Disclosures - Mark A. Frye M.D. 2016

- Grant Support - AssureRx, Janssen Research & Development, Mayo Foundation, Myriad, National Institute of Alcohol Abuse and Alcoholism (NIAAA), National Institute of Mental Health (NIMH), Pfizer
- Consultant (Mayo) - Janssen Research & Development, LLC, Mitsubishi Tanabe Pharma Corporation, Myriad Genetics, Neuralstem Inc., Sunovion, Supernus Pharmaceuticals, Teva Pharmaceuticals
- CME/Travel Support - American Physician Institute, CME Outfitters
- Speakers’ Bureau - NONE
- Financial Interest / Stock ownership / Royalties - NONE
- Mayo Clinic has a financial interest in AssureRx and the technology referenced in this presentation
Learning Objectives

• Use best available evidence to guide selection of pharmacotherapy for manic episodes
F.D.A. Indication Acute Mania

• Aripiprazole, Asenapine, Olanzapine, Risperidone, Quetiapine, Ziprasidone, Cariprazine (dopamine D2/D3 receptor partial agonist), Chlorpromazine all FDA approved for mania

• Carbamazepine ER and Divalproex Sodium all FDA approved for mania

• Lithium all FDA approved for mania

• Adasuve® (inhaled loxapine) is approved for acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults
Mania Matters
Episodes Associated With Neuroanatomic Change?

T1-weighted sagittal MRI anterior cingulate/medial prefrontal cortex
PRESS 1H-MRS (TR/TE = 3s/30ms voxel size 3x3x3 cm³)

Frye et al, Psychiatry Res. 2007; Tsai et al, Prog Neurobiol 1995;
Mania and the Law in California: Understanding the Criminalization of the Mentally Ill

“History seems to be repeating itself. There are again a substantial number of mentally ill individuals behind bars.”

Time from release to arrest N=66

Quanbeck, Frye, and Altshuler 2003 Am J Psychiatry
Acute mania outline

• Treatment goals and mood stabilization
  • Sleep restoration
  • Reduction of behavioral activation

• Review merits of mood stabilizing medications
  • Lithium
  • Core foundational anticonvulsant mood stabilizers
  • Atypical antipsychotic drugs

• Conclusion
Mania is an EMERGENCY

• Need rapid, safe stabilization
• Reduction of behavioral agitation
• Sleep restoration and management of withdrawal from drugs and alcohol
• Antimanic treatment based on
  • Manic episode (mixed vs manic)
  • Rapid cycling or psychotic symptoms
  • Patient’s medication history
  • Presence of comorbidities
  • Willingness to accept therapy
Acute management of agitated patient

• Agitation mild to moderate, cooperative, non-psychotic
  • Oral lorazepam 1-2 mg, repeat 1-2 mg Q 30-60 min until calm (or max dose 10-15 mg)

• Agitation mild to moderate, cooperative, (+) evidence of psychosis*
  • Oral olanzapine 5-10 mg
  • Oral risperidone 0.5-2.0 mg
  • Oral quetiapine 25-100 mg
  • Oral haloperidol 1-5 mg (anticholinergic is antipsychotic-naïve or EPS sensitive)

* Use lorazepam if suspected catatonia, NMS, or significant EPS.
Acute management of agitated patient

- Moderate to severe, uncooperative, +/- psychosis
  - **Haloperidol** 5-10 mg IM + **lorazepam** 1-2 mg IM (anticholinergic if neuroleptic naïve or EPS sensitive)
  - **Ziprasidone** 10-20 mg IM (repeat Q 2-4 hours as needed until calm, or max dose 40 mg/24 hours)
  - **Olanzapine** 10 mg IM (repeat after 2 hours until calm, or max dose 30 mg/day)
  - **Aripiprazole** 9.75 mg IM (repeat after 2 hours until calm, or max dose 30 mg/day)

Orally inhaled loxapine powder

- **Dosing:** 10 mg single inhaled dose (one/24 hrs)

