Psychopharmacology for the LTCF Provider

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ALMDA Winter Conference

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Knowledge that will change your world

Disclosures

- I have served as a consultant for Acadia Pharmaceuticals, and their product will be discussed in this talk.

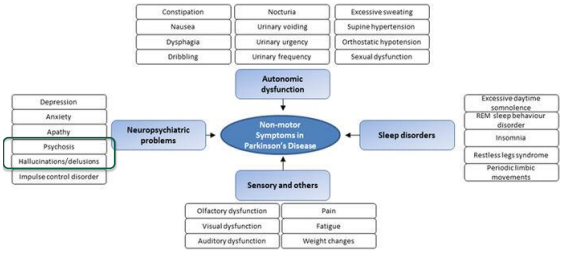
Psychopharmacology for the LTCF Provider

- Background on Psychosis / Receptor Theories
- General Treatment Principles
- Antipsychotics
- "Neuroleptic-sparing" therapy
  - Antidepressants
  - Mood stabilizers
- Non-pharmacologic treatment options
- Final thoughts

Have you seen this commercial on TV?

- https://www.youtube.com/watch?v=TyP7ZBbp8vQ

Non-motor symptoms in PD



Qamar et al, 2017

Some Definitions

- Hallucination – a perception of something that is not actually there
- Illusion – alteration of a real perception into something else
- Delusion – a fixed, false belief
  - Example: Believing some stranger is in the house when there is no one else there

Many Neurotransmitter Pathways Linked to Psychosis

There are 3 interconnected pathways that are believed to be linked to hallucinations and delusions[1,2]

Dopamine theory
Hyperactive dopamine in the mesolimbic pathway

Serotonin theory
5-HT_{2A} receptor hyperfunction in the cortex

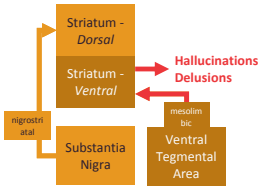
NMDA theory
NMDA receptor hypofunction

- Both serotonin and NMDA theories can result in hyperactivity of the mesolimbic dopamine pathway[1,2]
- It is likely that 1 or more of these pathways is involved in patients with psychosis[1,2]

1. Stahl SM. 4th ed. New York, NY: Cambridge University Press; 2013.
2. Stahl SM. *CNS Spectr.* 2016;21:355-359.

The Dopamine Theory of Psychosis

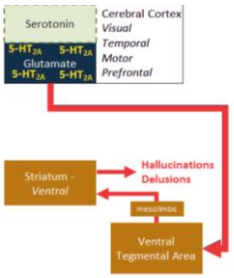
- Psychosis: hyperactivation of dopaminergic mesolimbic pathway
- Mesolimbic pathway projects from ventral tegmental area (VTA) to ventral striatum
- Dorsal striatum not thought to be affected by this hyperactivity because innervated via nigrostriatal pathway from substantia nigra



1. Stahl SM. 4th ed. New York, NY: Cambridge University Press; 2013.

The Serotonin Theory of Psychosis

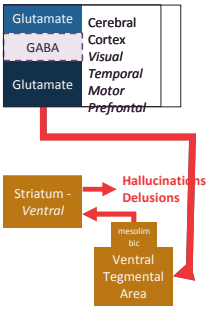
- Psychosis: hyperactivation of 5-HT_{2A} receptors on glutamate neurons
- May be due to excess serotonin, upregulated 5-HT_{2A} receptors, or a 5-HT_{2A} agonist, all of which could lead to downstream release of glutamate
- Glutamate release in VTA may activate mesolimbic pathway, resulting in excess dopamine in ventral striatum



1. Stahl SM. *CNS Spectr.* 2016;21:355-359.

The NMDA Theory of Psychosis

- Psychosis: hypofunctional NMDA receptors on GABA interneurons in cortex
- Hypofunction may lead to overactivation of downstream glutamate signaling to VTA
- Overactivation of this pathway may result in excess dopamine in ventral striatum via mesolimbic pathway



1. Stahl SM. 4th ed. New York, NY: Cambridge University Press; 2013.

General Principles

- Not all pharmacotherapy is bad
  - Though there are clear reasons to try to avoid neuroleptics, sometimes they are necessary
  - Can use meds from other classes to treat symptoms and prevent neuroleptic use
- Not all neuroleptics are the same
  - Use receptor profile differences to your advantage
- Medicating all the time for intermittent behavioral problems is extremely difficult
- Staff safety/sanity is an important consideration

