Maryland
DEPARTMENT OF HEALTH

EXPLORING ANTIPSYCHOTICS

Continuing Education Seminar

Saturday, May 6, 2023

A virtual program provided by the Maryland Department of Health Office of Pharmacy Services in collaboration with Kepro.

Continuing Medical Education (CME) &
Pharmacy Continuing Education (ACPE) Seminar

EXPLORING ANTIPSYCHOTICS

Virtual Live Program
on
Saturday, May 6, 2023

8:50 am – Introductions	Maryland Department of Health Office of Pharmacy Services
9:00 am – Out With the Old and In With the New? A Review and Update of Available Antipsychotics	Chelsea Di Polito, PharmD, BCPP University of Maryland School of Pharmacy
10:30 am – Use of Antipsychotics in the Pediatric Population: Is it too much?	Sandra Mitchell, PharmD, BCPP Virginia Commonwealth University School of Pharmacy
12:00 pm – Pharmacogenomics in Psychiatry: Is there a role?	Megan Ehret, PharmD, BCPP University of Maryland School of Pharmacy
1:00 pm – Closing Remarks	Maryland Department of Health Office of Pharmacy Services

1:15 pm - Adjourn

The views and opinions expressed by the speakers are not necessarily the views and opinions of the State of Maryland Department of Health.

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Activity Type: Knowledge-Based

OUT WITH THE OLD AND IN WITH THE NEW?

A REVIEW AND UPDATE OF AVAILABLE ANTIPSYCHOTICS

Chelsea Di Polito, PharmD, BCPP

Assistant Director, Pharmacy Administration – Clinical Services

University of Maryland School of Pharmacy

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Objectives

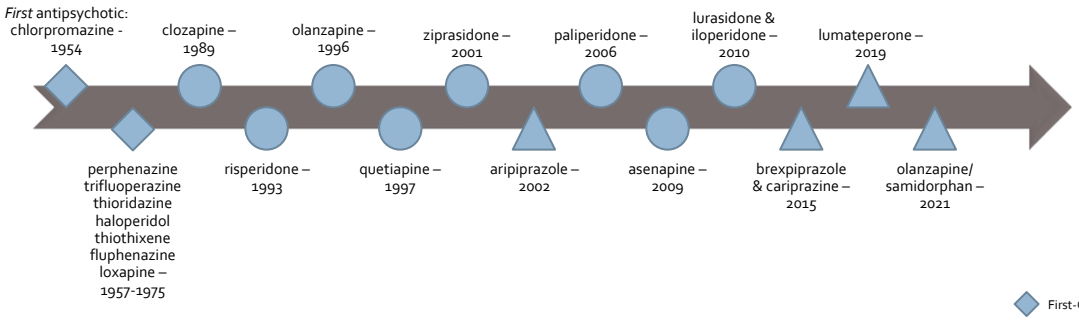
1. List the commercially available antipsychotics
2. Categorize the available antipsychotics by mechanism
3. Distinguish effectiveness and tolerability profiles of first and second-generation antipsychotics to the newer novel antipsychotics
4. Utilizing the current literature of novel antipsychotics, interpret statistical vs clinical significance of primary outcomes
5. Given a patient, recommend which antipsychotic(s) would be appropriate to prescribe and dispense

2

ANTIPSYCHOTIC OVERVIEW

3

Timeline of FDA-Approval



W W Shen. *Compr Psychiatry*. 1999 Nov-Dec;40(6):407-14.
Drugs@FDA: FDA-Approved Drugs. U.S. Food & Drug Administration. Retrieved April 5, 2023, from https://www.accessdata.fda.gov/scripts/cder/daf/

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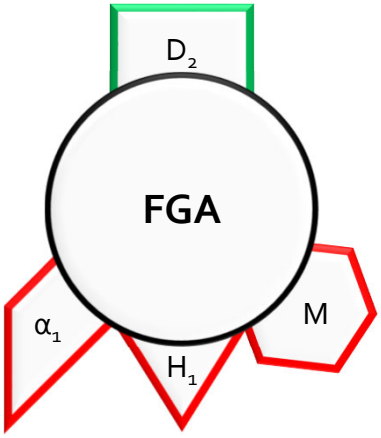
First-Generation Antipsychotics (FGAs)

Commercially Available*:

- Chlorpromazine
- Fluphenazine
- Haloperidol
- Loxapine
- Perphenazine
- Thiothixene
- Thioridazine
- Trifluoperazine



*Must be FDA-approved to treat schizophrenia and/or bipolar disorder

Richelson E. *J Clin Psychiatry.* 1999;60[suppl 10]:5-14.

5

First-Generation Antipsychotics (FGAs)

Dopamine, subtype 2 (D_2) - antagonist

- Relief of psychosis, worsening of negative symptoms*, prolactin elevation*, extrapyramidal symptoms*

Alpha, subtype 1 (α_1) - antagonist

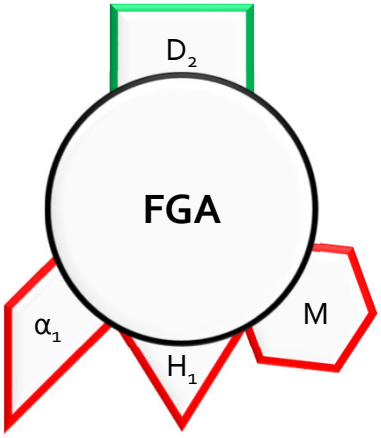
- Dizziness

Histamine, subtype 1 (H_1) – antagonist

- Sedation/somnolence, weight gain

Muscarinic receptors, *multiple* (M) – antagonist

- Anticholinergic symptoms (e.g. dry mouth, constipation, confusion, etc.)



*Undesirable effects

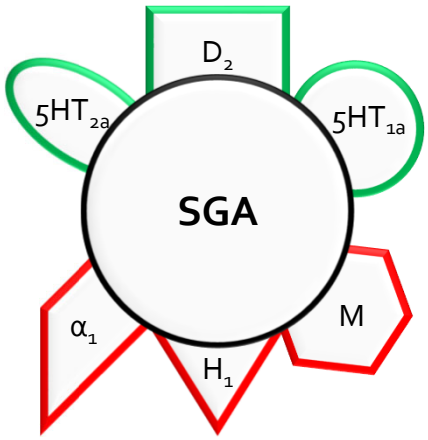
Richelson E. *J Clin Psychiatry.* 1999;60[suppl 10]:5-14.

6

Second-Generation Antipsychotics

Commercially Available*:

- Asenapine
- Clozapine
- Iloperidone
- Lurasidone
- Olanzapine
- Paliperidone
- Quetiapine
- Risperidone
- Ziprasidone



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Richelson E. *J Clin Psychiatry*. 1999;60[suppl 10]:5-14.
Stahl SM. (2014). *Stahl's essential psychopharmacology*

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Second-Generation Antipsychotics

Serotonin, subtype 2a ($5HT_{2a}$) - antagonist
- Reduction in undesirable side effects of D_2 antagonism, improvement in affective and cognitive symptoms

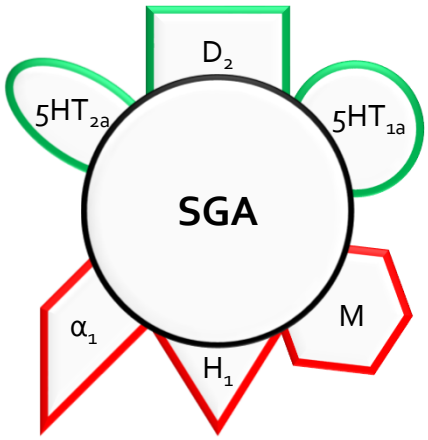
Serotonin, subtype 1a ($5HT_{1a}$) – agonist/partial
- Reduction in undesirable side effects of D_2 antagonism, improvement in affective and cognitive symptoms

Dopamine, subtype 2 (D_2) - antagonist
- Relief of psychosis, worsening of negative symptoms*, prolactin elevation*, extrapyramidal symptoms*

Alpha, subtype 1 (α_1) - antagonist
- Dizziness

Histamine, subtype 1 (H_1) – antagonist
- Sedation/somnolence, weight gain

Muscarinic receptors, *multiple* (M) – antagonist
- Anticholinergic symptoms (e.g. dry mouth, constipation, etc.)



*Undesirable effects

Richelson E. *J Clin Psychiatry*. 1999;60[suppl 10]:5-14.
Stahl SM. (2014). *Stahl's essential psychopharmacology*

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Differences between FGAs and SGAs

Receptor binding and selectivity

✓Rapid dissociation from D_2 receptors

✓Addition of $5HT_{2a}$ antagonism
- Ratio of $5HT_{2a}$ receptor binding > D_2 receptor binding

✓Addition of $5HT_{1a}$ agonism/partial agonism

Side effects

✓Less EPS, prolactin elevation, worsening of negative symptoms

✓More metabolic side effects

Richelson E. *J Clin Psychiatry*. 1999;60[suppl 10]:5-14.
Stahl SM. (2014). *Stahl's essential psychopharmacology*

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Novel Antipsychotics

*Aripiprazole (Abilify®)**

Brexpiprazole (Rexulti®)

Cariprazine (Vraylar®)

Lumateperone (Caplyta®)

Olanzapine/Samidorphan (Lybalvi®)

*Will not be the focus for today

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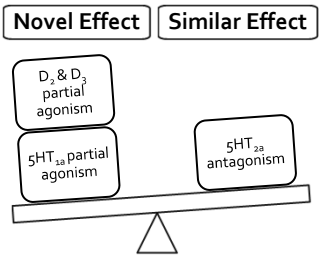
Novel Antipsychotics - **Aripiprazole**

- First "novel" antipsychotic on the market
  - Related to *partial* agonism (PA)
    - Activates receptors, but less than the ligand
    - High binding affinity
    - Acts as an antagonist to anything attempting to bind
- Benefit
  - D_2 PA: Fewer side effects
  - D_3 PA: Pro-cognitive effects? Negative symptom improvement?
  - $5HT_{1a}$ PA: Fewer side effects, improvement in cognition and affect
    - More potent than other SGAs



Potkin SG, et al. *Arch Gen Psychiatry*. 2003;60(7)681-90
Citrome, L. *Current Psychiatry*. 2018 Apr; 17(4): 24-34.
Stahl, S. M. (2014). *Stahl's essential psychopharmacology*

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Trouble with Aripiprazole

- Akathisia
- Agitation/aggression
- Insomnia/activation
- Nausea/vomiting

Why?

- Too much dopamine
  - Intrinsic activity
  - Upregulation of dopamine receptors after antagonist use

Siwek M, Et al. *Brain Sci*. 2023 Mar; 13(3):397.
Lea JW, Et al. *Pharmacotherapy*. 2007 Sep;27(9):1339-42.

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Novel Antipsychotics - **Brexpiprazole**

- Similar to aripiprazole
  - Partial agonism: D_2, D_3, & $5HT_{1a}$
  - Antagonism: $5HT_{2a}$

- Differences
  - Less D_2 partial agonism/intrinsic activity
  - More balanced ratio of D_2:$5HT_{2a}$ receptor binding
  - More potent at $5HT_{1a}$ & $5HT_{2a}$ receptors

Potentially less "troublesome" side effects observed with aripiprazole

Siwek M, Et al. *Brain Sci*. 2023 Mar; 13(3):397.
Eaves S, Et al. *P T*. 2016 Jul; 41(7):818-22.
Citrome, L. *Current Psychiatry*. 2018 Apr; 17(4): 24-34.
Stahl SM. *CNS Spectrums*. 2016 Feb, 21(1), 1-6.

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Novel Antipsychotics - **Cariprazine**

- Similar to aripiprazole & brexpiprazole
  - Partial agonism: D_2, D_3, & $5HT_{1a}$
    - D_2 intrinsic activity similar to brexpiprazole, lower than aripiprazole
  - Antagonism: $5HT_{2a}$

- Differences
  - D_3 PA > D_2 PA
    - Unknown advantage, if any
  - Lower affinity for $5HT_{2a}$
    - Unknown advantage, if any

Citrome L. *Current Psychiatry*. 2018 Apr; 17(4): 24-34.
Riva MA. *Riv Psichiatr*. 2021 Mar-Apr;56(2):1-9.
Stahl SM. *CNS Spectrums*. 2016 Apr, 21(2), 123-127.

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Novel Antipsychotics - **Lumateperone**

- Similarities to SGAs
  - D_2 and $5HT_{2a}$ receptor antagonist

- Differences
  - D_2 <<< $5HT_{2a}$ – much more selective for $5HT_{2a}$
    - Less side effects, less antipsychotic activity at lower doses
  - D_2 pre-synaptic receptor partial agonist
    - Reduces dopamine in the pre-synaptic cleft requiring less D_2 post-synaptic receptor blockade
  - Increases glutamatergic activity by augmenting NMDA and AMPA receptors
    - Antipsychotic and antidepressant effect
  - Serotonin reuptake inhibitor
    - Antidepressant effect

Cooper D, et al. *StatPearls [intenet]*. 2023 Jan.
Titulaer J, et al. *Eur Psychopharmacol*. 2022 Sep;62(22-35).

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Novel Antipsychotics - **Olanzapine/ Samidorphan**

- Similarities to SGAs
  - Olanzapine = olanzapine

- Differences
  - Addition of samidorphan - Mu (μ) opioid receptor antagonist
    - Mitigates weight gain observed with olanzapine monotherapy
      - No change in lipids, insulin sensitivity, glucose levels, nor *reduction* of weight
    - Mechanism not fully understood, but potentially decreases cravings

Haddad HW, et al. *Health Psychology Research*. 2022;10(2).
Das N, et al. *Alpha Psychiatry*. 2022 Jul; 23(4):210-211.

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FDA-Approved Indications

IBM Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Accessed April 12, 2023. http://www.micromedexsolutions.com

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Basic Prescribing Information

	Dosage	Half-Life (hours)	Interactions	How Supplied (mg)
Brexpiprazole	0.5 mg – 4 mg daily	91	Substrate of CYP3A4, CYP2D6	0.25, 0.5, 1, 2, 3, 4
Cariprazine	1.5mg – 6mg daily	48-96	Substrate of CYP3A4	1.5, 3, 4.5, 6
Lumateperone	42mg daily	13-21	Substrate of CYP3A4, UGT	42
Olanzapine/ samidorphan	5mg/10mg – 20mg/10mg	O = 35-52 S = 7-11	O = substrate of CYP1A2 and CYP2D6 S = substrate of CYP3A4, CYP2C19, CYP2C8	5/10, 10/10, 15/10, 20/10

o = olanzapine, s = samidorphan

Brexpiprazole (Rexulti®)[package insert]. Otsuka Pharmaceutical Co. Tokyo, Japan. 2021.
Cariprazine (Vraylar®)[package insert]. Allergan, Inc. Madison, NJ. 2022.
Lumateperone (Caplyta®)[package insert]. Intra-Cellular Therapies, Inc. New York, NY. 2022.
Olanzapine/samidorphan (Lybalvi®)[package insert]. Alkermes, Inc. Waltham, MA. 2021.

