Objectives

- At the completion of this training activity, the participant should be able to:
  - Explain the risks associated with anticholinergic and sedative medication use in older adults
  - Compare and contrast methods for quantifying anticholinergic and sedative burden
  - Describe how genetic variants may affect drug pharmacokinetics and pharmacodynamics for a series of drugs

Anticholinergic Pathophysiology

Cholinergic Hypothesis

A loss of cholinergic function in the CNS contributes significantly to the cognitive decline associated with advanced age and Alzheimer's disease (AD).
Pathophysiology
Cholinergic Hypothesis

- Alterations in high-affinity choline uptake / transport
- Impaired acetylcholine release
- Deficits in the expression of nicotinic and muscarinic receptors
- Dysfunctional neurotrophin support
- Deficits in axonal transport

Net Result
- Low level of the neurotransmitter acetylcholine (ACH)
- Leads to both cognitive and non-cognitive (e.g., behavioral) symptoms

Sedative Pathophysiology
Alterations in the BBB

Age-related alterations in the blood brain barrier (BBB) contribute significantly to the exaggerated response associated with medications affecting the CNS

Anticholinergic Pharmacology

P-glycoprotein activity of lymphocytes in young & elderly subjects as a function of age

Vd of (R)-verapamil in brain in young & elderly subjects as a function of age


Sedative Pathophysiology
Alterations in the BBB


Anticholinergic Pharmacology

Anticholinergic Pharmacology

Anticholinergic Hypothesis

- Most anticholinergics interact with muscarinic ACh receptors
  - A few can also affect the nicotinic ACh receptors (e.g., glycopyrrolate)

- The anticholinergic activity expressed by a drug is directly related to its potential to bind to muscarinic ACh receptors

- Presuming the cholinergic hypothesis is correct then one would expect the elderly & those with AD to be especially sensitive to the cognitive impairing effects of anticholinergic drugs
  - Indeed, substantial data to support this premise have been published

Anticholinergic Pharmacology

Anticholinergic Drug Interactions

- Clinically-important drug-drug interactions
  - Cholinergic / muscarinic agonists – Pharmacodynamic
    - Direct: Bethanechol
    - Indirect: Acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine)
  - CYP450-mediated drug interactions (competitive inhibition) – Pharmacokinetic
    - Drug specific

- Clinically-important drug-disease interactions
  - Benign prostatic hyperplasia
  - Constipation
  - Dementia
  - Glaucoma (narrow-angle)

Sedative Pharmacology

Multiple CNS Mechanisms

- Agonism of the benzodiazepine receptor (GABA-A complex)
  - Benzodiazepines & barbiturates

- Antagonism of histamine H₁ receptors
  - Antihistamines, antipsychotics, & TCAs

- Binding to the μ-opioid receptor
  - Opioids

- Antagonism of α₁-adrenergic receptors
  - Antipsychotics

- Blockage of muscarinic receptors
  - Smooth muscle relaxants (urinary antispasmodics)
Anticholinergic Pharmacology

Sedative Drug Interactions

- Clinically-important drug-drug interactions
  - CNS effects – Pharmacodynamic
    - Concomitant administration with other drugs that cause CNS depression
      e.g., Opioid + Benzodiazepine + Antidepressant
  - Respiratory effects – Pharmacodynamic
    - Concomitant administration with other drugs that cause respiratory depression
      e.g., Opioid + Benzodiazepine
  - CYP450-mediated drug interactions (competitive inhibition) – Pharmacokinetic
    - Drug specific (e.g., opioids are weak substrates for the CYP2D6 isoenzyme)

- Clinically-important drug-disease interactions
  - Use of opioids in patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve
    - COPD, cor pulmonale, morbid obesity
  - Use of sedative drugs in patients at high risk for falls
    - History of falls, orthostatic hypotension, syncope

Adverse Effects of Anticholinergic and Sedative Medications

Including Morbidity & Mortality

Anticholinergic & Sedative

THIS IS YOUR BRAIN ON DRUGS

YES, we have questions

Adverse Effects

Older Adults’ Susceptibility

- Older adults are particularly vulnerable to anticholinergic and sedative-related adverse effects for several reasons:
  - They have a high probability of being exposed
    - High medical comorbidity & polypharmacy
  - They are more sensitive to experience serious effects
    - Especially cognitive adverse effects (e.g., gait instability & falls)
  - Age-related physiological changes
    - Increase in blood brain barrier permeability
    - Decline in hepatic drug metabolism and renal drug clearance
    - Reduction in central cholinergic activities (i.e., decreased neurons & receptors, decreased acetylcholine-mediated transmission)
    - Increase in % of adipose tissue (increased distribution of lipophilic drugs, e.g., diazepam)

