

**Pharmacology Update:
Interactions of Oral
Contraceptives and Seizure
Medications to Drugs and
Herbal Remedies**

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Faculty

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Classifications of Interactions

- **Level 1: Severe - Avoid**
 - Using these medications together is contraindicated
 - Rare exceptions may exist
- **Level 2: Major**
 - Using these medications together may be contraindicated for a select group of patients

Classifications of Interactions

- Consider alteration in therapy and monitor patients
- **Level 3: Moderate**
 - Using these medications together may result in unintended clinical effects
 - Alterations in therapy may be required

Classifications of Interactions

- Monitor patients
- **Level 4: Minor**
 - Using these medications together usually does not result in clinically significant interactions

**Drug-Drug and Drug-Herbal
Interactions of
Oral Contraceptives**

Level 1 Interactions with OC

- **Amprenavir (Agenerase):**
HIV Protease Inhibitor
- **Fosamprenavir (Lexiva):**
HIV Protease Inhibitor
- **Aromatase Inhibitors:**
Hormonally-responsive cancers
- **Bosentan (Tracleer):**
Pulmonary arterial hypertension
- **Metopirone (Metyrapone):**
HPA Diagnosis

Protease Inhibitors

- **OC's decrease the serum concentrations of Amprenavir and Fosamprenavir**
- **Increase metabolism of OC's:**
Ritonavir, Lopinavir, Ritonavir, Nelfinavir, Saquinavir, Tipramavir
- **Decrease metabolism of OC's:**
Atazanavir and Indinavir

Protease Inhibitors

- **Report breakthrough bleeding and other adverse effects to physician and use barrier method of contraception**

Aromatase Inhibitors

- **Estrogens could interfere with action of aromatase inhibitors , decreasing circulating estrogen levels and inhibiting growth of hormonally-responsive cancers**
- **Estrogen therapy is not recommended due to opposing pharmacologic actions**

Aromatase Inhibitors

- **Includes:**
 - **Aminoglutethimide (cytadren)**
 - **Anastrozole (Arimidex)**
 - **Exemestane (Aromasin)**
 - **Letrozole (Femara)**
 - **Testolactone (Teslac)**

Bosentan (Tracleer)

- **Contraindicated**
- **Indicated for treatment of pulmonary arterial hypertension**
- **Significant inducer of CYP3A hepatic enzymes**
- **Decrease in norethindrone serum concentrations as high as 56% and ethinyl estradiol as high as 66%**
- **Teratogenic and contraindicated during pregnancy**

Metopirone (Metyrapone)

- Estrogen therapy can yield a sub - therapeutic response
- Indicated for Hypothalamic - pituitary - adrenal (HPA) suppression diagnosis
- Available only for compassionate use
- Discontinue estrogens prior to and during metyrapone administration

Question #1

- True or False
 - A patient taking an OC and a protease inhibitor should always use a barrier method of contraception, regardless of the interaction level

Answer #1

- True
 - The most common indication for Protease Inhibitors is HIV

Level 2 Interactions with OC

- HIV Protease Inhibitors:
 - Atazanavir
 - Indinavir
 - Lopinavir, Ritonavir
 - Nelfinavir
 - Ritonavir
 - Saquinavir
 - Tipranavir

Level 2 Interactions with OC

- Anti - seizure medications:
 - Carbamazepine
 - Felbamate
 - Fosphenytoin
 - Oxcarbazepine
 - Phenytoin
 - Topiramate

Level 2 Interactions with OC

- Tuberculosis
 - Rifabutin
 - Rifampin
 - Refapentine
- Antifungal:
 - Fluconazole
 - Griseofulvin

Level 2 Interactions with OC

- **Breast Cancer Prophylaxis**
 - Raloxifene
 - Tamoxifen
- **Other**
 - Bexarotene: Lymphoma
 - Charcoal: overdose, poisoning
 - Modafinil: Narcolepsy

Level 2 Interactions with OC

- Tizanidine: Muscle antispasmodic
- Warfarin: Blood thinner
- St. John's Wort
- Tobacco

Test Question #2

- **True or False:**
 - A medication listed as a level 2 interaction should never be given to a patient receiving oral contraceptives

Answer #2

- **False**
 - Should consider alternative therapies if possible
 - If not, closely monitor patients

CYP3A4 Inducers

- **Estrogens metabolized by CYP3A4, therefore susceptible to interactions with hepatic enzyme inducing drugs**
 - Anticonvulsants stimulate CYP3A4 thereby causing OC failure
 - Low - dose estrogen regimens at greater risk
(ethinyl estradiol < 50 mcg / day)

