Effects of CYP3A4 & CYP2D6-Mediated Drug Interactions and CYP2D6 Genetic Polymorphism on the Pharmacokinetics and Pharmacodynamics of Oxycodone – A Systematic Review

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Background

- Oxycodone is a semi-synthetic opioid analgesic used in the treatment of moderate to severe pain.
- Oxycodone may be subject to clinically significant drug-drug interactions because it undergoes extensive metabolism, mostly via CYP3A4 and CYP2D6 to form noroxycodone and oxymorphone, respectively.
- Interactions involving CYP3A4 are mediated through inhibitors such as ketoconazole and clarithromycin as well as inducers such as rifampin.
- While CYP2D6 is thought to not be inducible, it can be inhibited by drugs such as quinidine or paroxetine.
- CYP2D6 is subject to genetic polymorphism which is known to affect its catalytic function. Phenotypes include ultra-rapid, extensive, intermediate, or poor metabolizers.

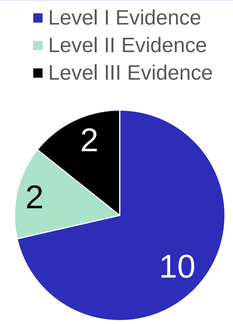
Methods

- This systematic review was completed using PubMed, EMBASE, CENTRAL, and Google Scholar from inception to November 2016.
- Search terms included: human, oxycodone, oxymorphone, noroxycodone, CYP3A4, CYP2D6, cytochrome P450, drug interactions, polymorphism, genetic, and genotype.
- Filters included English language and human population. Both *in vivo* and *in vitro* studies were included. Articles were considered irrelevant if they did not explore CYP3A4- or CYP2D6-mediated drug interactions or the effects of CYP2D6 polymorphisms on oxycodone clearance. Abstracts without an accompanying publication were excluded.
- Included articles were evaluated using the US Preventive Services Task Force levels of evidence. (USPSTF Procedure Manual. Available from: https://www.uspreventiveservicestaskforce.org)

Results – CYP3A4 Inhibitors

- CYP3A4 inhibitors such as voriconazole, clarithromycin and ritonavir have been shown to significantly impact the pharmacokinetics of oxycodone and its metabolites.
- An impact is also observed on the pharmacodynamics of oxycodone with increases in analgesia and toxicities including sedation, nausea, and vomiting.
- The changes in exposure to oxycodone make it likely that these interactions will be clinically relevant.

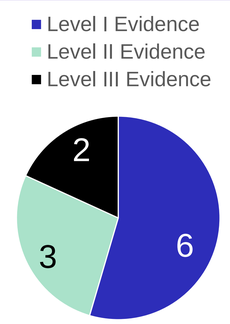
Figure 2: Included Studies



Results – CYP2D6 Inhibitors

- While CYP2D6 inhibitors such as paroxetine and quinidine did impact the pharmacokinetics of oxycodone's metabolites, minimal effects on the parent compound were seen.
- Minimal changes in analgesic efficacy were observed. However, increases in adverse effects such as sedation and nausea were observed in some studies.
- The potential for increased toxicity makes these interactions possibly clinically relevant.

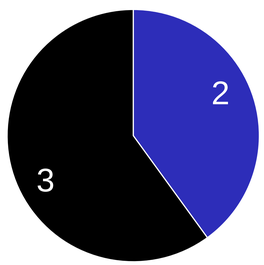
Figure 3: Included Studies



Results – CYP3A4 Inducers

- CYP3A4 inducers such as rifampin and St. John's wort have been shown to significantly reduce the exposures of oxycodone and its metabolites in addition to changes in other pharmacokinetic parameters.
- An effect is also observed on the pharmacodynamics of oxycodone with reduced analgesic efficacy. Limited data suggest no increase in adverse effects.
- The magnitude of changes in exposure to oxycodone make it likely that these interactions will be clinically relevant.