Anticholinergic Adverse Effects

Anticholinergic Risks

- Agitation / delirium
  - Onset or worsening BPSD
  - Loss of independence
  - Institutionalization

- Urinary retention
  - Increased UTI
  - Loss of independence
  - Acute kidney injury (AKI)

- Cardiac dysrhythmias
  - Arrhythmias

- Dry mouth
  - Dysphagia
  - Dental caries
  - Impaired communication

- Constipation
  - Fecal impaction
  - Paralytic ileus
  - Pain

- Urinary retention
  - Increased UTI
  - Loss of independence
  - Acute kidney injury (AKI)

- Constipation
  - Fecal impaction
  - Paralytic ileus
  - Pain

- Urinary retention
  - Increased UTI
  - Loss of independence
  - Acute kidney injury (AKI)

- Anticholinergic Morbidity

- Cognitive Function

  - Cause or worsen cognitive impairment & delirium
    - Myriad studies have found a significant association between anticholinergic burden and either cognitive impairment or delirium

  - Increase the risk of dementia & Alzheimer’s Disease
    - A recently published study (2015) demonstrated that higher cumulative anticholinergic drug use is associated with incident dementia
      - The risk was statistically significant among patients with the highest exposure (dementia: adjusted HR, 1.54 [95% CI, 1.21-1.96]; Alzheimer’s disease: adjusted HR, 1.63 [95% CI, 1.24-2.14]) compared with those with no use

Sedative Risks

- Daytime sleepiness
  - Sedentary
  - Social isolation

- Memory impairment
  - Anterograde amnesia

- Depression
  - Blurred vision (ACB) + Dizziness (SB)
  - Gait disturbances / falls

- Dependence
  - Physical
  - Psychological

- Tolerance
  - Abuse
  - Withdrawal

- Daytime sleepiness
  - Sedentary
  - Social isolation

- Memory impairment
  - Anterograde amnesia

- Depression
  - Blurred vision (ACB) + Dizziness (SB)
  - Gait disturbances / falls

- Dependence
  - Physical
  - Psychological

- Tolerance
  - Abuse
  - Withdrawal
Anticholinergic Morbidity

**Cognitive Function**

- Increased brain atrophy
  - A study published in 2016 found the use of drugs with moderate to strong anticholinergic activity was associated with brain atrophy
  - Whole brain & temporal lobe atrophy
  - In cognitively normal older adults
- As well as poorer cognition (e.g., immediate memory recall & executive function) and reduced glucose metabolism
- The effect appeared additive
  - An increased anticholinergic burden was associated with worsening executive function & increased brain atrophy

**Physical Function**

- Higher anticholinergic burden is significantly associated with falls
  - In a longitudinal study of community-dwelling older adults >65 years without dementia, in men, the use of drugs with definite anticholinergic activity was associated with greater risk of subsequent injurious falls (aRR, 2.55 [95% CI, 1.33-4.88])
- Recent study (2015) reveals 16% greater risk of injury in older adults currently using anticholinergic drugs compared with non-users
  - Included falls (with injury) but not exclusively injuries as a result of falls

**Pneumonia & Hospitalization**

- Possibly cause pneumonia
  - New study reveals link between anticholinergic drug use and CAP
    - Acute & chronic use
    - Low- & high-potency drugs
  - Possible mechanism involves:
    - Sedation & altered mental status
    - May contribute to poor pulmonary hygiene, atelectasis & aspiration
- Increase risk of hospitalization
  - When using ≥2 anticholinergic drugs

**Mortality**

- Association with increased risk of death has been reported
  - In a longitudinal study of community-dwelling and institutionalized participants, two-year mortality was greater for those taking definite & possible anticholinergics
    - Definite anticholinergics: OR, 1.68 (95% CI, 1.30-2.16), P<.001
    - Possible anticholinergics: OR, 1.56 (95% CI, 1.36-1.79), P<.001
  - For every additional point (above 5) scored on the ACB tool, the odds of dying increased by 26%
Sedative Morbidity

