The 2019-2020 Update and Review of Current Psychotropic Medications

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Special Acknowledgement: Jessica Greenwood, PharmD

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Learning Objectives

- Discuss the recently approved psychotropic medications, their mechanisms of action, and their intended role in the clinical care of the person with mental illness.
- Compare the newer agents to the historically effective agents and discuss their place in future treatment.
- Discuss the roles that formulations have in psychotropic medication use and potential impact on adherence or acceptance.

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What is a Psychotropic?

- **Any NeuroPsychopharmacological agent?**
- **May have a single or multiple approved and 'un-approved' or 'off-label' applications?**
  - **"Antidepressants" : SNRIs / SSRIs / NDRIs / others?**
  - **Some (not all) Anticonvulsants also effective Mood Stabilizers?**
  - **Use of Atypical Antipsychotics as Mood Stabilizers & Antidepressants / Anxiolytics / Other uses?**
- Why: Their Single vs Multiple pharmacological mechanisms of action (MoA)?
  - ***Are they 'Dirty Drugs' or have a 'Rich Pharmacological Profile'***

The "Ideal Psychotropic"

- **Manage or Treat**: **Positive & Negative symptoms of psychosis**
  Manic and/or Depressive symptoms
  Anxiety / Irritability / Aggression symptoms
- ***Effective for refractory patients***
- Have no risk for EPS, or tardive dyskinesia
- Have no side effects*
- Have no long-term adverse health consequences
- ***Have convenient dosage forms***:
  tablets / capsules / liquids / IM / SC / disintegrating or sublingual tablets / transdermal delivery systems (patches) / **long-acting injectables** / implantables / **nasal sprays** / inhalants
- Improve cognition
- Be affordable with a low acquisition cost
- ***Reduce relapse and hospitalization rates****
- Improve Quality of Life / Positive Outcomes

Are we treating…….
Target Symptoms or Diagnoses ?

- Is it a 'Cure' vs 'Disease Management'?
- Is the psychopathology acute and time-limited?
- Or is it chronic and enduring?
  - Genetics?

Psychotropic medications
FDA-approved
or 'changed' in recent years

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Approved Psychotropic Agents for 2007-2008

- **Armodafinil (Nuvigil™) 6/07**
  - Excessive sleepiness for specific conditions
- **Rivastigmine transdermal system (Exelon*Patch*™) 7/07**
  - Alzheimer's Disease
- **Desvenlafaxine (Pristiq™) 2/08**
  - Depression
- **Tetrabenazine (Xenazine™) 8/08** ***
  - Huntington's Chorea

Approved Psychotropic Agents for 2009

- **Iloperidone (Fanapt™) 5/09**
  - Acute Schizophrenia
- **Paliperidone LAI (Invega Sustenna™) 7/09**
  - Acute & Maintenance of Schizophrenia
  - Only agent approved for Schizoaffective Disorder
- **Asenapine (Saphris™) 8/09** ***
  - Acute Mania secondary to Bipolar Disorder
  - Acute Psychosis secondary to Schizophrenia
- **Olanzapine LAI (Relprevv™) 12/09**
  - Maintenance of Psychosis / Schizophrenia

Approved Psychotropic Agents for 2010

- **Doxepin (Silenor™) 3/10**
  - Insomnia
- **Guanfacine (Intuniv™) 3/10**
  - ADHD
- **Clonidine (Kapvay™) 10/10**
  - ADHD
- **Lurasidone (Latuda™) 10/10**
  - Schizophrenia
  - Bipolar Depression **6/13**
- **Dextromethorphan + Quinidine (Nuedexta™) 11/10**
  - Pseudobulbar affect

Approved Psychotropic Agents for 2011-2014

- **Vilazodone (Viibryd™) 2/11**
  - Depression
- **Aripiprazole LAI (Abilify Maintena™) 7/12**
  - Schizophrenia – Relapse Prevention
  - **Bipolar Disorder – Relapse Prevention 8/17**
- **Levomilnacipran (Fetzima™) 7/13**
  - Depression
- **Vortioxetine (Trintellix™) 10/13**
  - Depression
- **Tasimelteon (Hetlioz™) 1/14**
  - Non-24 Sleep-Wake Disorder

Approved Psychotropic Agents for 2015

- **Suvorexant (Belsomra™) 8/14* (Feb. 2015)**
  - Insomnia
- **Paliperidone Palmitate (Invega Trinza™) 6/15**
  - Schizophrenia – Relapse Prevention
- **Brexpiprazole (Rexulti™) 7/15**
  - Adjunctive Tx for MDD with Antidepressants
- **Aripiprazole LAI (Aristada™) 10/15**
  - Schizophrenia
- **Cariprazine (Vraylar™) 10/15**
  - Schizophrenia & Acute Mania
  - ***Bipolar Depression in 5/2019***

Approved Psychotropic Agents for 2016/17

- **Pimavanserin (Nuplazid™) 4/16**
  - Psychosis secondary to Parkinson's Disease
- **Buprenorphine (Probuphine™) 5/16**
  - MAT for opioid dependence
- **Valbenazine (Ingrezza™) 4/17** ***
  - Tardive Dyskinesia
- **Amantadine (Gocovri™) 8/17** ***
  - Parkinson's Disease
- **Deutetrabenazine (Austedo™) 8/17** ***
  - Tardive Dyskinesia & Huntington's Chorea

Approved Psychotropic Agents for 2018/19

- **Aripiprazole (Aristada Initio™) 7/18**
  - First Day Initiation of Aristada
- **Risperidone (Perseris™) 7/18**
  - Subcutaneous monthly LAI for Schizophrenia
- **Esketamine (Spravato™) 3/19**
  - Adjunct for Treatment Resistant Depression
- **Brexanolone (Zulresso™) 3/19**
  - Postpartum Depression
- **Solriamfeterol (Sunosi™) 3/19**
  - Excessive Daytime Sleepiness associated with Narcolepsy or OSA
- **Midazolam (Nayzilam™) 5/19**
  - Frequent Seizure Activity*

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Approved Psychotropic Agents for 2019/20

- **Pitolisant (Wakix™) 8/19**
  - Narcolepsy in Adults
- **Asenapine (Sacuado™) 10/19**
  - Treatment of Schizophrenia in Adults
- **Lumateperone (Caplyta™) 12/19**
  - Treatment of Schizophrenia in Adults
- **Lemborexant (Davigo™) 12/19**
  - Insomnia in Adults
- **Amisulpride (Barhemsys™) 2/20*****
  - Postoperative Nausea and Vomiting (PONV)

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Other Interesting Agents

- Istradefylline (Nourianz®) for PD "off" episodes
  - *August 28th, 2019*
- Opicapone- (Ongentys®) for PD "off" episodes
  - *April 27, 2020*
- Apomorphine sublingual (APL130277, Kynmobi®)- PD "off" episodes
  - *May 21st, 2020 (yesterday)*

- *And a lot of migraine treatments recently approved in last 18 months.*

- Rykindo® (risperidone microspheres LAI) NDA for Schizophrenia, Bipolar Disorder was submitted to FDA in 3/2019
  (Jan. 2020 was expected approval date, still waiting…..)

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Special ADHD Detour

or

Formulations, Formulations, Formulations at every turn

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Approved Psychotropic Agents for ADHD 2006 to 2019

- **Daytrana®** (Methylphenidate transdermal patch): **4/2006**
  - Initial: 10 mg/day on hip area, 15, 20, max 30 mg/day
- **Quillivant XR®** (MPH extended release ***suspension***): **1/2013**
  - Indicated for patients '6 years and above…..'
  - Initial: 20 mg once daily in AM, max 60 mg/day (study: 6-12 year olds)
- **QuilliChew XR®:** **12/2015**
  - 20-30-40 mg extended release chewable tablets
- **Adhansia XR®** (extended release MPH capsules): **7/2019**
  - 6 years and older, including adults
  - **25mg to 85mg/day*****

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Methylphenidate 'Delayed-Release' Formulation

- ***Jornay PM®*** *Extended Release MPH* **8/2018**
- Take between 6:30pm and 9:30pm
- May swallow whole capsule or
  may open and sprinkle onto applesauce (but don't chew)
- Efficacy Studies in PI report only ages 6-12 yo.
  - Hmmmmmmm……?
  - Small PK studies in adults (n=12)
  - https://www.jornaypm.com/

IRONSHORE PHARMACEUTICALS

Website Ad:
Mornings set the tone for the day

JORNAY PM isn't just for kids. In fact, JORNAY PM is indicated for people with ADHD aged 6 and older.

Adults with ADHD know all too well that ADHD can make mornings challenging. And all-day control is important, too.

JORNAY PM capsule

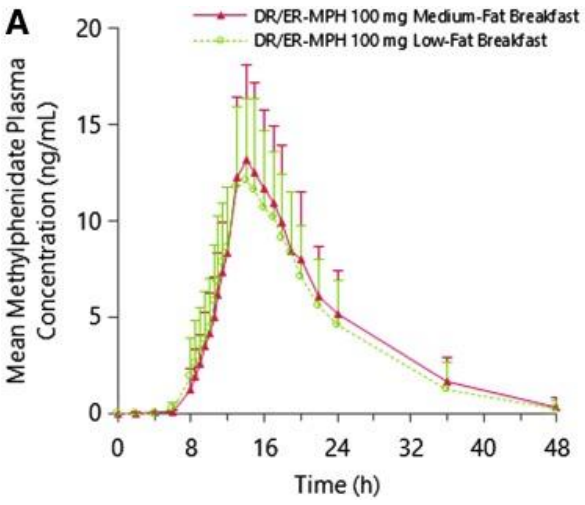
Microbead

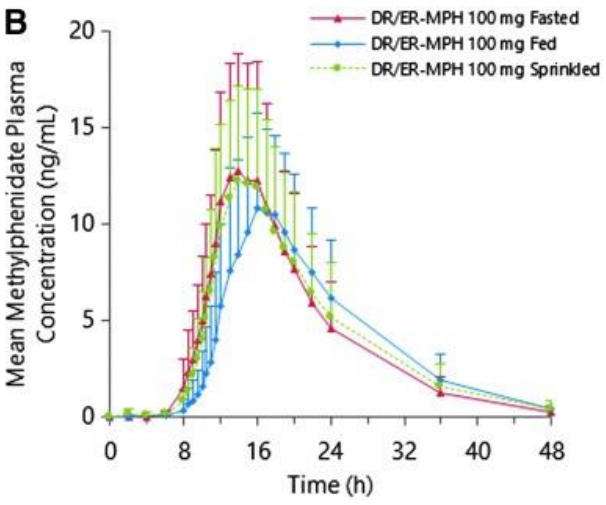
Delayed-release layer
The delayed-release layer keeps the medicine from working for about 12 hours, so it's working when you wake up to start the day.