- **Pooled analysis** of two Phase III randomized trials (one in schizophrenia, one in BP-I)

- **NNT (vs. PLC) for positive response:**
  - Loxapine 5 mg, NNT 4
  - Loxapine 10 mg, NNT 3

- **NNT (vs. PLC) for requiring only one dose of study drug without rescue medication:**
  - Loxapine 5 mg, NNT – n.s.
  - Loxapine 10 mg, NNT 7

*Citrome L. Int J Clin Pract. 2012*
Double-Blind Comparison of Clonazepam vs Lorazepam in Acute Mania

Double-blind comparison of clonazepam and lorazepam monotherapy (14 days) in 24 patients with acute mania

- Lorazepam: N=13 (Mean dose 12 ± 4.1 mg)
- Clonazepam: N=11 (Mean dose 11.3 ± 4.1 mg)

- 7-day Response
  - CGI Improvement 1 or 2: 46% (p < 0.10)
  - CGI Improvement 1 or 2: 9% (p < 0.10)

- 14-day Remission
  - CGI Improvement 1 or 2: 61% (p < 0.05)
  - CGI Improvement 1 or 2: 18%

- Remission
  - 39%
  - 0%

## FDA Approved Bipolar Disorder Treatments*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Manic</th>
<th>Mixed</th>
<th>Depression</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
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<tr>
<td>Asenapine</td>
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<td>+</td>
<td>–</td>
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</tr>
<tr>
<td>Cariprazine</td>
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<td>–</td>
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<tr>
<td>Lurasidone</td>
<td>–</td>
<td>–</td>
<td>+</td>
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<tr>
<td>Olanzapine</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
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<tr>
<td>Olanzapine/Fluoxetine</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Quetiapine/XR</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Risperidone (Oral / IM)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+ (IM)</td>
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<tr>
<td>Ziprasidone</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Chlorpromazine</td>
<td>+</td>
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<td>Carbamazepine ER</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Divalproex DR/ER</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Lamotrigine</td>
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<td>+</td>
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<tr>
<td>Lithium</td>
<td>+</td>
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</tbody>
</table>

*Aripiprazole, Asenapine, Olanzapine, Quetiapine, Risperidone indication as monotherapy and adjunct to Li or DVPX and with / without psychosis*
Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis

Andrea Cipriani, Corrado Barbui, Georgia Salanti, Jennifer Rendell, Rachel Brown, Sarah Stockton, Marianna Purgato, Loukia M Spinieli, Guy M Goodwin, John R Geddes

Systematic review of 68 randomized trials of pharmacotherapy for acute mania in adults (16,073 patients);

Any-cause early discontinuation is proxy for “acceptability”

Multiple treatments meta-analysis (accounts for direct and indirect comparisons)
Cariprazine for Acute Mania Associated With Bipolar I Disorder

Randomized, DB, PLC-controlled trial (2010-2011); cariprazine 3-6 mg/d vs. cariprazine 6-12 mg/d vs. PLC over 3 weeks; 497 patients with BP-I manic or mixed episodes; primary endpoint – change YMRS total score; secondary endpoints – response, remission

Calabrese et al., J Clin Psychiatry 2015
Atypical Antipsychotics in Acute Mania

Pros

• As a class, effective in acute mania and mixed episodes
• Rapid control of acute mania/mixed, rapid cycling, psychosis/no psychosis
• Sustained improvement of symptoms

Cons

• Tardive dyskinesia, neuroleptic malignant syndrome
• Weight gain, related dysmetabolic effects

Typical Antipsychotics in Acute Mania

Pros

• Efficacious for acute mania
• Haloperidol may be more rapidly efficacious than olanzapine, quetiapine, ziprasidone

Cons/adverse effects

• Acute EPS, tardive dyskinesia, akathisia, neuroleptic malignant syndrome

Negative impact on course of illness

• ↑ post-mania depressive symptom severity
• ↑ frequency of major depressive episodes