Cognitive Function

• Increase risk of cognitive decline / impairment
  • Complex relationship with other risk factors
  • In the Health, Aging and Body Composition Study, researchers found that combined use of CNS medications was associated with cognitive decline (adjusted HR, 1.37 [95% CI, 1.11-1.70]) over 5 years
  • Further, longer duration (adjusted HR, 1.39 [95% CI, 1.08-1.79]) & higher doses (adjusted HR, 1.87 [95% CI, 1.25-2.79]) of CNS medications conferred greater risk

Sedative Morbidity

Physical Function

• Cause or worsen physical inactivity
• Decline in muscle strength
• Reduced balance & mobility
• Impaired performance in ADLs/IADLs
• Increased risk of falling & fractures

A threat to independent living among older adults

Large-scale studies indicate that sedative-hypnotics increase the risk of postural instability, falls and fractures in the elderly

Non-benzodiazepine sedative-hypnotics do not appear to be safer

Sedative Morbidity

Accidents & Overdoses

• Cause or contribute to motor vehicle accidents
  • In a study of 72,685 drivers involved in injury-related road traffic accidents, the risk of being responsible for a traffic accident was higher in users of benzodiazepine hypnotics (OR, 1.39 [1.08-1.79]; P<0.01)
  • Plausibly related to impaired physical function (e.g., poorer performance in coordination, grip strength and/or mobility)

• Risk of respiratory failure, particularly in susceptible patients
  • Chronic obstructive pulmonary disease (COPD)
  • In a matched case-control study, the use of benzodiazepine receptor agonists was associated with an increased risk of respiratory failure (adjusted OR, 1.56 [95% CI, 1.14-2.13])

Sedative Morbidity

Accidents & Overdoses

• Increase risk of ED visits and hospitalizations
  • ADEs from the therapeutic use of psychiatric medications are responsible for nearly 90,000 ED visits annually in the United States, and almost 1 in 5 of those ED visits (19.3%, 95% CI, 16.3%-22.2%) results in hospitalization
  • Among psychiatric medications, antidepressants, antipsychotics, and anxiolytics and sedatives are the most implicated
  • The majority of ADE-related ED visits caused by psychiatric medications are from ADRs and unintentional overdoses or supratherapeutic dosages
Sedative Mortality

• No association overall
  • Between sedative drug use and mortality

• Certain drug classes
  • Antipsychotics have been linked to an increased risk of death (in dementia)
    • Plethora of good-quality evidence
    • A meta-analysis of 15 placebo-controlled trials, 10 to 12 weeks in duration and
      enrolling 5,110 patients, revealed a risk of death in antipsychotic users of
      approximately 1.6 times the risk of death in patients using placebo
    • Risk is greatest in the first 30 days
    • Nevertheless, risk appears to be unrelated to sedative effects (i.e., sudden death)
  • Results of studies with other sedative drugs in comparison are inconsistent

Sedative Mortality

• Overdose deaths
  • In 2010, the latest year for which these data are available, there were 38,329 drug
    ODs in the United States; most (57.7%; 22,134) involved pharmaceuticals
    • Of the pharmaceutical-related overdose deaths, the majority (74.3%; 16,451) were
      unintentional
    • Opioids (75.2%; 16,651), benzodiazepines (29.4%; 6,497), and antidepressants
      (17.6%; 3,889) were the pharmaceuticals most commonly involved in these
      overdose deaths
  • Further, among overdose deaths involving opioids, the pharmaceuticals most
    often also involved in these deaths were benzodiazepines (30.1%; 5,017),
    antidepressants (13.4%; 2,239), and antipsychotics and neuroleptics (4.7%; 783)

Quantifying Drug Burden

Basis of Drug Burden

• Different drugs, even within similar drug classes, have varying
degrees of anticholinergic and sedative activity
  • Affinity for muscarinic (anticholinergic) & other receptors (sedative)

  Some drugs have well-recognized activity
  • First-generation antihistamines (e.g., diphenhydramine)
  • Urinary antispasmodics (e.g., oxybutynin)
  • Anticholinergics (e.g., hyoscyamine)

  Opioids (e.g., morphine)
  • Anesthetics
  • Benzodiazepines & sedative hypnotics
Basis of Drug Burden

Anticholinergics Further Explored

- However, clinicians may not be aware that some commonly used drugs also have anticholinergic activity
  - Anticoagulants (e.g., warfarin)
  - Antidepressants (e.g., paroxetine)
  - Diuretics (e.g., furosemide)

