-	-/-
	Diuretics	Furosemide	-/-	-/-	-/-	-/-	-/-	-/-
		Hydrochlorothiazide	-/-	-/-	-/-	-/-	-/-	-/-
		Spironolactone	-/-	-/-	-/-	-/-	-/-	-/-
Dyslipidaemia	Statins	Rosuvastatin	↓/↓	-/-	↑↑/↑↑	-/-	-/-	-/-
		Atorvastatin	↓/↓	↓/↓	-/↑	-/-	-/-	-/-
		Simvastatin	-/↓	-/↓	-/↑	-/-	-/-	-/-
		Fluvastatin	-/↓	↓/↓	-/↑	-/-	-/-	-/-
		Pravastatin	-/↓	-/-	-/↑	-/-	-/-	-/-
		Pitavastatin	-/↓	-/-	-/↑	-/-	-/-	-/-
		Lovastatin	-/↓	-/↓	-/↑	-/-	-/-	-/-
	Fibrates	Gemfibrozil	-/-	-/-	-/-	↑/↑	↑↑/↑	-/-
Diabetes mellitus	Biguanides	Metformin	-/-	-/-	-/-	-/-	-/-	-/-
	Sulfonylureas	Gliclazide	-/↓	↓/↓	-/-	-/-	-/-	-/-
		Glimepiride	-/↓	↓/↓	-/-	-/-	-/-	-/-
		Glyburide	-/↓	↓/↓	-/↑	-/-	-/-	-/-
	DPP-4 inhibitors	Linagliptin	↓↓/↓	↓↓/↓	-/-	-/-	-/-	-/-
		Saxagliptin	↓/↓	↓/↓	-/-	-/-	-/-	-/-
	Meglitinides	Repaglinide	↓/↓	↓/↓	-/↑	-/-	-/-	-/-
	Insulin	Insulin	-/-	-/-	-/-	-/-	-/-	-/-

Source: Compiled by the authors based on the DDIs compendia Lexicomp®[25] and Drugs.com®[26].

Lexicomp® classifies interactions according to risk (X, D, C), severity (major, moderate, minor), and reliability (excellent, good, fair, poor). The risk rating provides different levels of urgency in responding to the identified DDI based on the likelihood of adverse events (X: the high probability of occurrence renders the combination of drugs contraindicated; D: the high probability of occurrence makes the combination desirable only when the benefits outweigh the possible harm and modification of the treatment is advocated whenever possible; C: the probability of occurrence does not discourage the combination, but therapy monitoring is warranted); the severity rating represents the possible magnitude of an interaction outcome (minor: adverse events would be considered tolerable in most cases; moderate: medical intervention may be required to treat adverse events, although they are not those needed in major rating; major: effects may result in death, hospitalization, permanent injury, or therapeutic failure); and the reliability rating represents the level of evidence and provides insight regarding the nature of reports (volume and credibility) available to support the interaction.

The Drug Interactions checker details drug–drug interaction mechanisms, severity, and management and also outlines drug–food interactions. Drugs.com similarly classifies interactions classified as either none, minor, moderate, and major/contraindicated.

ACE, angiotensin-converting enzyme, ARB, angiotensin II receptor blocker; DPP, dipeptidyl peptidase

L/D: stands for Lexicomp®/Drugs.com®. Only relevant DDIs are shown (i.e. 'minor' and category-B DDIs have been excluded as they do not give rise to modifications)

Lexicomp®: X(↓↓↓), avoid combination; ↓↓, decrease category D [consider modifying therapy]; ↓, decrease category C [monitor therapy]; ↑↑, increase category D [consider modifying therapy];
↑, increase category C [monitor therapy]

Drugs.com®: ↓↓, major decrease; ↓, moderate decrease; ↑↑, major increase, ↑, moderate increase, QT*, 'major' prolongation of the QT interval; QT, 'moderate' prolongation of the QT interval

meta-analyses of observational studies have shown positive associations with CV events and CV death[40,41]. The increase in CV risk appears to be particularly important among patients with prior CV risk factors or CVD[42] and seems to be driven by increased atherosclerosis, dyslipidemia, metabolic syndrome, and insulin resistance[40]. Compared to GnRH agonists, GnRH antagonists might be associated with less CV morbidity[43].

In the ARAMIS study[15], 37.7% of patients in the darolutamide arm and 34.7% patients in the placebo arm presented CVD, these being, in order of importance, first-degree atrioventricular block (9.0% and 8.8%, respectively), coronary artery disease (7.5% and 7.0%), myocardial ischemia (7.3% and 6.0%), atrial fibrillation (7.2% and 7.8%), and left bundle branch block (6.7% and 5.1%)[8]. Again, no information is available in this regard for nmCRPC patients participating in the SPARTAN (apalutamide)[10] and PROSPER (enzalutamide)[11] studies.

