

CARDIOVASCULAR AGENTS

Class of Dugs	Type of interaction	Clinical effects	Current labeling
<p><i>Nitrates:</i></p> <p>Nitroglycerin Isosorbide dinitrate Isosorbide mononitrate Amyl nitrate “popper” Nitrate</p>	<p>PDE5i-dependent reduction in the breakdown of cGMP induced by organic nitrates leading to a marked increase of cGMP signaling.</p>	<p>Synergic decrease in blood pressure leading to possible individual experiencing hypotension (SBP < 85 mmHg)</p>	<ul style="list-style-type: none"> • Contraindications for all PDE5is • Past use (> 2 weeks) not considered a contraindication • A period \geq 24 hours for short acting PDE5is (<i>avanafil, sildenafil and vardenafil</i>) and up to 48 hours for long acting (<i>tadalafil</i>) recommended against taking nitrates.
<p><i>Antihypertensive agents:</i></p> <ul style="list-style-type: none"> • α-blocker agents Doxazosin Tamsulosin Alfuzosin Terazosin Carvediol (mixed α-blocker) Labetol (mixed α-blockers) • other antihypertensives Selective β-blockers Calcium antagonists Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers Diuretics 	<p>Possible increase of hypotensive effects</p>	<p>Synergic decrease in blood pressure leading to possible individual experiencing hypotension (SBP < 85 mmHg)</p>	<ul style="list-style-type: none"> • Precautions for all PDE5is. • PDE5is should be initiated at the lowest recommended dose. • Patients already taking an optimal dose of PDE5 inhibitor the α-blocker should be initiated at the lowest dose. • None
<p><i>Antiarrhythmics</i></p> <p><u>Class 1 A</u> Quinidine Procainamide</p>	<p>QT interval prolongation</p>	<p>Torsade de pointes and ventricular tachycardia.</p>	<ul style="list-style-type: none"> • Precaution for vardenafil. • No limitation for other PDE5i

<u>Class III</u> Sotalol Amiodarone	QT interval prolongation	QT interval prolongation	<ul style="list-style-type: none"> • Precaution for vardenafil. • No limitation for other PDE5i
<u>Class IV</u> Verapamil	CYP3A4 inhibitor	Increase of systemic exposure	<ul style="list-style-type: none"> • Avanafil: precaution and maximum recommended dosage of 100 mg within 48 h after verapamil use • Precaution and possible dosage reduction for other PDE5i

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<p><i>Anticoagulant agents</i> warfarin</p> <p><i>Anti-platelet aggregating agents</i></p>	<p>Substrate of CYP2C9 metabolism</p> <p>Sildenafil increases inhibitory effects of nitric oxide donors on ADP-dependent platelet aggregation.</p>	<p>Possible increase in prothrombin time and increased risk of bleeding events.</p> <p>Possible increase in bleeding time and increased risk of bleeding events.</p>	<ul style="list-style-type: none"> • None for all PDE5i (no significant clinically interactions) • Precaution, in particular for sildenafil, for the high risk cardiovascular patient, commonly on multiple anti-thrombotic regiments or on warfarin
<p><i>Statins:</i></p>	<ul style="list-style-type: none"> • Increase the expression of eNOS • Activation of the serine/threonine kinase Akt which in turn, phosphorylates eNOS • Inhibition of the RhoA/RhoA-kinase pathway. 	<p>Possible improvement of PDE5is outcomes</p>	<ul style="list-style-type: none"> • None

ORAL HYPOGLYCEMIC AGENTS

Class of Dugs	Type of interaction	Clinical effects	Current labeling
<i>Hypoglycemic drugs</i> Sulfonylureas Benzoic acid derivates	Not reported	Not reported	<ul style="list-style-type: none"> • None
<i>Antihyperglycemic drugs</i> Biguanides α -Glucosidase inhibitors Thiazolidinediones	Not reported	Not reported	<ul style="list-style-type: none"> • None