- They also may not realize that using multiple drugs with weaker activity can be additive and/or synergistic
- Also there may be a cumulative effect (i.e., exposure [dose & duration])

Methods for Quantifying

Expert-Based Tools

- Based on experts’ experiences & opinions combined with available drug information (e.g., adverse effects, pharmacology)
- Simple list of drugs with known & different degrees of anticholinergic & sedative activity
- Help clinicians decide the degree of risk a drug & combination of drugs may pose for individual patients

May be the only method clinically useful for assessing the central or cognitive effects of drugs

Methods for Quantifying

Expert-Based Tools – Focus on ACB

- Prioritizes ranking criteria
  - Drugs with cognitive adverse effects and those that permeate the BBB
  - Drugs with peripheral anticholinergic activity also are included
  - Excludes topical, ophthalmic, otologic & inhaled drug preparations
- Uses categorical scoring
  - Possible anticholinergics = score of 1 (mild)
    - Score of 1 – in vitro data (i.e., SA or affinity for muscarinic receptors but little to no clinically relevant effects
  - Definite anticholinergics = score of 2 or 3
    - Score of 2 – clinical anticholinergic effect (moderate)
    - Score of 3 – drug may cause delirium (severe)
Methods for Quantifying Expert-Based Tools – Focus on ACB

- Cumulates on numerical scoring
- Sum (∑) drug scores for a cumulative ACB
- Clinically meaningful scores
  - ACB score ≥ 3
- Examples
  - Amitriptyline
  - Diphenhydramine
  - Paroxetine

Anticholinergic Cognitive Burden Scoring of Drugs

<table>
<thead>
<tr>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aclizolam</td>
<td>Loxapine</td>
<td>Atropine</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Oxcarbazepine</td>
<td>Tolterodine</td>
</tr>
</tbody>
</table>

Methods for Quantifying Expert-Based Tools – Focus on SLM

- Assigns sedative ratings categorically
- Bases ratings on drug characteristics
  - Primary sedatives = rating of 2
  - Prominent side effect = rating of 1
- Cumulates on numerical scoring
  - Sum (∑) drug scores for a sedative load
- Clinically meaningful scores
  - SLM score ≥ 3
  - ≥ 2 CNS-active drugs (e.g., Beers criteria)

REVISED Sedative Load Model Scoring of Drugs

<table>
<thead>
<tr>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide</td>
<td>Baclofen</td>
<td>Amantadine</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Morphine</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Paroxetine</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Quetiapine</td>
<td>Zolpidem</td>
</tr>
</tbody>
</table>
Limitations of Methodologies

Overall

• Hundreds of drugs are thought to have anticholinergic and/or sedative activity and, thus, these methods may not be all inclusive
  • Non-prescription drugs, namely herbals & supplements, may not be captured in these methods
  
• There are individual differences in pharmacodynamics, pharmacokinetics, especially drug interactions, and blood-brain barrier permeability that are not accounted for in these methods
  • Similarly, drug dosages can affect receptor potency yet may not be accounted for in these methods

Endogenous factors affect physiologic activity

Limitations of Methodologies

Expert-Based Tools

• Most clinically relevant but least standardized method (subjective)
  • Depends on the expert’s perspective, knowledge & experience
  
• Not routinely updated
  
• The combination of drug lists & clinical tools, such as the MMSE, is not sensitive enough to detect mild drug-induced cognitive changes
  
  • Intra-class variation in regard to drug activity is not accounted for (e.g., some antidepressants / antipsychotics are more sedating than others within the drug class)
  
• Should we be rating individual drugs on their anticholinergic/sedative potential?

Utility of Methodologies

Focus on Expert-Based Tools

• Expert-based tools are simple lists of medications with individual anticholinergic & sedative activity scores
  • Can be incorporated into clinical decision support (CDS) systems to determine cumulative drug burden
  
• These tools could be used as a component of MTM services to identify older adults who are at higher risk for potential anticholinergic and sedative effects
  
• Pharmacists are ideally positioned to address or prevent unintended sequelae of drug burden & preserve the QoL and overall health status of older patients
Reference


Take-Away Points

- Drugs with anticholinergic and sedative properties can negatively affect cognitive & physical function in older adults considerably
- Associated with poor outcomes
- Threat to independent living

