Attention-Deficit/Hyperactivity Disorder (ADHD) Pharmacotherapy - Drug Interactions		
Offending Agent(s)	**Possible Interaction**	**Response**
Amphetamines (AMP)		
Acidic agents (e.g., fruit juices, ascorbic acid)	May decrease amphetamine absorption, increase amphetamine excretion, decrease amphetamine plasma levels	Monitor response to therapy
Alkalizing agents Gastrointestinal (GI) (e.g., sodium bicarbonate) Urinary (e.g., acetazolamide)	May increase amphetamine absorption, decrease amphetamine excretion, increase amphetamine half-life	Alternative treatment should be considered
Antibacterial agent (linezolid)	May increase hypertensive effect of amphetamines	Combination of linezolid and amphetamines **should be avoided**
Antidepressants -monoamine oxidase inhibitor (MAOI) (e.g., phenelzine, selegiline)	May increase hypertensive effect that could lead to hypertensive crisis	Amphetamine products are **CONTRAINDICATED** during or within 14 days of MAOI therapy
Antidepressants – selective serotonin reuptake inhibitor (SSRI e.g., paroxetine) selective serotonin/norepinephrine reuptake inhibitor (SNRI, e.g. venlafaxine)	May increase adverse effects of SSRI and may increase risk of serotonin syndrome	Monitor for signs and symptoms of serotonin syndrome *Dosage may need to be reduced
Antidepressants -tricyclic (e.g., amitriptyline)	May increase stimulatory effect and cardiovascular effect of amphetamines	Monitor stimulant and cardiovascular response
Antihypertensives	May decrease hypotensive effects	Periodic evaluation of blood pressure is advisable
Antipsychotics (e.g., chlorpromazine, risperidone)	May decrease effect of amphetamines	Monitor response to AMP therapy
Decongestants (e.g., pseudoephedrine)	May increase heart rate and blood pressure	Blood pressure and heart rate should be monitored
Opioids	Amphetamines may enhance the analgesic effect of opioid agonists	Monitor therapy
Methylphenidate (MPH)		
Antibacterial agent – (linezolid)	May increase pharmacological effect of methylphenidate. Headache, GI symptoms, and hypertension may occur.	Combination of linezolid and methylphenidate **should be avoided**

Attention-Deficit/Hyperactivity Disorder (ADHD) Pharmacotherapy - Drug Interactions		
Offending Agent(s)	**Possible Interaction**	**Response**
Methylphenidate (MPH)		
Anticoagulant – (warfarin)	May increase serum concentration of warfarin	International normalized ratio (INR) should be monitored whenever MPH use is started or stopped and during dose changes. *Dosage may need to be reduced
Anticonvulsants (e.g., phenobarbital, phenytoin, primidone, fosphenytoin)	May increase serum levels of anticonvulsants	Anticonvulsant serum levels should be monitored at the start and stop of MPH use and during dose changes. *Dosage may need to be reduced
Antidepressants-MAOI (e.g., phenelzine, selegiline)	May increase hypertensive effect of MPH that could lead to hypertensive crisis	MPH products are **CONTRAINDICATED** during or within 14 days of MAOI therapy
Antidepressants*- *- selective serotonin reuptake inhibitor (SSRI), selective norepinephrine reuptake inhibitor (SNRI) (e.g., paroxetine, venlafaxine)	May increase adverse effects of SSRI and may increase risk of serotonin syndrome	Monitor for signs and symptoms of serotonin syndrome. *Dosage may need to be reduced
Antidepressants*-Tricyclic (e.g., amitriptyline)	May increase serum levels and adverse/ toxic effect of tricyclics antidepressants	Monitor serum levels and toxicity of tricyclic antidepressants. *Dosage may need to be reduced
Antihypertensives	May decrease hypotensive effects	Periodic evaluation of blood pressure is advisable
Decongestants (e.g., pseudoephedrine)	May increase heart rate May increase blood pressure	Blood pressure and heart rate should be monitored.
Antipsychotic- second generation (e.g., risperidone)	May increase risk for extrapyramidal symptoms (EPS) during dose changes of MPH or risperidone	Monitor for signs of EPS
Guanfacine (CYP3A4 substrate)		
Antihypertensives	May increase hypotensive effects	Periodic evaluation of blood pressure is advisable
Central Nervous System (CNS) depressants (e.g., alcohol, sedatives, hypnotics)	May increase sedation and somnolence	Monitor for additive CNS-depressant effects, avoid use of unprescribed CNS depressants
Strong and moderate CYP3A4 inhibitors (e.g., ketoconazole, fluconazole, and grapefruit juice)	Plasma concentrations can be significantly affected resulting in increased exposure	Consider guanfacine dose reduction
Strong and moderate CYP3A4 inducers (e.g., rifampin, efavirenz)	Plasma concentrations can be significantly affected resulting in decreased exposure	Consider guanfacine dose increase
Valproates	May increase plasma concentrations of valproic acid	Monitor response to valproic acid/ valproic acid derivatives when guanfacine is started or stopped
QTc prolonging agents (e.g., citalopram, quetiapine)	May increase QTc interval	Consider alternatives or closely monitor for evidence of QTc prolongation