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PRIMARY LITERATURE

19

BREXPIPRAZOLE

FDA-Approved Indications:

Schizophrenia

Major Depressive Disorder (MDD), Adjunct

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Brexpiprazole – Schizophrenia

- Three, six-week, randomized, double-blind, placebo-controlled trials
- Acute exacerbation of schizophrenia

Kane JM, 2015	Correll CU, 2015	Ishigooka J, 2018

• n = 674
• Placebo, 1mg, 2mg, 4mg
• Baseline PANSS = 94.9
  • Placebo = -13.53
  • 1mg = -16.90
  • 2mg = -16.61
  • **4mg = -20.00**
• No TEAEs were ≥5% or 2x placebo
	• n = 636
	• Placebo, 0.25mg, 2mg, 4mg
	• Baseline PANSS = 95.2
	  • Placebo = -12.01
	  • 0.25mg = -14.90
	  • **2mg = -20.73**
	  • **4mg = -19.65**
	• No TEAEs were ≥5% or 2x placebo
		• n = 459
		• Placebo, 1mg, 2mg, 4mg
		• Baseline PANSS = 97.3
		  • Placebo = -7.63
		  • 1mg = -8.26
		  • **2mg = -14.95**
		  • 4mg = -11.49
		• TEAEs: N/V/D, hyperprolactinemia, dental caries

PANSS = Positive and Negative Syndrome Scale; TEAE = Treatment-Emergent Adverse Events; N/V/D = Nausea/Vomiting/Diarrhea

Kane JM, et al. *Schizophr Res*. 2015 May;164(1-3):127-35.
Correll CU, et al. *Am J Psychiatry*. 2015 Sep 1;172(9):870-80.
Ishigooka J, et al. *Psychiatry Clin Neurosci*. 2018 Sep;72(9):692-700.

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Positive and Negative Syndrome Scale

- 30-item clinician-administered rating scale
- Three sub-scales
  - Positive
    - 7 questions, rated 1-7 (max = 49)
    - E.g. hallucinatory behavior, grandiosity
  - Negative
    - 7 questions, rated 1-7 (max = 49)
    - E.g. lack of spontaneity, emotional withdrawal
  - General
    - 16 questions, rated 1-7 (max = 112)
    - E.g. anxiety, guilty feelings

Score	Meaning
30	Absent
31-60	Minimal
61-90	Mild
91-120	Moderate
121-150	Moderate Severe
151-180	Severe
181-210	Extreme

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Brexpiprazole – Schizophrenia

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Ishigooka J, et al. *Psychiatry Clin Neurosci*. 2018 Sep;72(9):692-700.

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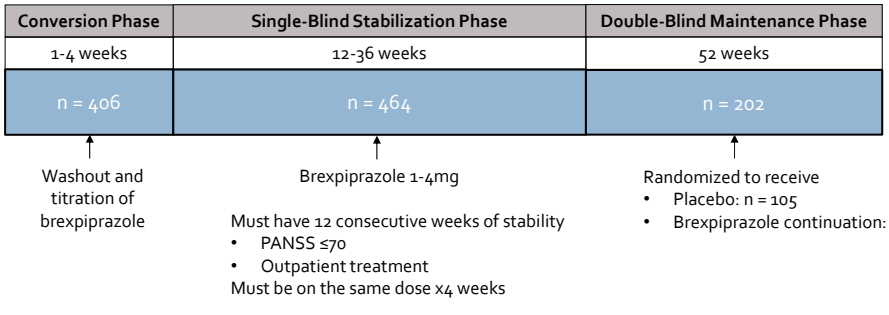
Brexpiprazole – Schizophrenia

- Fleischhacker WW – 2017; Randomized, double-blind, placebo-controlled trial
- Acute exacerbation of schizophrenia



Fleischhacker WW, et al. *Int J Neuropsychopharmacol*. 2017 Jan;20(1):11-21.

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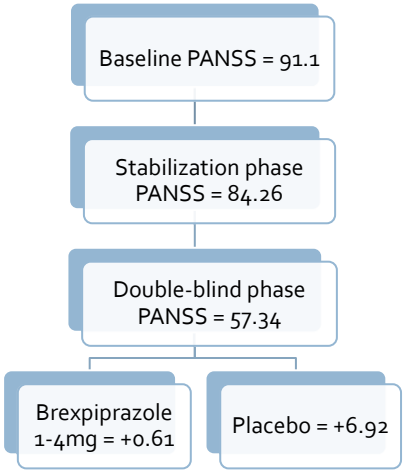
Brexpiprazole – Schizophrenia



- Average dose = 3.4mg
- The mean overall change was ***not*** significant
  - Baseline PANSS to double-blind phase was clinically significant
- Impending relapse at one year, p<0.0001
  - Brexpiprazole = 13.5%
  - Placebo = 38.5%
- TEAEs: insomnia, akathisia, agitation, increased weight, and headache

Fleischhacker WW, et al. *Int J Neuropsychopharmacol.* 2017 Jan;20(1):11-21.

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Brexpiprazole – Schizophrenia

- Two, 52-week open-label trials

Forbes A, 2018	Ishigooka J, 2018

• n = 1024
• New patients and patients from Kane, Correll, and Fleischhacker studies
• Brexpiprazole 1-4mg
  • Average dose: 3mg
• Baseline PANSS = 68.5
  • Change at 52 weeks = -12.2
  • No statistical analysis
• TEAEs: insomnia, weight gain, headache, agitation
	• n = 282
	• New patients and patients from Ishigooka study
	• Brexpiprazole 1-4mg
	  • Average dose: 3.1mg
	• Baseline PANSS = 72.7
	  • Change at 52 weeks = -7.67
	  • No statistical analysis
	• TEAEs: nasopharyngitis, akathisia, weight gain

PANSS = Positive and Negative Syndrome Scale; TEAE = Treatment-Emergent Adverse Events

Forbes A, et al. *Int J Neuropsychopharmacol.* 2018 May;21(5):433-41.
Ishigooka J, et al. *Psychiatry Clin Neurosci.* 2018 Jun;72(6):445-53.

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Brexpiprazole – MDD, Adjunct

- Three, six-week, randomized, double-blind, placebo-controlled trials
- Patients with MDD and an inadequate response during an 8-week, single-blind, active + placebo phase

Thase ME, 2015	Thase ME, 2015	Hobart M, 2018

• n = 669
• Placebo, 1mg, 3mg
• Baseline MADRS = 26.5
  • Placebo = -6.33
  • Brexpiprazole 1mg = -7.64
  • **Brexpiprazole 3mg = -8.29**
• TEAEs: akathisia, headache, somnolence, nasopharyngitis, weight gain
	• n = 378
	• Placebo, 2mg
	• Baseline MADRS = 26.9
	  • Placebo = -5.15
	  • **Brexpiprazole 2mg = -8.36**
	• TEAEs: weight gain, akathisia
		• n = 393
		• Placebo, 2mg
		• Baseline MADRS = 26.7
		  • Placebo = -8.1
		  • **Brexpiprazole 2mg = -10.4**
		• TEAEs: akathisia, restlessness, weight gain, upper respiratory infection

MDD = Major Depressive Disorder; MADRS = Montgomery-Asberg Depression Rating Scale; TEAE = Treatment-Emergent Adverse Events

Thase ME, et al. *J Clin Psychiatry*. 2015 Sep;76(9):1232-40.
Thase ME, et al. *J Clin Psychiatry*. 2015 Sep;76(9):1224-31.
Hobart M, et al. *J Clin Psychiatry*. 2018 Aug;79(4).

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Montgomery-Asberg Depression Rating Scale

- 10-item, clinician-administered rating scale, each rated 0-6
  1. Apparent sadness
  2. Reported sadness
  3. Inner tension
  4. Reduced sleep
  5. Reduced appetite
  6. Concentration difficulties
  7. Lassitude
  8. Inability to feel
  9. Pessimistic thoughts
  10. Suicidal thoughts

Score	Meaning
0-6	Normal/Absent
7-19	Mild depression
20-34	Moderate depression
35-60	Severe depression

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Brexpiprazole – MDD, Adjunct

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Thase ME, et al. *J Clin Psychiatry*. 2015 Sep;76(9):1224-31.
Hobart M, et al. *J Clin Psychiatry*. 2018 Aug;79(4).

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Brexpiprazole – MDD, Adjunct

- One, 24-week, randomized, double-blind, placebo-controlled trial
- Patients with MDD and an inadequate response during an 8-week, single-blind, active + placebo phase

Bauer M, 2019

• n = 885
• Placebo, 1mg-3mg
  • Average dose: 2.69mg
• Baseline MADRS = 25.9
  • Placebo = -12.3
  • Brexpiprazole 1-3mg = -11.9
  • Not statistically significant
• TEAEs: weight gain, headache, nasopharyngitis

MDD = Major Depressive Disorder; MADRS = Montgomery-Asberg Depression Rating Scale;
TEAE = Treatment-Emergent Adverse Events

Bauer M, et al. *Acta Neuropsychiatr*. 2019 Feb;31(1):27-35.

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Brexpiprazole Summary

- Use in schizophrenia
  - Ideal dose: 2-4mg
  - Effective at treating an acute exacerbation in six-weeks and preventing relapse at one year when compared to placebo
  - Common adverse events: akathisia, weight gain, headache

- Use as adjunct treatment in MDD
  - Ideal dose: 2-3mg
  - Effective at treating an acute episode of depression at six-weeks
    - Long-term effectiveness questionable
  - Common adverse events: akathisia, weight gain, headache

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CARIPRAZINE

FDA-Approved Indications:

Schizophrenia

Bipolar 1 Disorder, Acute mixed or manic episodes

Bipolar 1 Disorder, Depressed

Major Depressive Disorder, Adjunct

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Cariprazine – Schizophrenia

- One, six-week, randomized, double-blind, placebo-controlled proof of concept
- Exacerbation of schizophrenia

Durgam S, 2016

- n = 377
- Placebo, flexibly dosed at 1.5mg-4.5mg OR 6mg-12mg
  - Average dose: 3.83mg and 8.70mg (respectively
- Baseline PANSS = 95.05
  - Placebo = -9.74
  - Cariprazine 1.5mg-4.5mg = -14.53
  - Cariprazine 6mg-12mg = -12.62
    - Neither statistically significant
- TEAEs: akathisia, restlessness, tremor, back pain, extrapyramidal disorder

PANSS = Positive and Negative Syndrome Scale; TEAE = Treatment-Emergent Adverse Events

Durgam S, et al. *Int Clin Psychopharmacol.* 2016 Mar;31(2):61-8.

33

Cariprazine – Schizophrenia

- Two, six-week, randomized, double-blind, placebo-controlled trials
- Exacerbation of schizophrenia

Durgam S, 2014

- n = 711
- Placebo, 1.5mg, 3mg, 4.5mg, risperidone 4mg
- Baseline PANSS = 97.28
  - Placebo = -11.8
  - **1.5mg = -19.4**
  - **3mg = -20.7**
  - **4.5mg = -22.3**
  - **Risperidone 4mg = -26.9***
- TEAEs: insomnia, EPD, akathisia, nausea, sedation, dizziness, constipation

Kane JM, 2015

- n = 439
- Placebo, flexibly dosed at 3mg-6mg OR 6mg-9mg
  - Average dose: 5.2mg and 7.7mg
- Baseline PANSS = 96.4
  - Placebo = -16.0
  - **Cariprazine 3mg-6mg = -22.8**
  - **Cariprazine 6mg-9mg = -25.9**
- TEAEs: akathisia, EPD, tremor, vomiting, weight gain, diarrhea

*Risperidone used only for assay sensitivity
PANSS = Positive and Negative Syndrome Scale; TEAE = Treatment-Emergent Adverse Events; EPD = Extra-pyramidal Disorder

Durgam S, et al. *Schizophr Res.* 2014 Feb;152(2-3):450-7.
Kane JM, et al. *J Clin Psychopharmacol.* 2015 Aug;35(4):367-73.

34

Cariprazine – Schizophrenia

- Two, long-term, open-label trials

Durgam S, 2016

- n = 751, then 200
- 20 week trial, followed by double-blind up to 72 weeks
- Current exacerbation of schizophrenia
- Cariprazine 3-9mg (20 week); 3-9mg or placebo
  - Average dose: not defined; 4.5mg modal dose (67.7%)
- Relapse = 47.5% (placebo) vs **24.8% (cariprazine)**
- Baseline PANSS = 91.3
  - Change at 20 weeks = -22.8
- Baseline PANSS in extension = 50.9
  - Placebo = +13.2
  - Cariprazine = +5.0

No statistical analysis

- TEAEs: akathisia, headache, insomnia, tremor, back pain

Durgam S, 2017

- n = 92
- 48 week extension study to evaluate *safety/tolerability*
- Patients from the 2014 Durgam study
- Cariprazine flexibly dosed 1.5mg-4.5mg
  - Average dose: not defined
- Baseline PANSS = 65.6
  - Change at 48 weeks = -6.8
    - No statistical analysis
- TEAEs: akathisia, insomnia, weight gain, headache, nasopharyngitis, agitation, anxiety, dizziness, psychosis, tremor, extrapyramidal disorder, constipation, diarrhea, dyspepsia, sedation, somnolence

PANSS = Positive and Negative Syndrome Scale; TEAE = Treatment-Emergent Adverse Events

Durgam S, et al. *Schizophr Res.* 2016 Oct;176(2-3):264-71.
Durgam S, et al. *Psychipharmacology (Berl).* 2017 Jan;234(2):199-209.