Sustained Receptor Occupancy Is Thought to Be Necessary for Efficacy

Receptor Occupancy = $\frac{\text{\# receptors occupied by drug}}{\text{\# total receptors}}$

The effect of a drug should depend on the fraction of receptors occupied by drug[1]

- Antipsychotic efficacy is generally seen when at least 80% of D2 receptors are consistently occupied in the mesolimbic pathway[2]

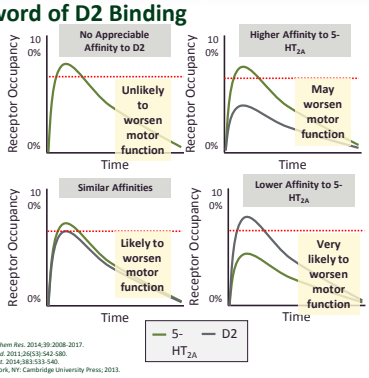
1. Salahudeen MS, et al. *Saudi Pharma J.* 2017;25:165-175.
2. Stahl SM. 4th ed. New York, NY: Cambridge University Press; 2013.

Typical Antipsychotics

- All are primarily active at D2 receptor
- Most commonly used is haloperidol (Haldol)
  - Available IM in addition to po
  - Long receptor occupancy: single dose can occupy D2 receptors for 30 days
  - Lots of affective blunting but not extremely sedating
  - Inexpensive (on the $4 list)
- Also fluphenazine (Prolixin) – high potency
- Chlorpromazine (Thorazine) – low potency but sedating

Double Edged Sword of D2 Binding

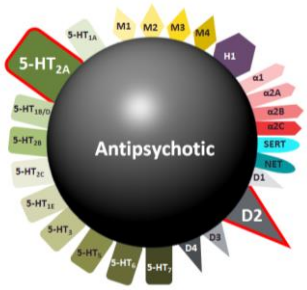
- D2 blockade is key for efficacy in psychosis
- D2 blockade is responsible for extrapyramidal symptoms/side effects (EPS) – parkinsonism/ dystonia[2,3]
- D2 blockade over time can cause tardive dyskinesia
- In patients with PD, high receptor occupancy at D2 receptors worsens motor function[1]



1. Hacksell U, et al. *Neurochem Res.* 2014;39:2008-2017.
2. Seppi K, et al. *Mov Disord.* 2011;26(S3):S42-S80.
3. Cummings J, et al. *Lancet.* 2014;383:533-540.
4. Stahl SM. 4th ed. New York, NY: Cambridge University Press; 2013.

Antipsychotics as a Class Have Activity at Many Receptors

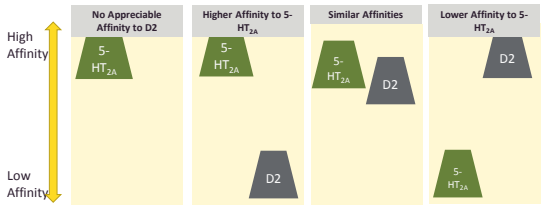
- Atypical antipsychotics bind many receptors but efficacy in psychosis thought to be primarily due to activity at D2 and 5-HT_{2A} receptors
- Atypical antipsychotics can be grouped based on their relative D2 and 5-HT_{2A} affinities



1. Stahl SM. 4th ed. New York, NY: Cambridge University Press; 2013.

Antipsychotic Groupings by Relative 5-HT2A and D2 Receptor Affinities

- Atypical antipsychotics can be grouped into 4 categories based on their relative 5-HT2A and D2 receptor affinities[1,2]



1. Stahl SM. 4th ed. New York, NY: Cambridge University Press; 2013.
2. Hacksell U, et al. *Neurochem Res*. 2014;39:2008-2017.