Attention-Deficit/Hyperactivity Disorder (ADHD) Pharmacotherapy - Drug Interactions		
Offending Agent(s)	**Possible Interaction**	**Response**
Guanfacine (CYP3A4 substrate)		
Beta blockers, calcium channel blockers	May increase risk of sinus bradycardia and atrioventricular (AV) block. May enhance the rebound hypertensive effects of clonidine	Closely monitor heart rate during treatment with a beta blocker and clonidine Withdraw beta blockers several days before clonidine withdrawal when possible and monitor blood pressure closely
Clonidine		
Antihypertensives	May increase hypotensive effects	Periodic evaluation of blood pressure is advisable
CNS depressants (e.g., alcohol, sedatives, hypnotics)	May increase sedation and somnolence	Monitor for additive CNS-depressant effects, avoid use of unprescribed CNS depressants
Beta blockers, calcium channel blockers	May increase risk of sinus bradycardia and AV block May enhance the rebound hypertensive effects of clonidine	Closely monitor heart rate during treatment with a beta blocker and clonidine Withdraw beta blockers several days before clonidine withdrawal when possible and monitor blood pressure closely
Atomoxetine (CYP2D6 substrate)		
Antidepressants -MAOI (e.g., phenelzine, selegiline)	May increase neurotoxic effects of atomoxetine (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma)	Atomoxetine is **CONTRAINDICATED** during or within 14 days of MAOI therapy
Antihypertensives	May decrease hypotensive effects	Periodic evaluation of blood pressure is advisable
Beta-2 agonists (e.g., albuterol)	Can increases in heart rate and blood pressure	Atomoxetine should be administered with caution to patients being treated with systemic (oral or IV) albuterol or other Beta-2 agonists
Strong inhibitors of CYP2D6 (e.g., paroxetine, fluoxetine, and quinidine)	Increase atomoxetine serum concentrations	Initiate atomoxetine at a reduced dose in patients receiving a strong CYP2D6 inhibitor. Increase to usual target dose after 4 weeks if needed. Consider therapy modification
QTc prolonging agents (e.g., citalopram, quetiapine)	May increase QTc interval	Consider alternatives or closely monitor for evidence of QTc prolongation