35

Cariprazine – Bipolar Acute Mixed/Manic

- Three, three-week, randomized, double-blind, placebo-controlled trials
- Bipolar 1 disorder, acute manic/mixed episode

Durgam S, 2015

- n = 235
- Placebo, 3mg-12mg
  - Average dose: 8.8mg
- Baseline YMRS = 30.4
  - Placebo = -8.9
  - **Cariprazine 3mg-12mg = -15.0**
- TEAEs: Extrapyramidal disorder, akathisia

Calabrese JR, 2015

- n = 492
- Placebo, 3mg-6mg OR 6mg-12mg
  - Average dose: 4.8mg and 9.1mg
- Baseline YMRS = 32.9
  - Placebo = -12.5
  - **Cariprazine 3mg-6mg = -18.6**
  - **Cariprazine 6mg-12mg = -18.5**
- TEAEs: akathisia, nausea, constipation, tremor

Sachs GS, 2015

- n = 310
- Placebo, 3mg-12mg
  - Average dose: not defined
- Baseline YMRS = 32.2
  - Placebo = -15.3
  - **Cariprazine 3mg-12mg = -19.6**
- TEAEs: akathisia, extrapyramidal disorder, tremor, dyspepsia, vomiting, dizziness, diarrhea, somnolence, restlessness, pyrexia

BiD = Bipolar 1 Disorder; YMRS = Young Mania Rating Scale; TEAE = Treatment-Emergent Adverse Events

Durgam S, et al. *Bipolar Disord.* 2015 Feb;17(1):63-75.
Calabrese JR, et al. *J Clin Psychiatry.* 2015 Mar;76(3):284-92.
Sachs GS, et al. *J Affect Disord.* 2015 Mar;174:296-302.

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Young Mania Rating Scale

- 11-item clinical interview scale with evaluation of symptoms over the previous 48 hours, all rated 0-4, except for items with a * (these are rated 0-8)
  1. Elevated mood
  2. Increased motor activity-energy
  3. Sexual interest
  4. Sleep
  5. Irritability*
  6. Speech (rate and amount)*
  7. Language-thought disorder
  8. Content*
  9. Disruptive-aggressive behavior*
  10. Appearance
  11. Insight

Score	Meaning
≤12	Absent/remission
13-19	Minimal symptoms
20-25	Mild mania
26-37	Moderate mania
38-60	Severe mania

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Cariprazine – Bipolar Acute Mixed/Manic

- Three, three-week, randomized, double-blind, placebo-controlled trials
- Bipolar 1 disorder, acute manic/mixed episode

Durgam S, 2015

- n = 235
- Placebo, 3mg-12mg
  - Average dose: 8.8mg
- Baseline YMRS = 30.4
  - Placebo = -8.9
  - **Cariprazine 3mg-12mg = -15.0**
- TEAEs: Extrapyramidal disorder, akathisia

Calabrese JR, 2015

- n = 492
- Placebo, 3mg-6mg OR 6mg-12mg
  - Average dose: 4.8mg and 9.1mg
- Baseline YMRS = 32.9
  - Placebo = -12.5
  - **Cariprazine 3mg-6mg = -18.6**
  - **Cariprazine 6mg-12mg = -18.5**
- TEAEs: akathisia, nausea, constipation, tremor

Sachs GS, 2015

- n = 310
- Placebo, 3mg-12mg
  - Average dose: not defined
- Baseline YMRS = 32.2
  - Placebo = -15.3
  - **Cariprazine 3mg-12mg = -19.6**
- TEAEs: akathisia, extrapyramidal disorder, tremor, dyspepsia, vomiting, dizziness, diarrhea, somnolence, restlessness, pyrexia

B1D = Bipolar 1 Disorder; YMRS = Young Mania Rating Scale; TEAE = Treatment-Emergent Adverse Events

Durgam S, et al. *Bipolar Disord*. 2015 Feb;17(1):63-75.
Calabrese JR, et al. *J Clin Psychiatry*. 2015 Mar;76(3):284-92.
Sachs GS, et al. *J Affect Disord*. 2015 Mar;174:296-302.

38

Cariprazine – Bipolar Depression

- Two, six-week, randomized, double-blind, placebo-controlled trials
- Bipolar 1 disorder, currently depressed

Earley W, 2019	Earley W, 2020

• n = 474
• Placebo, 1.5mg, 3mg
• Baseline MADRS = 30.6
  • Placebo = -12.6
  • **Cariprazine 1.5mg = -15.1**
  • **Cariprazine 3mg = -15.6**
• TEAEs: nausea, akathisia, dizziness, sedation
	• n = 478
	• Placebo, 1.5mg, 3mg
	• Baseline MADRS = 31.4
	  • Placebo = -12.4
	  • **Cariprazine 1.5mg = -14.8**
	  • Cariprazine 3mg = -14.1
	• TEAEs: akathisia, restlessness, nausea, fatigue

MADRS = Montgomery-Asberg Depression Rating Scale; TEAE = Treatment-Emergent Adverse Events

Earley WR, et al. *Am J Psychiatry*. 2019 Jun;176(6):439-48.
Earley WR, et al. *CNS Spectr*. 2020 Aug;25(4):502-10.

39

Cariprazine – Bipolar Depression

- Two, eight-week, randomized, double-blind, placebo-controlled trials

Durgam S, 2016	Yatham LN, 2020

• n = 571
• Bipolar 1 disorder, current depressive episode
• Placebo, 0.75mg, 1.5mg, 3mg
• Baseline MADRS = 30.6
  • Placebo = -11.1
  • Cariprazine 0.75mg = -13.0
  • **Cariprazine 1.5mg = -15.1**
  • Cariprazine 3mg = -13.7
• TEAEs: akathisia
	• n = 224
	• Bipolar 1 or 2 depression
	• Placebo, 0.25-0.5mg OR 1.5-3mg
	  • Average dose: 0.35mg and 1.52mg
	• Baseline MADRS = 30.5
	  • Placebo = -16.6
	  • Cariprazine 0.25-0.5mg = -16.8
	  • Cariprazine 1.5-3mg = -16.1
	  • Not statistically significant
	• TEAEs: insomnia, akathisia, dry mouth, nausea, weight gain, diarrhea, restlessness, vomiting, musculoskeletal stiffness, migraine, cough

MADRS = Montgomery-Asberg Depression Rating Scale; TEAE = Treatment-Emergent Adverse Events

Durgam S, et al. *Am J Psychiatry*. 2016 Mar;173(3):271-81.
Yatham LN, et al. *Int Clin Psychopharmacol*. 2020 May;35(3):147-56.

40

Cariprazine – MDD, Adjunct

- Two, short-term, randomized, double-blind, placebo-controlled trials
- Major depressive episode with inadequate response to an antidepressant alone

Durgam S, 2016	Sachs GS, 2023

• n = 808
• Eight week trial
• Adjunctive placebo, 1-2mg, 2-4.5mg
  • Average dose: 1.4mg and 2.6mg
• Baseline MADRS = 29.1
  • Placebo = -12.5
  • Cariprazine 1-2mg = -13.4
  • **Cariprazine 2-4.5mg = -14.6**
• TEAEs: akathisia, insomnia, nausea, restlessness, somnolence, fatigue, tremor, dizziness, constipation, increased appetite
	• n = 751
	• Six week trial
	• Adjunctive placebo, 1.5mg, 3mg
	• Baseline MADRS = 32.5
	  • Placebo = -11.5
	  • **Cariprazine 1.5mg = -14.1**
	  • Cariprazine 3mg = -13.1
	• TEAEs: akathisia, nausea

MDD = Major Depressive Disorder; MADRS = Montgomery-Asberg Depression Rating Scale; TEAE = Treatment-Emergent Adverse Events

Durgam S, et al. *J Clin Psychiatry*. 2016 Mar;77(3):371-8.
Sachs GS, et al. *Am J Psychiatry*. 2023 Mar;180(3):241-51.

41

Cariprazine – MDD, Adjunct

- Two, 16-week, randomized, double-blind, placebo-controlled trials
- Major depressive episode with an eight-week lead-in of antidepressant therapy alone

Earley WR, 2018	Fava M, 2018

• n = 527
• Adjunctive placebo, 1.5mg-4.5mg
  • Average dose: 2.97mg
• Baseline MADRS = 25.3
  • Placebo = -7.7*
  • Cariprazine 1.5-4.5mg = -7.8*
  • Not statistically significant
• TEAEs: akathisia, restlessness, somnolence
	• n = 230
	• Placebo, 0.1mg-0.3mg OR 1mg-2mg
	  • Average dose: 0.2mg and 1.1mg
	• Baseline MADRS = 26.4
	  • Placebo = -8.0
	  • Cariprazine 0.1-0.3mg = -7.5
	  • Cariprazine 1-2mg = -9.8
	  • Not statistically significant
	• TEAEs: headache, restlessness, fatigue, increased appetite, insomnia, dry mouth, constipation

*Approximate – not directly reported
MDD = Major Depressive Disorder; MADRS = Montgomery-Asberg Depression Rating Scale; TEAE = Treatment-Emergent Adverse Events

Earley WR, et al. *Psychopharmacol Bull*. 2018 Jun;48(4):62-80.
Fava M, et al. *Int Clin Psychopharmacol*. 2018 Nov;33(6)312-21.

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Cariprazine Summary

- Use in schizophrenia
  - Effective dose: 1.5mg-7.7mg (approved for 1.5mg-6mg)
  - Effective against placebo at treating acute psychosis at six weeks, preventing relapse at 20 weeks, and maintenance in up to 72 weeks
  - Common adverse events: akathisia, GI upset, headache, tremor, insomnia
- Use in bipolar mixed/mania
  - Effective dose: 3mg-9mg (approved for 3mg-6mg)
  - Effective against placebo at treating a manic/mixed episode at three weeks
  - Common adverse events: akathisia, tremor
- Use in bipolar depression
  - Effective dose: 1.5mg-3mg (approved for 1.5mg-3mg)
  - Effective against placebo at treating bipolar depression in up to eight weeks
  - Common adverse events: akathisia, nausea
- Use in major depressive disorder
  - Effective(?) dose: 1.5mg-2.6mg (approved for 1.5mg-3mg)
  - Questionable effectiveness for this indication (clinically significant difference from placebo?)
  - Common adverse events: akathisia, nausea

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LUMATEPERONE

FDA-Approved Indications:

Schizophrenia

Depressive episodes associated with Bipolar 1 or Bipolar 2 Disorder

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Lumateperone – Schizophrenia

- One, four-week, randomized, double-blind, placebo-controlled trial
- Acute exacerbation of schizophrenia

Correll CU, 2020

- n = 435
- Placebo, 28mg, 42mg
- Baseline PANSS = 89.8
  - Placebo = -12.4
  - Lumateperone 28mg = -13.7
  - **Lumateperone 42mg = -15.6**
- TEAEs: Somnolence/sedation, fatigue, constipation

PANSS = Positive and Negative Syndrome Scale;
TEAE = Treatment-Emergent Adverse Events

Correll CU, et al. *JAMA Psychiatry*. 2020 April;77(4):349-58.

45

Lumateperone – Bipolar Disorder

- Two, six-week, randomized, double-blind, placebo-controlled trials
- Bipolar disorder, type 1 or type 2 – currently depressed

Calabrese JR, 2021

- n = 376
- Monotherapy
- Placebo vs lumateperone 42mg
- Baseline MADRS = 30.5
  - Placebo = -12.1
  - **Lumateperone 42mg = -16.7**
- TEAEs: somnolence, nausea

Suppes T, 2023

- n = 519
- Adjunct to concurrent lithium or divalproex
- Placebo, 28mg, 42mg
- Baseline MADRS = 32.3
  - Placebo = -14.5
  - Lumateperone 28mg = -16.2
  - **Lumateperone 42mg = -16.9**
- TEAEs: somnolence, dizziness, nausea

MADRS = Montgomery-Asberg Depression Rating Scale; TEAE = Treatment-Emergent Adverse Events

Calabrese JR, et al. *Am J Psychiatry*. 2021 Dec;178(12):1098-106.
Suppes T, et al. *Bipolar Disord*. 2023 Feb; Online ahead of print.

46

Lumateperone Summary

- Use in schizophrenia
  - Ideal dose: 42mg
  - Effective against placebo at treating acute psychosis at 4 weeks
  - Common adverse events: somnolence/sedation, fatigue, constipation

- Monotherapy and adjunct (to lithium or valproate) in Bipolar 1 or Bipolar 2 disorder in a depressive episode
  - Ideal dose: 42mg
  - Effective against placebo at treating an acute episode depressive episode at six-weeks
  - Common adverse events: somnolence, nausea, dizziness

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OLANZAPINE/ SAMIDORPHAN

FDA-Approved Indications:

Schizophrenia

Bipolar 1 Disorder, Acute mixed or manic episodes

Bipolar 1 Disorder, Maintenance therapy

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Olanzapine/Samidorphan – Schizophrenia

- Martin WF – 2019; Randomized, double-blind, placebo-controlled trial
- Evaluation of weight gain and stability of psychosis

Lead-in Phase	Double-Blind Treatment Phase	Extension Phase
1 week	12 weeks	12 weeks
n = 309	Olanzapine + placebo (n = 75)	Placed on olanzapine + samidorphan 20mg (n = 54)
	Olanzapine + samidorphan 5mg (n = 80)	Olanzapine + samidorphan 5mg (n = 52)
	Olanzapine + samidorphan 10mg (n = 86)	Olanzapine + samidorphan 10mg (n = 57)
	Olanzapine + samidorphan 20mg (n = 68)	Olanzapine + samidorphan 20mg (n = 55)

Switch from current treatment to olanzapine 5-20mg/day

Must be clinically stable
- PANSS ≤80

Must have a stable body weight ≥3 months

Patients were aware of active samidorphan but were blinded by dose

Martin WF, et al. *Am J Psychiatry*. 2019 Jun;176(6):457-67.

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Olanzapine/Samidorphan – Schizophrenia

Weight Change at 12 Weeks

- Baseline 76.9 kg
  - Placebo = +4.1 kg
  - **5mg = +2.8 kg**
  - **10mg = +2.1 kg**
  - 20mg = +2.9 kg

Change in PANSS at 12 weeks

- Baseline: 62
  - Placebo = -2.9
  - 5mg = -1.5
  - 10mg = -2.7
  - 20mg = -2.5

- Both weight and PANSS remained stable in the extension phase
- TEAEs: somnolence, sedation, dizziness, and constipation

PANSS = Positive and Negative Syndrome Scale; TEAE = Treatment-Emergent Adverse Events

Martin WF, et al. *Am J Psychiatry*. 2019 Jun;176(6):457-67.