CV toxicity may be increased in nmCRPC patients treated with ARIs[44], as observed in Phase III studies with these drugs [10,11,15]. Again, DDIs with CV treatments should be especially considered in nmCRPC patients receiving ARIs.

CV risk factor optimization and treatment or prevention of new CV events are important in nmCRPC patients undergoing ADT[41]. The joint statement issued by the American Heart Association, American Cancer Society, and American Urologic Association in 2010 in the light of the first evidence supporting an increased CV risk in men with CVD undergoing ADT recommends secondary preventive measures including, when appropriate, lipid-lowering therapy, antihypertensive therapy, glucose-lowering therapy, and antiplatelet therapy[35]. These measures

Table 3. DDIs between ARIs and frequent treatments for common cardiovascular diseases in men with nmCRPC receiving ADT.

			Effect of ARIs on comedication exposure ('perpetrators')			Effect of comedications on ARI exposure ('victims')		
Condition	Drug class	Common treatments	Apalutamide	Enzalutamide	Darolutamide	Apalutamide	Enzalutamide	Darolutamide
CV disease†, deep vein thrombosis, atrial fibrillation	Antithrombotics	Warfarin	↓/↓	↓↓/↓	-/-	-/-	-/-	-/-
		Acenocoumarin	↓/↓	↓↓/↓	-/-	-/-	-/-	-/-
		Heparin	-/-	-/-	-/-	-/-	-/-	-/-
		Dabigatran	X(↓↓↓)/↓	-/↓	-/-	-/-	-/-	-/-
		Rivaroxaban	X(↓↓↓)/↓↓	↓↓/↓↓	-/↑	-/-	-/-	-/-
		Apixaban	X(↓↓↓)/↓↓	↓↓/↓↓	-/-	-/-	-/-	-/-
		Edoxaban	↓↓/↓	↓↓/↓	-/-	-/-	-/-	-/-
	Antiplatelet agents	ASA	-/-	-/-	-/-	-/-	-/-	-/-
		Clopidogrel	↓↓/-	↓/↓	-/-	-/-	-/-	-/-
		Ticagrelor	X(↓↓↓)/↓↓	X(↓↓↓)/↓↓	-/-	-/-	-/-	-/-
Cardiac arrhythmia, HF	Cardiac glycosides	Digoxin	↓/↓	-/↓	-/-	-/-	-/-	-/-
	Antiarrhythmics	Amiodarone	↓/↓↓	↓/↓↓	-/-	-/-	-/-	-/-
		Dronedarone	X(↓↓↓)/↓↓	X(↓↓↓)/↓↓	-/-	-/-	-/-	-/-

Source: Compiled by the authors based on the DDIs compendia Lexicomp®[25] and Drugs.com®[26].
ASA; acetylsalicylic acid; CV, cardiovascular; HF, heart failure
†Primary or secondary prevention
See legend in Table 2 for description of the signs used to describe the DDIs.

are even more important in men treated with ARIs. Most common treatments for these CV diseases are shown in Table 3.

3.3. Mental disorders

These have been reported in 12.6% of men aged 65–74 years in our setting and their prevalence increases slightly with age [30]. Mood disorders are frequent in the elderly and constitute the most common cause of psychiatric morbidity in this population[45]. The unipolar subtype (late-life depression) has been described in 10–38% of the elderly, while the bipolar subtype (manic–depressive) is reported in 0.1–0.5%, although the prevalence may be higher (4–8%) in inpatient psychogeriatric units[45]. Depression may in turn present with somatic symptoms like sleep disturbance, fatigue, psychomotor retardation [46], and slowed information processing, which affects all cognitive domains[47] and may be confounded with dementia ('pseudodementia')[45]. Insomnia is prevalent in the elderly; however, rather than aging, the prevalence of this disorder is associated with inactivity, dissatisfaction with their social life, and the presence of organic diseases and mental disorders [48], all of which are frequently present in the elderly.

Mental disorders themselves and the associated consequences greatly increase the drug burden associated with mood disorders in the elderly. The use of ADT in PC patients has been associated with an increased risk of mental disorders such as depression[49], dementia[49,50], anxiety[51], cognitive dysfunction[52], and Alzheimer's disease[53]. In the ARAMIS study[15], patients were unlikely to present mental disorders as these might have been considered by the investigator as a condition that impairs the patient's ability to comply with the study procedures (exclusion criteria). Unlike the SPARTAN [10] and PROSPER[11] studies, previous seizure or conditions predisposing to seizure were not exclusionary. In the ARAMIS study, the incidence of adverse events commonly associated with ARIs such as seizures and central nervous system (CNS)-related adverse events such as dizziness, falls, and cognitive impairment were similar in the darolutamide and placebo groups, which may be linked to the low penetration of the blood–brain barrier that has been reported in preclinical studies[54]. Conversely, falls and mental impairment disorders were more frequently reported with enzalutamide or apalutamide than placebo[10,11]. As mentioned above, differences in the duration of the studies and follow-up should be considered when interpreting these findings.