Typicals vs. Atypicals – Side Effects

Typicals	Atypicals
+ Weight Gain	**++ Weight Gain / Metabolic Syndrome ****
++ Tardive dyskinesia**	+/- Tardive Dyskinesia
+/- Sedation	**++ Sedation**
+ Dry mouth	Dry mouth
+ Orthostatic hypotension	Orthostatic hypotension
+ Parkinsonism	Parkinsonism
+ Dystonia	Dystonia

Receptor Selectivity of Various Treatment Options

Receptor	Pimavanserin	Haloperidol	Clozapine	Olanzapine	Quetiapine	Risperidone
5-HT2A	0.4	50	7	2.5	250	0.2
5-HT2B	nr	nr	40	80	1100	12
5-HT2C	16	nr	40	80	nr	100
5-HT1A	nr	nr	nr	nr	nr	nr
H1	nr	nr	0.5	4	5	60
M1	nr	nr	16	60	250	nr
M2	nr	nr	nr	nr	–	nr
M3	nr	nr	6	nr	200	nr
M4	nr	nr	nr	40	150	nr
M5	nr	nr	30	60	–	nr
D1	nr	100	nr	100	–	60
D2	nr	0.1	50	4	30	0.5
D3	nr	0.2	nr	25	9	13
Alpha 1A	nr	40	8	100	nr	3
Alpha 1D	–	nr	nr	nr	nr	50
Alpha 2A	nr	nr	nr	nr	nr	20
Alpha 2B	nr	nr	50	nr	nr	50
Alpha 2C	nr	50	40	nr	nr	13

K_i (nM)
≤ 1
≤ 10
≤ 100
≤ 1000
> 1000
-, not done; nr, no response

5-HT = serotonergic; H = histaminergic; M = muscarinic; D = dopaminergic; A = alpha-adrenergic.
Data are K_i values in nM derived from Receptor Selection and Amplification Technology™ (R-SATTM) platform[1]

1. Hacksell U et al. Neurochem Res. 2014;39:2008-2017

Small numbers means high binding, big numbers means low binding

Selected Atypical Antipsychotics

- Potency
  - Risperidone and olanzapine both with very high affinities for both D2 and 5HT2A, making them highly potent but also lots of potential for side effects
- Quetiapine and clozapine the most 'atypical:' the least D2 blockade and the most 5HT-2 blockade
  - Both have prominent wt gain and sedation (but quetiapine sedation goes away above 100mg/day)
  - True antipsychotic effect of quetiapine only present above 200mg/day
  - 1% of pts on clozapine develop BM suppression

Diagnosis of PDP

- PD-associated psychosis
  - Diagnosis of PD
  - At least 1: illusions, false sense of presence, hallucinations, delusions
    - These occur after the onset of PD
    - Continuous for >1 month
  - **Exclusion of other causes
  - Associated features
    - With/without insight
    - With/without dementia
    - With/without treatment for PD

Ravina et al, 2007

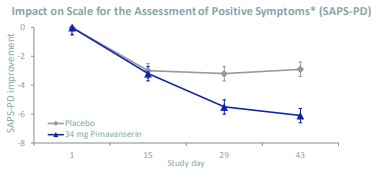
Pharmacologic Treatment Options for PDP

- Reduction of PD medication
  - Start with amantadine, trihexyphenidyl
  - Then reduce dopamine agonists
  - Then reduce levodopa
- Antipsychotic medications
  - Typical Antipsychotics
    - Generally contraindicated in PD
  - Atypical Antipsychotics
    - Not all are safe
- Newer treatment options
  - Cholinesterase inhibitors
  - NMDA receptor antagonist
  - Serotonin$_{2A}$ receptor inverse agonist (pimavanserin)

Pimavanserin and PDP

- New class of medication (Serotonin 2A inverse agonist)
- FDA-approved for treatment of PDP
  - Allows improvement of PDP symptoms with little to no risk of worsening PD motor symptoms
- Other unique qualities
  - Single dose (34mg once daily), auto-titrating
    - Has pros/cons
  - Branded and increased cost

ACP-103-020 Primary Outcome: SAPS-PD[1]



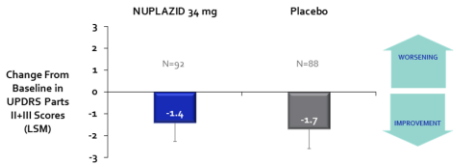
Day 43 Outcome Measure	Pimavanserin 34 mg† (n=95)	Placebo (n=90)	Treatment Change‡	*P* value	Effect Size
SAPS-PD (change from baseline to Day 43)	-5.79 (0.66)	-2.73 (0.67)	-3.06 (0.94)	0.0014	0.50
SAPS-PD % Change	-37% (4.6%)	-14% (4.7%)	-23% (6.6%)	0.0006	-

*Adapted for PD.