50

Olanzapine/Samidorphan – Schizophrenia

- ENLIGHTEN-1 Study (4 weeks) and 52-week extension
- Acute exacerbation of schizophrenia

Potkin SG, 2020 – Four Week Trial

- n = 397
- Placebo vs olanzapine vs olanzapine/samidorphan
- Baseline PANSS = 101.7
  - Placebo = -17.5
  - **Olanzapine 20mg = -22.8***
  - **Olanzapine 20mg/samidorphan 10mg = -23.9**
- TEAEs: increased weight, somnolence, dry mouth, anxiety, headache

Yagoda S, 2021 – 52 Week Extension

- n = 183
- All patients switched to olanzapine/samidorphan
  - Samidorphan 10mg and flexible dosing of 10mg, 15mg, or 20mg of olanzapine
    - Average dose: 15.45mg (olanzapine)
- Baseline weight (kg) = 79.1
  - Mean weight gain over study duration: 1.86kg
    - Not statistically evaluated
- PANSS continued to decline: Mean 78.9 to 62.7

*Olanzapine not directly compared
RCT = Randomized Controlled Trial; PANSS = Positive and Negative Syndrome Scale; TEAE = Treatment-Emergent Adverse Events

Potkin SG, et al. *J Clin Psychiatry*. 2020 Mar 3;81(2):19m12769.
Yagoda S, et al. *CNS Spectr*. 2021 Aug;26(4):383-92.

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Olanzapine/Samidorphan – Schizophrenia

- ENLIGHTEN-2 Study (24 weeks) and 52-week extension
- Evaluation of weight gain

Correll CU, 2020 – 24 Week Trial

- n = 550
- Olanzapine vs olanzapine/samidorphan 10mg
  - Olanzapine flexibly dosed 10-20mg
    - Average dose: 16.9mg
- Baseline weight = 77.37kg
  - Olanzapine = +6.59%
  - **Olanzapine/samidorphan = +4.21%**
- TEAEs: Weight gain, somnolence, dry mouth, increased appetite, increase waist circumference, CPK elevation

Kahn SR, 2021 – 52 Week Extension

- n = 167
- All patients switched to olanzapine/samidorphan
  - Equivalent olanzapine dose from ENLIGHTEN-2
    - Average dose: 17.8mg
- Baseline weight = 80.6kg
  - Olanzapine/samidorphan = -0.03kg
- TEAEs: Weight decrease, headache, weight gain

CPK = creatine phosphokinase; TEAE = Treatment-Emergent Adverse Events

Correll CU, et al. *Am J Psychiatry*. 2020 Dec;177(12)1168-78.
Kahn RS, et al. *Schizophr Res*. 2021 Jun;232:45-53.

52

Olanzapine/Samidorphan

- ENLIGHTEN-Early Study – Patients with Schizophrenia and Bipolar, Type 1 Disorder
- Evaluation of weight gain in patients with early illness (<4 years)

Kahn RS, 2023 – 12 Week Study

- n = 426
- Olanzapine 5-20mg, olanzapine 5-20mg/samidorphan 10mg
  - Average dose: 11.6mg
- Baseline BMI = 23.69
  - Olanzapine = +4.70kg
  - **Olanzapine/samidorphan = +3.37kg**
- TEAEs: Weight gain, somnolence, ALT elevation, headache, sedation, anxiety, increased waist circumference

BMI = Body Mass Index; TEAE = Treatment-Emergent Adverse Events; ALT = alanine aminotransferase

Kahn RS, et al. *J Clin Psychiatry*. 2023 Mar;84(3):22m14674.

53

Olanzapine/Samidorphan Summary

- Use in schizophrenia and/or bipolar disorder, type 1
  - PANSS changes are insignificant between olanzapine vs. olanzapine/samidorphan
  - Statistically significant difference in weight gain at 3 weeks, 12 weeks, 24 weeks
  - Extension trials show minimal, stable weight gain at 52 weeks
- Common adverse events included those typically seen with olanzapine
  - E.g. somnolence/sedation, dizziness, weight gain, increased waist circumference, and dry mouth

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HEAD-TO-HEAD TRIALS

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Why Head-To-Head Trials?

- We know these agents are effective
  - Are they *more* effective than the currently available agents?
  - Are they safer and/or better tolerated?
- If the agents are clinically superior, there may be an argument for use
- If the agents are clinically inferior, why would we use them?
- If we don't have head-to-head trials…what do we do then?

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Brexpiprazole vs Quetiapine XR

- Eight-week, randomized, double-blind, active-referenced, placebo-controlled trial
- Adjunctive treatment of major depressive disorder

Hobart M, 2018

- n = 495
- Inadequate response to antidepressant treatment for ≥6 weeks
- Placebo, brexpiprazole 2mg-3mg, quetiapine XR 150mg-300mg
  - Average dose: 2.2mg and 198.5mg
- Baseline MADRS = 25.5
  - Placebo = -4.6
  - **Brexpiprazole 2-3mg = -6.0***
  - Quetiapine XR 150-300mg = -4.9
- TEAEs: akathisia, somnolence, headache

*not directly compared to quetiapine XR
MADRS = Montgomery-Asberg Depression Rating Scale; TEAE = Treatment-Emergent Adverse Events

Hobart M, et al. *Curr Med Res Opin.* 2018 Apr;34(4):633-42.

NO DIRECT COMPARISON

57

Cariprazine vs Aripiprazole

- Six-week, randomized, double-blind, placebo- and active-controlled trial
- Acute exacerbation of schizophrenia

Durgam S, 2015

- n = 617
- Placebo, cariprazine 3mg, cariprazine 6mg, aripiprazole 10mg
- Baseline PANSS = 96.0
  - Placebo = -14.3
  - **Cariprazine 3mg = -20.2**
  - **Cariprazine 6mg = -23.0**
  - **Aripiprazole 10mg = -21.2***
- TEAEs: akathisia

*Aripiprazole not directly compared to cariprazine
PANSS = Positive and Negative Syndrome Scale; TEAE = Treatment-Emergent Adverse Events

Durgam S, et al. *J Clin Psychiatry.* 2015 Dec;76(12):e1574-82.

NO DIRECT COMPARISON

58

Cariprazine vs Risperidone

- 26-week, randomized, double-blind controlled trial
- Long-term stable schizophrenia with predominant negative symptoms

Nemeth G, 2017

- n = 456
- Cariprazine 3mg, 4.5mg, or 6mg vs risperidone 3mg, 4mg, or 6mg
  - Average dose: 4.2mg and 3.8mg
- Baseline PANSS for Negative Symptoms = 27.6
  - **Cariprazine = -8.63**
  - Risperidone = -7.16
- No difference in PANSS total score
- TEAEs common for both: akathisia, parkinsonism, insomnia, headache, anxiety

PANSS = Positive and Negative Syndrome Scale; TEAE = Treatment-Emergent Adverse Events

Nemeth G, et al. *Lancet*. 2017 Mar;389(10074):1103-13.

59

Lumateperone vs Risperidone

- Four-week, randomized, double-blind, placebo- and active-controlled trial
- Acute exacerbation of schizophrenia

Lieberman JA, 2016

- n = 311
- Placebo, lumateperone 60mg, lumateperone 120mg, risperidone 4mg
- Baseline PANSS = 91.25
  - Placebo = -7.4
  - **Lumateperone 60mg = -13.2**
  - Lumateperone 120mg = -8.3
  - **Risperidone 4mg = -13.4**
- TEAEs: dry mouth, nausea, dizziness

NO DIRECT COMPARISON

*Risperidone not directly compared to lumateperone
PANSS = Positive and Negative Syndrome Scale; TEAE = Treatment-Emergent Adverse Events

Lieberman, JA, et al. *Biol Psychiatry*. 2016 Jun;9(12):952-61.

60

Olanzapine/Samidorphan

- One, three-week, randomized, double-blind, placebo-controlled proof of concept
- Evaluation of weight gain in males with normal weight

Silverman BL, 2018

- n = 106
- Placebo, samidorphan 5mg, olanzapine 10mg, olanzapine 10mg/samidorphan 5mg
- Baseline weight = 67.9kg
  - Placebo = +0.1kg
  - Samidorphan 5mg = +0.8kg
  - **Olanzapine 10mg= +3.1kg**
  - **Olanzapine 10mg/samidorphan 5mg = +2.2kg***
- TEAEs in O/S group: orthostatic hypotension, somnolence, abnormal LFTs, sedation, dry mouth, nausea, increased appetite, dizziness, headache, increase in CPK

*Statistically significant compared to olanzapine for weight gain
O/S = olanzapine/samidorphan; LFTs = liver function tests; CPK = creatine phosphokinase

Silverman BL, et al. *Schizophr Res.* 2018 May;195:245-51.

61

Summary

- No head-to-head trials directly comparing second-generation antipsychotics to
  - Brexpiprazole
  - Lumateperone
- Cariprazine compared to risperidone for negative symptoms
  - Difference of 1.47
- Olanzapine/samidorphan compared to olanzapine for weight gain
  - Difference of 0.9kg
    - No comparison or discussion of treatment as usual with metformin

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PRICING

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Comparison of Available Agents

- Current costs would be without the mark-up of pharmacies

Medication	Cost/Day	Cost/Month (max)
Risperidone	$0.03-$0.07	$2.10
Aripiprazole	$0.08-$0.34	$10.20
Olanzapine	$0.05-$0.18	$5.40
Olanzapine + metformin	$0.04-$0.22	$6.60
Olanzapine/samidorphan	$42.50	$1275.00
Cariprazine	$44.37	$1331.10
Brexpiprazole	$45.70	$1371.00
Lumateperone	$50.50	$1515.00

Pulled from Spring Grove Hospital Center – Cardinal Contract

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NOVEL PIPELINE MEDICATIONS

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In the Pipeline

- $TAAR_1$ & $5HT_{1a}$ Agonist
  - Ulotaront
- Muscarinic (M_1 & M_4) agonist
  - Xanomeline-Trospium
- Glutamate (mGluR2/mGluR3) agonist
  - TS-134

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Ulotaront (SEP-856)

- Sunovion Pharmaceuticals

- Trace Amine-Associated Receptor 1 (TAAR1) agonist
  - Agonism = Inhibitory
    - Central activation = Internalization of pre- and post-dopaminergic receptors
    - Peripheral activation = decreased appetite, increased satiety, delay in gastric emptying, modulation of insulin, and reduced fasting glucose in the liver

- 5HT1a partial-agonist
  - Antidepressant and anxiolytic effects

Koblan KS, et al. *N Engl J Med*. 2020 Apr;382(16)1497-1506.
Dedic N, et al. *Int J Mol Sci*. 2021 Dec;22(24):13185.
Kantrowitz JT, et al. *Int J Neuropsychopharmacol*. 2023 Mar;pyad011.

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Ulotaront (SEP-856) – Continued

- Four-week randomized, double-blind, placebo-controlled trial
  - PANSS ↓ 17.2
  - Six-month, open-label extension
    - PANSS ↓ 22.6
    - No meaningful change in prolactin or movement disorder scales
    - Dyspepsia greatest side effect

- Likely apply for a New Drug Application (NDA) in 2024
  - Come to market in 2025?

Koblan KS, et al. *N Engl J Med*. 2020 Apr;382(16)1497-1506.
Kantrowitz JT, et al. *Int J Neuropsychopharmacol*. 2023 Mar;pyad011.

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Xanomeline/Trospium

- Karuna Therapeutics

- Muscarinic Receptor (M1 & M4) agonist
  - Brain
    - M4 activation decreases acetylcholine release leading to downstream reduction in dopamine
    - M1 on GABA interneurons leads to modulation of GABA, glutamate, and dopamine
  - Peripheral – M1
    - Activation leads to gastrointestinal side effects (e.g. nausea/vomiting) and syncope
    - Trospium = peripheral M1 antagonist
      - Utilized to mitigate undesirable side effects

Kantrowitz JT, et al. *Int J Neuropsychopharmacol.* 2023 Mar;pyad011.

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Xanomeline/Trospium – Continued

- Five-week randomized, double-blind, placebo-controlled trial
  - PANSS ↓ 17.4
  - No EPS, no metabolic side effects
    - Observed: constipation, nausea, dry mouth

- Future study(s) evaluating as augmentation

- Will submit NDA in 2023
  - Market 2024?

Kantrowitz JT, et al. *Int J Neuropsychopharmacol.* 2023 Mar;pyad011.

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TS-134

- Taisho Pharmaceuticals

- Metabotropic glutamate receptor (mGluR2/3) agonists
  - Decreases pre-synaptic glutamate release, which is toxic to working memory
    - Improves cognitive performance
  - Enhances post-synaptic receptor function, modulating NMDA and AMPA receptors
    - Decreases dopamine

- Phase 1 studies currently
  - Pomaglumetad discontinued by Eli Lilly in Phase III due to failure of therapeutic effects
    - Dose evaluated thought to be too low

Kantrowitz JT, et al. *Neuropsychopharmacology*. 2020 Oct;45(11):1842-50.
Li M-L, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. *2015 Jul;60:66-76.*

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Summary of Novel Pipeline Medications

- Ulotaront and xanomeline/trospium may soon come to market!
  - Unique mechanisms
  - Well tolerated
  - Similar reductions in PANSS to currently available antipsychotics

- TS-134
  - Early stages

- What does our future hold with these?

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CONCLUSION

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What do I need to know?

1. **Are the novel antipsychotics safe and effective?**
   - ✓ Yes – against placebo, they all have statistically and clinically significant therapeutic effects. Adverse events are similar to other SGAs.

2. **Should I be prescribing/recommending the novel antipsychotics over SGAs?**
   - ✓ Not necessarily – currently few head-to-head comparisons, and none with clinical significance warranting the high cost from either an efficacy or tolerability standpoint.

3. **What if a patient is interested in a novel antipsychotic?**
   - ✓ I would recommend checking first on insurance coverage and going from there.

4. **Will we ever have better options for treatment with antipsychotics?**
   - ✓ Pipeline medications offer some promise!

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Summary

- ✓All available antipsychotics have some degree of D_2 receptor involvement
- ✓Aripiprazole*, brexpiprazole, cariprazine, lumateperone, and olanzapine/samidorphan are the currently available novel antipsychotics
- ✓Mechanisms differ via partial agonism, varying ratios of D_2 and $5HT_{2a}$ selectivity, and involvement of other receptors
- ✓No current data exists showing a clinically meaningful advantage of a novel antipsychotic over currently available SGAs
- ✓Cost of novel antipsychotics will be unaffordable for most patients
- ✓Pipeline medications with no *direct* D_2 receptor involvement might be the future

*Not a new antipsychotic

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QUESTIONS?

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Notes

Use of Antipsychotics in the Pediatric Population: Is it too much?

