PHARMACY PHACTS

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Drug-Drug Interactions: Lamotrigine and Valproic Acid

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Pharmacists routinely focus on drug interactions whenever new medications are added to a patient's regimen. Some interactions deserve more attention than others depending on the potential risks. A high risk interaction takes place between lamotrigine *(Lamictal)* and valproic acid products *(Depakene, Depakote).* These medications all have FDA indications for bipolar I disorder and seizure control.[1]

Lamotrigine is known to be metabolized primarily by phase II conjugation in the liver. Thus, medications known to induce or inhibit glucuronidation will affect lamotrigine metabolism. Antiepileptic drugs including carbamazepine, phenobarbital and phenytoin, as well as estrogen containing compounds, and rifampin, all induce glucuronidation. Subsequently lamotrigine metabolism and clearance increase, lowering the plasma levels when prescribed in conjunction. Valproic acid decreases clearance of lamotrigine and can nearly double plasma concentrations requiring that-the lamotrigine dosage be decreased by 50% when these two drugs are co-administered.[2]

It is important to note that several medications that are concomitantly prescribed with lamotrigine do not interact to any appreciable extent. These include SSRIs, lithium, olanzapine, trazodone, and buspirone.

Escalation Regimen for LAMICTAL in Adults with Bipolar Disorder

	In Patients taking Valproate	**In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone or Valproate**	**In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital or Primidone and NOT taking Valproate**
Weeks 1 and 2	25mg every other day	25mg daily	50mg daily
Weeks 3 and 4	25mg daily	50mg daily	100mg daily, in divided doses
Week 5	50mg daily	100 mg daily	200mg daily, in divided doses
Week 6	100mg daily	200mg daily	300mg daily, in divided doses
Week 7	100mg daily	200 mg daily	Up to 400mg daily, in divided doses

References are available on request.

Drug-Drug Interactions: Antidepressants (SSRI)

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Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants that have the potential to cause serious clinical consequences when used with other interacting agents. In general, drug interactions can be classified as either pharmacodynamic or pharmacokinetic.

Pharmacodynamic drug interactions involve changes in the nature, magnitude, or duration of action and adverse effects when two drugs are used together. An example of a pharmacodynamic drug interaction with SSRIs is their use with other serotonin- enhancing agents which increases the potential for serotonin syndrome. Serotonin syndrome symptoms occur due to increased serotonin levels in the body which can be fatal if not treated. Symptoms include diarrhea, muscle rigidity, agitation, fever, heavy sweating, and confusion. Examples of serotonin-enhancing medications include tramadol, fentanyl, buspirone, lithium, ondansetron, linezolid, and St John's Wort. Another major pharmacodynamic interaction is the increased risk of gastrointestinal bleeding with concomitant use of SSRIs with NSAIDs, warfarin, or antiplatelet agents.

SSRI	Significant pharmacokinetic interactions (increased plasma levels and potential adverse effects)	Significant pharmacodynamic interactions
Fluvoxamine – a potent inhibitor of CYP 1A2, 2C19 and weak inhibitor of 3A4 and 2C9	Agomelatine* Some benzodiazepines (eg diazepam, alprazolam and bromazepam) Caffeine + Clozapine* Duloxetine* Haloperidol Melatonin Olanzapine + Proton pump inhibitors Phenytoin* Quetiapine Theophylline* Tricyclic antidepressants* (eg amitriptyline, clomipramine, desipramine, imipramine, maprotline and trimipramine) Warfarin*	Potential serotonin syndrome when combined with: Other serotonin-enhancing antidepressants Tramadol Fentanyl Buspirone St John's Wort Lithium Ondansetron Linezolid Increased risk of bleeding (particularly upper GI bleed) with: NSAIDs Warfarin and other anticoagulants Antiplatelets Other pharmacodynamic interactions to consider: Other drugs which can also cause sexual dysfunction (antipsychotics), GI effects (acetylcholinesterase inhibitors) or hyponatraemia (thiazide diuretics).
Fluoxetine, paroxetine – potent inhibitor of CYP 2D6	Aripiprazole Atomoxetine Carvedilol Clozapine + Donepezil Galantamine Metoprolol Risperidone + Tricyclic antidepressants* (eg amitriptyline, clomipramine, desipramine, imipramine, maprotline and trimipramine)	
Sertraline	Clozapine+ Unlikely to cause other clinically significant pharmacokinetic drug interactions	
Citalopram, escitalopram	Unlikely to cause clinically significant pharmacokinetic drug interactions but contra-indicated with other drugs which can prolong QT interval.	