†For numerical outcomes, data are least squares means (standard error); ‡Least squares means treatment change is pimavanserin minus placebo.

1. Cummings J et al. *Lancet.* 2014;383:533-340.

Pimavanserin Does Not Worsen PD Motor Symptoms



The UPDRS Parts II+III assesses motor function and the impact of motor function on daily living

LSM: least-squares mean

1. NUPLAZID Prescribing Information. 2016.

Pimavanserin Safety Data

	Percentage of Patients Reporting Adverse Reaction	
	NUPLAZID 34 mg N=202	Placebo N=231
Nausea	7%	4%
Peripheral edema	7%	2%
Confusional state	6%	3%
Hallucination[a]	5%	3%
Constipation	4%	3%
Gait disturbance	2%	<1%

Adverse Reactions Leading to Discontinuation of Treatment

- A total of 8% (16/202) of NUPLAZID 34 mg-treated patients and 4% (10/231) of placebo-treated patients discontinued because of adverse reactions
  - Hallucination (2% NUPLAZID 34 mg vs <1% placebo)
  - Urinary tract infection (1% NUPLAZID 34 mg vs <1% placebo)
  - Fatigue (1% NUPLAZID 34 mg vs 0% placebo)

[a] Hallucination includes visual, auditory, tactile, and somatic hallucinations

1. NUPLAZID Prescribing Information. 2016.

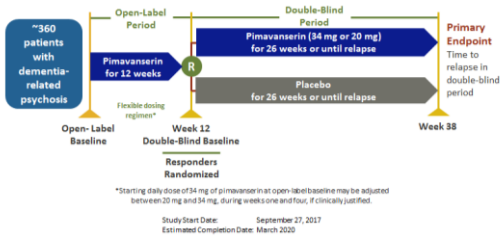
What about death risk with Pimavanserin?

Death Risk with PDP and Pimavanserin

Data Source	Mortality Rate per 100 patient-years (95% CI)
ACADIA Post-marketing Data	
PADER 2	11.5 (8.8-14.8)
PADER 3	12.5 (10.1-15.3)
PADER 4	11.8 (9.7-14.2)
PADER 5	10.6 (8.7-12.7)
PADER 6	11.5 (9.7-13.6)
PADER 7	16.8 (14.6-19.3)
PADER 8	14.5 (12.6-16.6)
OVERALL (29 April 2016-28 April 2018)	12.8 (12.0-13.7)
Literature: US Veterans Administration Data (Weintraub et al. 2016)	
Mortality rates for PD patients taking APs	Haloperidol 49.0 (37.4-63.0) Other typical AP 31.3 (19.1-48.3) Olanzapine 29.3 (24.1-35.2) Quetiapine 18.6 (16.9-20.3) Risperidone 31.0 (26.4-36.1) Other atypical AP 14.2 (7.6-24.3)
US Medicare Data (01 January 2012- 31 December 2015) (Weintraub et al. 2018)	Age Standardized Mortality Rates per 100 Person-Year of Follow Up per US Census 2010 (95% CI)
Parkinson's disease	7.31 (7.15-7.47)
Parkinson's disease psychosis	28.18 (27.53-28.8)

ACP-103-045: HARMONY

Randomized, double-blind, placebo-controlled, multi-center relapse prevention outpatient study



*Starting daily dose of 34 mg of pimavanserin at open-label baseline may be adjusted between 20 mg and 34 mg, during weeks one and four, if clinically justified.

Study Start Date: September 27, 2017
Estimated Completion Date: March 2020

1. ACADIA Pharmaceuticals. ACADIA Pharmaceuticals Initiates Phase III Study of Pimavanserin in Dementia-Related Psychosis. http://ir.acadia-pharm.com/phoenix.zhtml?c=125180&p=irol-newsArticle&ID=2304720. June 27, 2018.
2. Clinicaltrials.gov. Relapse Prevention Study of Pimavanserin in Dementia-related Psychosis. https://clinicaltrials.gov/ct2/show/NCT03325556. Accessed June 27, 2018.

Other Psychopharmacology

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Psychopharmacology – Antidepressants

- SSRI's
  - Include citalopram, escitalopram, paroxetine, fluoxetine, sertraline, fluvoxamine

Drug Name	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4	CYP2B6
Citalopram	+	0	0	+	0	0
Escitalopram	0	0	0	+	0	0
Fluoxetine	+	++	+/++	+++	+	+
Fluvoxamine	+++	++	+++	+	+	+
Paroxetine	+	+	+	+++	+	+++
Sertraline	+	+	+/++	+	+	+

Legend:
0 — no inhibition.
+ — mild inhibition.
++ — moderate inhibition.
+++ — strong inhibition.