- Knowing a patient’s medication risk aids in personalizing a medication care plan
- A tailored, systemic approach can reduce anticholinergic and sedative burden

Reference

DNA & Genes

- DNA... library or book
- Chromosome... cookbook or chapter
- Gene... recipe or sentence
  - Nucleotides... ingredients or alphabet
- Protein (Enzyme)... meal or paragraph

Pharmacogenomics

- Genetic variability is a key component of life
  - Changes protein expression and function
- Pharmacogenomics (PGx)
  - How a person's genes affect the way he or she responds to drugs
    - Relationship between variations in a large collection of genes (not just a single gene)
    - Change gene \( \rightarrow \) change protein's effect \( \rightarrow \) change drug's response
- Links genetic variations to clinically important events
  - Drug response or lack of response
  - Adverse drug reactions (ADRs) or adverse drug events (ADEs)
  - Dose requirements

Interindividual Variability

Drug Response

- One drug does NOT fit all
- Non-toxic and ineffective
- Toxic and ineffective
- Same Diagnosis & Same Drug
- Non-toxic and effective
PGx Principles
Focus on Drug Metabolism

Cytochrome P450 DMEs
Proportion of Drug Metabolism

Drug Metabolizing Enzymes (DMEs)
Cytochrome P450

- Genetic variants can affect the function and/or expression of drug metabolizing enzymes (DMEs)
  - Can differ between substrates
- The most well-studied DMEs are the cytochrome P450 (CYP) enzymes
  - Approximately 225 genes encode for DMEs
- A superfamily of enzymes responsible for the metabolism (chemical alteration) of substrates so they can be eliminated (excreted) from the body

<table>
<thead>
<tr>
<th>Species</th>
<th>Family</th>
<th>Subfamily</th>
<th>Isoform</th>
<th>Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUMAN</td>
<td></td>
<td></td>
<td>CYP2C19*1</td>
<td></td>
</tr>
</tbody>
</table>

**Cytochrome P450 DMEs**

CYP1A: 10%
CYP2A: 20%
CYP2B: 42%
CYP2D: 25%
CYP2E: 3%
CYP3A: 25%
**Cytochrome P450 DMEs**

**Example – CYP2C19**

<table>
<thead>
<tr>
<th>Definition (Diplotype)</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two increased function alleles, or more than 2 normal function alleles (e.g., CYP2C19*2/*2)</td>
<td>Ultra-Rapid Metabolizer (UM)</td>
</tr>
<tr>
<td>Combinations of normal function and increased function alleles (e.g., CYP2C19*2/*2)</td>
<td>Rapid Metabolizer (RM)</td>
</tr>
<tr>
<td>Combinations of normal function &amp; decreased function alleles (e.g., CYP2C19*1/*1)</td>
<td>Normal Metabolizer (NM)</td>
</tr>
<tr>
<td>Combinations of normal function, decreased function, and/or no function alleles (e.g., CYP2C19*1/*1)</td>
<td>Intermediate Metabolizer (IM)</td>
</tr>
<tr>
<td>Combination of no function alleles and/or decreased function alleles (e.g., CYP2C19*1/*1)</td>
<td>Poor Metabolizer (PM)</td>
</tr>
</tbody>
</table>

Cytochrome P450 DMEs

**Example – CYP2D6**

<table>
<thead>
<tr>
<th>Activity Score</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2</td>
<td>Ultra-Rapid Metabolizer (UM)</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>Normal Metabolizer (NM)</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>Intermediate Metabolizer (IM)</td>
</tr>
<tr>
<td>0</td>
<td>Poor Metabolizer (PM)</td>
</tr>
</tbody>
</table>

**PGx Applications**

**Drug-Gene Interactions (DGIs)**

- A DGI occurs when a patient’s genetic CYP450 type (e.g., CYP2D6 poor metabolizer) affects that patient’s ability to metabolize a drug.
- Drug-gene relationships can help identify patients at risk for undesired drug response (e.g., adverse drug reactions [ADRs], ineffectiveness).