*Avoid – high risk combination either due to the clinical significance or the potential toxicity of the affected drug
+ Use with caution – monitor the combination closely for any adverse effects

Pharmacokinetic drug interactions involve alterations in the absorption, distribution, metabolism, or elimination of one drug by another. SSRIs are metabolized by various CYP enzymes including CYP2D6, CYP1A2, and CYP3A4. Induction of these CYP enzymes would result in lower levels of SSRIs while inhibition would lead to higher levels. SSRIs themselves are also potent inhibitors of CYP enzymes and, thus, have the potential to increase levels of other medications. There are currently six agents within the class of SSRIs that are marketed in the United States: fluvoxamine, fluoxetine, paroxetine, sertraline, escitalopram, and citalopram.

SSRIs are effective antidepressants that should be used in caution with other agents due to both pharmacodynamic and pharmacokinetic drug interactions. Knowing these interactions before they occur is critical to the safety and health of patients. Prescribers should always weigh the risks and benefits of drug interactions with SSRIs before prescribing them as some are potentially fatal interactions, including serotonin syndrome and QT_c prolongation.

References are available upon request. Table referenced from Progress in Neurology and Psychiatry.

Misuse and Abuse of Over the Counter (OTC) Loperamide

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Beginning in the late 1990s, the use and abuse of prescription and non-prescription opioids has rapidly increased, which has demonstrated a positive correlation with opioid-related deaths. The continued growth of this epidemic in 2018 has brought new insight into patterns of abuse, including an increasing frequency of OTC loperamide use (Brand names: Imodium or Imodium A-D).

One known pharmacologic mechanism of loperamide is opioid (μ) agonism in the gastrointestinal wall; at therapeutic doses, there is no central nervous system (CNS) activity. It is indicated to treat acute and chronic diarrhea as well as traveler's diarrhea with a maximum daily recommended dose of 16 mg/day. In extremely high doses, however, loperamide may leak into the gut wall and activate the CNS, producing a "high" similar to the effect of abusing opioids such as heroin, fentanyl, and oxycodone.

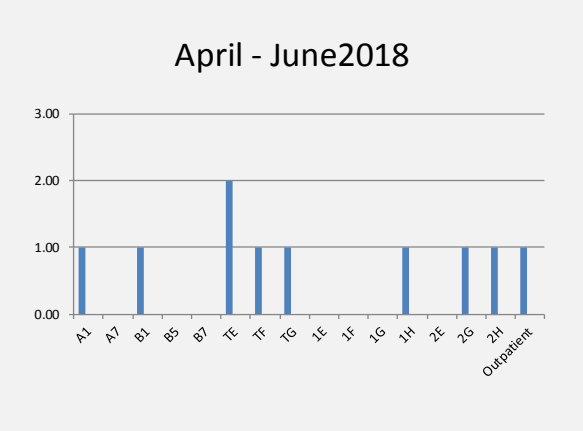
In May 2018, the FDA published an article addressing concerns of loperamide abuse due to the receipt of a number of reports of "serious heart problems and death" following the use of "as much as 100 times the recommended dose."[1] These reports led the FDA to implement a Drug Safety Communication. OTC and prescription loperamide labeling will now contain a warning about serious cardiac events that may occur at high doses, as loperamide overdose has a known association with symptoms such as fainting, rapid heartbeat or irregular rhythm, and unresponsiveness.[2] Cardiac events such as QTc prolongation, torsades de pointes, and cardiac arrest have been reported as well.[2]

To reduce the risk of loperamide abuse, a number of abuse deterrents are in the process of being implemented. The FDA is encouraging the use of blister packs in addition to a reduction in bottle size from online suppliers in order to restrict the quantity sold. Online suppliers often sell large quantities of loperamide (up to 200 caplets) in a single bottle, which are frequently sold in boxes containing more than 1,000 caplets. With the implementation of these abuse deterrents, it is also important that this medication remains accessible to patients for whom it is indicated. Currently, Walmart, Amazon, eBay, and Sam's Club are implementing the aforementioned FDA recommendations to assist in the prevention of loperamide abuse; however, these preventative changes are not predicted to affect the current price of loperamide. The FDA will "continue to assess the loperamide safety issue, and monitor adverse events, scientific literature, and data submitted by the public."[1] Healthcare professionals or patients who note cases of toxicity, adverse events, or side effects from loperamide are encouraged to submit a report to www.fda.gov/MedWatch/report.

References are available upon request.

Adverse Drug Reactions (ADRs)

Number of ADRs reported



You may report an ADR by calling x3784 or entering the data into the Sunrise Allergies System.

Formulary changes

- Remove Terbinafine from formulary
  - Only 2 tablets used in over a year
- Rifaximin remains non-formulary
  - $38 per tablet; will only order if clinically necessary
  - In most cases, recommendation for use comes from outside GI specialist

Drug shortages

- Fluphenazine injection
- Concerta tablets 36mg, 27mg: Towson campus has in stock but still sporadically unavailable. EC campus can order as bulk bottles.