CYP3A4 Inducers

- Patients at higher risk of folate deficiency
- Greater risk of neural tube defects when failure occurs

Anti - Seizure Medications CYP3A4 Inducers

- May decrease level of contraceptive and efficacy:
 - Carbamazepine (Tegretol)
 - Oxcarbazepine (Trileptal)
 - Felbamate (Felbatol)
 - Topiramate (Topamax): May decrease levels of contraceptive and efficacy if dose is over 200 mg / day

Anti - Seizure Medications CYP3A4 Inducers

- No adverse effect if dose is 50 - 200 mg / day
 - Phenytoin (Dilantin)
 - Fosphenytoin (Cerebyx)

Tuberculosis treatments CYP3A4 Inducers

- May decrease level of contraceptive and efficacy:
 - Rifampin (Rifadin):
 - Increases elimination of estrogens and progestins
 - Increases estrogenic protein binding activity

Tuberculosis treatments CYP3A4 Inducers

- 70% of women taking estrogen-containing OC and rifampin experience menstrual abnormalities and 6% become pregnant
 - Rifabutin (Mycobutin)
 - Rifapentine (Priftin)

Anti - Fungal Medications

- Fluconazole (Diflucan):
 - Clinical significance is unknown
 - Variations in increase and decrease of hormonal concentrations
- Griseofulvin (Fulvicin):
 - CYP3A4 Inducer
 - May decrease levels of contraceptive and efficacy

Breast Cancer Prophylaxis Medications

- Tamoxifen (Nolvadex):
 - Contraindicated in most, but not all, patients
 - Oral contraceptives may aggravate conditions being treated by tamoxifen

Breast Cancer Prophylaxis Medications

- **Raloxifene (Evista):**
 - Blocks estrogen receptors
 - Illogical to give with estrogen

Warfarin (Coumadin)

- Generally avoid OC's in patients taking Warfarin due to Thromboembolism risks
- Weigh risks versus benefits
- OC's can alter INR

Warfarin (Coumadin)

- OC's products containing $> / = 50$ mcg Ethinyl Estradiol are associated with the greatest risk of Thromboembolic complications
- Addition of progestins may increase Thromboembolic risks

Tizanidine (Zanaflex)

- May increase tizanidine levels
- Tizanidine clearance is decreased 50%
- Risk of hypotension, bradycardia, psychomotor impairment and other adverse effects

Other

- **Modafinil (Provigil):**
 - Indicated for narcolepsy
 - CYP3A4 Inducer - May decrease levels of contraceptive and efficacy
 - May cause failure of OC's and hormonal containing implants or devices

Other

- **Bexarotene (Targretin):**
 - CYP3A4 Inducer
 - Indicated for T- cell lymphoma
 - May decrease levels of contraceptive and efficacy

Other

- **Tobacco:**
 - Increase risk of thromboembolic disease
 - Increased risk for patients 35 years or older or those who smoke 15 or more cigarettes per day

Other

- **Charcoal:**
 - Possible absorption issue with oral contraceptives
 - Should take 3 hours after but at least 12 hours before oral contraceptive

Other

- **St. John's Wort:**
 - CYP3A4 inducer
 - Loss of contraceptive efficacy

Level 3 Interactions with OC

- Ambrisentan
- Amoxicillin
- Ampicillin
- Aprepitant: Fosaprepitant
- Chloramphenicol
- Clarithromycin
- Clindamycin

Level 3 Interactions with OC

- Cyclosporine
- Dantrolene
- Dirithromycin
- Doxercalciferol
- Echinacea
- Erythromycin
- Lamotrigine

Level 3 Interactions with OC

- Lincomycin
- Mycophenolate
- Neomycin
- Nitrofurantoin
- Penicillin V
- Selegiline
- Somatropin, rh-GH

Level 3 Interactions with OC

- Soy Isoflavones
- Sulfonamides
- Tetracycline
- Theophylline, Aminophylline

Anti - Infectives

- Disruption of normal GI flora may decrease effectiveness of estrogen-containing OC's
- Includes: amoxicillin, ampicillin, chloramphenicol, clindamycin, lincomycin, neomycin, nitrofurantoin, penicillin V, sulfonamides, tetracyclines

Anti - Infectives

- Macrolide anti - infectives may increase estrogen metabolism
 - Dirithromycin, erythromycin, clarithromycin
- Incidence of the interaction between anti - infectives and OC's is unpredictable and those most at risk for OC failure cannot be identified

