

In the name of God

Drug Interactions in Headache Treatment



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September 2015

Headache Treatment



- Headaches are very common and sometimes last for years
- Abortive therapy for relieving the attack
- Prophylactic drugs for prevention
- Patients sometimes seek over the counter drugs

Ref: [Headache](#). 2015 *The Epidemiology of Exertional Headache in the General Population of Tehran, Iran (Abstract)*

[Rabiee B](#)¹, [Mohammadinejad P](#)¹, [Kordi R](#)¹, [Yunesian M](#)².

Importance of Drug Interactions



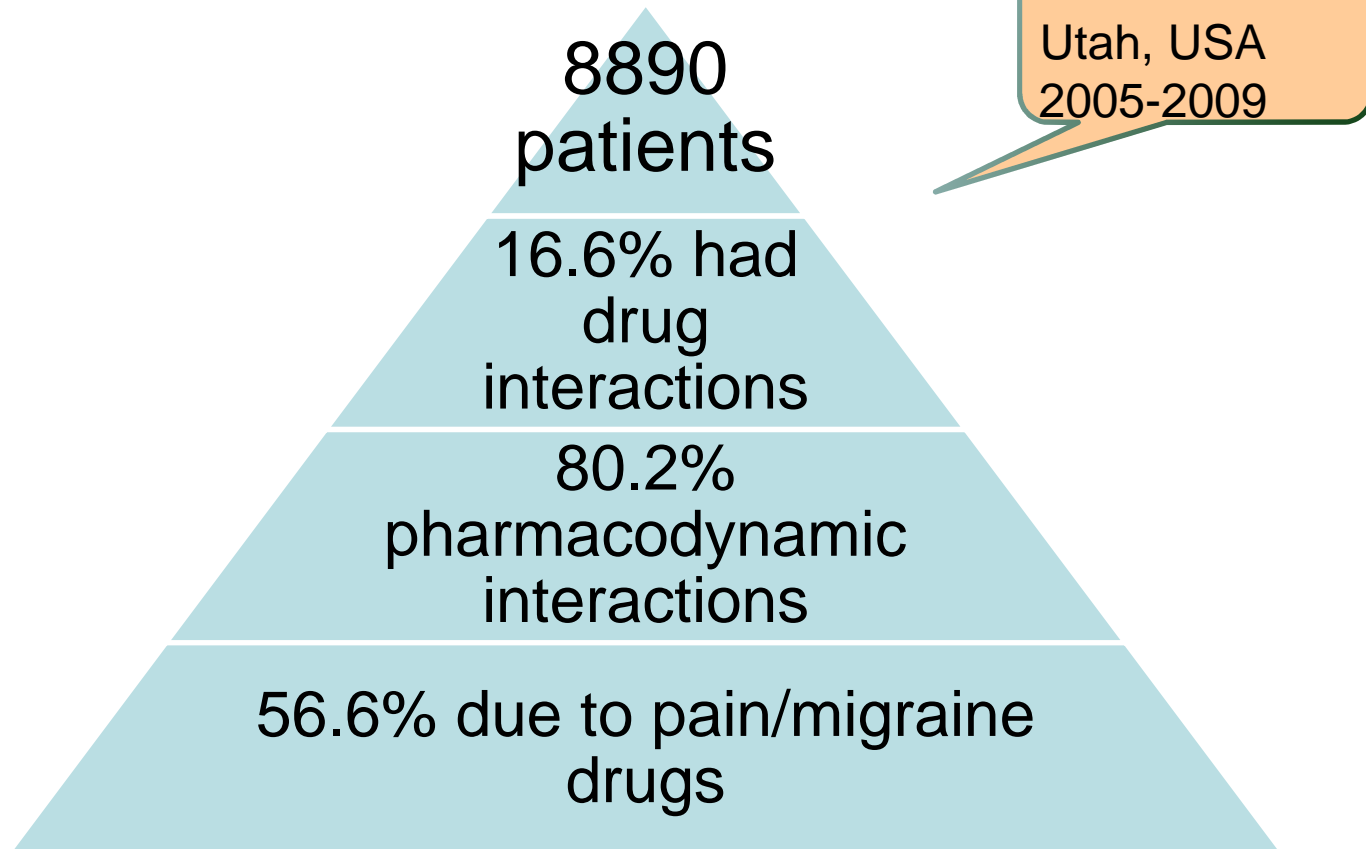
- When a condition is common, episodic, chronic, mixed (like headaches), drug-drug interactions (DDIs) are important
- Patients with comorbid medical problems and multiple drug therapy regimens have increased risk of drug interactions



Studies on drug-drug interactions

*Identifying and Communicating Clinically
Meaningful Drug-Drug Interactions*

J Pharm Pract 2014





Drug interactions in abortive therapy



Clinical outcome of the interaction: vasoconstriction



- Triptans and Ergot alkaloids mechanism: agonists of 5HT_{1B},_{1D} receptors: vasoconstrictive properties
- Concomitant use with other vasoconstrictive drugs*: enhanced effect: might lead to dangerous outcomes (ergotism)
- Gangrene and amputation

