Objectives

- Assess a patient’s risk for developing steroid-induced psychosis, fluoroquinolone-induced central nervous system effects, and interferon-induced depression
- Either rule out or recognize drug-induced psychiatric conditions
- When possible, take measures to prevent or treat drug-induced psychiatric conditions
We’re not talking about anabolic steroids.

Steroids treat inflammation.

What is steroid-induced psychosis?

Euphoria
Anger, Agitation

Anxiety, Depression, Mood lability

Hallucinations/Delusions

Delirium
Alzheimer’s-type dementia
Cognitive impairment
3-10% of patients on corticosteroids

- Mania
- Depression
- Mania+Depression
- Delirium
- Psychosis

Risk factors for steroid-induced psychosis:

Female gender (?)
Hypoalbuminemia

Normal albumin concentrations
Hypoalbuminemia

Risk factor for steroid-induced psychosis:

**Dose**

- >80 mg/day prednisone = 18.6%
- 41-80 mg/day prednisone = 4.6%
- ≤ 40 mg/day prednisone = 1.3%
When does steroid-induced psychosis occur?

- Steroid Psychosis (not delirium)
- Steroid Psychosis (not delirium)
- Delirium

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid Psychosis</td>
<td>Day 4</td>
</tr>
<tr>
<td>Steroid Psychosis</td>
<td>Week 2-3</td>
</tr>
<tr>
<td>Steroid Psychosis</td>
<td>Month 2-4</td>
</tr>
</tbody>
</table>

Treating Steroid Psychosis

Option 1: Taper Steroid Dose

Day 1 → Day 2 → Day 3 → Day 4 → Day 5

Treating Steroid Psychosis

Option 2: Divide Steroid into Multiple Daily Doses

Steroid Serum Concentration

Day 1 → Day 2

Treating Steroid Psychosis

Option 3: Switch to Different Steroid

- New chemical structure
- Different specificity or potency
- Alterations in absorption, protein binding, metabolism, excretion, membrane permeability

Day 1 → Day 2
Treating Steroid Psychosis
Option 4: Start Medication to Treat Symptoms

Antidepressant
Mood Stabilizer
Antipsychotic
Anxiolytic

Not Ideal for Monotherapy. Do WITH Another Option.

Carol is a 52-year-old female who had a hysterectomy in your hospital 12 days ago. Following the procedure, she had intractable nausea and vomiting, and was started on 8 mg IV dexamethasone BID. She is now being transferred to your inpatient psychiatric unit with auditory hallucinations and religious delusions. What is the likelihood (given as a % risk) that her current symptoms were caused by the steroid?

1. 18.6%
2. 4.6%
3. 1.3%

Mild:
- Dizziness
- Headache
- Drowsiness
- Insomnia
- Anxiety
- Nightmares

CNS Effects of Fluoroquinolones
Severe and Rare:
Psychosis
Agitation
Confusion
Depression

Second most common ADR of fluoroquinolones:

CNS (0.2-11%)

Diary Card
Incidence:
Headache 13.2%
Dizziness 9.2%
Somnolence 1.3%

Spontaneous Reporting
Incidence:
Headache 2.3%
Dizziness 3%
Somnolence 1.8%

Theory One:
Decreased GABA activity means CNS activation

Fluoroquinolones bind here
Theory Two:

Uninhibited NMDA activity means CNS activation

Regardless of theory...

Which fluoroquinolones are most likely to cause CNS ADRs?

Norfloxacin

Moxifloxacin

Ciprofloxacin

Ofloxacin

Levofloxacin

What about NSAIDs?

Interaction with FQ’s unlikely.
Who is at risk?

High Dose  Renal Impairment  Elderly

CNS ADRs in 177 Elderly Patients

*Levofloxacin 500 mg QDay*

<table>
<thead>
<tr>
<th></th>
<th>Elderly</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Headache</td>
<td>5.3%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Managing Patients on Fluoroquinolones

Mild CNS ADRs resolve with continued use. Avoid by giving with food or at bedtime.

Rose is an 86-year-old female with Alzheimer’s disease presenting with acute delirium. She has been admitted to your inpatient psychiatric unit, and a urinalysis reveals that Rose has a urinary tract infection. You would like to treat with an oral antibiotic, and you know that Rose has a sulfa allergy. Which fluoroquinolone would be most appropriate?