Extended-release layer
The extended-release layer keeps controlling ADHD symptoms throughout the day.

Medicine core
The medicine core contains methylphenidate—a medicine that has been prescribed for ADHD for decades.

Jornay PM





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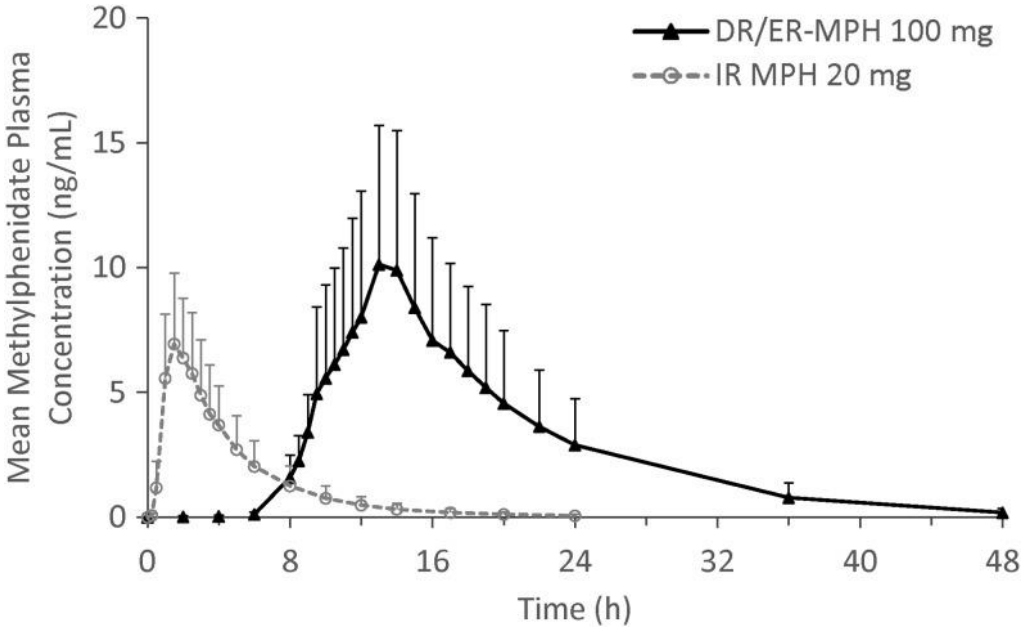

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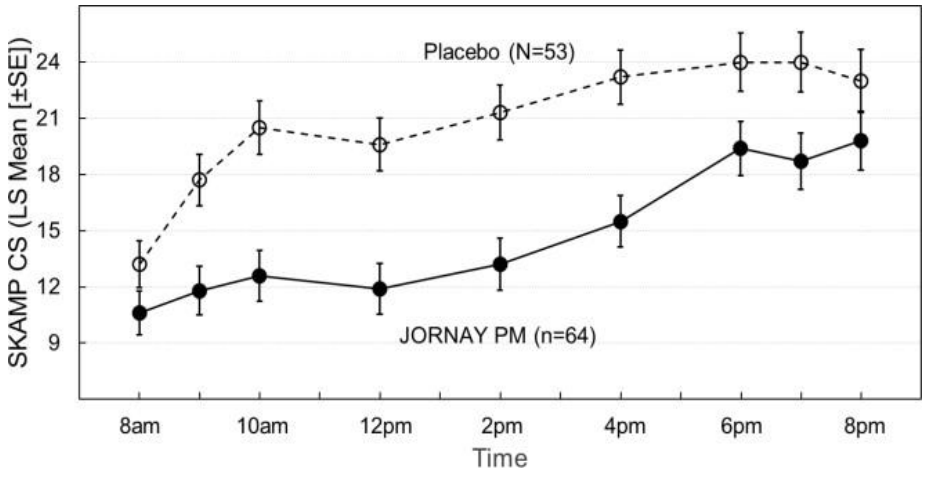
Jornay PM: Teacher ratings: ages 6-12



Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP), a 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting.

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d95dede0-b1ff-4489-8f91-3bbe122852bf

Dextroamphetamine

- **Zenzedi®** (dextroamphetamine sulfate) **5/2014**
  - Duration: 5-8 hours, Max dose: 40 mg/day tablets
- **ProCentra®** (dextroamphetamine sulfate) **1/2008**
  - colorless, bubble gum flavored ***oral solution***
  - each teaspoonful (5 mL) of oral solution contains 5 mg
  - ***Warning letter from FDA in Feb. 2020 for misleading advertising***
- ***Vyvanse®*** *(lisdexamfetamine dimesylate)**** **2/2007**
  - First and only 'pro-drug' stimulant for ADHD
  - First and only drug approved for Binge Eating Disorder in 2015

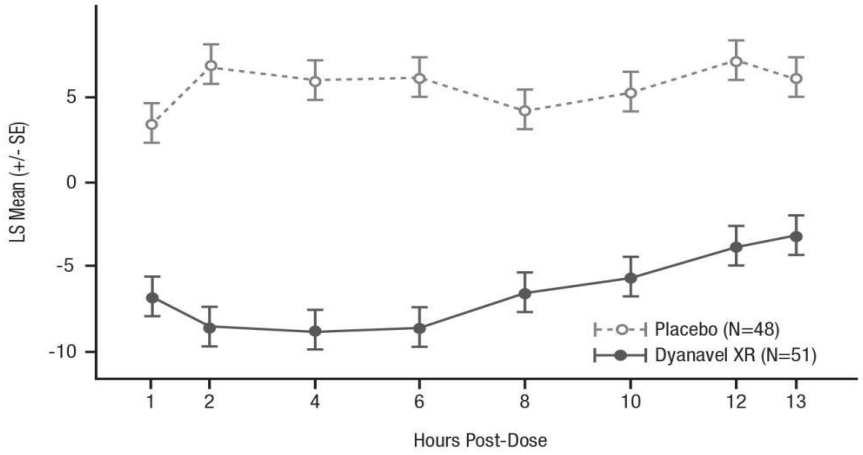
Mixed Amphetamine
(Isomers or Salts)

- **Adzenys ER® and Adzenys XR-ODT®** **1/2016**
  - Ages: 6 to 17 years & adults
  - Initial: 3.1 to 18.8 mg/day, Max: 18.8 mg/day in 6-12 year olds; 12.5 mg/day in 13+ yo
- **Mydayis®** (extended release capsules) **6/2017**
  - Initial: 12.5 mg to 25 mg/day, then up to 37.5 or 50 mg/day
  - Ages: 13 to 17 years; Max: 25 mg/day, Ages: 18 to 55 years; Max: 50 mg/day
  - Duration: up to 16 hours
- **Evekeo® and Evekeo ODT®** (IR tablet) **8/2019**
  - Amphetamine Sulfate (d- & l- isomers)
  - Ages: 3-17 years
- **Dyanavel®** (Extended release oral solution) **10/2015**
  - 2.5 mg/ml, Max 20 mg/day, Duration: 4-6 hrs
  - Ion exchange resin (sodium polystyrene sulfonate), contains immediate release and extended-release components

Change from pre-dose in SKAMP-Combined Score after treatment with **DYANAVEL XR or Placebo**.

		LS Mean Change from Pre-Dose at 4 Hours Post-Dosing (SE) Difference a (95% CI)	Placebo-subtracted
DYANAVEL XR	17.3 (8.88)	-8.8 (1.14)	-14.8 (-17.9, -11.6)
Placebo	15.5 (7.35)	6.0 (1.19)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
a Difference (drug minus placebo) in least-squares mean change from pre-dose.



Back on the road to the Newer (Non-ADHD) Psychotropics

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Asenapine Transdermal System

Secuado (asenapine) transdermal system

- SECUADO is indicated for the treatment of schizophrenia.

- **MoA**: Serotonin and Dopamine antagonist
- **Dosing**:
  - For transdermal use only. Apply one SECUADO transdermal system every 24 hours.
  - Apply SECUADO to one of the following sites:
    the hip, abdomen, upper arm, or upper back area.
  - The recommended starting dose of SECUADO is 3.8 mg/24 hours.
    May increase dosage to 5.7 mg/24 hours or 7.6 mg/24 hours after one week.