Lithium in Acute Mania

- Gold standard – benchmark
- Lithium non-response differs from other mood stabilizers
- Clinical predictors account for <50% of variance, suggesting genetic factors
- Prophylactic response familial
- Numerous side effects, narrow therapeutic index
- Believed to reduce suicide rates via unknown mechanism

Advertisement from *Harper's New Monthly Magazine*, 1892, from the author's collection

### Variable Lithium Response Rate

Based on Bipolar Subtype

<table>
<thead>
<tr>
<th>Poor Response (30%)</th>
<th>Rapid Cycling</th>
<th>Mixed Mania</th>
<th>Substance Abuse</th>
<th>(+) Family History</th>
<th>&gt;3 Episodes</th>
<th>DMI Pattern</th>
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<table>
<thead>
<tr>
<th>Good Response (70%)</th>
<th>Nonrapid Cycling</th>
<th>Euphoric Mania</th>
<th>No Substance Abuse</th>
<th>(+) Family History</th>
<th>Few Lifetime Episodes</th>
<th>MDI Pattern</th>
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</table>

**DMI** = Depression → mania → euthymic interval; **MDI** = Mania → depression → euthymic interval

National Institute of Mental Health (NIMH)
International Group for The Study of Lithium Treated Patients (IGSLI)

• 4 linked SNPs chromosome 21 associated with lithium response (rs79663003, p=1.37 × 10^{-8}; rs78015114, p=1.31 × 10^{-8}; rs74795342, p=3.31 × 10^{-9}; and rs75222709, p=3.50 × 10^{-9})
• Replicated prospective study (n=73) lithium monotherapy x 2 years (p=0.03268, hazard ratio 3.8, 95% CI 1.1-13.0)
• Response-associated region-2 genes for long, non-coding RNAs (IncRNAs) increasingly recognized regulators of gene expression AL157359.3 and AL157359

Hou et al., Lancet 2016
Valproate for Mania: Dose-response effect

Prospective study of 374 patients with acute mania stratified into 6 groups based on VPA serum level ranges (lowest level ≤ 55.0 mcg/mL)

RESULTS

• Linear relationship between VPA serum level and therapeutic response

• Efficacy significantly > PLC beginning at 71.4-85.0 mcg/mL (consistent at all higher VPA concentrations)

• ES was associated with highest VPA serum levels (>94 mcg/mL)

Divalproex & Carbamazepine in Acute Mania

Pros
- Effective in manic and mixed episodes
- Effective in alcohol withdrawal & relapse prevention
- Several effective in migraine prevention

Cons
- Ineffective in acute mania (LTG, TPX, GBP)
- P450 3A/4 heteroinduction
- Weight gain & endocrine disturbances (VAL)
- Teratogenicity (VAL, CBZ)
- Rash risk

CBZ = carbamazepine; VAL = valproate; LTG = lamotrigine; GBP = gabapentin; OLZ = olanzapine.
DVPX = divalproex; TPX = topiramate
Other anticonvulsant drugs

- **Oxcarbazepine**
  - One negative randomized, DB, PLC-controlled trial
  - No PLC-controlled studies in adults

- **Lamotrigine**
  - Two unpublished negative trials

- **Gabapentin**
  - Negative PLC-controlled add-on study (LI, VPA)

- **Topiramate**
  - Four negative PLC-controlled trials

References:
ECT for Acute Mania

• Electroconvulsive therapy (ECT) is a mood stabilizer

• 2 controlled studies of acute mania
  • ECT vs lithium
  • ECT vs lithium + haloperidol,