Question #3

- True or False
 - Patients should always be counseled to use an alternative means of contraception while taking antibiotics

Answer #3

- True
 - At least for me
 - It is a liability issue

Lamotrigine (Lamictal)

- Indicated for seizures and bipolar disorder
- May decrease hormone level resulting in contraceptive failure
- Estradiol and mestranol may decrease lamotrigine levels resulting in a need for increased dosing

Lamotrigine (Lamictal)

- Side effects
 - Ex: dizziness, ataxia, and diplopia may occur during placebo / off week
- Progestin - only products are not known to change lamotrigine levels

Theophylline (Theo-24)

- Indicated for asthma and bronchospasm
- May increase theophylline levels
- Risk of theophylline toxicity
- CYP3A4 and CYP1A2 substrate
- Inhibits hepatic metabolism

Cyclosporine

- Indicated for organ transplant rejection prophylaxis, rheumatoid arthritis and psoriasis
- CYP3A4 substrate with moderate CYP3A4 inhibitor characteristics
- May increase cyclosporine levels with risk of toxicity
- Increased risk of hyperkalemia

Selegiline (Eldepryl)

- Indicated for Parkinson disease
- May increase selegiline total concentrations as much as 20 - fold due most likely to decreased metabolism of selegiline
- May be necessary to reduce dose of selegiline

Ambrisentan (Letairis)

- Indicated for pulmonary arterial hypertension
- Restricted distribution in the United States
- CYP3A4 substrate

Aprepitant (Emend)

- Aprepitant:
 - Indicated for prevention of chemo-related nausea and vomiting
 - Fosaprepitant (Emend Injection)
 - Minor CYP3A4 inducer and moderate CYP3A4 inhibitor

Other

- **Mycophenolate Mofetil (CellCept):** Indicated for prevention of organ transplant rejection
 - One study showed decreased level of levonorgestrel
- **Dantrolene:** Indicated for spasticity
 - Increased risk of hepatotoxicity
- **Doxercalciferol:** Indicated for hyperparathyroidism

Other

- **Somatropin, rh - GH (growth hormone):**
 - Indicated for growth hormone deficiency
 - Induced hepatic metabolism may decrease hormonal contraceptive levels resulting in failure
 - May accelerate epiphysial maturation

Herbs and OTC's

- **Echinacea:**
 - Inhibits intestinal CYP3A4 but induces hepatic CYP3A4
 - Clinical significance unknown
- **Soy Isoflavones:**
 - Similar chemical structure to synthetic and natural estrogens
 - Clinical significance unknown
 - Use with caution

Level 4 Interactions with OC

- Antidiabetic Agents
- Antihypertensive Agents
- Ascorbic Acid, Vitamin C
- Atorvastatin
- Benzodiazepines
- Caffeine
- Calcium salts

Level 4 Interactions with OC

- Cimetidine
- Clofibrate
- Delavirdine
- Food
- Grapefruit juice
- Green tea
- Guarana
- Hydrocortisone

Level 4 Interactions with OC

- Mineral Oil
- Nefazodone
- Neuromuscular Blockers
- Prednisolone
- Rosuvastatin
- Thyroid hormones
- Tricyclic antidepressants
- Ursodeoxycholic Acid, Ursodiol

Anti - Diabetic Medications

- OC's decrease hypoglycemic effect by impairing glucose tolerance
- More common in patients receiving > 50 mcg ethinyl estradiol per day
- Closely monitor patients when OC therapy is initiated and when discontinued

Anti - Diabetic Medications

- Pioglitazone (Actos) may decrease OC effectiveness by increasing metabolism of estrogens
- Exenatide (Byetta) may reduce rate and/or extent of absorption of OC's
 - Take OC at least one hour prior to exenatide injection

Anti - Hypertensives

- Estrogen can induce fluid retention and may increase blood pressure in some patients
- Monitor patients to confirm target blood pressure is achieved

Statins

- Atorvastatin (Lipitor) and Rosuvastatin (Crestor)
- Indicated for hypercholesterolemia
- May increase contraceptive hormonal levels, mostly likely, due to competition for CYP3A4 substrate
- Clinical significance unknown

Benzodiazepines

- Ethinyl estradiol may increase levels of some benzodiazepines, including:
 - Chlordiazepoxide (Librium)
 - Clorazepate (Tranxene)
 - Clonazepam (Klonopin)
 - Diazepam (Valium)
 - Triazolam (Halcion), and others