- **ADRs**:
  - Application Site Reactions, Weight Gain,
  - ***EPS: 8-13% for SECUADO and 2% for placebo***

noven

Secuado® Clinical Trials

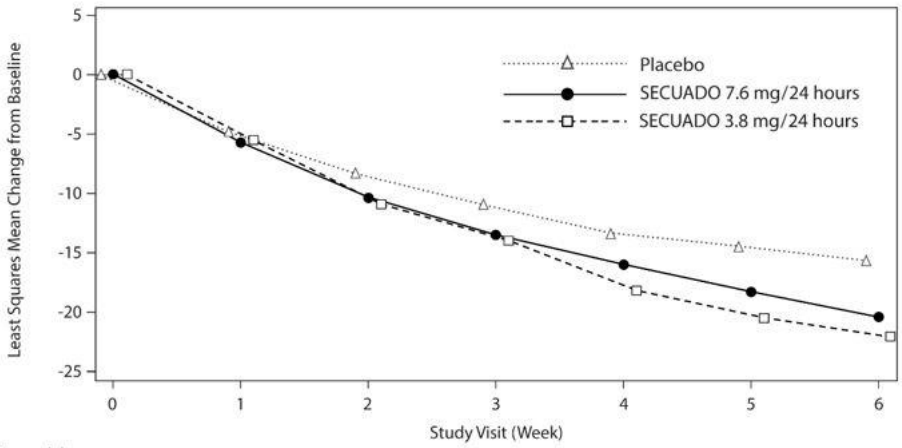
Table 8: Primary Efficacy Results for Change from Baseline in PANSS Total Score Week 6 (Study 1)

Treatment Group	Primary Efficacy Measure: PANSS Total Score		
	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE) to Week 6	Placebo-subtracted Difference[a] (95% CI)
SECUADO 3.8 mg/24 hours*	97.0 (9.78)	-22.1 (1.2)	– 6.6 (-9.81, -3.40)
SECUADO 7.6 mg/24 hours*	95.6 (8.68)	-20.4 (1.2)	– 4.8 (-8.06, -1.64)
Placebo	97.4 (10.07)	-15.5 (1.2)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline. A negative value for the placebo subtracted difference represents improvement.
*: Statistically significant after multiplicity adjustments.

Noven is a fully-integrated specialty pharmaceutical company with industry-leading transdermal expertise. Noven. http://www.noven.com/secuado.php. Accessed February 1, 2020.

Asenapine Transdermal



Number of patients remaining at each time point							
Placebo	203	201	193	185	179	174	165
SECUADO 7.6 mg/24 hours	203	203	194	188	182	174	164
SECUADO 3.8 mg/24 hours	201	201	196	186	180	178	168

Lumateperone

NEW CAPLYTA™ (lumateperone) capsules 42 mg — NOW APPROVED FOR YOUR ADULT PATIENTS WITH SCHIZOPHRENIA

- CAPLYTA is indicated for the treatment of schizophrenia in adults.

- **MoA**: Serotonin and Dopamine receptor antagonist
- **Dosing**:
  - 42 mg once per day
- **ADRs**:
  - Somnolence, dizziness,
  - Dry mouth, N/V
  - ***EPS: 6.7% for CAPLYTA and 6.3% for placebo***

Intra-Cellular THERAPIES
BUILT ON NOBEL PRIZE–WINNING SCIENCE

Caplyta® Clinical Trials

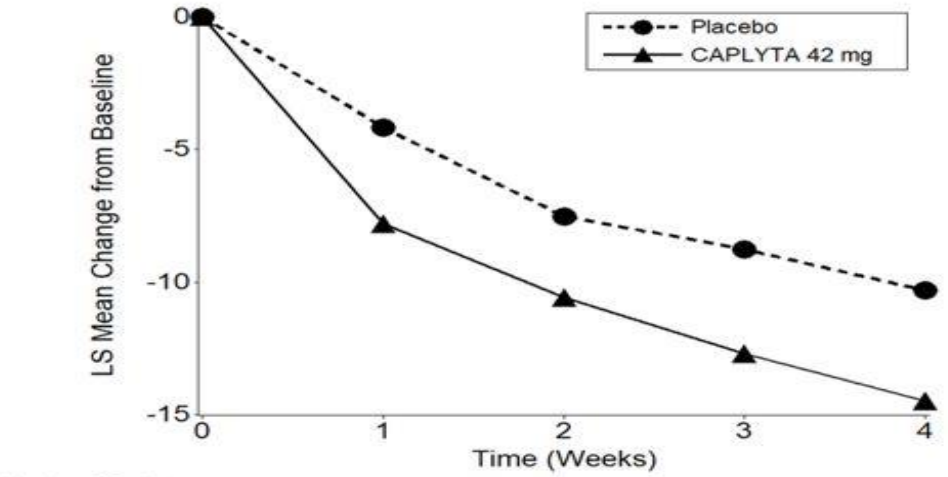
Table 3: Primary Efficacy Results for Change from Baseline in PANSS Total Score in Patients with Schizophrenia (Studies 1 and 2)

Study Number	Treatment Group	N	Primary Efficacy Endpoint: PANSS Total Score		
			Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI)
1	CAPLYTA (42 mg)*	84	88.1 (11.0)	-13.2 (1.7)	-5.8 (-10.5, -1.1)[a]
	Placebo	85	86.3 (13.1)	-7.4 (1.7)	--
2	CAPLYTA (42 mg)*	150	90.0 (9.6)	-14.5 (1.3)	-4.2 (-7.8, -0.6)
	Placebo	150	89.0 (10.3)	-10.3 (1.3)	--

The PANSS total score may range from 30 to 210; higher scores reflect greater symptom severity. SD: standard deviation; SE: standard error; LS Mean: least squares mean; CI: unadjusted confidence interval.
[a]Difference (drug minus placebo) in LS mean change from baseline not adjusted for sample size increase after unblinded interim analysis.
*Statistically significantly superior to placebo.

CAPLYTA® (lumateperone): https://www.caplyta.com. Accessed February 1, 2020

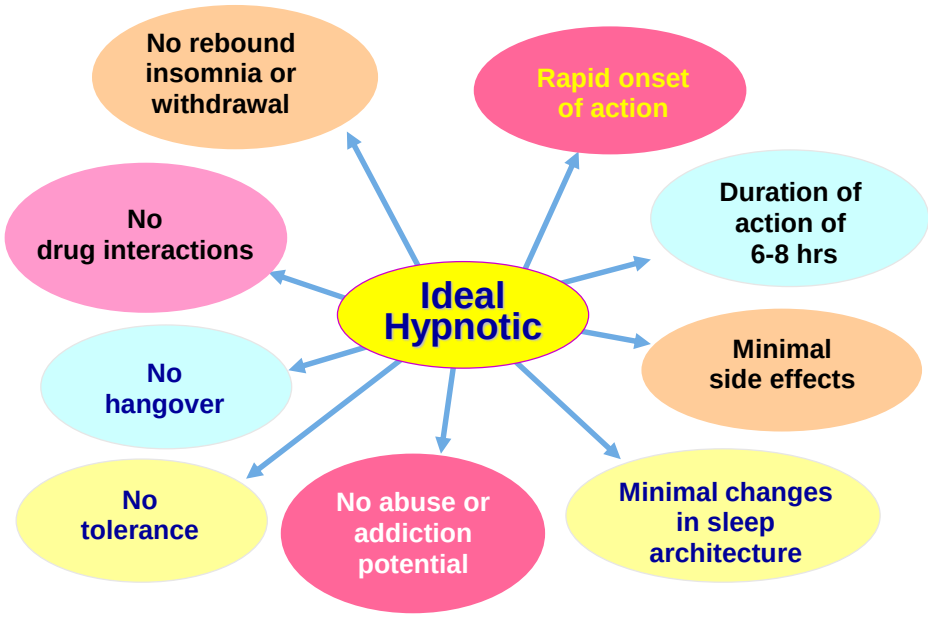
Lumateperone



Insomnia Management

- In the U.S. 33% report insomnia symptoms and 80% of elderly have sleep complaint
- Chronic insomnia disorder affects 10-15% of the population
- **Non-pharmacological treatments**
  - Therapy for any medical condition, psychiatric illness, substance abuse, or sleep disorder that may be precipitating or exacerbating the insomnia
  - Behavioral counseling about sleep hygiene and stimulus control
- **Pharmacological treatments**
  - Benzodiazepines, nonbenzodiazepine sedatives, melatonin agonists, doxepin, and suvorexant, an orexin antagonist

Pharmacological Management of Insomnia



FDA-Approved Treatments for Insomnia

Benzodiazepines

Temazepam (Restoril®)
Flurazepam (Dalmane®)
Triazolam (Halcion®)
Quazepam (Doral®)
Estazolam (Prosom®)

Melatonin-Receptor agonists

Ramelteon (Rozerem®)
Tasimelteon (Hetlioz®)
Melatonin is not approved

- **BZD_1-Receptor agonists**
  - Zolpidem (Ambien®)
  - Zaleplon (Sonata®)
  - Eszopiclone (Lunesta®)

- **Histamine antagonists**
  - Doxepin (Silenor®)
  - Diphenhydramine

Others

Suvorexant **(Belsomra®)**
Lemborexant **(Dayvigo®)**

Lemborexant (Dayvigo®)

- **Indication**: insomnia, difficulties with sleep onset and/or sleep maintenance
- **MoA:** orexin receptor antagonist
- **Dosing:**
  - 5 mg taken no more than once per night, immediately before going to bed, with at least 7 hours remaining before the planned time of awakening
  - May be increased to 10 mg based on clinical response and tolerability; max 10 mg/day
  - Time to sleep onset may be delayed if taken with, or soon after, a meal
- **ADRs:**
  - Somnolence
  - **Warnings:**
    - CNS Depressant Effects and Daytime Impairment
    - ***Sleep Paralysis, Hypnogogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms***
    - ***Complex Sleep Behaviors***; Compromised Respiratory Function;
    - Worsening of Depression/Suicidal Ideation

Dayvigo (lemborexant) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; December 2019

Dayvigo® Clinical Trials

- Study 1
- 6-month, randomized, double-blind, placebo-controlled
- adult patients age 18 or older who met DSM-5 criteria for insomnia disorder
- placebo (n=325), DAYVIGO 5 mg (n=323), or DAYVIGO 10 mg (n=323) once nightly
- Primary efficacy endpoint was the mean change from baseline to end of treatment at 6 months for log transformed patient-reported (subjective) sleep onset latency (sSOL)
- Secondary efficacy endpoints for sleep maintenance were change from baseline to end of treatment at 6 months for patient-reported sleep efficiency (sSEF) and wake after sleep onset (sWASO)

Dayvigo (lemborexant) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; December 2019

Dayvigo® Clinical Trials

Table 3: Primary and Secondary Efficacy Results for Change from Baseline in Sleep Onset and Sleep Maintenance at 6 Months in Patients with Insomnia (Study 1)