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Virginia Commonwealth University Health

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Objectives

- Review indications for antipsychotics in children and adolescents
- Compare adverse effects of antipsychotics used in children and adolescents
- Differentiate metabolic side effects and monitoring parameters of antipsychotics
- Evaluate the use of antipsychotics in the pediatric population
- Determine when to initiate an antipsychotic in a child or adolescent

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Cases to Ponder

16 y/o slender female endorses being pregnant but not sexually active and endorsing physical abuse by parents

Mental status exam: elevated mood, disorganized and tangential thinking, delusional thoughts, hyper religious beliefs, inappropriate laughing, ideas of reference, decreased sleep, cooperative, incongruent affect, mood “great”, poor insight and judgement, memory limited

14 y/o obese male presenting to emergency department with bizarre behaviors for several days such as dealing drugs to friends and having a “hit list”

Mental status exam: disorganized and delusional thinking, clang associations, thought broadcasting, looseness of associations, responding to auditory hallucinations, endorses visual hallucinations of shadows and deceased grandmother, mood “stressed out”, affect anxious and constricted, poor insight and judgement

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Antipsychotics in Youth

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Antipsychotics in Youth

- Increase use since 1990
  - Residential care > group homes > foster care > general population
  - Publicly vs. privately insured
- Most frequently prescribed
  - Risperidone: 42.1%
  - Aripiprazole: 28%
  - Quetiapine: 19.2%
  - Olanzapine: 4.4%
- Most frequent target: aggression

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Prescribing Patterns Among Young People

Age (years)	Stimulant (%)	Antidepressant (%)	Antipsychotic (%)
3-5	0.5	0.2	0.2
6-12	4.6	1	0.8
13-18	3.7	2.8	1.2
19-24	1.6	4	0.8

- Prevalence among youth with one or more prescription filled in the US in 2008
- Highest prescribing among general psychiatry or child psychiatry for all age groups except stimulants
- Females prescribed antidepressants more than males as age increased
- Males aged 6-18 years prescribed antipsychotics and stimulants more than females

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At-Risk Youth

- At least 20% of US youth are considered highly vulnerable
- Factors impacting vulnerability
  - Connection with juvenile justice system
  - Child welfare system involvement
  - Living in a restrictive setting
  - Disruptions in parenting
  - Intellectual disability
  - Poverty
  - Trauma
- High-rate antipsychotic prescriptions
  - Polypharmacy
  - Off-label use
  - Long-term use

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Over Prescribing Causes

Lack of access to mental health services	Expansion of FDA-approved indications	Off-label use	Shorter hospitalizations
Difficulty obtaining acute care hospitalizations	Lack of shared decision making	Need for quick response to manage behavior	Advertising

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Antipsychotics
- Indications
- Dosing
- Treatment guidelines

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Antipsychotics

First Generation Antipsychotics (FGA)	Second Generation Antipsychotics (SGA)

• **Mechanism of action**
  • D2 receptor antagonist
  • H1 and 5-HT2 receptor antagonism
  • Alpha2-adrenergic receptor agonism
• **Adverse effects (AE)**
  • Extrapyramidal symptoms (EPS)
  • Gynecomastia
  • QTc prolongation
  • Neuroleptic malignant syndrome (NMS)
	• **Mechanism of action**
	  • D2 receptor antagonism
	  • 5-HT2a receptor antagonism
	  • Variable affinity for muscarinic, histaminergic and alpha-adrenergic receptors
	• **Adverse effects (AE)**
	  • Orthostasis
	  • Sedation
	  • Weight gain

Black boxed warning for <u>all</u> antipsychotics: increased risk of mortality in elderly patients with dementia-related psychosis

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Antipsychotic Receptor Binding

	D_1	D_2	D_3	D_4	5-HT_{1A}	5-HT_{1B}	5-HT_{2A}	5-HT_{2B}	5-HT_{2c}	5-HT_6	5-HT_7
Chlorpromazine	++	+++	+++	+++			+++	+++	++	+++	+++
Haloperidol	+	+++	+++	+++		+	+				+
Aripiprazole		+++	+++	+	+++	+	+	++++	++	+	++
Asenapine	+++	+++	++++	+++	+++	+++	++++	++++	++++	++++	++++
Brexpiprazole	+	++++	+++	+++	++++	++	++++	+++	+	++	+++
Cariprazine		++++	++++		+++		++	++++	+		+
Clozapine	+	+	+	++	+	+	++	+++	++	++	++
Iloperidone	+	+++	+++	++	++	++	+++		++	+	+
Lumateperone	++	++		+++			+++				
Lurasidone	+	+++			+++		+++		+		++++
Olanzapine	++	++	++	++		+	+++	++	++	+++	++
Paliperidone	+	+++	+++	+++	+	++	+++		++	+	+++
Quetiapine	+	+	+		++		++		+	+	++
Risperidone	+	+++	+++	+++	+	++	++++	++	++		+++
Ziprasidone	+	+++	+++	++	+++	+++	++++	++	++++	++	+++

+ weak association; ++ moderate association; +++ strong association; yellow = partial agonism

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Selected FGA and Indications in Youth

	Chlorpromazine	Haloperidol	Thiothixene	Thioridazine
Schizophrenia		X	X	X
Control of tics or Tourette's disorder		X		
Severe behavioral problems	X	X		
Short-term hyperactivity	X	X		

https://dailymed.nlm.nih.gov/dailymed/
J Am Acad Child Adolesc Psychiatry. 2013;52(9): 976-90.

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Selected FGA Dosing

Medication	Age (yrs)	Starting dose	Recommended Dose	Maximum dose
Chlorpromazine	1-12	Oral: 0.55 mg/kg/dose every 4-6 hours IV/IM: 0.28-0.55 mg/kg/dose every 6-8 hours or 25 mg/dose	Oral: 50-100 mg/day IV/IM: 25-50 mg/dose	Oral: 500 mg/day IV/IM: - <5 yrs or <22.7 kg: 40 mg/day - ≥ 5 yrs or ≥ 22.7 kg: 75-100 mg/day
Haloperidol	≥3	0.25-0.5 mg/day in 2-3 divided dose	0.05-0.15 mg/kg/day in 2-3 divided doses	15 mg/day
Thioridazine	≥6	0.5 mg/kg/day or 50 mg/dose divided	200-800 divided BID to TID	3 mg/kg/day or 800 mg divided BID to TID
Thiothixene	≥12	2 mg TID or 5 mg BID	15-30 mg/day in divided doses	60 mg/day divided TID

BID = twice daily; IM = intramuscular; IV = intravenous; TID = three times a day

https://dailymed.nlm.nih.gov/dailymed/

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SGA Indications in Youth

	Aripiprazole	Asenapine	Brexpiprazole	Cariprazine+	Clozapine+	Iloperidone+	Lumateperone+	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone+
Schizophrenia	X	X	X	X	X*	X	X	X	X	X	X	X	X
Bipolar disorder (mania)	X	X		X					X		X	X	X
Bipolar disorder (depression)							X	X	X^		X		
Schizoaffective disorder										X			
Depression (adjunct)	X	X							X^		X		
Tourette's disorder	X												
Autism (irritability)	X											X	
Reducing suicidality in schizophrenia or schizoaffective disorder					X								

+ Not FDA approved for children and adolescents *Treatment-resistant schizophrenia

^Olanzapine-fluoxetine (Symbyax®) is approved for bipolar depression and treatment resistant depression

https://dailymed.nlm.nih.gov/dailymed/

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Selected SGA Dosing

Medication	Indication	Age (yrs)	Starting dose (mg/day)	Recommended Dose (mg/day)	Maximum dose (mg/day)
Aripiprazole (ARI)	Irritability with autism	≥6	2	5	10
	Tourette's disorder	≥6	<50 kg: 2 ≥50 kg: 2	<50 kg: 5 ≥50 kg: 10	<50 kg: 10 ≥50 kg: 20
	Bipolar disorder	≥10	2	10	30
	Schizophrenia	≥13	2	10	30
Risperidone (RIS)	Irritability with autism	≥5	<20 kg: 0.25 ≥20 kg: 0.5	<20 kg: 0.5 ≥20 kg: 1	0.5-3
	Bipolar disorder	≥10	0.5	1-2.5	1-6
	Schizophrenia	≥13	0.5	3	1-6

https://dailymed.nlm.nih.gov/dailymed/

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Selected SGA Dosing

Medication	Indication	Age (yrs)	Starting dose (mg/day)	Recommended Dose (mg/day)	Maximum dose (mg/day)
Asenapine (ASN)	Bipolar disorder	≥10	5 divided BID	2-10 divided BID	20 divided BID
Lurasidone (LUR)	Bipolar depression	≥10	20	20-80	80
	Schizophrenia	≥13	40	40-80	80
Olanzapine (OLZ)	Bipolar disorder	≥13	2.5-5	10	20
	Bipolar depression (combo with fluoxetine)	≥10	3/25	6/25-12/50	12/50
	Schizophrenia	≥13	2.5-5	10	20
Paliperidone (PAL)	Schizophrenia	≥12	<51 kg: 3 ≥ 51 kg: 3	<51 kg: 3-6 ≥ 51 kg: 3-12	<51 kg: 6 ≥ 51 kg: 12
Quetiapine (QTP)	Bipolar disorder	≥10	50 divided BID	400-600	600
	Schizophrenia	≥13	50 divided BID	400-800	800

BID = twice daily

https://dailymed.nlm.nih.gov/dailymed/

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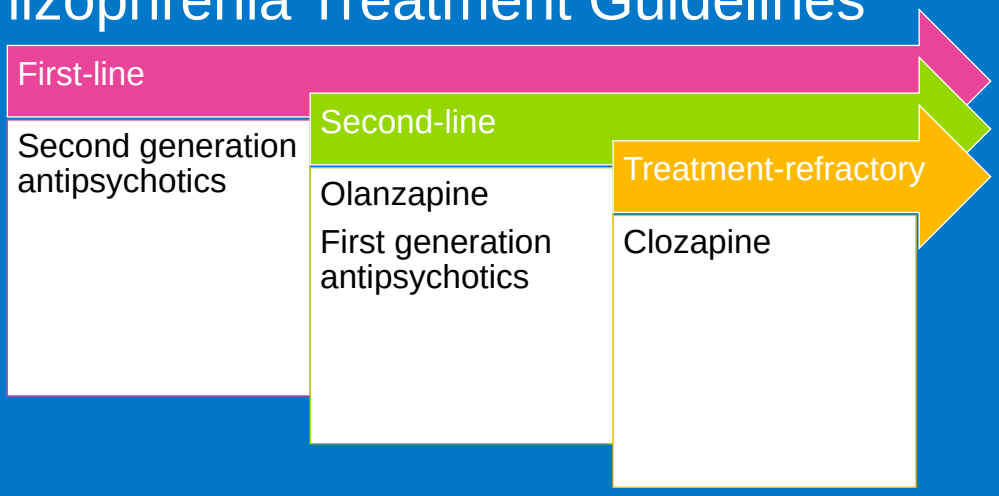
Schizophrenia Treatment Guidelines



- Monotherapy preferred before adjunctive treatment
- Non-pharmacologic treatments used in combination with medication
- Lifelong treatment required

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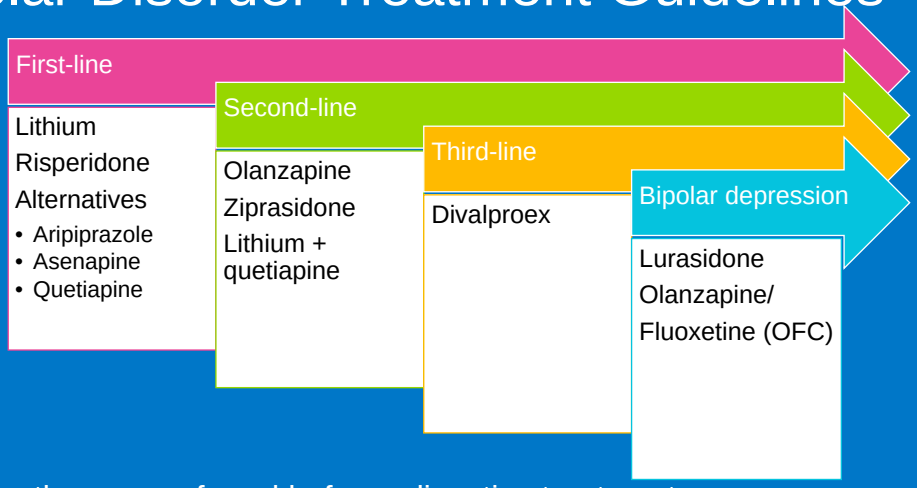
Bipolar Disorder Treatment Guidelines



- Monotherapy preferred before adjunctive treatment
- Non-pharmacologic treatments used in combination with medication
- Lifelong treatment required

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Other Treatment Guidelines

- Tourette's Disorder
  - Antipsychotics reserved for second- and third-line options
- Autism
  - Risperidone and aripiprazole
    - After first-line therapeutic options fail
    - Activities of daily living are impacted
    - Education is disrupted
    - Family life effected
    - Self injury occurs
  - Other antipsychotics reserved as second- and third-line options

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Evidence-Based Medicine

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Schizophrenia

Study	Population	Intervention	Results
McGorry, 2013	14-30 yrs ultra high risk for psychosis (N=115) Duration: 52 weeks	• RIS 0.5-2 mg/day + CBT • CBT+PBO • supportive therapy + CBT	• No difference between groups in rate of transition to psychosis • Negative symptoms and overall functioning improved in all groups
Correll, 2017	13-17 yrs with schizophrenia (N=146) Duration: 52 weeks	ARI 10-30 mg/day	• Mean dose = 19.2 ± 6.7 mg/day • Longer time to relapse and discontinuation • Insomnia greater in PBO group
Pagsberg, 2017	12-17 yrs with first episode psychosis (N=113) Duration: 12 weeks	• ARI 2.5-30 mg/day • QTP ER 50-800 mg/day	• No different between ARI or QTP ER groups on PANSS positive score • Weight gain higher in QTP ER group • Sedation, akathisia, EPS treatment higher in ARI group

CBT = cognitive behavior therapy; ER = extended-release; PANSS = Positive and Negative Syndrome Scale; PBO = placebo