Attention-Deficit/Hyperactivity Disorder (ADHD) Pharmacotherapy - Drug Interactions		
Offending Agent(s)	**Possible Interaction**	**Response**
Viloxazine (CYP1A2- strong inhibitor, CYP2D6- weak inhibitor, and CYP3A4-weak inhibitor)		
Antidepressants-MAOI (e.g., phenelzine, selegiline)	May increase hypertensive effect that could lead to hypertensive crisis	Viloxazine products are **CONTRAINDICATED** during or within 14 days of MAOI therapy
Antihypertensives	May decrease hypotensive effects	Periodic evaluation of blood pressure is advisable
CYP1A2 substrates- sensitive or within a narrow therapeutic range (e.g., duloxetine, tizanidine, theophylline)	Increased exposure of CYP1A2 substrates which may increase the risk of adverse events	Coadministration with viloxazine is **CONTRAINDICATED**
CYP1A2 substrates- moderate (e.g., clozapine, olanzapine, caffeine)	Increased exposure of CYP1A2 substrates which may increase the risk of adverse events	Not recommended for coadministration with viloxazine. Dose reduction may be warranted if co-administered.
CYP2D6 substrates (e.g., dextromethorphan, nortriptyline, venlafaxine)	Increases the exposure of CYP2D6 substrates when co-administered	Monitor for adverse reaction and adjust dosages of the CYP2D6 substrate as clinically indicated
CYP3A4 substrates (e.g., tacrolimus, lurasidone, buspirone)	Increases the exposure of CYP3A4 substrates when co-administered	Monitor for adverse reaction and adjust dosages of the CYP3A4 substrate as clinically indicated
Bupropion (CYP2B6- substrate, CYP2D6- inhibitor)		
Alcohol	Enhancement of the adverse/toxic effects of alcohol	Consumption of alcohol should be minimized or avoided
Antidepressants -MAOI (e.g., phenelzine, selegiline)	May increase hypertensive effect that could lead to hypertensive crisis	Bupropion products are **CONTRAINDICATED** during or within 14 days of MAOI therapy
Citalopram	Bupropion may increase the serum concentration of citalopram which may also enhance the adverse/toxic effect of citalopram	Monitor therapy and/or consider therapy modification
CYP2D6 substrates (e.g., venlafaxine, aripiprazole, paroxetine)	Can increase the exposures of drugs that are substrates of CYP2D6	Dosage decrease of the dose of CYP2D6 substrates may be necessary, particularly for drugs with a narrow therapeutic index
Dopaminergic drugs (e.g., levodopa and amantadine)	CNS toxicity (restlessness, agitation, tremor, etc.) has been reported with concurrent use of bupropion	Use caution and monitor therapy when using concurrently
Drugs that lower seizure threshold (e.g., antipsychotics, antidepressants)	Risk of seizures with bupropion which can be increased with other drugs lowering seizure threshold	Use extreme caution. Use low initial doses of bupropion and increase gradually. Do not exceed max dose.

Attention-Deficit/Hyperactivity Disorder (ADHD) Pharmacotherapy - Drug Interactions		
Offending Agent(s)	**Possible Interaction**	**Response**
Bupropion (CYP2B6- substrate, CYP2D6- inhibitor)		
Drugs that require activation by CYP2D6 (e.g., tamoxifen)	Could have reduced efficacy if concurrent use with bupropion	May require increased doses of the drug
Inhibitors of CYP2B6 (e.g., ticlopidine, clopidogrel)	Can increase bupropion exposures but decrease hydroxybupropion exposure	Dosage adjustment of bupropion may be necessary when co-administered with CYP2B6 inhibitors
Inducers of CYP2B6 (e.g., ritonavir, lopinavir, efavirenz)	Can decrease bupropion and hydroxybupropion exposure	Dosage increase of bupropion may be necessary when co-administered with inducers of CYP2B6 but should not exceed the maximum recommended dose
Amantadine (OCT2- Substrate)		
Alcohol	May increase the potential for CNS effects (dizziness, confusion, lightheadedness)	Concomitant use with alcohol is not recommended
Anticholinergic drugs	May potentiate the anticholinergic-like side effects	Dose reductions may be necessary
Live attenuated influenza vaccines	Amantadine may interfere with efficacy of live attenuated influenza vaccines.	Live vaccines are not recommended. Inactivated influenza vaccines may be used, as appropriate.
OCT2 Inhibitors	OCT2 Inhibitors may increase serum concentrations of amantadine	Monitor therapy and/or consider therapy modification
QTc prolonging agents (e.g., citalopram, quetiapine)	May increase QTc interval	Consider alternatives or closely monitor for evidence of QTc prolongation
Modafinil (CYP2C19- inhibitor, CYP3A4- moderate inducer)		
Antidepressants -MAOI (e.g., phenelzine)	Could induce severe cardiovascular reactions, such as hypertensive crisis with concurrent use	Caution should be used when concomitantly administering MAOIs and modafinil
CYP2C19 substrates (e.g., phenytoin, diazepam)	Higher systemic exposure of CYP2C19 substrate may occur	Dosage adjustments may be necessary
CYP3A4 substrates (e.g., cyclosporine, steroidal contraceptives, guanfacine)	Lower systemic exposure of CYP3A4 substrates	Dosage adjustments should be considered Alternative or concomitant methods of contraception are recommended for patients taking steroidal contraceptives (e.g., ethinyl estradiol) when treated concomitantly with modafinil and for one month after discontinuation of modafinil treatment
Warfarin	Modafinil may increase or decrease the effect of warfarin	Closely monitor INR if coadministration is necessary