Seizure and CNS-related adverse events may impact quality of life and treatment discontinuation, which reinforces the importance of their early identification[55]. Most common treatments for mental disorders are shown in Table 4.

3.4. Other common conditions

Common conditions in elderly people aged 65–74 years include chronic back pain, arthrosis, and prostate problems, the prevalence of which increases with age (Table 1). Other comorbid conditions like respiratory diseases, urinary incontinence or urine control problems, kidney disorders, and chronic constipation are found in a lower percentage of men at this age, although their prevalence at older ages is significantly higher. The prevalence of other common conditions at the age of 65–74 years, like chronic allergy, appears to remain relatively stable (Table 1)[30]. This picture resembles that of the ARAMIS study[15], where osteoarthritis (darolutamide arm: 12.8%; placebo arm: 11.7%), benign prostatic hyperplasia (10.8% and 11.4%, respectively), arthralgia (7.4% and 4.9%), constipation (7.3% and 4.7%), back pain (6.5% and 6.9%), nocturia (6.3% and 5.2%), and gastrointestinal reflux disease (5.2% and 6.9%) were present in >5% of the total population. This latter is not included in the Spanish National Health Survey, although its prevalence in Western culture is ~20% [56]. Insomnia, which is frequently associated with depression [46], was reported in 6.2% of patients in the darolutamide arm and 6.5% of patients in the placebo arm[8]. In the ARAMIS study, patients were unlikely to present infections as these would have made the patient inappropriate for enrollment according to the study protocol[15]. Nonetheless, these were

Table 4. DDIs between ARIs and frequent treatments for common mental disorders in men with nmCRPC receiving ADT.

			Effect of ARIs on comedication exposure ('perpetrators')			Effect of comedications on ARI exposure ('victims')		
Condition	Drug class	Common treatments	Apalutamide	Enzalutamide	Darolutamide	Apalutamide	Enzalutamide	Darolutamide
Depression	SSRIs	Citalopram	↓/QT*	↓/QT*	-/-	-/-	-/-	-/-
		Escitalopram	↓/QT*	↓/QT*	-/-	-/-	-/-	-/-
		Sertraline	↓/QT*	↓/QT*	-/QT	-/-	-/-	-/-
		Trazodone	↓↓/QT	↓↓/QT	-/QT	-/-	-/-	-/-
		Amitriptyline	-/QT	-/QT	-/QT	-/-	-/-	-/-
	NSSAs	Mirtazapine	↓/↓	↓/↓	-/QT	-/-	-/-	-/-
Anxiety, agitation	Anxiolytics	Diazepam	↓/↓	↓/↓	-/-	-/-	-/-	-/-
		Midazolam	↓/↓	↓/↓	-/-	-/-	-/-	-/-
	Antipsychotics	Haloperidol	↓/QT*	↓/QT*	-/-	-/-	-/-	-/-
Epilepsy, mood disorders	Anti-seizure agents	Carbamazepine	-/-	-/-	-/-	↓/-	↓↓/↓	X (↓↓↓)/↓↓
		Oxcarbazepine	↓/-	↓/-	-/-	-/-	-/↓	-/↓
		Phenobarbital			-/-	-/-	↓↓/↓	-/↓↓
		Phenytoin	↓/-	↓↓/-	-/-	-/-	-/↓	X (↓↓↓)/↓↓
		Primidone			-/-	-/-	↓↓/↓↓	-/↓↓
		Valproic acid	-/↓		-/-	-/-	-/-	-/-

Source: Compiled by the authors based on the DDIs compendia Lexicomp®[25] and Drugs.com®[26].
NNSAs, noradrenergic and specific serotonergic agents; SSRIs, Selective serotonin reuptake inhibitors
See legend in Table 2 for description of the signs used to describe the DDIs.

not reported among those present in >5% of the total population (full analysis set)[8].

Notably, patients included in the ARAMIS study also reported hot flushes (5.3% and 6.3%) and erectile dysfunction (5.1% and 6.5%), both known adverse events of ADT[5]. Osteoporosis, which affects up to 1.7% of men aged 65–74 years and older to 5% of men aged 85 years or older in the Spanish population[30], is likely to have a greater prevalence in patients with nmCRPC as ADT is thought to contribute to a high prevalence of osteoporosis in up to 53% of men with PC[57].

Most common treatments for these conditions are shown in Table 5.

4. Pharmacokinetic DDI profile of ARIs

4.1. ARIs as 'perpetrators': effect of ARIs on other medical products

Apalutamide and enzalutamide are potent inducers of many metabolizing enzymes and efflux and hepatic uptake transporters, which leads to the loss or reduction of the clinical effect of medicinal products that are substrates of these enzymes or transporters as a consequence of the reduction of their plasma concentrations. There is also a risk of increased formation of active metabolites[20,21].