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Schizophrenia

Study	Population	Intervention	Results
Findling, 2012	13-17 yrs with schizophrenia (N=326) Duration: 6 week	• QTP 400 or 800 mg/day • PBO	• Both QTP groups significant improvement PANNS total score compared to PBO • QTP groups exhibited greater changes in weight and metabolic parameters
Savitz, 2015	12-17 yrs with schizophrenia (N=226) Duration: 8 weeks + 18-week maintenance	• PAL ER 3-9 mg/day • ARI 5-15 mg/day	• No difference between ARI or PAL ER groups on PANSS positive score • No significant differences for any secondary endpoints • More weight gain in PAL ER group
Savitz, 2015	12-17 yrs with schizophrenia (N=220) Duration: 2 years	PAL ER 6 mg/day (range 1.5-12 mg/day)	• Improvement in PANSS total score by ≥ 20%; remission in 41.7% • No significant change in growth-adjusted z-scores Hyperprolactinemia in 56%

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Schizophrenia

Study	Population	Intervention	Results
Findling, 2015	12-17 yrs with schizophrenia (N=306 then 196) Duration: 8 weeks + 26-week OLE	• ASN 2.5 or 5 mg BID • PBO	• No different between ASN or PBO groups on PANNS total score at 8 weeks • Continued improvement in the OLE for the PANSS total score and CGI-S for both groups
Goldman, 2017	13-17 yrs with schizophrenia (N=326) Duration: 6 week	• LUR 40 or 80 mg/day • PBO	• Both LUR groups significant improvement PANNS total score compared to PBO • Minimal effects on weight gain

OLE = open-label extension; CGI-S = Clinical Global Impression scale - Severity

- No available studies for brexpiprazole, iloperidone and lumateperone
- Negative evidence for ziprasidone
- Combined evidence with bipolar disorder for cariprazine and quetiapine

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Schizophrenia + Bipolar Disorder

Study	Population	Intervention	Results

Findling, 2013	13-17 yrs with schizophrenia or manic episode of BPI (N=505)
	
	Duration: 26 weeks
		• QTP 200-800 mg/day	• Mean dose and duration
			  • Schizophrenia: 632 mg and 156 days
			  • BPI: 571 mg and 137 days
			• Most common TEAEs were somnolence, headache, sedation, weight gain, and vomiting

Riccobene, 2022	13-17 yrs with schizophrenia or BPI (N=50) Duration: 42 days	CAR 1.5-4.5 mg/day	• PK profile similar to adults • Most common TEAEs were sedation and parkinsonism

BPI = bipolar I disorder; CAR = cariprazine; PK = pharmacokinetics; TEAE = treatment emergent adverse effects

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Bipolar Disorder

Study	Population	Intervention	Results
Kowatch, 2015	3-7 yrs BPI mixed or manic episode ± psychosis (N=115) Duration: 6 weeks	• RIS 0.5-0.75 mg/day • VPA 10 mg/kg/day; target serum level 80-100 mcg/mL • PBO	• YMRS scores improved for RIS and VPA groups compared to PBO and also with RIS compared to VPA • More endocrine and metabolic effects for RIS
Pathak, 2013	10-17 yrs BPI manic episode (N=284) Duration: 3 weeks	• QTP 400 or 600 mg/day • PBO	• QTP group significantly greater reduction YMRS score • No differences in CGI-BP • QTP greater increased in weight gain • Change in QT interval greater with Li
Patino, 2021	10-17 yrs BPI mixed or manic episode (N=109) Duration: 6 weeks	• QTP 400-600 mg/day • Li target serum level 1-1.2 mEq/L	• QTP group significantly greater improvements YMRS total score • CGI-BP improved in QTP groups • CDRS-R improved between QTP 600 mg/day vs. PBO • TEAEs in QTP group were somnolence, sedation, dizziness, headache

BP= bipolar disorder; CDRS-R = Children's Depression Rating Scale – Revised; CGI-BP = Clinical Global Impression scale – bipolar disorder; Li = lithium; VPA = valproic acid; YMRS = Young Mania rating Scale

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Bipolar Disorder

Study	Population	Intervention	Results
Findling, 2013	10-17 yrs BPI manic or mixed episode ± psychotic features (N=210) Duration: 30 weeks	• ARI 10 or 30 mg/day • PBO	• ARI groups significantly greater reduction YMRS score from week 1 to 30 • Significant improvement in mania symptoms on CGAS and CGI-BP for ARI groups • EPS emergence was dose dependent
Findling, 2022	10-17 yrs BPI manic episode (N=171) Duration: 4 weeks	• ZIP 20 or 80 mg/day • PBO	• ZIP group significantly greater reduction YMRS score • Somnolence, fatigue, and nausea were most common with ZIP • ZIP moderately prolonged QT interval
Findling, 2022	10-17 yrs BPI manic episode (N=23) Duration: 26 weeks OLE	ZIP 20 or 80 mg/day	• Continued improvement in mania symptoms • Somnolence, fatigue, and nausea were most common with ZIP • Minimal effects on metabolic parameters, weight, and BMI

BMI = body mass index; CGAS = clinical global assessment scale; ZIP = ziprasidone

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Bipolar Disorder

Study	Population	Intervention	Results
Joshi, 2013	6-17 yrs BPI, II, or NOS manic, hypomanic, or mixed episode (N=15) Duration: 8 weeks	• ≥20 kg: PAL 3 mg/day • >45 kg: PAL 6 mg/day	• PAL groups significantly greater reduction YMRS total score • Significant increase weight for PAL groups
Findling, 2015	10-17 yrs BPI manic or mixed episode (N=403) Duration: 3 weeks	• ASN 2.5, 5, or 10 mg BID • PBO	• All ASN groups significantly greater reduction YMRS score • Somnolence, sedation, oral hypoesthesia, and increased appetite were most common with ASN • ASN groups higher incidence of weight gain and changes in metabolic parameters
Findling, 2016	10-17 yrs BPI manic or mixed episode (N=321) Duration: 50 weeks OLE	ASN 2.5-10 mg BID	• Continued improvement in mania symptoms • Somnolence, sedation, and hypersomnia were most common • One-third experience clinically significant weight gain

NOS = not otherwise specified

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Bipolar Depression

Study	Population	Intervention	Results
Detke, 2015	10-17 yrs BPI, current episode depressed (N=255) Duration: 8 weeks	• OFC 6/25 or 12/50 mg/day • PBO	• Significant difference in CDRS-R by study endpoint for both OFC groups • Mania symptoms remained low through the study for all groups • Weight gain, increased appetite, somnolence, tremor, and sedation higher in OFC groups
DelBello, 2009	12-18 yrs BPI, current episode depressed (N=32) Duration: 8 weeks	• QTP 300-600 mg/day • PBO	• No statistically significant between groups on CDRS-R • No difference in response or remission • Dizziness most common with QTP
Findling, 2014	12-18 yrs BPI or II, current episode depressed (N=193) Duration: 8 weeks	• QTP XR 150-300 mg/day • PBO	• No statistically significant between groups on CDRS-R • No difference in response or remission

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Bipolar Depression

Study	Population	Intervention	Results
DelBello, 2017	10-17 yrs BPI, current episode depressed (N=347) Duration: 6 weeks	• LUR 20-80 mg/day • PBO	• Significant improvement on CDRS-R total score and CGI-BP-S depression score for LUR group • Most common side effects were nausea and somnolence • No significant weight effect between groups
DelBello, 2021	10-17 yrs BPI, current episode depressed (N=168) Duration: 2 years OLE	LUR 20-80 mg/day	• Continued improvement on CDRS-R • Most common side effects were headache and nausea • Minimal changes in weight and metabolic parameters

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Irritability with Autism

Study	Population	Intervention	Results
Kent, 2013	5-17 yrs with autism (N=96) Duration: 6 weeks	• Low dose RIS: 0.125 or 0.175 mg/day • High dose RIS: 1.25 or 1.75 mg/day • PBO	• ABC-I improved in high dose RIS compared to PBO but not low dose • CGI-S and CGI-I improved for high dose RIS • TEAEs were increased appetite, sedation, somnolence, and weight gain
Kent, 2013	5-17 yrs with autism (N=79) Duration: 26 weeks OLE	• <45 kg: RIS 0.125-1.25 mg/day • ≥45 kg: RIS 1.25-1.75 mg/day	• Continued improvement on ABC-I for all treatment groups with improved response rate • CGI-S improved in all groups • Most common side effects were increased appetite, weight gain, and vomiting
Findling, 2014	6-17 yrs with autism (N=85) Duration: 13-26 weeks followed by 26 weeks	• ARI 2-15 mg/day • PBO	• No statistical differences between groups for time to relapse • Most common side effects were weight gain, somnolence, and vomiting • No differences in EPS between groups

ABC-I = Aberrant behavior Checklist – Irritability

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Irritability with Autism

Study	Population	Intervention	Results
Stigler, 2012	12/21 yrs with irritability with autism (N=21) Duration: 8 weeks	PAL 3-12 mg/day	• Improvement ABC-I and CGI-I • Most common side effects were increased appetite, weight gain, and tiredness
Loebel, 2016	6-17 yrs with irritability with autism (N=150) Duration: 6 weeks	• LUR 20 or 60 mg/day • PBO	• No difference in ABC-I • CGI-I improvement for LUR 20 mg/day but not 60 mg/day compared to PBO • Most common side effects were vomiting and somnolence • Modest changes in weight
DeVane, 2019	6-17 yrs with autism (N=80) Duration: 10 weeks followed by 12-week blinded extension	• ARI 2-15 mg/day • RIS 0.25-3 mg/day	• No difference in psychiatric, ABC-I, or metabolic parameters • Prolactin decreased in ARI group and increased in RIS group

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Tourette's Disorder

Study	Population	Intervention	Results
Ghanizadeh, 2014	6-18 yrs with Tourette's disorder (N=60) Duration: 8 weeks	• ARI 1.25-15 mg/day • RIS 0.25-3 mg/day	• Both groups significantly decreased YGTSS-TTS, motor, phonic, and total tic severity scores • QOL scores increased for both groups • Side effects in both groups were increased appetite and drowsiness

Sallee, 2017	7-17 yrs with Tourette's disorder (N=133)
	
	Duration: 8 weeks
		• ARI (low vs. high dose)
		  • <50 kg: 5-10 mg/day
		  • ≥50 kg: 10-20 mg/day
		• PBO
			• Significant decrease in YGTSS-TTS for both ARI groups
			• Significant improvement in CGI-TS for both ARI groups
			• Most common AEs were sedation, somnolence, increased appetite, and fatigue

Tao, 2017	6-16 yrs with first episode psychosis (N=24)
	
	Duration: 1.5 weeks
		• ARI
		  • <50 kg: 2.5-5 mg/day
		  • ≥50 kg: 5-10 mg/day
		• VPA injection 15 mg/kg BID
			• YGTSS-TTS decreased in both groups with more marked reduction in VPA compared to ARI
			• Motor, phonic, and impairment scores improved in both groups
			• Most common AEs were sedation, somnolence, increased appetite, and fatigue

CGI-TS = Clinical Global Impression scale – tic severity; QOL = quality of life; YGTSS – TTS = Yale Global Tic Severity Scale – total tic score

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ADHD and Disruptive Behavior Disorders

- Risperidone – mixed results
  - Shorter trials with some improvement in aggression
  - Maintenance studies with minimal to no improvement on aggression
  - Possible benefit when combined with methylphenidate
- Safety Data
  - Elevated prolactin
  - Weight gain

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Long-Acting Injectable Antipsychotics (LAI) – Place in Therapy

- No prospective studies; majority case reports and case series
- Most reported LAI: RISP then PAL and ARI
- Decrease in severity of symptoms and lower remission rates
- Possible decrease in AEs
- Barriers to administration
  - Providers knowledge
  - Clinic administration
  - Patient and guardian acceptance of LAI treatment
  - Insurance approval

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Adverse effects

Evidence	• Short-term studies currently available • Need for long-term studies on brain development
Common AEs	• Somnolence/sedation, gastrointestinal distress, weight gain
Additional Effects	• Metabolic parameters (lipids, glucose, insulin resistance) • Hormonal effects (prolactin, amenorrhea, breast development) • QTc prolongation • NMS
Extrapyramidal symptoms	• Decreased with SGA vs. FGA • Increased incidence in children and adolescents compared to adults

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Receptor Binding and AEs

	H_1	H_2	H_3	M_1	M_3	α_1	α_{2A}	α_{2B}	α_{2c}
Chlorpromazine	+++	+	+	++	++	+++	+	++	++
Haloperidol		+				++	+	+	+
Aripiprazole	++					++	++	++	++
Asenapine	+++	+++				+++	+++	++++	+++
Brexpiprazole	++					+++	++	++	++++
Cariprazine	++					+			
Clozapine	+++	+		+++	++	+++	++	++	++
Iloperidone	+					+++	+	+	++
Lumateperone						+++			
Lurasidone						++	++		+++
Olanzapine	+++	++	+	++	++	++	+	++	++
Paliperidone	++	+				+++	+++	+++	+++
Quetiapine	+++			+	+	++	+	+	++
Risperidone	+++	+				+++	++	++	+++
Ziprasidone	++					++	+	++	++

+ weak association; ++ moderate association; +++ strong association

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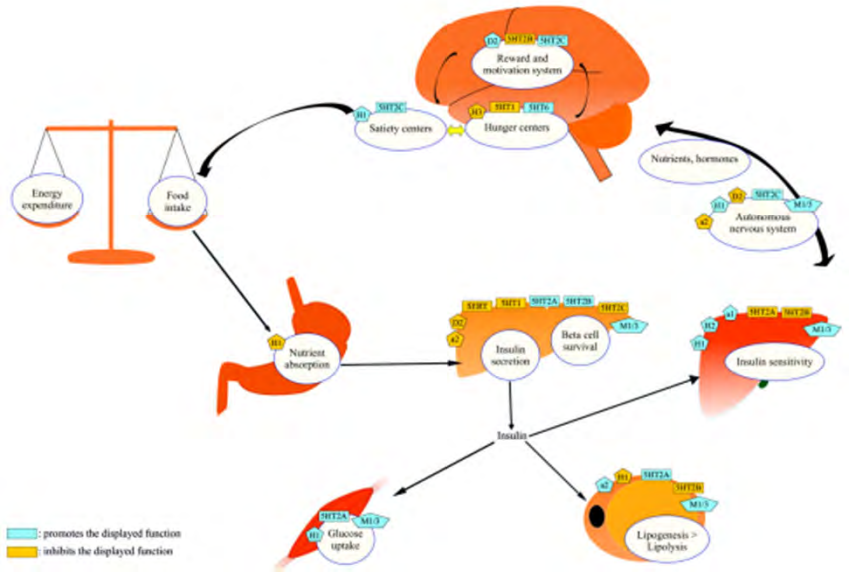
Receptor Metabolic Effects



