Psyched about ID
Clinical Pearls at the Intersection of Neuropsychiatry and Infectious Disease

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PGY1 Pharmacy Resident
Pharmacy Grand Rounds
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Objectives

• Review properties that potentiate a medication’s ability to act on the central nervous system (CNS)

• Discuss key neuropsychiatric adverse reactions of antimicrobials and their management

• Discuss potential therapeutic uses of antimicrobials in neuropsychiatric conditions
The Intersection of Neuropsychiatry and Infectious Disease

Infections Causing Neuropsychiatric Disease
- HAND
- Neurosyphilis

Antimicrobials Causing Neuropsychiatric Adverse Events

Antimicrobials As Treatment for Neuropsychiatric Disease

Complex Drug Drug Interactions Between Antimicrobials and Neuropsychiatric Agents
Drug Entry into the Central Nervous System

- **Low Molecular Weight**
- **Low Protein Binding**
- **Lipophilic (log P >0)**

CSF Penetration

### Relative CNS Penetrations of Antimicrobials

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Daptomycin</th>
<th>Cefotaxime</th>
<th>Meropenem</th>
</tr>
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<tbody>
<tr>
<td>Protein Binding</td>
<td>&gt;90%</td>
<td>~30%</td>
<td>~2%</td>
</tr>
<tr>
<td>Weight</td>
<td>1,619 Daltons</td>
<td>455 Daltons</td>
<td>383 Daltons</td>
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<td>Lipophilicity</td>
<td>logP 0.88</td>
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Images Public Domain
Daptomycin, Cefotaxime, Meropenem. Micromedex 2.0. Truven Health Analytics, Inc. Greenwood Village, CO
Based on chemical properties, which antimicrobial would you predict to have better CSF penetration?

- A. Daptomycin
- B. Cefotaxime
- C. Meropenem
Relative CNS Penetrations of Antimicrobials

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</tr>
<tr>
<td>$\text{AUC}_{\text{CSF}}/\text{AUC}_S$</td>
<td>0%</td>
<td>12%</td>
<td>20%</td>
</tr>
</tbody>
</table>


Images Public Domain
Daptomycin, Cefotaxime, Meropenem. Micromedex 2.0. Truven Health Analytics, Inc. Greenwood Village, CO
Antimicrobials and Reported Neuropsychiatric Effects

- Seizures
  - Beta-lactams
  - Fluoroquinolones
  - Isoniazid
- Serotonin Syndrome
  - Linezolid
- Vivid Dreams/Psychosis
  - Efavirenz
  - Mefloquine
  - Voriconazole
- Encephalopathy
  - Cefepime
- Mania
  - Macrolides
  - Fluoroquinolones
  - Isoniazid
  - Metronidazole
  - Penicillins

Antimicrobials and Seizures

- Beta-lactams
- Fluoroquinolones

Normal GABA function

Antimicrobials Block GABA Function

- Pyridoxine (B6)
- Isoniazid

GABA

Presynaptic Terminal

GABA

Cl-

Beta-Lactams
Fluoroquinolones

Action

Potential

Postsynaptic Terminal

Beta-Lactams: Seizure Risk

Highest Risk
0.3-0.9% or >7 cases
- Cefepime ≈ Penicillin ≈ Cefazolin ≈ Imipenem-Cilastatin

Moderate Risk
6 Cases
- Aztreonam

Low-Moderate Risk
<0.1% or 4-5 Cases
- Ampicillin ≈ Piperacillin ≈ Meropenem

Low Risk
1-3 Cases
- Ceftriaxone ≈ Cefotetan ≈ Ceftazidime ≈ Cefotaxime ≈ Cefixime

Minimal Risk
0 Cases
- Doripenem ≈ Amoxicillin

Fluoroquinolones: Seizure Risk

• Seizures limited to isolated case reports
• Almost universally reported with risk factors
  • Renal insufficiency
  • Underlying neurologic disease
  • Theophylline
• Incidence <1% in Micromedex

Ciprofloxacin, Levofloxacin. Micromedex 2.0. Truven Health Analytics, Inc. Greenwood Village, CO
Fluoroquinolones: Case Reports of Seizure since 1960