Endpoint	Treatment Group	Number of Patients ITT	Baseline Mean[a] (SD)	Month 6 LS Mean[a] (SE)	Treatment Effect (95% CI)
Sleep Onset sSOL (minutes)	DAYVIGO 5 mg*	316	43.0 (31.5)	20.0 (1.1)	0.7 (0.6, 0.8)
	DAYVIGO 10 mg*	315	45.0 (33.4)	19.2 (1.1)	0.7 (0.6, 0.8)
	Placebo	318	45.0 (31.8)	27.3 (1.4)	(ratio vs placebo)[b]
Sleep Maintenance sSEF (%)	DAYVIGO 5 mg*	316	63.1 (18.2)	75.9 (0.9)	4.5 (2.2, 6.9)
	DAYVIGO 10 mg*	315	62.0 (17.2)	75.9 (0.9)	4.7 (2.4, 7.0)
	Placebo	318	61.3 (17.8)	71.4 (0.8)	(%)[c]
Sleep Maintenance sWASO (minutes)	DAYVIGO 5 mg*	316	132.8 (82.5)	87.9 (3.7)	-17.5 (-27.3, -7.6)
	DAYVIGO 10 mg*	315	136.8 (87.4)	92.7 (3.7)	-12.7 (-22.4, -3.0)
	Placebo	318	132.5 (80.2)	105.3 (3.6)	(minutes)[c]

Dayvigo (lemborexant) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; December 2019

Dayvigo® Clinical Trials

- Study 2
- 1-month, randomized, double-blind, placebo- and active-controlled
- Adult female patients age 55 and older and male patients 65 years and older who met DSM-5 criteria for insomnia disorder
- Placebo (n=208), DAYVIGO 5 mg (n=266) or 10 mg (n=269), or active comparator (n=263) once nightly
- The primary efficacy endpoint was the mean change in log-transformed latency to persistent sleep (LPS) from baseline to end of treatment (Days 29/30), as measured by overnight polysomnography (PSG) monitoring
- Secondary efficacy endpoints were the mean change from baseline to end of treatment (Days 29/30) in SEF and WASO measured by PSG

Dayvigo (lemborexant) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; December

Dayvigo® Clinical Trials

Table 4: Primary and Secondary Efficacy Results for Change from Baseline in Sleep Onset and Sleep Maintenance at 1 Month in Patients with Insomnia (Study 2)

Endpoint	Treatment Group	Number of Patients ITT	Baseline Mean[a] (SD)	Day 29/30 LS Mean[a] (SE)	Treatment Effect (95% CI)
Sleep Onset LPS (minutes)	DAYVIGO 5 mg*	266	33.0 (27.2)	15.5 (0.8)	0.8 (0.7, 0.9)
	DAYVIGO 10 mg*	269	33.3 (27.2)	14.5 (0.7)	0.7 (0.6, 0.8)
	Placebo	208	33.6 (25.9)	20.0 (1.1)	(ratio vs. placebo)[b]
Sleep Maintenance SEF (%)	DAYVIGO 5 mg*	266	68.4 (11.3)	80.7 (0.5)	7.1 (5.6, 8.5)
	DAYVIGO 10 mg*	269	67.8 (10.8)	82.7 (0.5)	8.0 (6.6, 9.5)
	Placebo	208	68.9 (9.6)	74.6 (0.6)	(%)[c]
Sleep Maintenance WASO (minutes)	DAYVIGO 5 mg*	266	113.4 (39.0)	68.3 (2.2)	-24.0 (-30.0, -18.0)
	DAYVIGO 10mg*	269	114.8 (40.0)	66.9 (2.2)	-25.3 (-31.4, -19.3)
	Placebo	208	111.7 (37.2)	92.2 (2.5)	(minutes)[c]

Narcolepsy Management

- Types of Narcolepsy
  - Type 1: either narcolepsy with cataplexy or hypocretin deficiency syndrome
  - Type 2: narcolepsy without cataplexy
- Estimated that 0.01-0.16% of the population affected
- **Excessive daytime sleepiness (EDS)** is usually the first and most disabling symptom
- Common co-occurring disorders include REM behavior disorder, **obstructive sleep apnea (OSA),** restless leg syndrome and depression

- First line: modafinil or armodafinil ± sodium oxybate (if severe EDS)
- Second line: stimulants and/or nonpharmacological scheduled naps
- Third line: antidepressants / selegiline

Billiard M, Bassetti C, Dauvilliers Y, et al. EFNS guidelines on management of narcolepsy. Eur J Neur.2006; 13(10):1035-48

Solriamfetol

- Indicated to treat excessive daytime sleepiness in adults with **Narcolepsy or Obstructive Sleep Apnea (OSA)**
- **MoA:** Dopamine and Norepinephrine reuptake inhibitor **(DNRI)**
- **Dosing**: 75-150 mg once per day
- **ADRs**:
  - Headache, nausea, decreased appetite, insomnia, anxiety
  - Increased BP/HR

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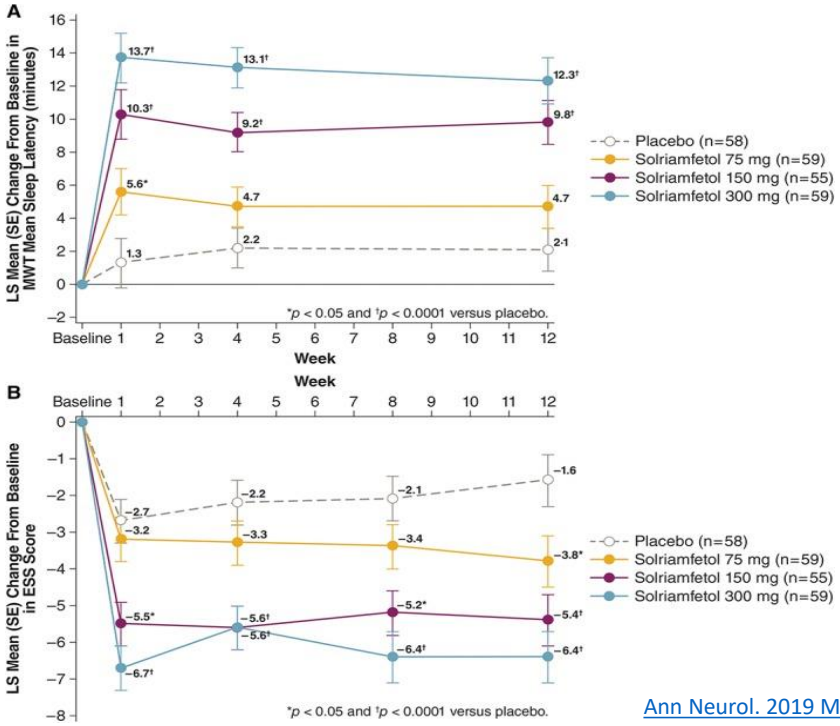
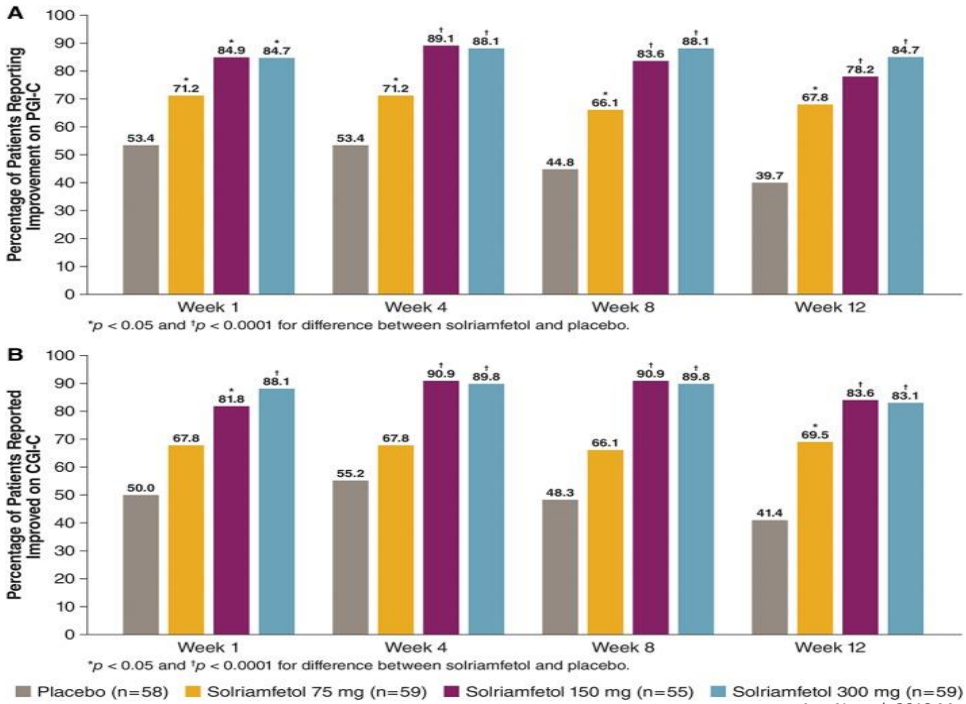


43

Ann Neurol. 2019 Mar; 85(3): 359–370.

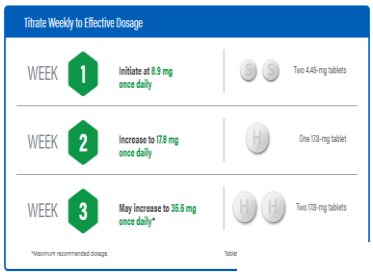


44

Ann Neurol. 2019 Mar; 85(3): 359–370.