* *alpha1 agonists (e.g. phenylephrine) & central alpha2 agonists (e.g. clonidine)*



Clinical outcome of the interaction : Serotonin Syndrome



- When serotonergic drugs* are used concomitantly
- Signs and symptoms: weakness, hyperreflexia, incoordination, confusion, agitation, sweating, change in blood pressure, nausea, tremor,
- In severe cases might lead to seizure and unconsciousness

**Triptans and Ergot alkaloids are agonists of serotonin(5HT).*



Serotonin Syndrome when Triptans are used with:



- MAOInhs

Reduce the metabolism of Rizatriptan and Zolmitriptan
2 weeks interval

- SSRIs*
- SNRIs*
- Ergot alkaloids
- Lithium

** In 2007, two studies evaluated the 29 case reports of this interaction and FDA alert on co-administration of SSRIs, SNRIs and Triptans and suggested that these evidences do not support limiting the use of Triptans with SSRIs/SNRIs*

Ref:

- 1.Shapiro, R. E., Tepper, S. J. The Serotonin Syndrome, Triptans, and the Potential for Drug–Drug Interactions. Headache, 2007; 47: 266–269.*
- 2.Randolph W. Evans. The FDA Alert on Serotonin Syndrome With Combined Use of SSRIs or SNRIs and Triptans: An Analysis of the 29 Case ReportsMedGenMed. 2007; 9(3): 48.*

Serotonin Syndrome when Ergot alkaloids are used with:



- MAOInhs (2 weeks interval)
- SSRIs
- Triptans (24h interval)



Type of interaction: Inhibition of Metabolism



- Almotriptan and Eletriptan are influenced by cytochrome P-450 (CYP) 3A4 inhibitors: reduced clearance and increased exposure to these agents
- Almotriptan: different studies suggest no dose adjustments
- Eletriptan: concomitant use must be under great precaution
- Eletriptan and potent CYP3A4 inhibitors (ketoconazole, itraconazole, nefazodone, clarithromycin, ritonavir, and nelfinavir) should not be used together: 72hours time interval



Type of interaction: Inhibition of Metabolism



- Ergot alkaloids and:
 - Clarithromycin
 - Erythromycin
 - HIV protease inhibitors
 - Azole antifungals
 - Heparin
 - Cyclosporin
 - Tacrolimus

Outcome: increased side effects (especially vasoconstriction) and toxicity



Old and New drugs



- Ergotamine and dihydroergotamine: most of their DDIs are known
- New generations of Triptans might still have interactions which haven't been discussed in pre-marketing studies



Nonsteroidal Anti-inflammatory Drugs



- Cyclosporine
- Methotrexate
- Diuretics
- Lithium
- Phenytoin
- SSRIs
- Warfarin



Opioids



- CYP3A inhibitors:
Some anti HIV drugs
Some anti tuberculosis drugs
Some antidepressants
...



Drug interactions in prophylaxis of headaches

Propranolol



- Reduces the metabolic clearance of Zolmitriptan, Rizatriptan, and Eletriptan: patients might be over exposed to these drugs
- Other interactions that increase its side effects
- In doses 160 mg/d and up: increases the level of antipsychotic drugs → enhances the efficacy → A good interaction!



Anti Seizure Drugs



- Enzyme inducers and inhibitors
- Several steroidal drugs
- Cyclosporin A
- Oral anticoagulants
- Many cardiovascular, antineoplastic and psychotropic drugs
- Each other!



*Ref: Emilio Perucca Clinically relevant drug interactions with antiepileptic drugs
Br J Clin Pharmacol. 2006 Mar; 61(3): 246–255.*

SSRIs



- SSRIs may inhibit CYP450 enzymes
- Citalopram & Escitalopram inhibit enzymes less than others: choice when DDIs are a concern
(Reasonable alternative to these two: Sertraline)
- Fluoxetine, paroxetine and sertraline at doses over 200 mg/d are potent inhibitors of 2D6
- Fluvoxamine potently inhibits 1A2 & 2C19
- Most important DDI: Tamoxifen use with fluoxetine or paroxetine



Tricyclic Antidepressants



- MAOIs (high fever, convulsion)
- SSRIs (Serotonin Syndrome)
- SNRIs (Serotonin Syndrome)
- Cimetidine (increased level of TCAs)
- Epinephrine (severe high blood pressure)
- Acetylcholine blockers (paralytic ileus)



Lithium



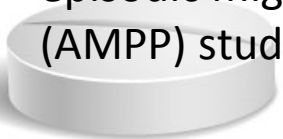
- Nonsteroidal anti-inflammatory drugs
- ACE Inhibitors
- Thiazides
- Sodium
- Diuretics
- High amounts of caffeine



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- J Neurol Sci. 2013 Mar 15;326(1-2):10-7. doi: 10.1016/j.jns.2012.12.020. Epub 2013 Feb 8.
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Thank You for Your Attention



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