Apalutamide is a strong inducer of metabolizing enzymes such as CYP3A4 and CYP2C19 and a weak inducer of CYP2C9. It is also a substrate of uridine 5'-diphospho-glucoronosyl transferase (UGT). Clinically, it is a weak inducer of the drug transporters P-gp, BCRP, and organic anion transporting polypeptide 1B1 (OATP1B1). Based on *in vitro* data, inhibition of organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3), and multidrug and toxin extrusion (MATE) proteins cannot be excluded[21].

Enzalutamide is a strong inducer of CYP3A4, CYP2B6, CYP2C9, CYP2C19, and UGTs – glucuronide conjugating enzymes. The transport protein P-gp may also be induced, and probably other transporters such as multidrug resistance-associated protein 2 (MRP2), BCRP, and OATP1B1 as well[20]. Overall, it is recommended that these medicinal products should be substituted whenever possible or a potential loss of activity evaluated if medication is continued.

Darolutamide is an inhibitor of BCRP and OATP1B1/1B3. Co-administration of darolutamide with other BCRP substrates should be avoided where possible. Co-administration of darolutamide may increase the plasma concentrations of other concomitant BCRP and OATP1B1/1B3 substrates. No clinically relevant drug–drug interaction is expected in case of P-gp substrate administration. Darolutamide is a mild inducer of CYP3A4. No clinically relevant DDI is expected in case of administration[19].

In all three cases, since ADT may prolong the QT interval, co-administration with medicinal products that are known to prolong the QT interval or medicinal products that are able to induce *Torsade de pointes* should be carefully evaluated [19–21].

4.2. ARIs as 'victims': potential for other medicinal products to affect ARI exposure

Apalutamide is a substrate of CYP2C8 (major) and CYP3A4 (minor), which are involved in the elimination of apalutamide and the formation of its active metabolite N-desmethyl apalutamide. No clinically meaningful changes in their overall exposure are expected as a result of drug interaction with inducers or mild or moderate inhibitors of CYP2C8 or CYP3A4, and a dose reduction based on tolerability should only be considered when it is co-administered with strong inhibitors of these cytochromes[21].

Enzalutamide is a major substrate of CYP2C8, which plays an important role in the elimination of enzalutamide and the formation of its active metabolite. Conversely, CYP3A4 plays a minor role in the metabolism of this ARI. Strong inhibitors of CYP2C8 are to be avoided or used with caution during enzalutamide treatment. The dose of enzalutamide should be reduced when it is co-administered with strong inhibitors of CYP2C8, but not with inhibitors of CYP3A4. No dose

Table 5. DDIs between ARIs and frequent treatments for other common disorders in men with nmCRPC receiving ADT.