<table>
<thead>
<tr>
<th>Year</th>
<th># Pts</th>
<th>Contributing Factors</th>
</tr>
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<tbody>
<tr>
<td>1989</td>
<td>1</td>
<td>Theophylline</td>
</tr>
<tr>
<td>1989</td>
<td>1</td>
<td>Seizure History</td>
</tr>
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<td>1992</td>
<td>1</td>
<td>Theophylline</td>
</tr>
<tr>
<td>1993</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>2001</td>
<td>1</td>
<td>Renal Insufficiency</td>
</tr>
<tr>
<td>2005</td>
<td>1</td>
<td>ECT</td>
</tr>
<tr>
<td>2009</td>
<td>1</td>
<td>Renal Insufficiency</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>11</strong></td>
<td></td>
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</tbody>
</table>

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<tr>
<th>Year</th>
<th># Pts</th>
<th>Contributing Factors</th>
</tr>
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<td>2001</td>
<td>1</td>
<td>Renal Insufficiency</td>
</tr>
<tr>
<td>2005</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>2005</td>
<td>1</td>
<td>Epilepsy and Renal Insufficiency</td>
</tr>
<tr>
<td>2012</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>5</strong></td>
<td></td>
</tr>
</tbody>
</table>

Pts = Patients

Antimicrobial Seizure Risk

- **Highest Risk**
  - 0.3-0.9% or >7 cases
  - Cefepime ≈ Penicillin ≈ Cefazolin ≈ Imipenem-Cilastatin → Ciprofloxacin

- **Moderate Risk**
  - 6 Cases
  - Aztreonam

- **Low-Moderate Risk**
  - <0.1% or 4-5 Cases
  - Ampicillin ≈ Piperacillin ≈ Meropenem → Levofloxacin

- **Low Risk**
  - 1-3 Cases
  - Ceftriaxone ≈ Cefotetan ≈ Ceftazidime ≈ Cefotaxime ≈ Cefixime

- **Minimal Risk**
  - 0 Cases
  - Doripenem ≈ Amoxicillin

*SMX-TMP= Sulfamethoxazole-Trimethoprim, Aminoglycosides, Glycopeptides, Lipopeptides, Clindamycin, Tetracyclines*

References:
Risk Factors: Antimicrobial-Induced Seizures

- Extremes of Age
- Meningitis
- Renal dysfunction
- History of Seizures
- Head Injury
- Route
  - Intraventricular $>\,$ Intravenously $>\,$ Oral

Management of Beta-lactam or Fluoroquinolone induced Seizure

- Most occur 12-72 hours after initiation of antimicrobial, but some reported up to 14 days after initiation.
- Remove or reduce dose of inciting medication.
- Benzodiazepines, Barbiturates.
- Phenytoin or other agents that do not have GABA agonist activity likely do not work.
- Hemodialysis if refractory.
- Reversal typically occurs within 12-72 hours of discontinuation.

45 year old female, no significant past medical history, develops ESBL urinary tract infection and is started on meropenem. She develops a seizure on day 2 of meropenem. What drug would you select to manage her seizure?

A. Phenytoin
B. Valproic Acid
C. Lorazepam
D. B or C would be good options
What drug would you select to manage her seizure?

A. Phenytoin
B. Valproic Acid
C. Lorazepam
D. B or C would be good options
Linezolid as a Reversible and Weak Monoamine Oxidase (MAO) Inhibitor

Serotonin (5-HT) Serotonin (5-HT)
Serotonin (5-HT) Serotonin (5-HT)

Linezolid

Agents with Serotonergic Properties

• Increased 5-HT release
  • Amphetamines
  • Cocaine
  • Mirtazepine

• Inhibition of serotonin metabolism
  • Linezolid
  • MAOIs
  • St. John’s Wort

• Impaired presynaptic reuptake
  • SSRIs
  • St. John’s Wort
  • Fentanyl
  • Trazadone
  • SNRIs
  • Tramadol
  • Dextromethorphan