Benzodiazepines

- Conversely, ethinyl estradiol may enhance metabolism of Lorazepam (Ativan), Oxazepam (Serax), and Temazepam (Restoril)
- Observe patients for evidence of increased or decreased response

Corticosteroids

- May potentiate the anti - inflammatory effects of hydrocortisone
- May delay clearance of prednisolone
- Monitor patients receiving hydrocortisone and prednisolone
- No evidence of interaction with dexamethasone, methylprednisolone and prednisone

Thyroid Hormones

- Estrogens cause abnormal thyroid function test results
- Estrogens increase serum thyroxine binding globulin
- Patients may have a decreased clinical response due to decreased free thyroxine levels
- Thyroid hormone dose adjustments may be necessary

Tricyclic Antidepressants

- Ethinyl estradiol may decrease metabolism of tricyclic antidepressants, thereby, increasing serum concentrations
- Side effects of imipramine may be increased
- More significant interaction probable with ethinyl estradiol doses of 50 mcg or greater per day

Other

- Neuromuscular Blockers: Prolonged neuromuscular blockade may occur
- Cimetidine (Tagamet): Reduces hepatic clearance of estradiol - Monitor for estrogen related side effects
- Ursodiol (Actigall): OC may increase hepatic cholesterol secretion and increase cholesterol gallstone formation, thereby, counteracting the effectiveness of ursodiol

Other

- Nefazodone (Serzone):
 - Indicated for depression
 - Inhibits CYP3A4 isoenzyme
 - May increase estrogen - related side effects
 - Clinical significance unknown

Other

- Delavirdine (Rescriptor):
 - Indicated for HIV infection
 - Serum concentration of ethinyl estradiol may be increased
 - Clinical significance is unknown

Question #4

- True or False
 - Patients should always be asked what prescription medications, vitamins, herbals and over - the - counter medications they are taking

Answer #4

- True
 - Most people do not consider vitamins and “natural” products as part of their medication regimen but these can affect how their medications work

Other CYP3A4 Inhibitors

- Grapefruit juice:
 - Decreases estradiol metabolism
 - Estrogen levels may increase up to 30%
 - Clinical significance is unknown

Other CYP3A4 Inhibitors

- Vitamin C (ascorbic acid):
 - May increase ethinyl estradiol bioavailability up to 50%
 - May see increase in estrogen related side effects

Other

- Calcium salts:
 - Estrogen increase calcium absorption which can be beneficial
- Caffeine:
 - Includes coffee, green tea, other teas, colas, guarana, and chocolate
 - Serum concentrations of caffeine may be increased by ethinyl estradiol
 - Monitor for caffeine - related side effects

Other

- Mineral Oil
 - Simultaneous administration may decrease absorption of estrogens
 - Separate doses by giving estrogens 1 hour before or 2 hours after mineral oil

Drug-Drug and Drug-Herbal Interactions of Seizure Medications

Gabapentin (Neurontin)

- Indicated for treatment of partial seizures
- Has high lipid solubility
- Not metabolized by the liver
- Has no protein binding
- No enzyme induction - related drug interactions

Gabapentin (Neurontin)

- Does not alter serum concentration of other anticonvulsants and other anticonvulsants do not alter serum concentration of Gabapentin
- No level 1 interactions

Gabapentin (Neurontin)

- Level 2 interactions:
 - Antacids (aluminum hydroxide and magnesium hydroxide):
 - When taken together reduces bioavailability by 20%
 - Take gabapentin at least 2 hours after antacid

Gabapentin (Neurontin)

- Ethanol:
 - With gabapentin enacarbil (Horizant Extended Release), Gabapentin is released faster
 - All gabapentin there is a increased risk of drowsiness and dizziness
 - Patients should avoid alcohol consumption

Gabapentin (Neurontin)

- Sevelamer (Renagel):
 - Potential for reduces drug absorption
 - Separate dose of Gabapentin at least 1 hour before or 3 hours after Sevelamer

Gabapentin (Neurontin)

– Level 3 interactions:

- **Morphine:** May increase Gabapentin serum concentration
 - Monitor patient for signs of CNS depression and adjust dose of each as necessary
- **Naproxen:** Increases amount of Gabapentin absorbed by 12 - 15%
 - Clinical significance unknown

Gabapentin (Neurontin)

- **Hydrocodone:** May decrease concentration of Hydrocodone and increase concentration of Gabapentin
 - Is Gabapentin dose dependent, with lower doses having less effect
 - Monitor patients and adjust doses of each

Gabapentin (Neurontin)

- **Colesevelam:** For safety, give gabapentin at least 4 hours before colesevelam