			Effect of ARIs on comedication exposure ('perpetrators')			Effect of comedications on ARI exposure ('victims')		
Condition	Drug class	Common treatments	Apalutamide	Enzalutamide	Darolutamide	Apalutamide	Enzalutamide	Darolutamide
Insomnia	Benzodiazepines	Flurazepam	-/↓	-/↓	-/-	-/-	-/-	-/-
		Clonazepam	↓/↓	↓/↓	-/-	-/-	-/-	-/-
		Levetiracetam	-/-	-/-	-/-	-/-	-/-	-/-
		Triazolam	↓↓/↓	↓↓/↓	-/-	-/-	-/-	-/-
		Alprazolam	↓/↓	↓/↓	-/-	-/-	-/-	-/-
		Zolpidem	↓/↓	↓/↓	-/-	-/-	-/-	-/-
		Zopiclone	↓/↓	↓/↓	-/-	-/-	-/-	-/-
GER	Proton pump inhibitors	Omeprazole	X (↓↓↓)/↓	↓/↓	-/-	-/-	-/-	-/-
		Pantoprazole	-/↓	-/↓	-/-	-/-	-/-	-/-
		Lansoprazole	X (↓↓↓)/↓	-/↓	-/-	-/-	-/-	-/-
		Rabeprazole	-/↓	-/↓	-/-	-/-	-/-	-/-
	H2RAs	Famotidine	-/-	-/QT	-/-	-/-	-/-	-/-
Bacterial infections	Antibiotics	Amox-clav	-/-	-/-	-/-	-/-	-/-	-/-
		Levofloxacin	-/QT	-/QT	-/QT	-/-	-/-	-/-
		Ciprofloxacin	-/QT	-/QT	-/-	-/-	-/-	-/-
		Fosfomycin	-/-	-/-	-/-	-/-	-/-	-/-
		Piperacillin/ tazobactam	-/-	-/-	-/-	-/-	-/-	-/-
		Clarithromycin	↓↓/↓	↓↓/↓	-/-	-/-	-/-	↑/↑
		Rifampicin	-/-	-/-	-/-	-/-	↓↓/↓	X (↓↓↓)/↓↓
		Doxycycline	-/-	-/-	-/-	-/-	-/-	-/-
		Erythromycin	-/↓	-/↓	-/-	-/-	-/-	-/-
		Trimethoprim	-/-	-/↓	-/-	-/-	-/-	-/-
Rheumatic, inflammatory, autoimmune diseases	Corticoids	Dexamethasone	↓↓/-	↓↓/-	-/-	-/-	-/↓	-/↓↓
		Prednisone	↓/-	↓/-	-/-	-/-	-/-	-/-
Pain and inflammation	Analgesics	Paracetamol	-/↓	-/-	-/-	-/-	-/-	-/-
		Metamizole	-/-	-/-	-/-	-/-	-/-	-/-
		Fentanyl	↓/↓↓	↓/↓↓	-/-	-/-	-/-	-/-
		Tramadol	↓/ seizure risk	↓/ seizure risk	-/QT	-/-	-/-	-/-
		Methadone	↓/↓↓	↓/↓↓	-/-	-/-	-/-	-/-
		Oxycodone	↓/↓↓	↓/↓↓	-/-	-/-	-/-	-/-
		Buprenorphine	↓/↓	↓/↓	-/QT	-/-	-/-	-/-
		Morphine	-/↓	-/-	-/-	-/-	-/-	-/-
	Anti-seizure agents‡	Pregabalin	-/-	-/-	-/-	-/-	-/-	-/-
		Gabapentin	-/-	-/-	-/-	-/-	-/-	-/-
	NSAIDs	Ibuprofen	-/↓	-/↓	-/-	-/-	-/-	-/-
		Diclofenac	-/↓	↓/↓	-/-	-/-	-/-	-/-
		Dexketoprofen	-/-	-/-	-/-	-/-	-/-	-/-
		Celecoxib	-/↓	↓/↓	-/-	-/-	-/-	-/-
ED	PDE-5i	Sildenafil	↓/↓	↓/↓	-/-	-/-	-/-	-/-
		Vardenafil	-/QT	-/QT	-/QT	-/-	-/-	-/-
		Tadalafil	↓↓/↓	↓↓/↓	-/-	-/-	-/-	-/-
BPH†	Alpha blockers	Tamsulosin	-/↓	-/↓	-/-	-/-	-/-	-/-
DTD	Antidiarrheics	Loperamide	-/↓	-/↓	-/-	-/-	-/-	-/-
	Antiemetics	Ondansetron	↓/QT	↓/QT	-/QT	-/-	-/-	-/-
		Metoclopramide	-/-	-/-	-/-	-/-	-/-	-/-
	Anticholinergic	Hyoscine butylbromide	-/-	-/-	-/-	-/-	-/-	-/-
Osteoporosis	Bone-modifying agent	Denosumab	-/-	-/-	-/-	-/-	-/-	-/-
	Bisphosphonate derivative	Zoledronic acid	-/-	-/-	-/-	-/-	-/-	-/-
	Electrolyte supplement	Calcium carbonate/ Vitamin D	-/-	-/-	-/-	-/-	-/-	-/-

Source: Compiled by the authors based on the DDIs compendia Lexicomp®[25] and Drugs.com®[26].
Amox-clav, amoxicillin-clavulanic acid; DTD, digestive tract disorders; ED, erectile dysfunction; GER; gastroesophageal reflux disease; H2RAs, histamine H_2 receptors inhibitors, NSAIDs, non-steroidal anti-inflammatory drugs; BPH, benign prostatic hyperplasia; PDE-5i, phosphodiesterase 5 inhibitor;
†Used to treat neuropathic pain
‡In general, urinary incontinence or urine control problems.
See legend in Table 2 for description of the signs used to describe the DDIs.

adjustment is needed when it is co-administered with inducers of these cytochromes[20].

Darolutamide is a substrate of CYP3A4 (minor), P-glycoprotein (P-gp) (minor), and breast cancer resistance protein (BCRP). No clinically relevant DDI is expected in case of CYP3A4, P-gp, or BCRP inhibitor administration, although co-administration of darolutamide with P-gp and a strong CYP3A4 inhibitor increases darolutamide exposure, which may increase the risk of adverse reactions to darolutamide. The use of strong and moderate CYP3A4 inducers and P-gp

inducers during treatment with darolutamide is not recommended unless there is no other therapeutic alternative. Darolutamide is also a substrate of UGT1A9. No clinically relevant DDI is expected when it is co-administered with a UGT1A9 inhibitor[19].