Figure 4: Included Studies



Results – CYP2D6 Genetic Polymorphism

- The effects of CYP2D6 genetic polymorphism on the pharmacokinetics of oxycodone and its metabolites are mostly limited to changing the relative exposure of oxymorphone with minimal changes to the parent compound.
- In many cases, phenotype did not affect pharmacodynamic parameters. However, certain studies suggested reduced analgesia and increased adverse effects in poor metabolizers.
- In most cases, CYP2D6 phenotype is unlikely to be clinically relevant.

Figure 5: Included Studies

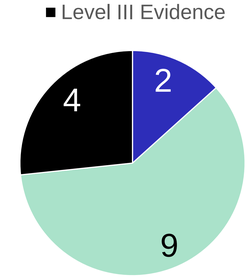


Figure 1: PRISMA Flow Diagram for Systematic Review

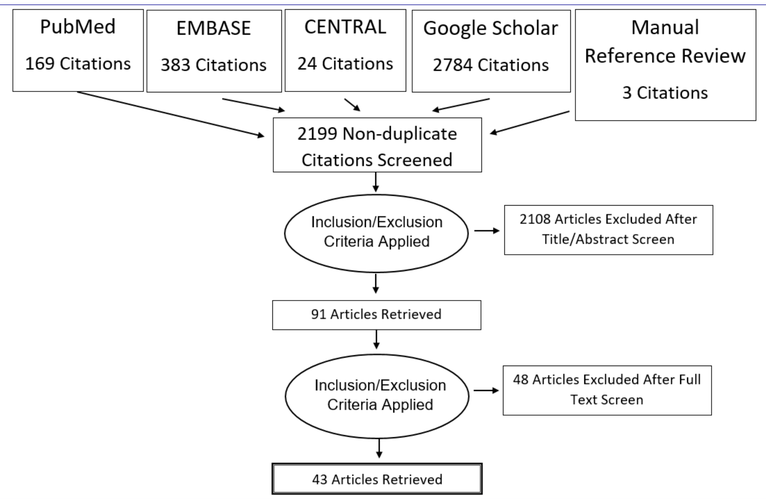


Table 1: Likelihood of a Clinically Relevant Interaction

If ≥3 criteria met then likely, if 1-2 then possible, if 0 then unlikely:

1. ≥ 2-fold increase in exposure or increase in clearance ≥ 50% OR ≥ 50% decrease in exposure or ≥ 2-fold increase in clearance
2. Evidence of impact of drug interaction on efficacy of oxycodone
3. Evidence of impact of drug interaction on toxicity of oxycodone
4. Supported by level I evidence

CYP3A4 Inhibitors		CYP2D6 Inhibitors	
Ketoconazole	Likely	Paroxetine	Possible
Itraconazole	Likely	Quinidine	Possible
Voriconazole	Likely	Quinine	Unlikely
Miconazole	Possible		
Telithromycin	Possible	**CYP3A4 Inducers**	
Clarithromycin	Likely	Rifampin	Likely
Grapefruit juice	Possible	St. John's wort	Likely
Ritonavir	Likely	Carbamazepine	Possible
Ritonavir/lopinovir	Likely	Fosphenytoin	Possible
Aprepitant	Unlikely		

Limitations

- The heterogeneity of the available studies does not allow for meta-analysis of the impact of drug-drug or drug-gene interactions on the pharmacokinetics of oxycodone. Therefore, it is challenging to approximate the overall magnitude of these interactions.
- Due to a lack of randomized data for all interaction types, conclusions were made with lower quality data.

Conclusions

- When used together with oxycodone, moderate or strong CYP3A4 inhibitors or inducers are likely to result in clinically relevant drug interactions with effects on both pharmacokinetic and pharmacodynamic parameters.
- CYP2D6 inhibitors may possibly result in increased toxicity when combined with oxycodone thereby warranting additional monitoring.
- CYP2D6 phenotype is unlikely to result in clinically relevant interactions in most cases, but may provide an explanation to otherwise undetermined treatment failure in a patient taking oxycodone.

Acknowledgements

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