Antidepressants – SSRI's

- Fluvoxamine (Luvox) primarily used for OCD
- Paroxetine (Paxil) is most potent, shortest half-life
- Fluoxetine (Prozac) has longest action due to active metabolite that lasts weeks
- Citalopram (Celexa) and escitalopram (Lexapro) [just S-isomer of citalopram] are most selective SSRI's
- Paxil most classically known for anxiety disorders, Zoloft good for anxious depression

Psychopharmacology – Antidepressants

- SNRI's
  - Venlafaxine (Effexor) is prototypical, has SSRI activity at low doses and SNRI activity at high doses – beware resulting HTN
  - Duloxetine (Cymbalta) – dual SSRI/SNRI
  - Desvenlafaxine (Pristiq) – active metabolite of Effexor, bypasses some of HTN problems but attractiveness is ease of use (one dose, no titration needed)
  - Milnacipran (Savella) – FDA-approved for fibromyalgia, structurally different from other SNRI's, favorable PK's, very low P450 interations
  - Levomilnacipran (Fetzima) – L isomer of above, effective for MDD

Psychopharmacology – Antidepressants

- Bupropion
  - Mixed dopamine/NE reuptake inhibition, has no 5HT activity
  - Activating, good adjunct to SSRI for refractory depression, no sexual side effects
  - **Lowers seizure threshold

Psychopharmacology – Antidepressants

- Tricyclics (TCA's)
  - Amitryptyline more potent but also more side effects than nortryptyline
  - Imipramine increases risk of heart block
  - Side effects primarily anticholinergic (dry mouth, constipation, orthostatic hypotension, wt. gain)
    - Therefore not recommended in geriatric population
- Tetracyclics
  - Mirtazapine (Remeron) and trazodone have prominent antihistamine side effect (sedation)
  - Trazodone used primarily for this and needs >200mg/day to have antidepressant effect
  - Remeron also stimulates appetite and loses antihistamine effect above 45mg/day

Other Recommendations

- Depression / Anxiety
  - Treat aggressively medically as many times behavioral problems are a manifestation of mood
  - Don't forget about counseling, even in geriatric population
- Paranoia / Suspiciousness / Obsessiveness / Perseveration / Irritability / Explosiveness
  - Identify triggers, behavioral modification
  - Antipsychotics, use oral-dissolving or IM preparations prn in addition to scheduled
  - Distraction / engagement in other activities

Other Recommendations

- Impulsivity
  - Consider mood stabilizer
  - Environmental strategies (bed/seat alarm)
- Screaming
  - In otherwise mute patient, often indicates terminal stages of disease
  - May not be experiencing discomfort (but check for sources of pain/infection)
  - Consider palliative/hospice care

Caregiver Burnout

- Make sure to take care of mental health of caregivers as well!

Huntington's Disease Society of America

HUNTINGTON'S DISEASE SOCIETY OF AMERICA LAUNCHES FIRST-OF-ITS-KIND FREE TELEHEALTH COUNSELING FOR HD FAMILIES

To utilize HDSA's free telehealth portal, visit www.hdsa.amwell.com or download the free Amwell® app and use the codes HDSA or HD to access the Huntington's disease practice. On the site, patients can schedule personal appointments with social workers and psychologists licensed in their state. The session is free for families affected by HD, and no insurance is required.

disease that causes the progressive breakdown of nerve cells in the brain. Best estimates from mental health professionals indicate that approximately 50 percent of patients seen at HD clinics, such as HDSA Centers of Excellence, are referred to counseling for issues ranging from anxiety and depression to stress management and suicidal thoughts. Unfortunately, it is estimated that only between 15 and 25 percent of those referred for counseling actually seek treatment.

"By partnering with American Well, we are confident that we can greatly improve access to care for families impacted by the

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Summary / Final Thoughts

- Care of LTCF patient with behavioral problems is both valiant and challenging
- A little pharmacology nerdiness can help to guide choice of pharmacotherapy
- Don't forget antidepressants and mood stabilizers
- Take time for yourself to avoid caregiver burnout

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