5. The most common DDIs expected in patients with nmCRPC receiving ARIs

5.1. ARIs as 'perpetrators': effect of ARIs on the PK of common treatments

Most drugs in clinical use are metabolized by at least one of the metabolic enzymes of the cytochrome P450 (CYP) family [58]. As a consequence, most PK DDIs are the result of the inhibition of these enzymes[18,59]. Given that enzalutamide and apalutamide are strong CYP inducers[20,21], treatment with these ARIs results in decreased plasma levels of comedications metabolized through CYP3A4, CYP2C19, and CYP2C9. In patients with nmCRPC receiving enzalutamide or apalutamide, these DDIs increase the risk of suboptimal treatment of the typical common comorbid conditions seen in these patients (especially those managed with treatments with a narrow therapeutic index), which requires close monitoring or modification of therapy[8,20,21,60–63]. The induction of several efflux and hepatic uptake transporters by enzalutamide and apalutamide also adds to this effect[20,21]. Among the common diseases in men with nmCRPC, this potential for DDIs especially affects the PK of common treatments for hypertension (calcium channel blockers, angiotensin II receptor blockers [ARBs], and beta-blockers), dyslipidemia (statins), diabetes mellitus (sulfonylureas, dipeptidyl peptidase 4 inhibitors, and meglitinides) (Table 2), CV diseases (antithrombotic, antiplatelet agents, cardiac glycosides, and antiarrhythmics) (Table 3), mental disorders (selective serotonin reuptake inhibitors [SSRIs], noradrenergic and specific serotonergic agents [NSSAs], antipsychotics, and anti-seizure agents) (Table 4), insomnia (benzodiazepines), gastroesophageal reflux disease (proton pump inhibitors), bacterial infections (certain antibiotics), rheumatic, inflammatory, and autoimmune diseases (corticosteroids), pain and inflammation (analgesics and non-steroidal anti-inflammatory drugs [NSAIDs]), erectile dysfunction (phosphodiesterase 5 inhibitors [PDE-5i]), benign prostatic hyperplasia (tamsulosin), and digestive tract disorders (anti-diarrheics, certain antiemetics) (Table 5). Prolongation of the QT interval must be carefully evaluated when enzalutamide and apalutamide are co-administered with SSRIs, the antipsychotic haloperidol, the antibiotics levofloxacin and ciprofloxacin, the PDE-5i vardenafil, and the antiemetic ondansetron (Tables 4 and 5). The risk of seizure has to be taken into account when co-administering enzalutamide or apalutamide with tramadol (Table 5).

To our knowledge, no studies analyzing the burden of DDIs with enzalutamide and apalutamide in men with nmCRPC are available. DDIs with enzalutamide have been analyzed in the metastatic stage of CRPC (mCRPC), for which enzalutamide (but not apalutamide) is licensed[20]. A study conducted in Spain has revealed that up to 93.0% of mCRPC patients treated with enzalutamide in a single center had at least one DDI, most of them related to CYP3A4-mediated metabolism of comedications. Sixty percent were classified as major severity and 52% as risk level D according to the Lexicomp® DDI compendium. The most common treatments showing DDIs with enzalutamide in mCRPC patients in our setting were omeprazole, atorvastatin, fentanyl, prednisone, and tramadol [63]. The high rate and severity of DDIs with enzalutamide in the mCRPC setting has also been reported in other studies [60,64].

Darolutamide, the most recently available ARI, is structurally differently from enzalutamide and apalutamide[65]. Overall, darolutamide has shown few inhibitory or inducing interactions at therapeutic concentrations, with increased exposure of BCRP and OATP substrates probably being the main interaction[19,54]. This potential for DDIs does not affect the PK of common treatments for hypertension except for valsartan, diabetes mellitus except for glyburide and repaglinide (Table 2), CV diseases except for rivaroxaban (Table 3), mental disorders (Table 4), insomnia, gastroesophageal reflux disease, bacterial infections, rheumatic, inflammatory, and autoimmune diseases, pain and inflammation, erectile dysfunction, benign prostatic hyperplasia, or digestive tract disorders (Table 5). Conversely, the inhibitory effect of darolutamide on BCRP and OATP1B1/1B3 may increase the plasma concentration of statins (commonly substrates of these transporters), especially rosuvastatin (concomitant BCRP, OATP1B1/1B3, and OAT3 substrates), which results in an increased risk of myotoxicity[8]. (Table 5). Prolongation of the QT interval has to be carefully evaluated when darolutamide is co-administered with the SSRIs sertraline, trazodone, and amitriptyline, the NSSA mirtazapine, the antibiotic levofloxacin, the analgesics tramadol and buprenorphine, the PDE-5i vardenafil, and the antiemetic ondansetron (Tables 4 and 5).

Conversely to enzalutamide and apalutamide, an exploratory *post hoc* population PK analysis has been conducted with darolutamide in a valid subset of patients with nmCRPC from the ARAMIS study. In this study, the most frequently prescribed comedications were antihypertensives and agents for other CV disorders, along with a need for analgesia, treatments for urological and acid-related gastrointestinal disorders, antidepressants, anxiolytics, and dementia treatments [8]. Darolutamide showed few effects on the concomitant drugs administered to these patients except for rosuvastatin [8], which is the only clinically relevant interaction of note of darolutamide[19,54]. Moreover, these comedications showed no significant effect on the PK of darolutamide. In this study, the incidence of adverse events resulting from DDIs was negligible as this was similar in the darolutamide and placebo arms despite the high use of comedications in both arms[8]. The effect of concomitant use of statins was also analyzed in the ARAMIS study. The use of statins was similar in the darolutamide and placebo arms (32.1% and 36.5%, respectively). In a safety subgroup analysis in statin users and non-users, no significant differences were found between both subgroups with respect to the adverse event rate and the type of adverse events. However, when only analyzing patients using statins that were BCRP substrates (~30% of the overall population),

the adverse event rate was higher among statin users (8.6%) compared to non-users (3.5%). According to the authors, this difference was due to the greater incidence of laboratory parameters and was independent of statin exposure[8]. Given the possibility of DDIs, concomitant use of darolutamide with statins that are either BCRP or OATP1B1/1B3 substrates requires monitoring patients for adverse reactions[19].