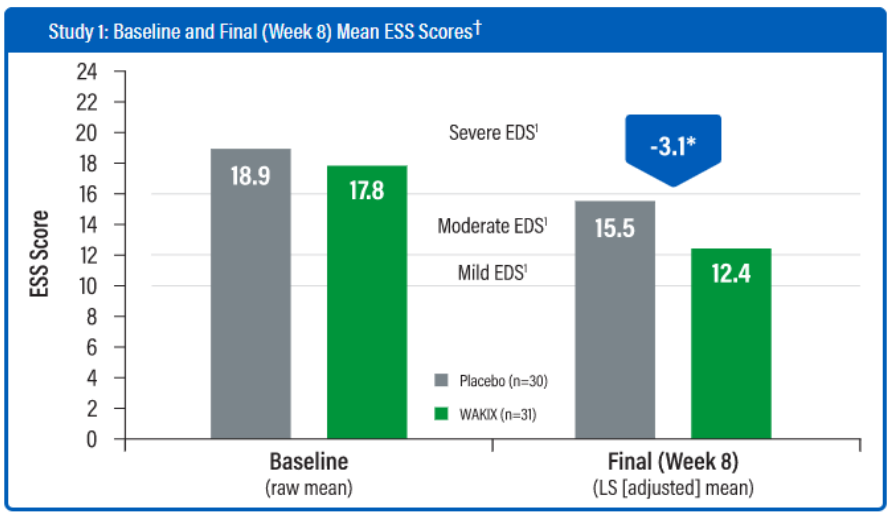
Pitolisant

- **Indication:**
  - treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy
- **MoA:**
  - antagonist/inverse agonist at histamine type-3 (H_3) receptors
  - Increase synthesis and release of Histamine
- **Dosing:**
  - 17.8 mg to 35.6 mg taken once daily in the morning upon wakening
  - It may take up to 8 weeks for some patients to achieve a clinical response with WAKIX
- **ADRs:**
  - (occurring in ≥5% of patients and 2x the rate of placebo)
  - Insomnia (6%), nausea (6%), and anxiety (5%)
  - Possible QT prolongation
  - Drug Interactions: Strong CYP2D6 Inhibitors/Strong CYP3A4 Inducers & Histamine-1 (H1) Receptor Antagonists
  - Use alternate form of birth control (non-hormonal contraception)



Narcolepsy is Characterized by Unstable Wakefulness1,2. Narcolepsy | WAKIX® (itolisant) tablets. https://wakixhcp.com/narcolepsy/. Accessed February 1, 2020

Wakix® Clinical Trials



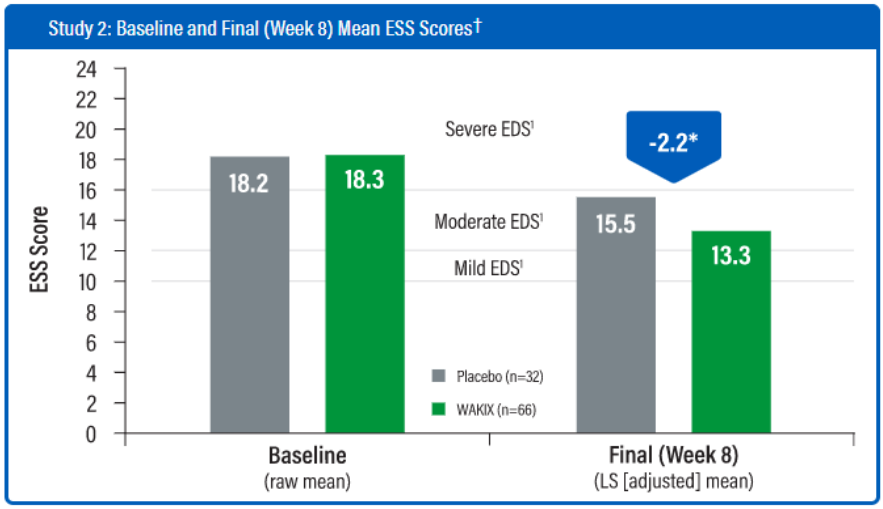
Study 1: 8-week, multicenter, randomized, double-blind, placebo-controlled study in 61 adults with narcolepsy (based on *International Classification of Sleep Disorders*, Second Edition [ICSD-2] criteria). WAKIX was initiated at 8.9 mg once daily and could be increased at weekly intervals to 17.8 mg or 35.6 mg once daily based on efficacy response and tolerability. Between Weeks 3 and 8, patients were maintained on a stable dosage of 8.9 mg, 17.8 mg, or 35.6 mg once daily.

*Placebo-subtracted difference (95% CI -6.73, -0.46); results were statistically significant.

†Lower ESS score represents improvement; scores range from 0 (no symptoms) to 24 (worst symptoms). Baseline values shown as raw mean values; final values shown as least square (LS) mean (e.g., adjusted for baseline).

Narcolepsy is Characterized by Unstable Wakefulness1,2. Narcolepsy | WAKIX® (pitolisant) tablets. https://wakixhcp.com/narcolepsy/. Accessed February 1, 2020.

Wakix® Clinical Trials



Study 2: 8-week, multicenter, randomized, double-blind, placebo-controlled study in 98 adults with narcolepsy (based on *International Classification of Sleep Disorders*, Second Edition [ICSD-2] criteria). WAKIX was initiated at 4.45 mg once daily and could be increased at weekly intervals to 8.9 mg or 17.8 mg once daily based on efficacy response and tolerability. Between Weeks 3 and 8, patients were maintained on a stable dosage of 4.45 mg, 8.9 mg, or 17.8 mg once daily.

*Placebo-subtracted difference (95% CI -4.17, -0.22); results were statistically significant.

†Lower ESS score represents improvement; scores range from 0 (no symptoms) to 24 (worst symptoms). Baseline values shown as raw mean values; final values shown as least square (LS) mean (e.g., adjusted for baseline).

Narcolepsy is Characterized by Unstable Wakefulness1,2. Narcolepsy | WAKIX® (pitolisant) tablets. https://wakixhcp.com/narcolepsy/. Accessed February 1, 2020.

Midazolam

- Indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (seizure clusters, acute repetitive seizures) in patients 12 years of age and older.

  "*Nayzilam now provides patients and caregivers with the first and only FDA-approved nasal option for treating seizure clusters" May, 2019.*

- **MoA:** Benzodiazepine, so GABA receptor modulator
- **Dosing:** 5mg per nostril, may repeat x1
- **ADRs:** Somnolence, HA, nasal discomfort

But Wait…..Jan.2020……for ages 6 years and older……

Amisulpride

- BARHEMSYS is a drug used in adults to prevent or treat postoperative nausea and vomiting (PONV).

- **MoA**: selective Dopamine type-2 (D_2) & also D_3 receptor antagonist
- **Dosing**:
  - 5 to 10mg given ***Intravenous infusion*** (1-2 minutes)
- **ADRs**:
  - Increased Prolactin, chills, low potassium, orthostasis, abdominal distension
  - infusion site pain.
  - QT Prolongation

- ***History:***
  Over 20 years in Europe as an atypical AP with impressive efficacy

Esketamine

Spravato™ (esketamine) CIII nasal spray

- Spravato® is indicated as adjunct/combination treatment for Treatment Resistant Depression (TRD)

- Dose:
  - Nasal Spray application for in-office administration
  - 28mg units (**dosed at 56mg or 84mg per treatment**)
  - 2x/week, then weekly, then every 1-2 weeks for maintenance
  - Non-competitive N-methyl-D-aspartate receptor antagonist

- BBWs:
  - Sedation/Dissociation; Misuse & Abuse; Suicidality
- ADRs:
  - Nausea/Vomiting, Increased Blood Pressure

Esketamine

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

Sedation

- **Patients are at risk for sedation after administration of SPRAVATO** ***[see Warnings and Precautions (5.1)]*****.**

Dissociation

- **Patients are at risk for dissociative or perceptual changes after administration of SPRAVATO** ***[see Warnings and Precautions (5.2)]*****.**

Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting ***[see Warnings and Precautions (5.1, 5.2)]*****.**

Abuse and Misuse

- **SPRAVATO has the potential to be abused and misused. Consider the risks and benefits of prescribing SPRAVATO prior to use in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse** ***[see Warnings and Precautions (5.3)]*****.**

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, SPRAVATO is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS ***[see Warnings and Precautions (5.4)]*****.**

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. SPRAVATO is not approved in pediatric patients ***[see Warnings and Precautions (5.5)]*****.**

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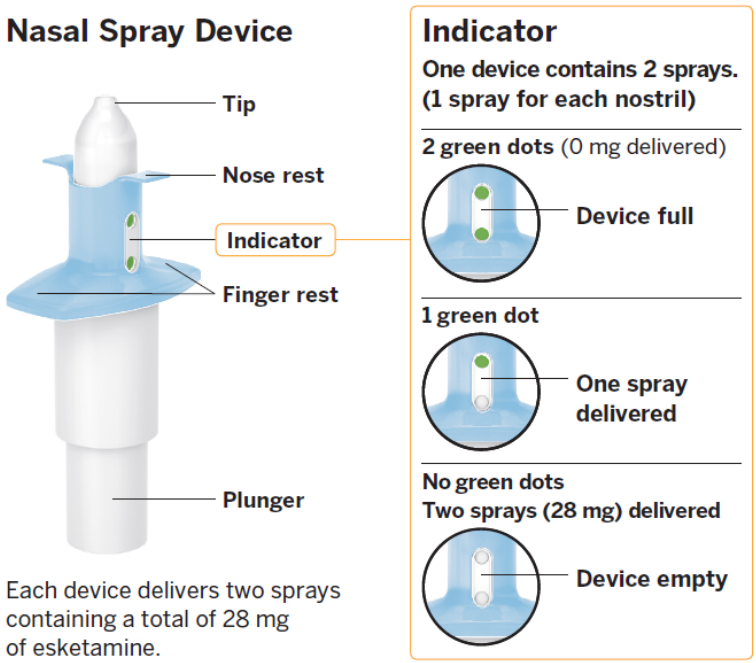