• Serotonin Receptor Agonism
  • Buspirone
  • Carbamazepine
  • Lithium

### Serotonin Syndrome

<table>
<thead>
<tr>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>Hypertension</td>
<td>Autonomic instability</td>
</tr>
<tr>
<td>Shivering</td>
<td>Hyperthermia</td>
<td>Shock</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Hyperactive Bowels</td>
<td>Delirium</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>Clonus of the Extremities</td>
<td>Metabolic Acidosis</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Ocular Clonus</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Restlessness</td>
<td>Agitation</td>
<td>Renal Failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disseminated Intravascular Coagulation</td>
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<tr>
<th>Recommendation Regarding The Simultaneous Use of Linezolid and SSRIs/Venlafaxine</th>
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<td><strong>Micromedex – Prior to 2011</strong></td>
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<td>“Wait at least 14 days after discontinuing linezolid before initiating therapy with an SSRI. Wait at least 14 days after discontinuing the SSRI before initiating therapy with linezolid.”</td>
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### Linezolid + SSRI Study at Mayo Clinic Rochester

<table>
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<tr>
<th><strong>Objective</strong></th>
<th>To report the incidence of serotonin syndrome in patients receiving linezolid and SSRIs or the SNRI Venlafaxine</th>
</tr>
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<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Retrospective chart review of inpatients at Mayo Clinic Rochester from 2000-2004</td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>Serotonin syndrome, defined by Sternbach or Boyer criteria</td>
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</table>
High Probability Serotonin Syndrome

Documented diagnosis in chart

≥ 3 Sternbach criteria or ≥ 1 Boyer criteria and no clear alternative explanation or symptoms reversed with discontinuation of therapy

Sternbach
- Mental status changes
- Agitation
- Myoclonus
- Hyperreflexia
- Diaphoresis
- Shivering
- Tremor
- Diarrhea
- Incoordination
- Fever

Boyer
- Tremor and hyperreflexia
- Spontaneous clonus
- Muscle rigidity, a body temperature 138°C, and either ocular clonus or inducible clonus
- Ocular clonus and either agitation or diaphoresis
- Inducible clonus and either agitation or diaphoresis

Patients who Received Linezolid plus an SSRI / Venlafaxine within 14 Days of each other

N= 72 patients

52 Patients received concomitant linezolid + SSRI therapy

2 – high probability SS

20 patients received linezolid + SSRI within 14 days

0 – high probability SS

SS- Serotonin Syndrome

Discussion

• Of the 72 patients who received linezolid + venlafaxine/SSRI within 14 days of each other, only 2 patients (2.8%) had high probability of serotonin syndrome

• In both patients, symptoms reversed 1-2 days on discontinuation of either the SSRI or linezolid
  • Patient #1 - linezolid, sertraline, trazodone and fentanyl
  • Patient #2 - linezolid, venlafaxine → citalopram

• 90% of patients received at least 1 other serotonergic agent

Conclusion

• Because serotonin syndrome is uncommon, and self-limited when recognized, linezolid may be used concomitantly with SSRI s, if the clinical situation warrants it, without a 14 day washout period, with careful monitoring for signs and symptoms of serotonin syndrome

• Recognition is key
  • Self-limited only if recognized and suspected agent discontinued

## Recommendation Regarding The Simultaneous Use of Linezolid and SSRIs/Venlafaxine

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<tr>
<td>“Wait at least <strong>14 days</strong> after discontinuing linezolid before initiating therapy with an SSRI. Wait at least <strong>14 days</strong> after discontinuing the SSRI before initiating therapy with linezolid.”</td>
<td>“If urgent treatment with linezolid is necessary, <strong>promptly discontinue SSRI and then administer linezolid</strong>. Monitor for serotonin syndrome for 2 weeks. SSRI can be resumed 24 hours after the last dose of linezolid.”</td>
</tr>
</tbody>
</table>
Decision Tree for patients on SSRIs, wanting to start linezolid

Critically ill, hemodynamically unstable, or sedated?

- Yes
  - Discontinue SSRI
  - Start Linezolid
  - Monitor for SS x 2 weeks

- No
  - Can another antimicrobial be used?
    - Yes
      - Select other antimicrobial
      - Continue SSRI
    - No
      - Is the patient’s psychiatric condition dependent on the SSRI?
        - Yes
          - Discontinue SSRI
          - Start Linezolid
          - Monitor for SS x 2 weeks
        - No
          - Consider concomitant SSRI + Linezolid
          - Frequent monitoring for SS

SS- Serotonin Syndrome

Potential Roles of Antimicrobials in Treating Neuropsychiatric Illness

- Reduced negative symptoms in Schizophrenia
  - Minocycline, Cycloserine
- Attenuation of Alcohol Withdrawal
  - Ceftriaxone
- Attenuation of hypersexuality in elderly persons with dementia
  - Ketoconazole