5.2. ARIs as 'victims': effect of common treatments on the PK of ARIs

CYP2C8 inhibitors can increase the composite area under the plasma concentration–time curve from time zero to infinity of enzalutamide plus its active metabolite by 2.2-fold[61]. These interactions affect the concomitant use of some common treatments with enzalutamide like the Ca channel blocker verapamil and the fibrate gemfibrozil (Table 2). The use of strong or moderate CYP2C8 and/or CYP3A4 inducers such as the anti-seizure agents carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and primidone, the antibiotic rifampicin, the corticosteroid dexamethasone, requiring either modification of therapy or monitoring (Tables 4 and 5).

No major changes in the PK of apalutamide are expected with strong CYP3A4/CYP2C8 inhibitors or inducers[66]. Of the common treatments analyzed, only gemfibrozil and carbamazepine may influence the PK of apalutamide, although less so than for enzalutamide (Tables 2 and 4).

No clinically relevant DDIs are expected between darolutamide and CYP3A4, P-gp, or BCRP inhibitors[19]. However, concomitant use with a strong CYP3A4 inhibitor like clarithromycin should be monitored. None of the common treatments analyzed was a combined P-gp and strong CYP3A4 inhibitor, which would increase the risk of adverse reactions with darolutamide as a result of increased exposure to this agent[19]. The use of strong and moderate CYP3A4 inducers and P-gp inducers may have an effect on the PK of darolutamide and so their use is not recommended unless there is no therapeutic alternative[19]. Among the common treatments analyzed, these included the anti-seizure agents carbamazepine, oxcarbazepine, and phenobarbital, the corticoid dexamethasone, and the antibiotic rifampicin. The combination of darolutamide and carbamazepine, phenytoin, or rifampicin should also be avoided according to Lexicomp®. These medications were rarely used in the ARAMIS study[15].

6. Conclusion

Enzalutamide, apalutamide, and darolutamide are the standard of care in the treatment of high-risk nmCRPC patients. Considering the comorbidity burden in these patients and the potential for DDIs between these ARIs ('perpetrators') and medications commonly used to treat common comorbidities ('victims') in these men, a careful selection of first-line treatment is essential if we are to avoid undertreatment of these comorbidities. Darolutamide offers an option to safely treat these patients given that no relevant DDIs are expected when it is co-administered with CYP substrates, except with statins that are either BCRP or OATP1B1/1B3 substrates. Using enzalutamide or apalutamide to treat nmCRPC requires a careful identification of potential DDIs with comedications and subsequent modification of therapy or close patient monitoring. The role of 'perpetrator' of common treatments for frequent comorbidities on ARIs is less common but still relevant and should also be considered before starting treatment with a given ARI. The consideration of potential DDIs between common treatments for age-related comorbidities (or ADT side effects) and ARIs are thus a fundamental component in clinical decision-making.

7. Expert opinion

Optimal selection of ARIs in patients with nmCRPC is a complex decision based on several factors. Among these, poly-medication due to the presence of comorbidities typically found in old age, in addition to those caused by ADT, is of special interest given the deleterious consequences of PK DDIs. Age-related declines in renal and hepatic function make these patients more vulnerable to DDIs[67]. Together with the consideration of adverse events that are known to be associated with next-generation ARIs[5], potential DDIs are a fundamental component of clinical decision-making [8,68,69].

The addition of an ARI to men with high-risk nmCRPC receiving ADT should not only focus on PC treatment but on the patient himself and his overall management[31]. A comprehensive review of the medical history and other medications taken is therefore crucial. Despite this information commonly being available in medical records, it should be further discussed with patients with the aim of confirming its accuracy and updating it[70]. Likewise, potential interactions with over-the-counter (OTC) or alternative medicines and herbal medicines when starting treatment and during follow-up should not be underestimated[59,63,71,72]. The role of each ARI as a DDI 'perpetrator' or 'victim' should be carefully analyzed on the basis of this background to evaluate potential deleterious effects on the treatment of chronic conditions or on the adverse effect profile and therapeutic benefit/risk ratio of ARIs[31].