**Gabapentin (Neurontin)
Level 3 Interactions**

- **Medications that may enhance CNS depression (e.g. drowsiness and dizziness):**
 - Anxiolytics, Sedatives and Hypnotics
 - Antipsychotics:

**Gabapentin (Neurontin)
Level 3 Interactions**

- Olanzapine, Clozapine, Haloperidol, Molindone, Pimozide, Quetiapine, Risperidone
- **Antiparkinson's Disease:**
 - Entacapone, Pramipexole, Ropinirole, Tolcapone

**Gabapentin (Neurontin)
Level 3 Interactions**

- Carisoprodol (Soma), Methocarbamol (Robaxin)
- **Phenothiazines and Tricyclic anti - depressants:**
 - Amoxapine, Maprotiline, Mirtazapine, Nefazodone, Trazodone

Gabapentin (Neurontin) Level 3 Interactions

- Tramadol (Ultram)
- Sedating H1 blockers
- Opiate antitussive or expectorant combinations; opioid agonist and combinations

Gabapentin (Neurontin)

- Level 4 interactions:
 - Cimetidine (Tagamet)
 - Gabapentin clearance reduced but not clinically significant
 - Propranolol (Inderal)
 - Higher doses of propranolol may induce dystonia
 - Monitor patient and lower propranolol dose if necessary

Lamotrigine (Lamictal)

- Indicated for partial seizures and tonic - clonic seizures
- Off-label use in absence seizures
- Metabolized via glucuronidation
- Caution when adding and discontinuing medications once seizure control has been achieved
- No level 1 interactions

Lamotrigine (Lamictal)

- Level 2 interactions:
 - Acetaminophen (Tylenol):
 - Doses of 900 mg tid or more accelerates lamotrigine clearance by 15%
 - Atazanavir (Reyataz):
 - Increases metabolism of lamotrigine

Lamotrigine (Lamictal)

- Adjust dose with addition or discontinuation of Atazanavir
- Cabamazepine:
 - May stimulate metabolism of Lamotrigine, decreasing level of Lamotrigine as much as 40%

Lamotrigine (Lamictal)

- Clozapine:
 - Can increase Clozapine concentration by 3 fold
 - Lowering of seizure threshold dose dependent
- Desmopressin (DDAVP):
 - Increase risk of water intoxication with Hyponatremia

Lamotrigine (Lamictal)

- **Level 2 interactions:**
 - **Methsuximide (Celontin):**
 - **Reduces serum concentrations of Lamotrigine by up to 70%**
 - **Caution when discontinuing Methsuximide**

Lamotrigine (Lamictal)

- **Rifampin:**
 - **Increased Lamotrigine clearance resulting in decrease anticonvulant efficacy**
- **Sevelamer (Renagel):**
 - **Potential for reduces absorption**
 - **Separate Lamotrigine doses by at least one hour before or three hours after Sevelamer**

Lamotrigine (Lamictal)

- **Level 2 interactions:**
 - **Oral and non - oral combination contraceptives:**
 - **May require close clinical monitoring**
 - **Estrogen may increase Lamotrigine clearance**

Lamotrigine (Lamictal)

- **Increased side effects during placebo / off week are possible**
- **Clinical significance of clearance changes is unknown**
- **Changes limited to the pill free week are not recommended**
- **May consider progestin - only contraceptives or extended cycle combined hormonal contraceptive**

Lamotrigine (Lamictal)

- **Level 3 Interactions:**
 - **Phenytoin and Fosphenytoin:**
 - **Induces hepatic enzymes**
 - **When added to regiment, can reduce steady state concentration of Lamatrigine up to 50%**

Lamotrigine (Lamictal)

- **May require lamotrigine dose adjustment**
- **Barbiturates (phenobarbital, mephobarbital, primidone):**
 - **Induces hepatic enzymes**
 - **When added to regiment, can reduce steady state concentration of lamatrigine up to 40%**

Lamotrigine (Lamictal)

- May require lamotrigine dose adjustment
- Oxcarbazepine:
 - Increases clearance of lamotrigine up to 29%
 - Monitor for headache, dizziness, nausea and somnolence

Lamotrigine (Lamictal)

- Level 3 Interactions:
 - Valproic acid:
 - More than doubles the elimination half - life and steady - state concentration of Lamatrigine
 - Adjust dose if Valproic acid is discontinued

Lamotrigine (Lamictal)

- Topiramate:
 - May decrease Topiramate serum concentration
 - Clinical significance is unknown
- Bupropion:
 - A drug - disease interaction
 - Should not be used in patients with a pre - existing seizure disorder