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Metabolic Risks

	Glucose Abnormalities	Lipid Abnormalities	Weight Gain
Chlorpromazine	+/++	+/++	+++/++++
Haloperidol	+	+	+
Aripiprazole	+	+	++
Asenapine	+	+	++
Brexpiprazole	+(LD)	+(LD)	+(LD)
Cariprazine	+(LD)	+(LD)	+(LD)
Clozapine	++	++	+++/++++
Iloperidone	+/++	+/++	+++/++++
Lumateperone	+	+	+
Lurasidone	+	+	+
Olanzapine	++	++	++++
Paliperidone	+/++	+/++	+++
Quetiapine	+/++	++	+++
Risperidone	+/++	+/++	+++
Ziprasidone	+	+	+

Glucose and Lipid abnormalities: maximum ++; Weight gain: maximum ++++;
LD = limited data

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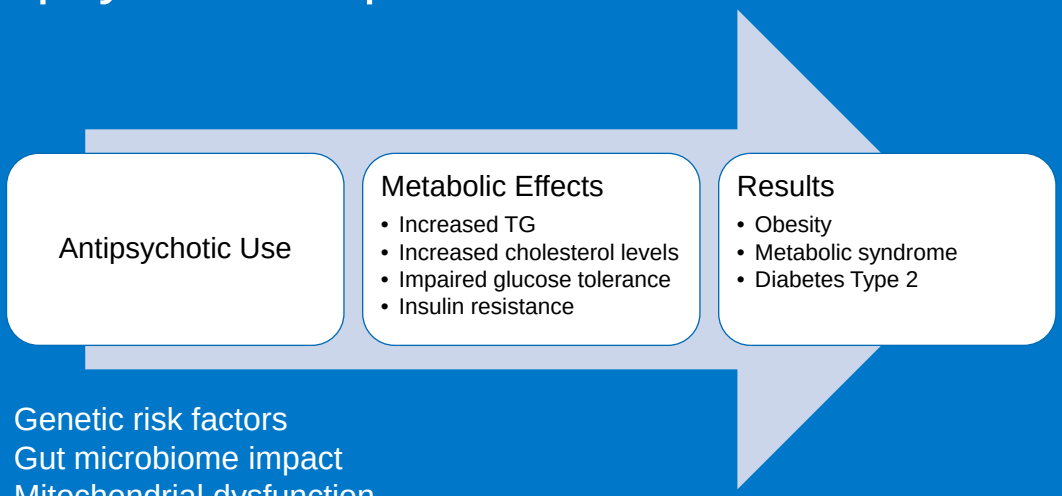
Antipsychotic Impact



- Genetic risk factors
- Gut microbiome impact
- Mitochondrial dysfunction
- Ghrelin and leptin hormonal signaling

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Monitoring Recommendations

Treatment Response		Adverse Effects		Cardiometabolic Monitoring		Review of Continued Use	
Medication effect	Regularly	Common AEs	Regularly	Height, weight, BMI	Baseline, weeks 4, 8, 12, 6 months, annually	Monitor effect and stabilization	Annually
		EPS		Waist circumference	Baseline, annually		
				Blood pressure, pulse	Baseline, week 12, 6 months, annually		
		Prolactin-related		Glucose levels			
				Lipid profile			

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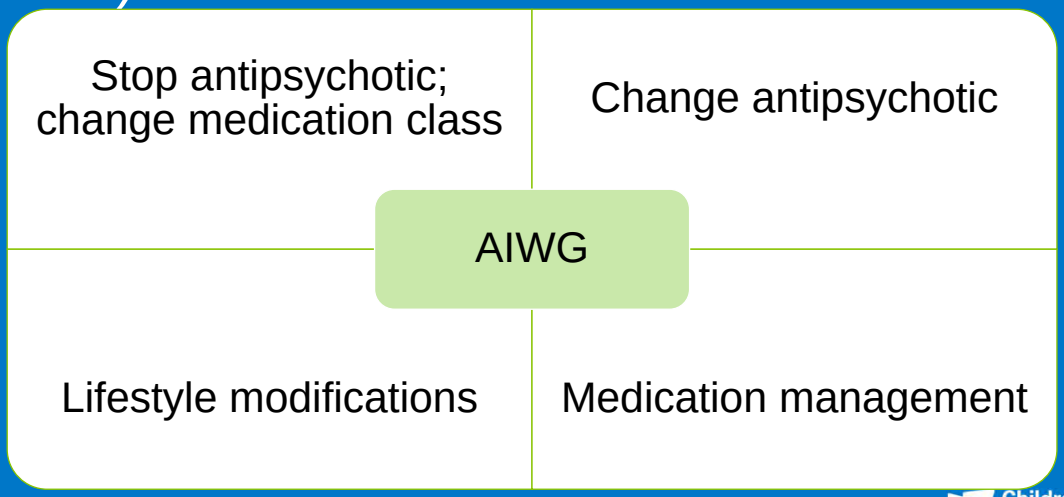
Antipsychotic Induced Weight Gain Treatment (AIWG)



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AIWG Lifestyle Modifications

- Diet changes
- Increased physical activity
- Adequate sleep
- Stress management
- Probiotics

- Barriers
  - Paucity of data
  - Difficulty with adherence
  - Lack of self-motivation

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Prevention AIWG

Metformin	Topiramate	Glucagon-like Peptide Agonists
• Decreases hepatic gluconeogenesis • Reduces insulin resistance • Decreases total cholesterol elevations • Max dose: 1,000 mg BID	• Prevention • Improves insulin sensitivity • Decreases leptin concentrations and visceral fat • Max dose: 150-200 mg/day	• Prevention • Decreases appetite • Delays gastric emptying • Increases visceral and intra-organ lipolysis • No specific dosing recommendations

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IMPACT Trial

Study Design
- Randomized, 24 weeks
- Bipolar spectrum, schizophrenia spectrum, major depression with psychotic features
- 8-19 years
- BMI >85th percentile
- Baseline weight gain >10%

Interventions
- Metformin add-on (MET)
- Switch to aripiprazole, perphenazine, molindone (SWITCH)
- Current SGA continued with lifestyle modifications (CONTROL)

Results (N=127)
- BMI z-score significantly decreases in MET and SWITCH vs. CONTROL
- No difference between MET and SWITCH for BMI z-score
- MET increased gastrointestinal distress

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Topiramate add-on therapy

Study design
- Open-label, 8 weeks
- 6-17 years
- Bipolar disorder spectrum

Interventions
- OLZ
- OLZ + topiramate (TPX)

Results (N=40)
- Weight gain in OLZ group statistically significantly more then OLZ+TPX
- No difference in YMRS

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Monitoring Antipsychotic Prescribing Patterns

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System-wide Interventions

- Child and Family Services Improvement and Innovation Act of 2011
  - Required states to develop protocols for appropriate use and monitoring
  - Expansion from 2008 Fostering Connections to Success and Increasing Adoptions Act
    - Designed to improve healthcare outcomes for youth in foster care
- National Committee for Quality Assurance release quality metrics on safe and effective use of antipsychotics

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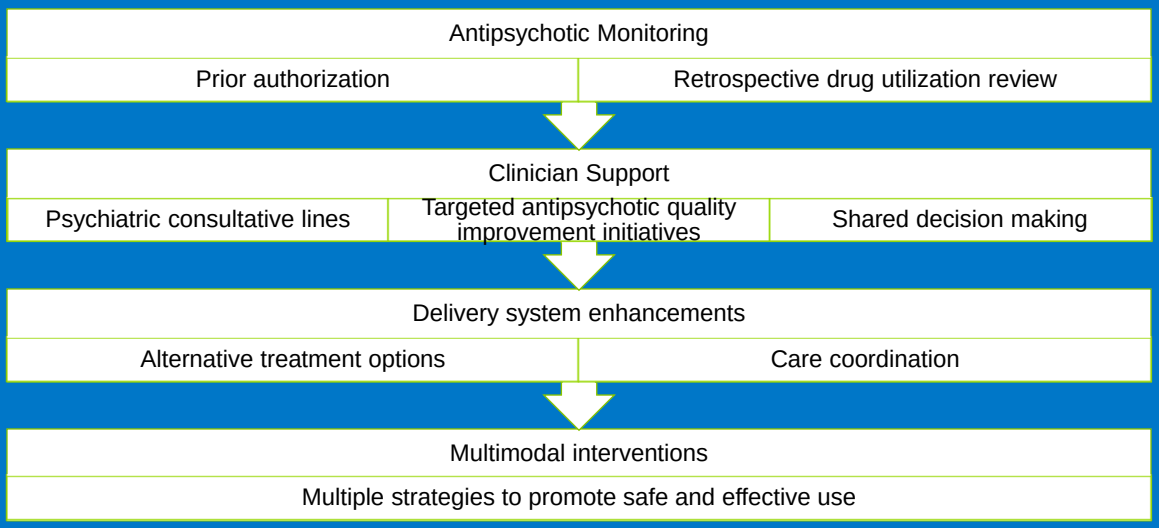
Operational Supports



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Antipsychotic De-escalation

- Polypharmacy is common in pediatrics
  - Defined as ≥5 low risk drugs or ≥3 high risk drugs
  - Increased risk of ADRs
  - Risk for medication discrepancy or non-adherence
  - Unintended consequences such as drug-drug interactions
- Process to de-prescribe in adults
  - Is there an indication for all medications
  - Is there any drug-induced harm
  - What is the current or future benefit of the medication
  - Prioritize discontinuation based on lowest likelihood of withdrawal effects and lowest benefit:harm ratio
  - Implement discontinuation regimen and monitor outcomes

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Clinical Practice Examples

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Bipolar Disorder Case

16 y/o slender female endorses being pregnant but not sexually active and endorsing physical abuse by parents

Mental status exam: elevated mood, disorganized and tangential thinking, delusional thoughts, hyper religious beliefs, inappropriate laughing, ideas of reference, decreased sleep, cooperative, incongruent affect, mood “great”, poor insight and judgement, memory limited, superficial burn near left eye

Past medical history:

- No psychiatric history
- Two previous concussions (2022, 2023)
- Surgery in Mexico for intussusception

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Bipolar Disorder Case

No current medications

Family history – maternal aunt: bipolar disorder

Labs/Vitals
- Serum pregnancy – negative
- BMI: 15.4 kg/m2

Other pertinent information
- Amish heritage
- No medical or prescription insurance

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Bipolar Disorder Case

Which of the following medications is the best option?

A. Aripiprazole
B. Lithium
C. Lurasidone
D. Risperidone

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Bipolar Disorder Case

Which of the following should be obtained at baseline and six months?

A. Lipid profile and hemoglobin A1c
B. Prolactin level and EPS measures
C. Weight, height, waist circumference
D. Blood pressure and electrocardiogram

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Schizophrenia Case

14 y/o obese male presenting to emergency department with bizarre behaviors for several days indicating he has been dealing drugs to friends and has a "hit list". "I'm really good at lying".

Mental status exam: disorganized and delusional thinking, clang associations, thought broadcasting, looseness of associations, responding to auditory hallucinations, endorses visual hallucinations of shadows and deceased grandmother, mood "stressed out", affect anxious and constricted, poor insight and judgement

Hobbies: watches Daniel Tiger's Neighborhood

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Schizophrenia Case

Past medical history:

- Autism spectrum disorder, diagnosed December 2022
- Attention-deficit/hyperactivity disorder
- Nut allergy

Current medications

- Quetiapine 50 mg bedtime
- Lithium 300 mg bedtime

Past medications

- Aripiprazole 5 mg daily
- Divalproex 250 mg BID (caused drooling and shaking)
- Methylphenidate ER 18 mg daily
- Clonidine 0.1 mg bedtime

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Schizophrenia Case

Family history – none

Labs/Vitals

- Lithium level – 0.2 mEq/L at 13:30
- BMI: 30.2 kg/m2

Other pertinent information

- Mom reports mood "cycling"
- Difficulty swallowing medications
- Sees dietician for weight gain

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Schizophrenia Case

What is the best treatment plan for this patient?

A. Add haloperidol 5 mg BID
B. Change medications to olanzapine 5 mg BID
C. Change quetiapine to aripiprazole, continue lithium 300 mg at bedtime
D. Titrate lithium to therapeutic level, continue quetiapine 50 mg at bedtime

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Schizophrenia Case

With the initiation of olanzapine and BMI >30 mg/kg2, which of the following is the best option?

A. Dextroamphetamine
B. Metformin
C. Liraglutide
D. Topiramate

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Summary

- Majority of SGAs are approved for bipolar disorder and schizophrenia in children and adolescents
- Most common adverse effects, based on receptor binding, include orthostatic hypotension, increased appetite, weight gain, and sedation
- Changes in glucose and lipids are highest for clozapine and olanzapine
- Numerous studies support the use of SGAs for psychiatric disorders in youth
- Treatment plans should be based on available treatment guidelines

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Use of Antipsychotics in the Pediatric Population: Is it too much?

Sandy Mitchell, PharmD, BCPP
Clinical Pharmacy Specialist – Child and Adolescent Psychiatry
Children's Hospital of Richmond – Virginia Treatment Center for Children
Virginia Commonwealth University Health

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Notes

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SCHOOL OF PHARMACY

Pharmacogenomics in Psychiatry: Is there a role?

Megan J. Ehret, PharmD, MS, BCPP
Professor
University of Maryland, School of Pharmacy

1

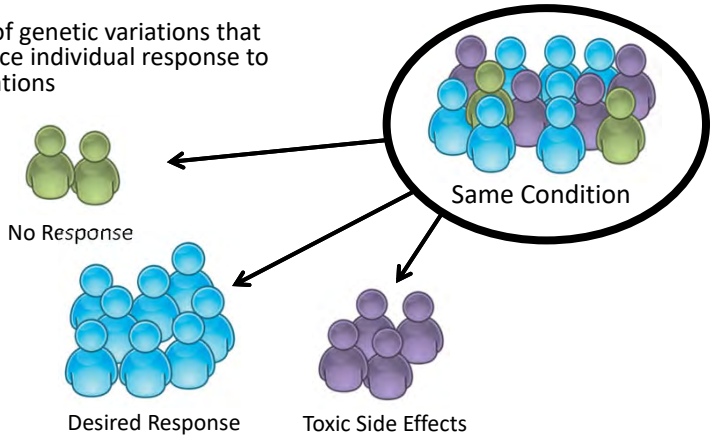
Objectives/Discussion Points

- Describe pharmacogenomics in the current literature regarding the treatment of serious mental illness
- Contrast available pharmacogenomic tests
- Describe current utilization of pharmacogenomic testing in clinical practice
- Discuss implementation of pharmacogenomic testing in practice

2

What is Pharmacogenomics?