Two relevant aspects should be taken into account when considering comorbidities and comedications before starting treatment with an ARI. First of all, the CVD risk, as the addition of ARIs is associated with an increase in the CV toxicity burden, among other toxicities[44]. This aspect not only affects the selection of ARIs, as these vary regarding their CVD risk, but it is also relevant because it results in an increase in the treatment burden in the short term while on treatment with the ARI. The second relevant aspect relates to the fact that the patients' comorbidity burden (and therefore the likelihood of new comedications) increases with age, which may result in an increase in the treatment burden in the medium/long term. This view implies that at the time of starting an ARI, the evaluation of DDIs should focus on the present, with an eye on the medium/long-term future. The ABCDE (Awareness, Blood pressure, Cholesterol/Cigarettes, Diet/Diabetes, and Exercise) algorithm proposed by Guan et al [73] . for heart and vascular wellness in patients following a PC diagnosis could be useful for the follow-up of age- and treatment-related CVD risk during treatment with ARIs. New medications

used for the conditions included in this algorithm should be selected based on the patient profile but also on DDIs with the ARI being administered. A low potential for DDIs may allow new comedications to be added as needed without changing the nmCRPC treatment. Other modifying factors that may increase (risk factors) or decrease (mitigating factors) susceptibility to DDIs should also be carefully analyzed when evaluating or reporting evidence of DDIs. These should include those related to the patient (age, sex, pharmacogenomics, comorbidity, clinical status, vital signs, laboratory values, and indication for the drug) and to the drug (dose, duration, route and order of administration, and timing of dose)[74].

A multidisciplinary approach is needed to determine the optimal management of the patient based on the gathered information. This approach should include the expertise of the clinical pharmacist, together with the oncologist/urologist in charge of the patient, in order to decide on the ARI to be used and, when appropriate, the changes needed in comedications. All this information should be shared with the other healthcare professionals involved in the patient's care – especially the family doctor- to avoid duplicate prescriptions (and subsequent new potential DDIs)[18,71] and to establish a collaborative follow-up strategy. Despite these efforts, there are still relevant issues that must be addressed in order to improve the assessment and management of DDIs. One of them is the lack of guidelines or standards for determining the clinical relevance of DDIs via consistent systematic evaluation and classification[75]. Determining the clinical relevance of a DDI is of the utmost importance to focus on those which are relevant to the patient among all the theoretical ones[76]. In an effort to overcome this problem, an expert consensus work group defined a 'clinically relevant DDI' as 'one associated with either toxicity or loss of efficacy that warrants the attention of healthcare professionals'[74]. However, high-quality evidence on many DDIs is still lacking[74], and more interaction studies are needed to ensure appropriate antineoplastic PK in clinical practice[77]. The existence of several subscription-based and free DDI compendia to assess DDIs may also be confusing. The different approaches to identifying and evaluating evidence on DDIs of these compendia has been shown to lead to discrepancies in the evaluation of DDIs[67,76,78,79]. Many of these may be explained by differences in the sources of information and in assumptions that consider DDIs as a 'class effect'[79]. Among the available DDI compendia, the subscription-based Lexicomp® and the free Drugs.com® have shown the highest performance out of the nine analyzed for screening DDIs of oral oncolytics in a prospective study[67]. This study also showed that, overall, the nine DDI compendia evaluated (the subscription-based PEPID®, Micromedex®, Lexicomp®, and Facts & Comparisons®, and the free ones Epocrates Free®, Medscape®, Drugs®, RxList®, and WebMD®) were better at ensuring that DDIs categorized as severe were clinically relevant (as shown by a narrow range of positive predictive values [PPVs]: 0.88–0.97) than ensuring that DDIs categorized as severe were actually not clinically relevant (as shown by a relative wide range of negative predictive values [NPVs]: 0.38–0.83) when assessing DDIs with oral oncolytics[67]. These results point to the need to harmonize the definition and classification of DDIs among the different compendia. Given the high performance of free DDI compendia like Drugs®, the authors encourage the use of this compendium when no subscription-based one is available[67].

These reflections, far from being limited to the nmCRPC setting, can be extended to all stages of PC where ARIs are licensed. Moreover, the management of advanced prostate cancer is likely to become even more complex in the near future due to the numerous clinical trials analyzing the use of several drug combinations. In this context, two clinical trials have already established the combination of ADT–docetaxel combined with abiraterone–prednisone (PEACE-1)[80] or darolutamide (ARASENS)[81] as new standard-of-care treatment options for patients with hormone-sensitive metastatic prostate cancer (mHSPC), after showing an increase in overall survival in their respective clinical trials compared to ADT–docetaxel alone. Similarly, other clinical trials are currently investigating the combination of ARIs with poly (ADP ribose) polymerase (PARP) inhibitors or immune checkpoint inhibitors, among other combinations[82]. Consequently, DDIs and optimal selection of ARIs will become even more crucial in the near future for the management of advanced PC in order to avoid synergistic toxicities or a negative impact on patients' quality of life. These new treatment combinations make the careful assessment of potential DDIs even more necessary and challenging, for which protocols and resources are urgently needed.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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