Lamotrigine (Lamictal)

- Level 3 Interactions:
 - Ritonavir:
 - Increases hepatic metabolism resulting in decreased Lamatrigine concentrations
 - Dose increase of Lamotrigine may be necessary

Lamotrigine (Lamictal)

- Dihydrofolate reductase inhibitors (fluorouracil, 5-FU, methotrexate, pyrimethamine, trimethoprim):
 - All inhibit dihydrofolate reductase
 - Use with caution

Lamotrigine (Lamictal)

- Colesevelam:
 - Change in concentration can be clinically significant
 - Give Lamotrigine at least 4 hours before Colesevelam

Topiramate (Topamax)

- Indicated for partial seizures, tonic - clonic seizures and Lennox - Gastaut seizures
- Metabolized minimally by the liver
- Is a minor CYP3A4 inducer and a weak CYP2C19 inhibitor
- Avoid alcohol consumption

Topiramate (Topamax)

- Alcohol withdrawal or excessive use may lower seizure threshold
- Avoid doses over 200 mg / day if using hormonal contraceptives

Topiramate (Topamax)

- Level 1 Interaction:
 - Probenecid:
 - Significant increase in renal clearance of Topiramate
 - May lower Topiramate levels
 - Shown in animals only; no human trials

Topiramate (Topamax)

- Level 2 Interactions:
 - Metformin:
 - Topiramate can cause metabolic acidosis and may increase serum concentration of metformin
 - Best to avoid taking both but if necessary, closely monitor patients

Topiramate (Topamax)

- Oral and non - oral contraceptives:
 - Increase clearance of Ethinyl Estradiol
 - More risk at doses over 200 mg / day

Topiramate (Topamax)

- Level 2 Interactions:
 - Ethanol:
 - Alters pattern of Topiramate release from extended - release capsules
 - Do not consume alcohol within 6 hours (before and after) taking Topiramate

Topiramate (Topamax)

- Dolutegravir:
 - Decrease Dolutegravir levels
- Tramadol:
 - May cause CNS depression and cognitive and / or neuropsychiatric reactions
 - Decrease seizure threshold

Topiramate (Topamax)

- Level 2 Interactions:
 - Hydrochlorothiazide (HCTZ):
 - May potentiate potassium - wasting
 - Clinical significance is unknown
 - May require reduction in Topiramate dose when HCTZ is added and dose increase when HCTZ is discontinued

Topiramate (Topamax)

- Carbonic Anhydrase inhibitors:
 - Increased risk of renal stone formation
 - Increased risk for heat - related disorders, e.g. heat stroke
 - Increased risk of bleeding
 - Includes Acetazolamide, Methazolamide, Dichlorphenamide

Topiramate (Topamax)

- Level 2 Interactions:
 - Telithromycin:
 - May cause subtherapeutic levels of Telithromycin
 - May result in increase serum concentration of Topiramate with increase in adverse effects

Topiramate (Topamax)

- Sevelamer:
 - Potential for reduced drug absorption with potential for loss of efficacy
 - Separate dose of Topiramate at least 1 hour before or 3 hours after Sevelamer

Topiramate (Topamax)

- Linagliptin:
 - May decrease Linagliptin to subtherapeutic levels
 - Alternative to Linagliptin is recommended

Topiramate (Topamax)

- **Level 2 Interactions:**
 - **Valproic acid:**
 - **May result in decrease in Valproic acid and Topiramate serum concentrations**
 - **Associated with hyperammonemia**
 - **Associated with hypothermia**
 - **May increase risk of bleeding**

Topiramate (Topamax) Level 3 Interactions

- **Amitriptyline**
- **Anticoagulants**
- **Antimuscarinics**
- **Aspirin**
- **Barbiturates**
- **Benzodiazepine**
- **Carbamazepine**

Topiramate (Topamax) Level 3 Interactions

- **Colesevelam**
- **Dasabuvir**
- **Ombitasvir**
- **Paritaprevir**
- **Ritonavir**
- **Digoxin**
- **Estrogens**

Topiramate (Topamax) Level 3 Interactions

- **Ethotoin**
- **Ezogabibe**
- **Felbamate**
- **Fosphenytoin**
- **Lamotrigine**
- **Levetiracetam**
- **Lithium**

Topiramate (Topamax) Level 3 Interactions

- **Loop Diuretics**
- **Metformin**
- **NSAIDS**
- **Opiate Agonists**
- **Oxcarbazepine**
- **Phenytoin**
- **Pioglitazone**