ANTIDEPRESSANTS

<i>SSRI:</i> Fluvoxamine Fluoxetine	CYP3A4 inhibitors	Increase of systemic exposure	<ul style="list-style-type: none"> • Precaution: starting dose of sildenafil 25 mg is suggested for patients on fluvoxamine therapy • No specific studies for tadalafil and vardenafil but similar precautions should be advised. • No specific studies have been reported for Fluoxetine • Contraindication for simultaneous use of avanafil and nefazodone
Citalopram Escitalopram Paroxetine Sertraline Venlafaxine	No significant effects on CYP3A4	None	<ul style="list-style-type: none"> • None.
<i>iMAO:</i>	Possible additive hypotensive effects	Possible individual experiencing hypotension	<ul style="list-style-type: none"> • Precaution for all PDE5is

ANTIEPILEPTICS

Phenobarbital Phenytoin Carbamazepin	CYP3A4 inducers	Reduction of systemic exposure	<ul style="list-style-type: none"> Potentially required higher dose of PDE5is
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CHEMIOTERAPICS

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<i>Macrolid antibiotics</i> Erythromycin Clarithromycin Troleanddomycin	CYP3A4 inhibitors	Increase of systemic exposure	<ul style="list-style-type: none"> Sildenafil: precaution and dose reduction. Vardenafil: precaution, not to exceed a single 2.5-5mg dose of vardenafil in a 24-hour period. Tadalafil: precaution not to exceed a single 10 mg dose, and should not be taken more than once for 72 hour-period. Avanafil: controindication concomitant use with claritromycin and troleandromycin, precaution and maximum recommended dosage of 100 mg within 48 h after eritromycine use
Azithromycin	Not involved in CYP3A4	None	<ul style="list-style-type: none"> None
<i>Rifampin</i>	CYP3A4 inducer	Reduction of systemic exposure	<ul style="list-style-type: none"> Precaution: potentially required higher dose of PDE5is.
<i>Azole antifungals</i> Ketoconazole Itraconazole Fluconazole Voriconazole	CYP3A4 inhibitors	Increase of systemic exposure	<ul style="list-style-type: none"> Sildenafil: precaution and dose reduction. Vardenafil: precaution, not to exceed a single 2.5-5mg dose of vardenafil in a 24-hour period. Tadalafil: precaution not to exceed a single 10 mg dose, and should not be taken more than once for 72 hour-period. Avanafil: controindication with use of ketoconazole, itraconazole and voriconazole, precaution not to exceed a single 100 mg dose, and should not be taken more than once for 48 hour-period with fuconazole

<ul style="list-style-type: none"> • <i>Antiretroviral protease inhibitors</i> Ritinar Saquinavir Tipranavir Indinavir Fosamprenavir	CYP3A4 inhibitors	Increase of systemic exposure	<ul style="list-style-type: none"> • Sildenafil: precaution not to exceeded a single dose of 25 mg of sildenafil in 48-hour period. • Vardenafil: precaution, not to exceed a single 2.5-5mg dose of vardenafil in a 24-hour period. • Tadalafil: precaution not to exceed a single 10 mg dose, and should not be taken more than once for 72 hour-period. • Avanafil: contraindication with use of ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, precaution not to exceed a single 100 mg dose, and should not be taken more than once for 48 hour-period with aprenavir, fosamprenavir
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H2 INHIBITOR/ANTIACID AGENTS

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<p><i>H2 inhibitors:</i> Cimetidine Ranitidine</p>	<p>Non specific CYP inhibitor Not involved in CYP metabolism</p>	<p>Increase of systemic exposure None</p>	<ul style="list-style-type: none"> • Precaution: potentially required lower dose of PDE5is • None.
<p><i>Antacids</i> Aluminum hydroxide/magnesium hydroxide</p>	<p>Reduction of the tadalafil absorption by 30% No effect on vardenafil and sildenafil absorption</p>	<p>Reduction of systemic exposure</p>	<ul style="list-style-type: none"> • Precaution: potentially required higher dose of tadalafil

Supplementary Table 1. Principal phosphodiesterase 5 (PDE5) inhibitor- drug interaction and current labeling.