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Administration Technique

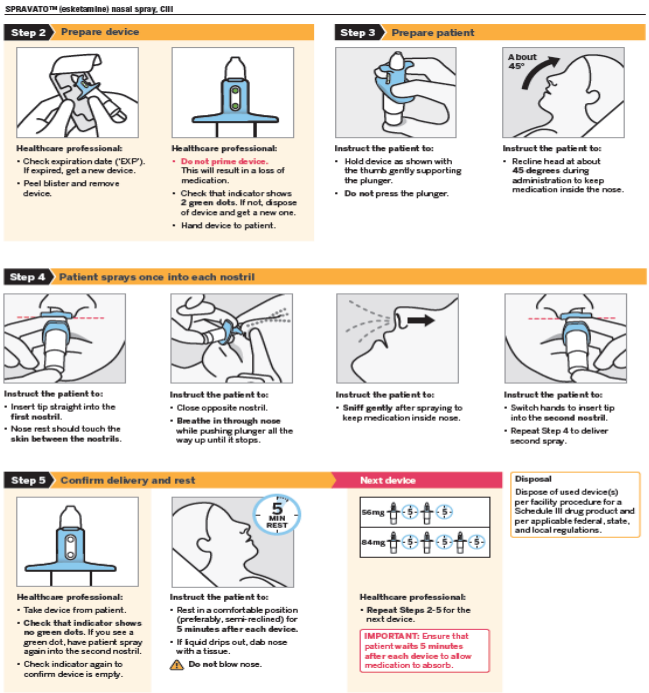
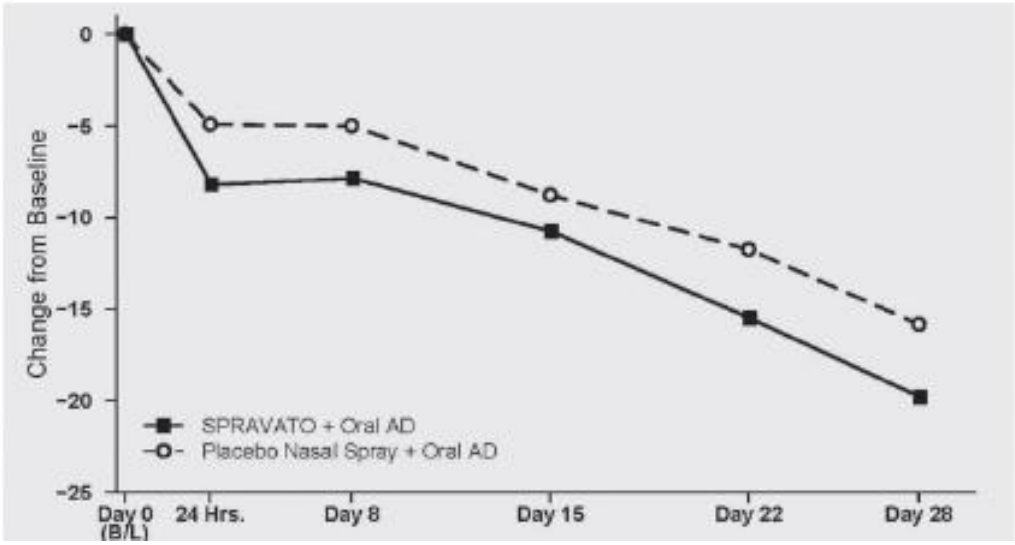


Figure 4: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in Patients with TRD in Study 1* (Full Analysis Set) – MMRM Analysis

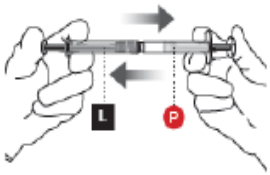


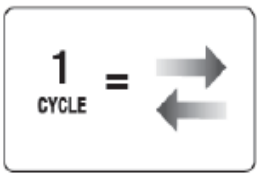
Risperidone

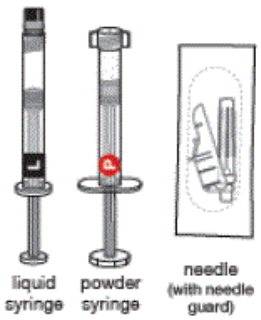
once-monthly PERSERIS™ (risperidone) for extended-release injectable suspension 90 mg · 120 mg

- Perseris® is indicated for treatment of schizophre
- **MoA:**
  - $5HT_{2a}$ + D_2 antagonism
- **Dosing:**
  - Subcutaneous injection in abdomen by HCP every month.
  - 90mg (~3mg/d) or 120mg (~4mg/d)
- ADRs: ***same as the last 27 years***
- **BBW:**
  - Increased Mortality* when used for dementia-related psychosis

Perseris™







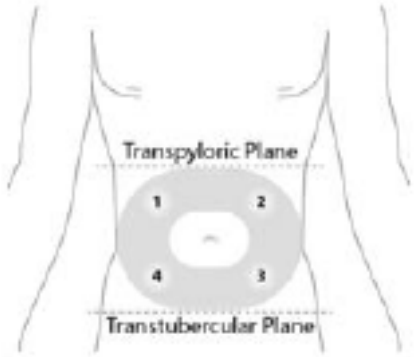
Premixing

- Transfer the contents of the Liquid Syringe into the Powder Syringe.
- Gently push the Powder Syringe plunger until you feel resistance (to wet powder an compacting).
- Repeat this gentle back-and-forth process for 5 cycles.

Complete mixing

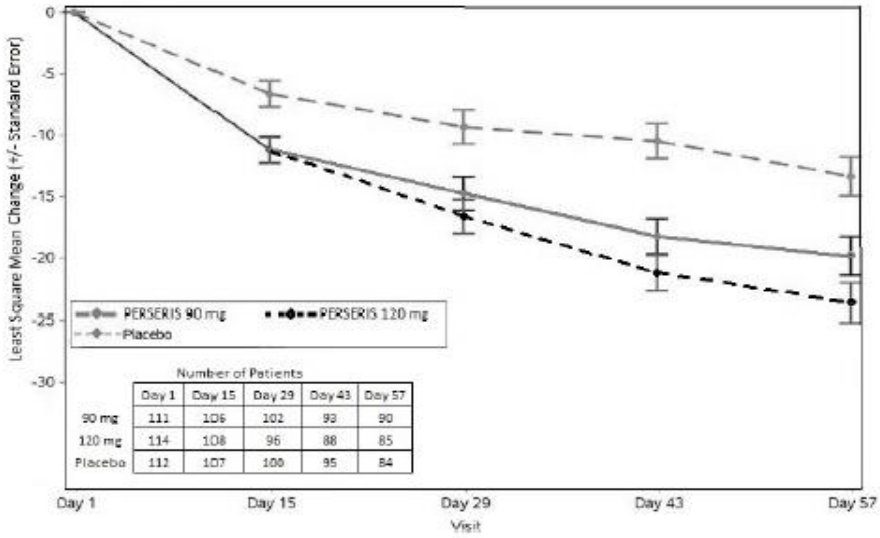
- Continue mixing the syringes for an additional 55 cycles.
- This mixing can be more vigorous than when premixing.

Figure 7



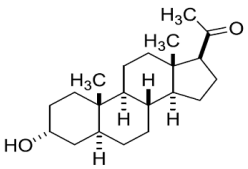
Perseris™

Figure 14. Least Square Mean Change from Baseline (+/- Standard Error) in PANSS Total Scores by Days



57

Brexanolone



- **Zulresso®** is indicated for Post Partum Depression (PPD)
- **MoA**:
  - Allopregnanolone = naturally produced steroid
  - Gamma-aminobutyric acid A ($GABA_A$) receptor positive allosteric modulator

- **Dose**: (100 mg/20 mL (5 mg/mL) single-dose vial)
  - ***60-hour inpatient infusion***
  - 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
  - 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
  - 24 to 52 hours: Increase dosage to 90 mcg/kg/hour
  - 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
  - 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour

- **ADRs:** Excessive Sedation / Loss of consciousness
- **BBW**: Suicidality

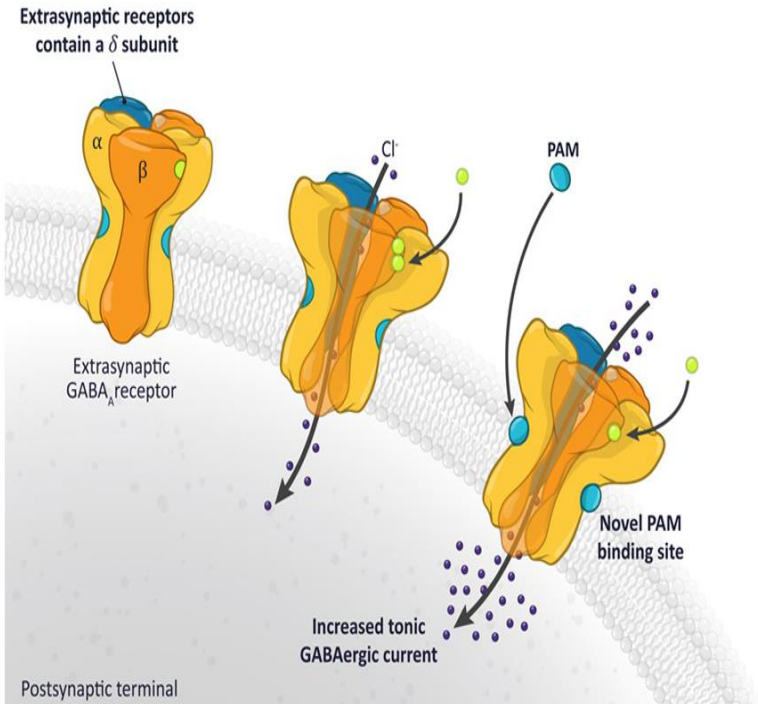
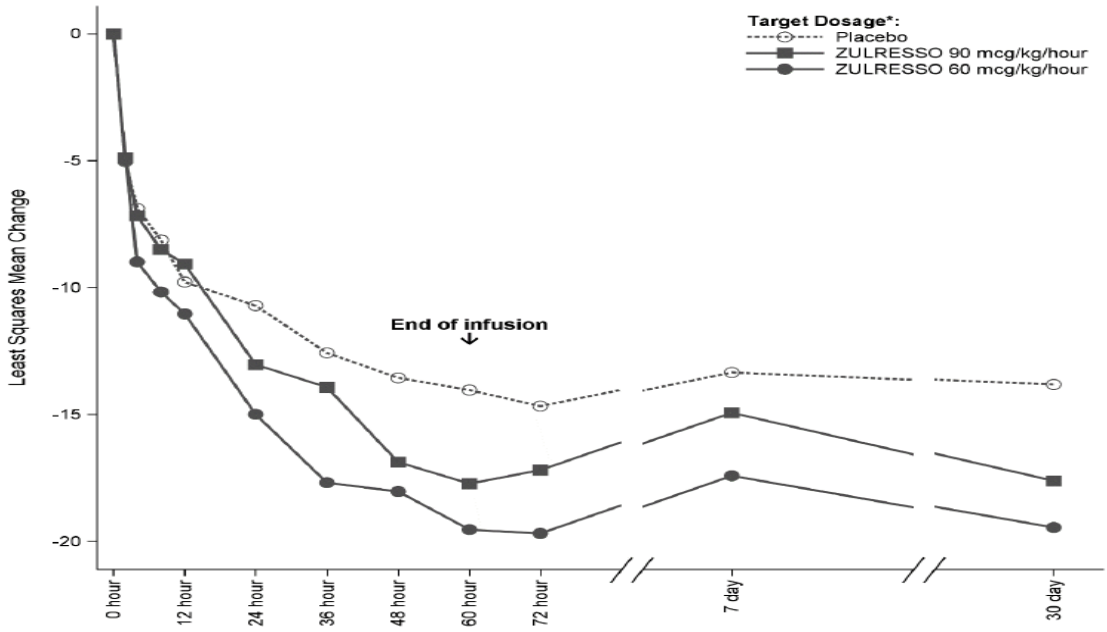