Topiramate (Topamax) Level 3 Interactions

- **Platelet Inhibitors**
- **Pregabalin**
- **Risperidone**
- **Rufinamide**
- **Salicylates**
- **SSRIs**
- **Thiazide diuretics**

Topiramate (Topamax) Level 3 Interactions

- Tiagabine
- Tretinoin

Topiramate (Topamax)

- Level 4 Interactions:
 - Voriconazole (Vfend)
 - An antifungal
 - May result in an increase in Voriconazole concentrations
 - Clinical significance is unknown

Pregabalin (Lyrica)

- Indicated for partial seizures
- No drug interactions of clinical significance due to inhibition of the CYP450 enzymes have been reported
- No level 1 or level 4 interactions
- Raw ginkgo seeds: May decrease anticonvulsant efficacy

Pregabalin (Lyrica)

- Level 2 Interactions:
 - Angiotensin - converting enzyme inhibitors (ACE Inhibitors):
 - May cause life - threatening angioedema with respiratory compromise

Pregabalin (Lyrica)

- Examples of ACE inhibitors:
 - Accupril
 - Benazepril
 - Enalapril
 - Lisinopril

Pregabalin (Lyrica)

- Level 3 Interactions:
 - Thiazolidinediones (pioglitazone, rosiglitazone, troglitazone):
 - Higher rates of peripheral edema and weight gain
 - May exacerbate or lead to heart failure

Pregabalin (Lyrica) Level 3 Interactions:

- **May potentiate CNS effects such as sedation and cognitive and gross motor function:**
 - Opioids
 - Ethanol
 - Phenothiazines
 - Sedating H1- blockers

Pregabalin (Lyrica) Level 3 Interactions:

- Anxiolytics, Sedatives and Hypnotics
- Barbiturates
- Butorphanol
- General Anesthetics
- Buprenorphine
- THC, Dronabinol

Pregabalin (Lyrica) Level 3 Interactions:

- Nabilone
- Nalbuphine
- Pentazocine
- Tolcapone
- Tricyclic Antidepressants
- Carbinoxamine
- Carbidopa, Levodopa, Entacapone

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- Indicated for absence, myoclonic, partial and tonic - clonic seizures
- No Level 1 interactions
- Metabolized by hepatic CYP450 microsomal enzymes, CYP2C19 and CYP2C9, and UGT
 - Therefore, interactions can be significant

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- Ginkgo: May decrease anticonvulsant efficacy
- Omacetaxine mepesuccinate and tositumomab: May increase risk of bleeding

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- Carbinoxaine and Doxylamine: Increased risk of CNS depression, psychomotor impairment and adverse effects

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- **Level 2 Interactions:**
 - **Carbapenems:**
 - Includes doripenem, ertapenem, imipenem, and meropenem
 - May decrease valproic acid to subtherapeutic levels

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- **Carbamazepine:**
 - May increase clearance and decrease serum concentration of valproic acid
 - May decrease metabolism of carbamazepine's active metabolite causing vomiting and tiredness, especially in children

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- **Level 2 Interactions:**
 - **Rifampin:**
 - May increase clearance of valproic acid and rifampin
 - Adjust valproic dose as necessary

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- **Isoniazide (INH):**
 - May inhibit valproic acid hepatic metabolism
 - Increases valproic acid concentrations and hepatotoxicity

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- **Topiramate:**
 - May cause hyperammonemia.
 - May cause hypothermia
- **Interactions that may cause additive CNS depression and can lower seizure threshold:**

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- Haloperidol
- Loxapine
- Maprotiline
- Monoamine oxidase inhibitors (MAOIs)

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- **Level 2 Interactions:**
 - Dasabuvir, Ombitasvir,
Paritaprevir, Ritonavir, Tipranavir,
Lopinavir:
 - May decrease valproic acid
concentration and efficacy

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- Sodium oxybate:
 - May increase systemic exposure
of sodium oxybate
 - May impair attention and
memory tests

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- Reduce sodium oxybate dose by
at least 20% when valproic acid
treatment is initiated
- Closely monitor patient and
make further dose adjustments if
necessary

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- Cholestyramine:
 - May decrease bioavailability of
valproic acid
 - Separate valproic acid dose at
least 2 hours before or 6 hours
after cholestyramine

Divalproex Sodium (Depakote) and Valproic Acid (Depakene)

- Sevelamer:
 - Potential for reduced absorption
 - Separate valproic acid dose by at
least 1 hour before or 3 hours
after sevelamer