1. Ciprofloxacin
2. Levofloxacin
3. Moxifloxacin
Interferon-Induced Depression

Types of IFN

- **IFN-α**
  - Hepatitis C
  - CML
  - Melanoma
  - Kaposi’s sarcoma
  - Multiple myeloma

- **IFN-β**
  - Multiple sclerosis

- **IFN-γ**
  - Osteopetrosis
  - Chronic Granulomatous Disease

CML = Chronic myeloid leukemia

**IFN Indications**


Image from: http://pamhemp.med.sc.edu/mayer/v13.jpg
**Proposed Mechanism of IFN-Induced Depression**

- Interferon (IFN)
- + IDO Induction
- IDO = Indolamine

**IDO** → **Tryptophan** → **L-kynurenine** → **Acetyl CoA** → **Picolinic Acid** → **Nicotinic Acid**

**Diet**

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**Incidence of MDD with IFN-α**

- Hepatitis C: ~ 20-40% develop MDD
  - Develops ~3 months after initiation

**Incidence of MDD with IFN-β**

- *Cancer*: Limited data compared to HCV

**Depression in 1200 melanoma patients**

<table>
<thead>
<tr>
<th></th>
<th>Interferon Group (n=608)</th>
<th>Observation Group (n=613)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>360 (59%)</td>
<td>38 (6%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>153 (25%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>11 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

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**Incidence Before IFN**

- Moderate: 14%
- Severe: 1%
- None: 85%

**Incidence After 12 months of IFN**

- Moderate: 40%
- Severe: 4%
- None: 56%

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**Zephir et al. Multiple Sclerosis 2003; 9: 284.**
Incidence of MDD with IFN-γ

• Limited data and small studies
• Two efficacy studies reported no incidence of MDD:
  – Metastatic carcinoid tumor, n=51
  – Chronic granulomatous disease, n=76

Risk Factors IFN-Induced MDD

- History of Mental Illness
- History of Substance Abuse
- Concomitant Ribavirin
- History of Suicidal Ideation
- Family History of Mental Illness
- Interferon Rechallenge

Treating IFN-Induced Depression

• Randomized, double-blind, placebo-controlled
• Excluded: history of psychiatric illness or active substance abuse
• 100 patients with HCV on IFN-α + ribavirin
• Patients:
  – Hospital Anxiety and Depression Scale (HADS) score ≥ 9
  – n=28
• Treatment:
  – 20 mg citalopram daily (n=14) or placebo (n=14)
Evaluating Kraus Study

• Weaknesses
  – Effect of ribavirin?
  – Patient population
  – Low citalopram dose
• Strengths
  – Use of HADS scale
  – Study design
  – Appropriately powered

Depression Prophylaxis During Interferon Therapy

• Patients (n=40):
  – Resected malignant melanoma
  – 12 wks of IFN-α
  – Excluded: bipolar disorder, schizophrenia
• Intervention:
  – Randomized, double-blind, placebo-controlled
  – 10-40 mg paroxetine (mean 31 mg, n=20) v placebo (n=20)
  – Started 2 weeks before IFN therapy

• Primary outcome:
  – Decrease in Hamilton Depression Rating Scale (HAM-D) score
• HAM-D Scale:
  – 0-6: No depression
  – 7-17: Mild depression
  – 18-24: Moderate depression
  – > 25: Severe depression
• Secondary outcome:
  – Development of MDD during interferon treatment

Results:
  – Development of MDD:
    – 11% paroxetine, 45% placebo (p=0.04)
  – Change in HAM-D Score:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>4 wk</th>
<th>8 wk</th>
<th>12 wk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5 ± 4.4</td>
<td>11.8 ± 7.6</td>
<td>14.5 ± 9.9</td>
<td>15.2 ± 9.9</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>5.6 ± 4.7</td>
<td>9.1 ± 5.2</td>
<td>7.8 ± 5.2</td>
<td>8.4 ± 5</td>
</tr>
</tbody>
</table>

* p<0.001
Evaluating Musselman Study

- Weaknesses
  - Inadequate length of paroxetine therapy?
  - Inadequate starting dose of paroxetine
  - Did not account for use of concomitant mood-altering medications

- Strengths
  - Patient population

Recommendations

- When starting a patient on IFN
  - Recognize that the incidence of IFN-induced MDD is largely unknown
  - Identify risk factors for MDD in that patient
  - Determine whether prophylaxis or watchful waiting is more appropriate
  - Recall that evidence surrounding both treatment and prophylaxis of IFN-induced MDD is focused on SSRIs

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Questions?

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