Study of genetic variations that influence individual response to medications



3

Pharmacogenomic Mechanisms

- Pharmacokinetic
- Pharmacodynamic
- Immunologic Mechanisms

Bousman CA, et al. Pharmacopsychiatry 2021;54:5-17.

4

Pharmacokinetics

- CYP Enzymes
  - CYP2C9, CYP2C19, CYP2D6
- UDP-glucuronosyltransferase (UGT)
- Catechol-O-methyltransferase (COMT)
- P-glycoprotein (ABCB1)

Caudle KE, et al. Genet Med 2017;19:31-54.

5

Standardization Terms (CPIC)

Term/Gene Category	Final Term	Example
Allele functional status: all genes	Increased, normal, decreased, no, unknown, uncertain function	CYP2C19*17
Phenotype: drug-metabolizing enzymes	Ultrarapid, rapid, normal, intermediate, poor metabolizers	CYP2C19*17/*17
Phenotype: transporters	Increased, normal, decreased, poor function	SLCO1B1*1/*14
Phenotype: high-risk genotype status	Positive, negative	HLA-B*15:02

Genet Med 2016 doi: 10.1038/gim.2016.87

6

Pharmacodynamics

- Biochemical, cellular, and physiologic effects of medications and MOA
  - Neurotransmitter receptors
  - Reuptake transporters
  - Signal transduction
  - Gene transcription
  - Protein folding and trafficking

Blumenthal D. Goodman & Gilmans The Pharmacological Basis of Therapeutics. 13th ed 2018: 31-54

7

Immunologic Mechanisms

- Drug hypersensitivity reactions
  - Human leukocyte antigen (HLA) genes

Tangamornsuksan W, et al. JAMA Dermatol 2013;149:1025-1032.

8

Available Guidelines

- Clinical Pharmacogenetic Implementation Consortium (CPIC)
- Dutch Pharmacogenetics Working Group (DPWG)

9

Antidepressants

10

Guidelines and Product Labels

- 17 antidepressants
- CYP2C19 PM: 50%↓ in starting dose of citalopram, escitalopram, sertraline, tertiary amine TCAs
- CYP2C19 RM/UM: citalopram, escitalopram, tertiary amine TCAs- inadequate response
- CYP2D6 PM: 50%↓ TCAs, fluvoxamine, paroxetine
- CYP2D6 UM: select an alternative antidepressant not metabolized by CYP2D6

Hicks JK, et al. Clin Pharmacol Ther 2015;98:127-134.
Hicks JK, et al. Clin Pharmacol Ther 2016;102:37-44.

11

	Actionable Guidelines Available		Product Label- FDA
Antidepressant	**CPIC**	**DPWG**	
Amitriptyline	CYP2C19, CYP2D6	CYP2D6	CYP2D6
Amoxapine	-	-	CYP2D6
Citalopram	CYP2C19	CYP2C19	CYP2C19
Clomipramine	CYP2C19, CYP2D6	CYP2D6	CYP2D6
Desipramine	CYP2D6	-	CYP2D6
Doxepin	CYP2C19, CYP2D6	CYP2D6	CYP2D6
Duloxetine	-	-	CYP2D6
Escitalopram	CYP2C19	CYP2C19	-
Fluvoxamine	CYP2D6	-	CYP2D6
Imipramine	CYP2C19, CYP2D6	CYP2C19, CYP2D6	CYP2D6
Nortriptyline	CYP2D6	CYP2D6	CYP2D6
Paroxetine	CYP2D6	CYP2D6	-
Protriptyline	-	-	CYP2D6
Sertraline	CYP2C19	CYP2C19	-
Trimipramine	CYP2C19, CYP2D6	-	CYP2D6
Venlafaxine	-	CYP2D6	CYP2D6
Vortioxetine	-	-	CYP2D6

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Genomics Tests and The FDA

WARNING LETTER

Inova Genomics Laboratory

MARCS-CMS 577422 – 04/04/2019

Share Tweet LinkedIn Email Print

Product: Medical Devices

Recipient:
Ramaswamy Iyer, Ph.D.
Director
Inova Genomics Laboratory
3300 Gallows Road
Claude Moore Building, 2nd Floor
Falls Church, VA 22042
United States

Issuing Office:
Center for Devices and Radiological Health
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
United States

Inova ends genetic tests that elicited FDA warning

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Antipsychotics

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Guidelines and Product Labels

- 10 antipsychotics
- CYP2D6 PM: lower starting doses or alternative drug not metabolized by CYP2D6

- Genetic variation in D2 receptor: inconsistent results for efficacy or adverse reactions

Swen JJ, et al. Clin Pharmacol Ther 2011;89:662-673.
Yoshida K, et al. Mol Neuropsychiatry 2020; 5:1-26.

15

	Actionable Guideline Available		**Product Label- FDA**
Antipsychotic	**CPIC**	**DPWG**	
Aripiprazole	-	CYP2D6	CYP2D6
Brexpiprazole	-	CYP2D6	CYP2D6
Clozapine	-	-	CYP2D6
Haloperidol	-	CYP2D6	-
Iloperidone	-	-	CYP2D6
Perphenazine	-	-	CYP2D6
Pimozide	-	CYP2D6	CYP2D6
Risperidone	-	CYP2D6	-
Thioridazine	-	-	CYP2D6
Zuclophenthixol	-	CYP2D6	-

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Mood Stabilizers/Anticonvulsants

17

Guidelines and Product Labels

- Carbamazepine and oxcarbazepine: HLA-B*1502 allele “genetically at risk populations”
- Carbamazepine: HLA-A*31:01
- CYP2C9 PM: 50%↓ for phenytoin, assuming not a carrier of HLA-B*1502 allele
- Valproic acid: contraindicated or recommend genetic tests to individuals suspected of having certain rare metabolic disorders

Caudle KE, et al. Clin Pharmacol Ther 2014;96:542-548.
Philips EJ, et al. Clin Pharmacol Ther 2018;103:574-581.
Finsterer J, et al. Drug Chem Toxicol 2010;33:138-151.

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	Actionable Guideline Available		Product Label-FDA
Mood Stabilizer/Anticonvulsant	**CPIC**	**DPWG**	
Carbamazepine	HLA-A, HLA-B	-	HLA-A, HLA-B
Oxcarbazepine	HLA-B	-	HLA-B
Phenytoin	CYP2C9, HLA-B	CYP2D6	HLA-B
Valproic Acid	-	-	OTC, POLG

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Anxiolytics/Hypnotics

20

Guidelines and Product Labels

- CYP2C19 PM: starting dose of 5 mg/day for clobazam with titrations proceeding slowly according to body weight
- CYP2C19 PM: diazepam could present with marked differences in drug clearance, suggesting caution and additional monitoring is warranted

Seo T, et al. Pharmacogenomics 2008;9:527-537.
de Leon J, et al. Ther Drug Monit 2013;35:30-47.

21

ADHD Medications

22

Guidelines and Package Inserts

- CYP2D6 inhibitor or CYP2D6 PM: atomoxetine to start at the same dose as NM, but to approach dose escalation differently by only considering increases after 4 weeks if the medication is tolerated and symptoms don't improve

Brown JT, et al. Clin Pharmacol Ther 2019;106:94-102.

23

Pharmacogenomic Testing In Psychiatry- Logistic Considerations

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Test Providers

- Commercial
  - Gatekeeper
  - Direct-to-consumer
- Non-commercial: healthcare organizations/systems

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Test Content

- Single gene versus panel of genes
  - Often includes genes lacking sufficient evidence to guide prescribing
- Number of gene sequence variations or alleles
  - Lack of regulatory standards
- AMP and CAP: published recommendations for CYP2C9, CYP2C19 allele selection (CYP2D6 underway)

Pratt VM, et al. J Mol Diagn 2019;21:746-755.
Pratt VM, et al. J Mol Diagn 2018;20:269-276.

26

Test Analytical Validity

- Variability
  - Accurately calling “star” alleles from the variants tested
  - Identification of structural variations
  - Presence of novel or rare allelic variations

Ingelman-Sunberg M, et al. Hum Genomics 2018;107:154-170.

27

Test Feasibility

- Availability of testing
- Patient and provider acceptability of testing
- Testing turnaround time
- Test affordability

28

Test Clinical Efficacy and Cost-Effectiveness

- Mixed data on efficacy
  - 2 meta-analytic evaluations of the clinical efficacy of commercial PGx testing: improves the likelihood of achieving symptom remission compared to TAU
  - Inconclusive and negative trial findings
- Cost-Effectiveness
  - Most evaluations concluded it is cost-effective or a cost-saving strategy relative to TAU
  - Most completed by PGx testing companies

Bousman CA, et al. Pharmacogenomics 2019;20:37-47 Rosenblat JD, et al. J Affect Disord 2018;241:484-491. Greden JF, et al. J Psychiatr Res 2019;111:59-67. Perlis RH, et al. Depress Anxiety 2020; 37:834-841. Benitez J, et al. Per Med 2018;15:481-494. Maciel A, et al. Neuropsychiatr Dis Treat 2018;14:225-230. Berm EJ, et al. PLoS One 2016;11:e0146262.

29

Test Results Interpretation and Delivery

- Assigning a function to the alleles possessed
- Combining the functions to derive a phenotype
- Process is inconsistent; no gold standard approach exists
- Proprietary algorithms- potential discordant recommendations

30

Test Results Interpretation and Delivery

- Other factors:
  - Age
  - Sex
  - Concomitant medications
  - Renal/hepatic function
  - Inflammation
  - Lifestyle (smoking; diet)
  - Weight
- Therapeutic drug monitoring

Caudle KE, et al. Clin Transl Sci 2019;13:116-124. Bousman CA, Braz J Psychiatry 2020;42:113-115. Bousman CA, et al. Pharmacogenomics J 2018; 18:613-622. Tandy-Connor S, et al. Genet Med 2018;20:1515-1521.

31

Test Results Interpretations and Delivery

- Ancestry
  - "One-size-fits-all"
  - European ancestry

Franconi F, et al. Curr Med Cehm 2017;24:2561-2575.

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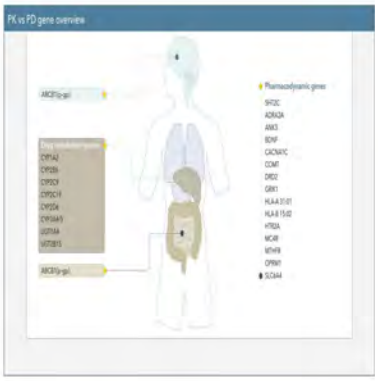
Genesight®

33

34

Genomind



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Circle DNA

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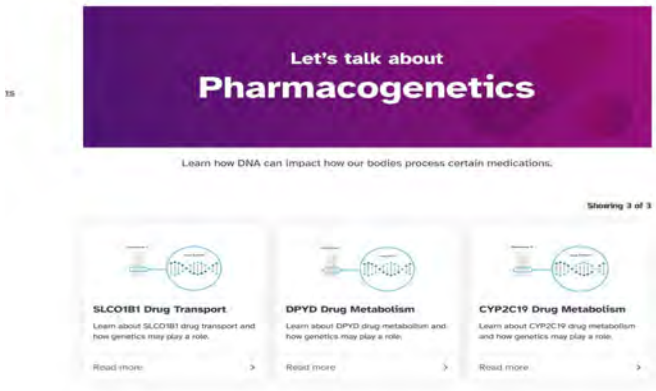
23andMe®



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Other Laboratories

- Tempus
- Admera
- Quest
- Lab Corp
- Others…….

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Capturing it all

39

Electronic Medial Record

- Laboratory Results
- Pharmacogenomic Consults- present statically in the EMR
- Automated alerts- fire only when an affected drug is ordered or dispensed to a pt. with an actionable pharmacogenetic test result

Hicks JK, et al. Clin Pharmacol Ther 2012

40

How to Capture the Impact

- Novel research study designs that reflect heterogeneity and complexity of real-world pts.
  - Medical comorbidity
  - Polypharmacy
  - Diversity in genetic ancestry
  - Age
  - Gender
  - Environmental exposures

Hamilton S. Biol Psychiatry 2015

41

Routine Clinical Practice

- Clear, curated, peer-reviewed pharmacogenetic guidelines
- Compare costs of utilization of genomic testing to standard of care
  - Costs of genomic testing
  - Medications costs
  - Cost of pharmacist time
  - Hospitalization costs
  - Quality of Life costs

42

Available Laboratories

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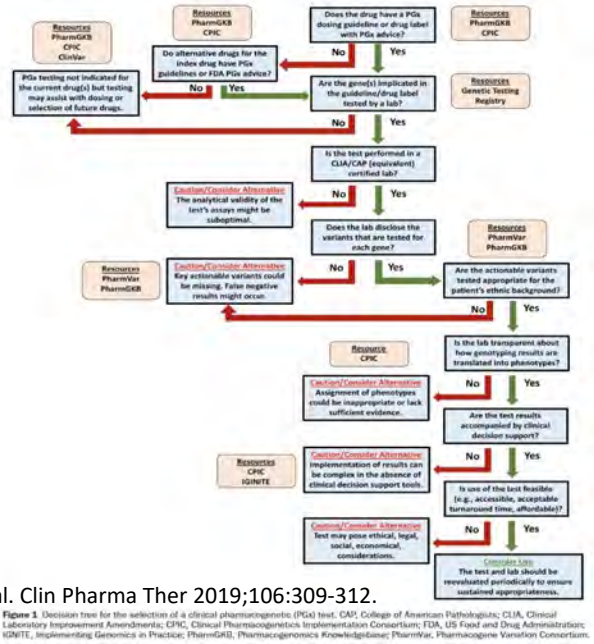

Bousman CA, et al. Clin Pharma Ther 2019;106:309-312.

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Conclusions

- Decision-support tool
- Supplement demographic, clinical, and lifestyle information
- CYP2C19, CYP2D6, CYP2C9, HLA-A, HLA-B have evidence/guidance
- Pharmacodynamic genes: no current evidence
- Education or consult an expert

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Discussion/Questions

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Notes

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201 W. Preston Street, Baltimore, MD 21201
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https://health.maryland.gov/mmcp/pap