Divalproex Sodium (Depakote) and Valproic Acid (Depakene) Level 3 Interactions

- Barbiturates
- Bupropion
- Clonazepam
- Clozapine
- Colesevelam
- Ethanol

**Divalproex Sodium
(Depakote) and Valproic
Acid (Depakene)
Level 3 Interactions**

- Ethosuximide
- Ethotoin
- Felbamate
- Fosphenytoin
- Lamotrigine
- Mefloquine

**Divalproex Sodium
(Depakote) and Valproic
Acid (Depakene)
Level 3 Interactions**

- Methsuximide
- NSAIDs
- Paliperidone
- Phenothiazines
- Phenytoin
- Salicylates

**Divalproex Sodium
(Depakote) and Valproic
Acid (Depakene)
Level 3 Interactions**

- Temozolomide
- Tricyclic antidepressants
- Voriconazole
- Warfarin
- Zolpidem

**Divalproex Sodium
(Depakote) and Valproic
Acid (Depakene)
Level 4 Interactions**

- Antacids
- Asenapine
- Diazepam
- Lorazepam
- Oxcarbazepine

**Divalproex Sodium
(Depakote) and Valproic
Acid (Depakene)
Level 4 Interactions**

- Risperidone
- Tolbutamide
- Zidovudine

Levetiracetam (Keppra)

- Adjunctive therapy in treatment of partial, myoclonic and generalized tonic - clonic seizures
- Minimal interactions with other antiepileptic medications
- No drug interactions with commonly prescribed medications
- Not an inhibitor nor has high affinity for hepatic P450 enzymes
- No Level 1 interactions

Levetiracetam (Keppra)

- **Level 2 Interactions:**
 - **Sevelamer:**
 - **Potential for reduced absorption**
 - **Separate levetiracetam dose by at least 1 hour before or 3 hours after sevelamer**

Levetiracetam (Keppra)

- **Level 4 Interactions:**
 - **Probencid:**
 - **The major metabolite of levetiracetam was approximately doubled**
 - **Renal clearance of metabolite may decrease up to 60%**
 - **Clinical significance unknown**

Levetiracetam (Keppra)

- **Level 3 Interactions:**
 - **Ethanol:**
 - **May lead to loss of seizure control**
 - **May increase drowsiness and dizziness**

Levetiracetam (Keppra)

- **Colesevelam:**
 - **May alter levetiracetam serum concentrations**
 - **Give levetiracetam dose at least 4 hours before colesevelam**

Levetiracetam (Keppra)

- **Carbamazepine:**
 - **Pharmacodynamic interaction**
 - **Carbamazepine toxicity symptoms of ataxia, nystagmus and unsteady gait reported with levetiracetam doses equal to or greater than 500 mg twice a day**

Phenytoin (Dilantin)

- **Indicated for tonic – clonic and partial seizures with complex symptomatology**
- **Mechanisms of drug interactions may be complex**
- **Induces of hepatic P450 enzymes (CYP3A4, CYP2C9, CYP2C19)**
- **Interactions also influenced by patient's age, presence of liver disease and cigarette smoking history**

Phenytoin (Dilantin) Level 1 Interactions

- Artemether, Lumefantrine
- Dasabuvir, Ombitasvir, Paritaprevir, Ritonavir
- Delavirdine
- Etravirine
- Ibrutinib
- Nifedipine

Phenytoin (Dilantin) Level 1 Interactions

- Olaparib
- Ranolazine
- Telaprevir

Phenytoin (Dilantin)

- Over 70 drugs listed as having the potential for a level 2 interaction
- Includes:
 - Oral and non - oral contraceptives
 - Rifampin
 - Isoniazid
 - Protease inhibitors

Phenytoin (Dilantin)

- Ethanol
- Fluconazole
- St. John's Wort
- Vinca alkaloids

Phenytoin (Dilantin)

- Over 90 drugs listed as having the potential for a level 3 interaction
- Includes:
 - Antacids
 - PPIs
 - Miconazole
 - Ciprofloxacin

Phenytoin (Dilantin)

- Estrogens
- Opiates
- Sulfonamides
- Topiramate
- Trimethoprim
- Valproic acid
- Vitamin D

Phenytoin (Dilantin)

- Over 30 drugs listed as having the potential for a level 4 interaction
- Includes:
 - Acetaminophen
 - Acyclovir
 - Antidiabetic medications
 - Caffeine

Phenytoin (Dilantin)

- Folic acid
- Green tea
- Guarana
- Flu vaccine
- Aspirin

Contact Information

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