Figure 1: Change from Baseline in HAM-D Total Score Over Time (Days) in Study 1



Pimavanserin

NUPLAZID™ (pimavanserin) tablets

- NUPLAZID® is indicated for the treatment of hallucinations and delusions associated with **Parkinson's Disease Related Psychosis**
- **Off-label use: ? Alzheimer's Disease Related Psychosis ?**
  - **Research is ongoing**
- **Dose:**
  - 34 mg QD, as 2x17 mg strength tablets once daily
- **ADRs:**
  - QT Interval Prolongation, Peripheral Edema, Nausea, Confusion
- **BBW:** Increased Mortality….. same as all antipsychotics

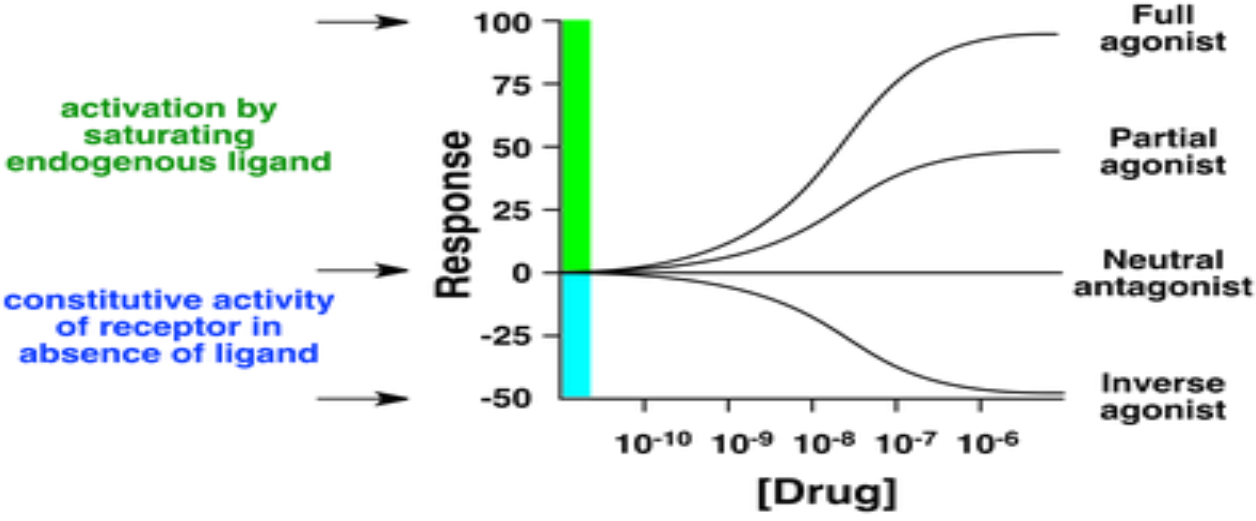
https://www.nuplazidhcp.com/

Pimavanserin

- The effect may be mediated through a combination of….

inverse agonist and antagonist activity at serotonin 5-HT_{2A} receptors and to a lesser extent at serotonin 5-HT_{2C} receptors.

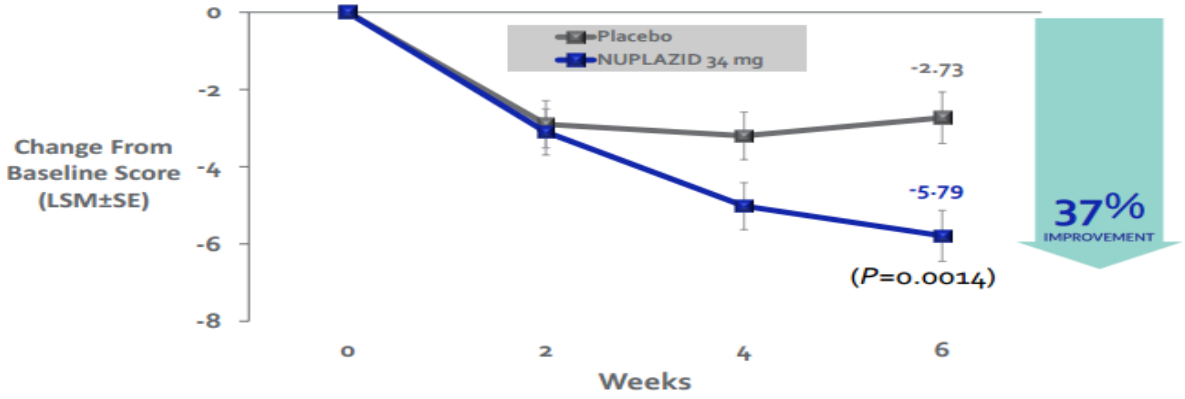
- *in vitro,* inverse agonist and antagonist at:
  - 5-HT_{2A} receptors with high binding affinity (Ki value 0.087 nM)
  - 5-HT_{2C} receptors with lower binding affinity (Ki value 0.44 nM)



SAPS-PD Change From Baseline Through 6 Weeks

ACADIA Pharmaceuticals

NUPLAZID 34 mg showed a 37% improvement in SAPS-PD from baseline at Week 6 versus 14% for placebo



The effect of NUPLAZID on SAPS-PD improved through the six-week trial period

LSM: least-squares mean; SE: standard error

NUPLAZID Prescribing Information. 2016.

Cummings J, et al. *Lancet*. 2014;383:533-540.

Valbenazine

INGREZZA™ (valbenazine) capsules

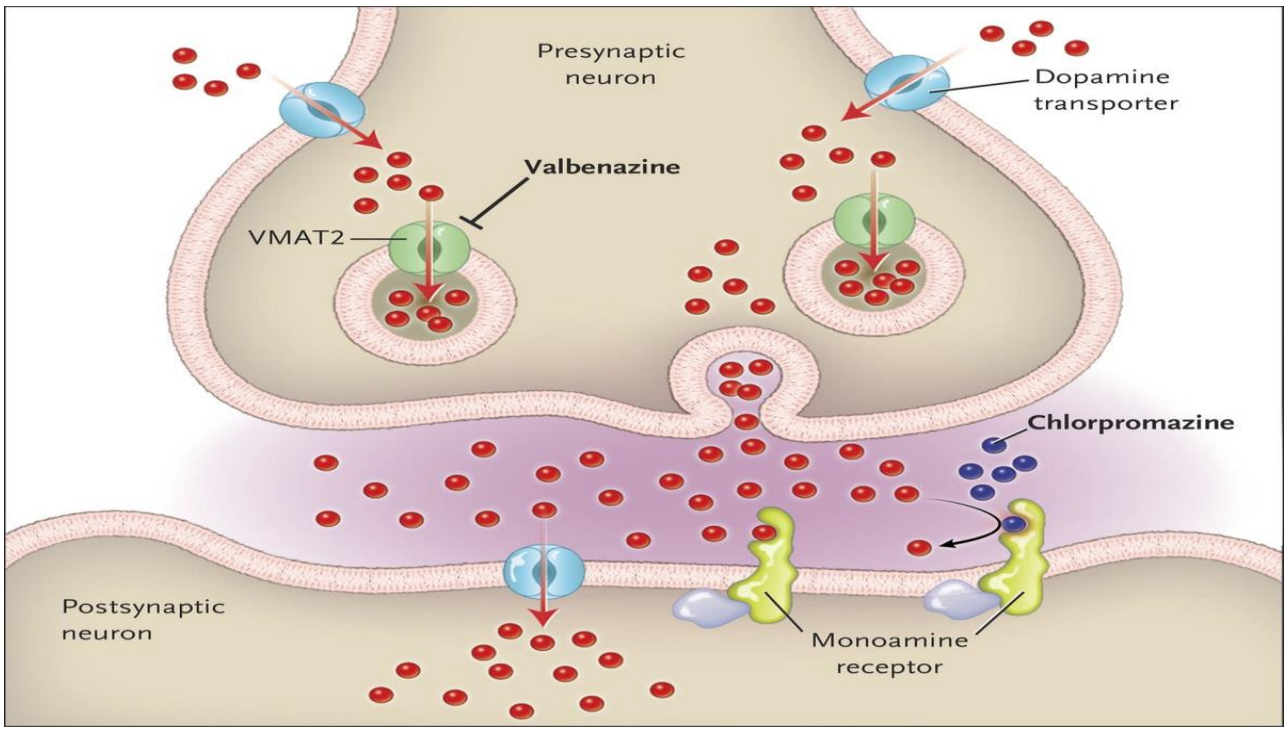
- INGREZZA is indicated for the treatment of adults with **tardive dyskinesia**
- **MoA**:
  - VMAT2 Inhibitor
  - **Valbenazine** is a **prodrug** of the (+)-α-isomer of **tetrabenazine**
- **Dosing**:
  - 40mg/day x 1 week; then 80mg/day
- **ADRs**:
  - **Somnolence**, anticholinergic effects, balance disorders / falls
  - HA, akathisia, parkinsonian EPS, vomiting, nausea, and arthralgia
  - May prolong the QT interval.