Attention-Deficit/Hyperactivity Disorder (ADHD) Pharmacotherapy - Drug Interactions		
Offending Agent(s)	**Possible Interaction**	**Response**
Tricyclic Antidepressants (TCA) Desipramine (CYP1A2- minor substrate, CYP2D6- major substrate) Imipramine (CYP1A2, CYP2B6, CYP3A4 and CYP2C19- minor substrate, CYP2D6- major substrate) Nortriptyline (CYP1A2 & CYP2C19- minor substrate, CYP2D6 major substrate)		
Amphetamines	May enhance the adverse/toxic effect and cardiovascular effects of amphetamines Amphetamines may enhance the serotonergic effect of imipramine resulting in serotonin syndrome	Monitor therapy
Anticholinergics agents	May enhance the adverse/toxic effect of other anticholinergic agents	Monitor therapy/avoid combination depending on individual agent
Antipsychotic agents	May enhance the serotonergic effect resulting in serotonin syndrome	Monitor therapy
Antidepressants -MAOI (e.g., phenelzine)	Could induce severe cardiovascular reactions, such as hypertensive crisis with concurrent use	Caution should be used when concomitantly administering MAOIs and imipramine.
CYP2D6 inhibitors (e.g., fluoxetine, paroxetine)	Higher systemic exposure of TCA may occur	Monitor therapy: dosage adjustments may be necessary
Methylphenidates	May enhance the serotonergic effect resulting in serotonin syndrome	Monitor therapy
Serotonergic agents (e.g., paroxetine, venlafaxine)	May increase adverse effects of SSRI and may increase risk of serotonin syndrome	Monitor for signs and symptoms of serotonin syndrome *Dosage may need to be reduced
QTc prolonging agents (e.g., citalopram, quetiapine)	May increase QTc interval	Consider alternatives or closely monitor for evidence of QTc prolongation

Drug disclaimer:

The authors do not endorse or recommend the use of any particular drug mentioned in this publication. Before prescribing a new drug to a patient, practitioners are advised to check the product information accompanying each drug to ensure it is appropriate for a specific patient and to identify appropriate dosage, contraindications, side effects and drug-to-drug interactions.

References for Appendix 2.9: ADHD Pharmacotherapy – Drug Interactions

Concordia Pharmaceuticals, Inc. (2020). *Kapvay: Highlights of Prescribing.* https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022331s021lbl.pdf

Desipramine Oral (Drug Facts and Comparisons). (2022). In *Facts and Comparisons [online]*. Available from Wolters Kluwer Health, Inc. Retrieved December 23, 2021, from Facts and Comparisons

Eli Lilly and Company. (2022). *Strattera: Highlights of Prescribing Information*. https://pi.lilly.com/us/strattera-pi.pdf

Janssen Pharmaceuticals, I. (2022, April). *Concerta: Highlights of Prescribing Information*. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/CONCERTA-pi.pdf

Modafinil Oral (Drug Facts And Comparisons). (2023). In *Facts and Comparisons [online]*. Available from Wolters Kluwer Health, Inc. Retrieved November 30, 2021

Supernus Pharmaceuticals, Inc. (2021). *Qelbree: Highlights of Prescribing Information*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211964s003lbl.pdf

Takeda Pharmaceuticals America, Inc. (2021). *Intuniv: Highlights of Prescribing Information*.