Minocycline and Schizophrenia

- Negative Symptoms – notoriously difficult to treat
  - Apathy
  - Emotional Blunting
  - Social Withdrawal
  - Anhedonia

- 25-30% of patients with schizophrenia have inadequate response to antipsychotics

- Persistent negative symptoms → poor social and occupational functioning

Mechanism of Action

- **Schizophrenia Pathophysiology**
  - Glutamate neurotoxicity $\rightarrow$ loss of dopaminergic neuron innervation of the prefrontal cortex

- **Minocycline**
  - Inhibits microglia activation $\rightarrow$ neuroprotection $\rightarrow$ preservation of dopaminergic neurons in prefrontal cortex $\rightarrow$ decreased negative symptoms

Double-Blind, Placebo-controlled, Randomized, Multicenter Trial in China

N= 92 patients with Schizophrenia onset <5 years ago, treated with risperidone monotherapy

N=46 Minocycline 200mg/day

N=46 Placebo

Primary Outcomes: Scale for Assessment of Negative Symptoms (SANS) Score at 16 weeks

Results

• Primary Outcome: SANS score at 16 weeks

<table>
<thead>
<tr>
<th></th>
<th>Minocycline</th>
<th>Placebo</th>
<th>p-value</th>
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<tr>
<td>Baseline SANS score</td>
<td>59.54</td>
<td>61.20</td>
<td>P= 0.618</td>
</tr>
<tr>
<td>SANS score at 16 weeks</td>
<td>32.33</td>
<td>47.80</td>
<td>P&lt;0.001</td>
</tr>
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</table>

• Secondary Outcomes:
  • Percentage of subjects with ≥ 50% improvement in SANS score at 16 weeks
    • Minocycline 43.6%  
    • Placebo 10.0%  
    \[ P<0.05 \]

Conclusion

• The addition of minocycline to atypical antipsychotic drugs in early schizophrenia had significant efficacy on negative symptoms, and shows promise as an adjunctive treatment.

• However, not yet being used clinically
  • Long term effects of minocycline, including antibiotic resistance, need to be evaluated

Ceftriaxone and Attenuation of Alcohol Withdrawal

- Ceftriaxone induces up-regulation of glutamate transporter EAAT2
  - Reuptake transporter of glutamate
  - Decreases glutamate concentration in neuronal synapse

GLUT = glutamate

Ceftriaxone in Rats with Alcohol Dependence
Mayo Clinic Rochester

| Methods: | • Ethanol 4g/kg q6h administered to rats for 3-5 consecutive days  
• Ethanol stopped x 12 hours, then rats randomized to ceftriaxone 100 mg/kg BID or normal saline BID  
• Withdrawal manifestations captured via continuous video recording x 36 hours and reviewed via blinded evaluator  
• Head jerks, twitching, body jerks, spontaneous unprovoked startle, seizure |
| Results | Ceftriaxone 100mg/kg BID significantly reduced severity of withdrawal symptoms |
| Other Findings | Brain content was analyzed; EAAT2 significantly upregulated in ceftriaxone group |

Clinical Implications

• While targeting EAAT2 is a novel mechanism for alcohol withdrawal, it has only been studied in animal models.

• Ceftriaxone 100mg/kg would yield human doses of ~ 7-10g BID.

• Not likely useful clinically, but this study highlights an interesting mechanism by which future drugs may be developed for alcohol withdrawal.
Which of the following is the proposed mechanism by which ceftriaxone attenuates alcohol withdrawal?

• A. GABA\textsubscript{A} antagonism  
• B. GABA\textsubscript{A} agonism  
• C. EAAT2 upregulation  
• D. EAAT2 downregulation
Summary

• Complex interaction exists between fields of neuropsychiatry and infectious disease

• Overall seizure risk with antibiotics is low, but some are associated with higher risk than others

• Key drug interactions
  • Linezolid + SSRIs
  • Concomitant therapy may be appropriate in some situations, but recognition of SS is key for appropriate management
  • Carbapenems + Valproic acid → undetectable valproic acid levels

• Novel mechanisms of antimicrobials are being explored for treatment of schizophrenia and alcohol withdrawal, but further research is needed to establish role
Questions?
Gamble.Christine@mayo.edu