• ECT reported significant benefits for acute mania
<table>
<thead>
<tr>
<th>AGENT</th>
<th>MONO</th>
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<tbody>
<tr>
<td>Lithium</td>
<td>0.8 - 1.2 mmol/L</td>
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<tr>
<td>Divalproex</td>
<td>90 - 125 mg/L</td>
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<tr>
<td>Carbamazepine</td>
<td>4-12 mcg/ml vs 800 mg</td>
</tr>
<tr>
<td>Asenapine</td>
<td>10 mg bid sublingual</td>
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<tr>
<td>Olanzapine</td>
<td>10-20 mg/d</td>
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<tr>
<td>Risperidone</td>
<td>4 - 5 mg/d</td>
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<tr>
<td>Quetiapine</td>
<td>600 - 800 mg/d</td>
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<tr>
<td>Ziprasidone</td>
<td>80-120 mg/d</td>
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<tr>
<td>Aripiprazole</td>
<td>15 - 30 mg/d</td>
</tr>
<tr>
<td>Clozapine</td>
<td>150-450 mg</td>
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<tr>
<td>Cariprazine</td>
<td>3-6 mg/d</td>
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## Mood Stabilizer
### Safety and Tolerability Concerns

<table>
<thead>
<tr>
<th></th>
<th>Lithium</th>
<th>Valproate</th>
<th>Carbamazepine</th>
<th>Lamotrigine</th>
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<tr>
<td>Gastrointestinal</td>
<td>Gastrointestinal</td>
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<td>Gastrointestinal</td>
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<td>Weight gain</td>
<td>Weight gain</td>
<td>Weight gain</td>
<td>Rash</td>
<td>Rash</td>
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<tr>
<td>Neurotoxicity</td>
<td>Tremor</td>
<td>Neurotoxicity</td>
<td>Headache</td>
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<tr>
<td>Renal toxicity</td>
<td>Hepatotoxicity</td>
<td>Hepatotoxicity</td>
<td>Dizziness</td>
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<tr>
<td>Thyroid toxicity</td>
<td>Thrombocytopenia</td>
<td>Thyroid changes</td>
<td>Pruritis</td>
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<tr>
<td>Hair Loss</td>
<td>Hair Loss</td>
<td>Blood dyscrasias</td>
<td>Dream abnormality</td>
<td></td>
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<tr>
<td>Cardiac toxicity</td>
<td>Pancreatitis</td>
<td>Cardiac toxicity</td>
<td></td>
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<tr>
<td>Acne, Psoriasis</td>
<td>PCOS</td>
<td>Hyponatremia</td>
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<td>Teratogen</td>
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<tr>
<td>Suicidality (?)</td>
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= boxed warning in prescribing information; (?) = recent alert


All Mood Stabilizers Have at Least One Boxed Warning
# Antipsychotic Safety and Tolerability Concerns

## First-Generation
- Depression
- Akathisia
- Acute dystonia
- Tardive dyskinesia<sup>a</sup>
- Weight gain
- Sedation
- Anticholinergic
- Cardiac, Orthostasis
- Hyperprolactinemia
- Neuroleptic malignant<sup>a</sup>
- Cardiac/pneumonia in older adults<sup>a</sup>

## Second-Generation
- Weight gain
- Sedation
- Hyperglycemia, Diabetes<sup>b</sup>
- Suicidality in age ≤ 24<sup>c</sup>
- Akathisia
- Hyperprolactinemia
- Cerebrovascular in elderly<sup>d</sup>
- Cardiac, Orthostasis
- Tardive dyskinesia<sup>a</sup>
- Neuroleptic malignant<sup>a</sup>
- Cardiac/pneumonia in older adults<sup>a</sup>

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Warnings - boxed; <sup>a</sup> antipsychotic class warning; <sup>b</sup> Second generation antipsychotic class warning; <sup>c</sup> aripiprazole, quetiapine, olanzapine + fluoxetine combination (antidepressant class warning); <sup>d</sup> risperidone, olanzapine, aripiprazole


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**All Antipsychotics Have at Least One Boxed Warning**
Mania Matters

• Treat the illness
  • Short term high dose benzodiazepine, sleep restoration, containment

• Individualize treatment
  • Right medication to the right patient

• Improve psychoeducation

• Enhance treatment adherence and minimize side effect burden