**It is estimated that 1 in 4 patients (25%) take >1 drug that commonly causes ADRs due to genetic variation in drug metabolism**
Cytochrome P450 DMEs
Genotype to Phenotype

1. Poor Metabolizer (PM)
   - Drug A (e.g., *3/*3)

2. Intermediate Metabolizer (IM)
   - Drug B (e.g., *1/*3)

3. Normal Metabolizer (NM)
   - Drug C (i.e., *1/*1)

4. Ultra-Rapid Metabolizer (UM)
   - Drug D (e.g., *17/*17)

Phenotype Expression

Exception: Prodrugs


DGIs Principles

Active Drug A

Inactive Metabolite

Inactive Drug B

Active Metabolite

CYP

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PGx Applications
Drug-Gene Interaction Examples

Clopidogrel Metabolic Pathway

Clopidogrel Response | Guidelines

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Interpretation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>UM</td>
<td>Increased platelet inhibition &amp; decreased residual platelet aggregation.</td>
<td>Label-recommended dosage and administration. <strong>Monitor for bleed.</strong></td>
</tr>
<tr>
<td>EM</td>
<td>Normal platelet inhibition &amp; normal residual platelet aggregation.</td>
<td>Label-recommended dosage and administration.</td>
</tr>
<tr>
<td>IM</td>
<td>Reduced platelet inhibition, increased residual platelet aggregation, &amp; increased risk for adverse CV events.</td>
<td>Alternative antplatelet therapy (if no contraindication) such as prasugrel or ticagrelor.</td>
</tr>
<tr>
<td>PM</td>
<td>Significantly reduced platelet inhibition, increased residual platelet aggregation, &amp; increased risk for adverse CV events.</td>
<td>Alternative antplatelet therapy (if no contraindication) such as prasugrel or ticagrelor.</td>
</tr>
</tbody>
</table>

Alternative Metabolic Pathways

**Prasugrel (inactive)**

- Esterases
- Thiolactone (inactive)

**CYP2B6 CYP3A4**

- CYP2C9
- CYP2C19

R-138727*

**Ticagrelor**

- CYP3A4/S

AR-C124910X*

*Active

NOT a prodrug
Opioids

<table>
<thead>
<tr>
<th>Opioid</th>
<th>CYP2D6</th>
<th>CYP3A4</th>
<th>CYP2B6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>5*</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>NON P450</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15*</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>NON P450</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>10*</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>NON P450</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>10</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Tapentadol</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Oxycodone Metabolic Pathway

Oxycodone Response

Normal Response

Oxycodone → CYP2D6 → Oxymorphone

Reduced Response

Oxycodone → CYP2D6 → Oxymorphone

Oxycodone Response
Enhanced Response

Oxycodone → Oxymorphone

CYP2D6

CYP2D6 ♦/♦2
Ultra-rapid Metabolizer (UM)

CYP2D6 ♦/♦1
Normal Metabolizer (NM)

CYP2D6 ♦/♦2
Intermediate Metabolizer (IM) or Poor Metabolizer (PM)

Oxycodone Response
Altered Response – Phenoconversion

Oxycodone → Oxymorphone

CYP2D6

Bupropion

CYP2D6 ♦/♦1
Normal Metabolizer (NM)

CYP2D6 behaves like an Intermediate Metabolizer (IM) or Poor Metabolizer (PM)

This can be mitigated by giving Oxycodone 2-4 hours prior to Bupropion

Oxycodone Response
Altered Response – Phenoconversion

Oxycodone → Oxymorphone

CYP2D6

Amiodarone

CYP2D6 ♦/♦1
Normal Metabolizer (NM)

CYP2D6 ♦/♦2
Intermediate Metabolizer (IM) or Poor Metabolizer (PM)

This can NOT be mitigated by changing time of administration

Oxycodone Response | Guidelines

• DPWG (Dutch Pharmacogenetics Working Group)

<table>
<thead>
<tr>
<th></th>
<th>NM</th>
<th>IM</th>
<th>PM</th>
<th>UM</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>Select ALTERNATIVE or be ALERT to symptoms of insufficient pain relief</td>
<td>Select ALTERNATIVE or be ALERT to symptoms of insufficient pain relief</td>
<td>Select ALTERNATIVE or be ALERT to ADEs</td>
<td></td>
</tr>
</tbody>
</table>

Alternatives: Acetaminophen, NSAID, morphine (not tramadol or codeine)
Take-Away Points

- PGx is a rapidly developing field that has important clinical applications for personalizing drug therapy to maximize effectiveness (benefits) and/or minimize toxicity (risks).

- It will become increasingly difficult to practice medicine & to provide high quality health care in the future without a fundamental knowledge of PGx.

With their knowledge of the principles discussed herein, PACE clinicians should consider the utility of PGx in their practices.

PGx References


Questions?