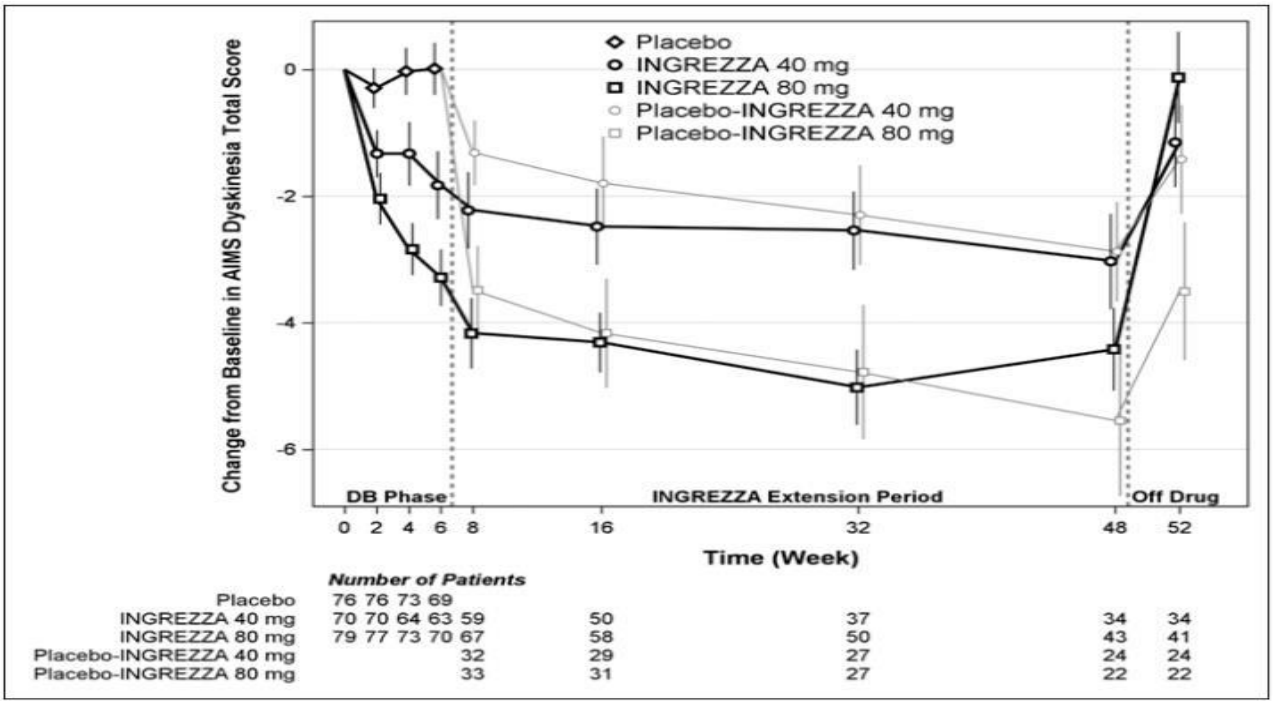
Neurocrine BIOSCIENCES

Valbenazine:
Mechanism of Action

- Mediated through the **reversible inhibition of vesicular monoamine transporter 2 (VMAT2),**
  a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and later release.

- Active metabolite:
  - after removal of valine AA….
    [+]-α-dihydrotetrabenazine ([+]-α-HTBZ)





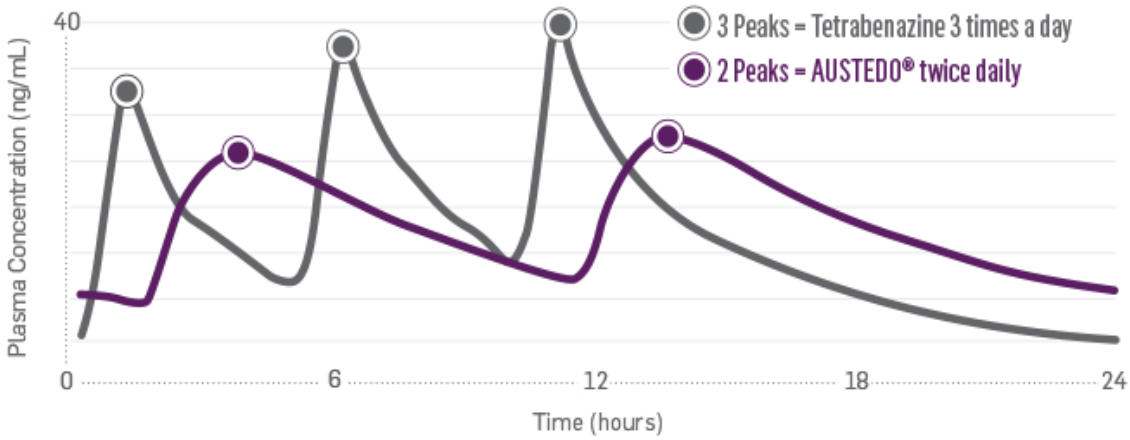
Deutetrabenazine

Austedo (deutetrabenazine) 6 mg, 9 mg, and 12 mg tablets

- AUSTEDO is indicated for the treatment of adults with **Tardive Dyskinesia & Huntington's Chorea**
- **MoA**: **VMAT2 inhibitor**
  - **deuterium,** resulting in stronger molecular bonds, **'kinetic isotope effect'**
  - Bonds 6-10x more strongly with carbon atoms
  - Extends the half-life of active therapeutic metabolites to 9-10 hours
  - alpha & beta metabolites of **dihydrotetrabenazine**
- **Dosing**:
  - 12mg/day x 1 week; then titrate by 6mg to 48 mg/day
- **ADRs**:
  - Somnolence, dry mouth, diarrhea, fatigue, nasopharyngitis, insomnia
  - May worsen psychiatric disorders, May prolong the QT interval
  - **BBW for Suicidality with use in Huntington's**

teva

Plasma Concentrations of Alpha and Beta Metabolites Over 24 Hours—PK Model[7]



The correlation between plasma levels and clinical efficacy has not been established.

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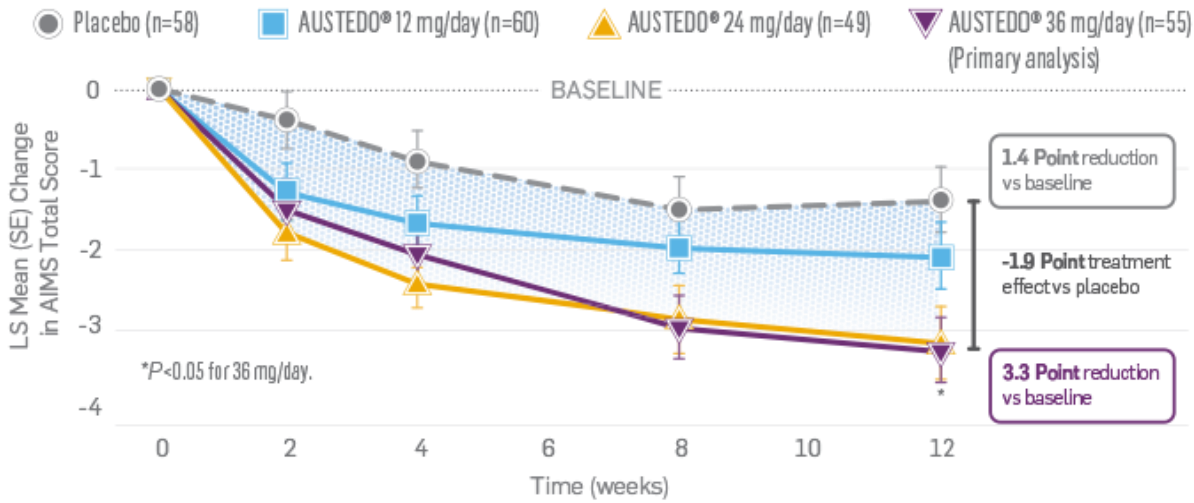
Deutetrabenazine for TD

AIM-TD: Change in AIMS Total Score from Baseline to Week 12 (N=222)[1]
(Primary endpoint)



Reserpine

- Classes: Antihypertensive, 'Other'
- MoA: non-selective VMAT inhibition
- Dosing & Uses: 0.1mg, 0.25mg
- Hypertension:
  - Initial = 0.5 mg daily for 1 or 2 weeks,
  - Maintenance = 0.1-0.25 mg PO qDay
  - *Use higher dosages cautiously occurrence of mental depression or other adverse reactions may increase*
- **Psychiatric Disorders**:
  - 0.5 mg daily, but may range from 0.1 to 1 mg; titrate dose according to patient response
- **Tardive Dyskinesia**:
  - 0.25 mg q6hr; may increase by 0.1-0.25 mg to a total of 5 mg daily

Antidepressant Selection and Treatment

NSU Florida
NOVA SOUTHEASTERN UNIVERSITY

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Historical, Research & Clinical Applications of *'Antidepressants'*

- ***Depression***
- **Obsessive-Compulsive Disorder**
- **Panic Disorder**
- **Social Anxiety Dis.**
- **Generalized Anxiety Disorder**
- **PMDD (PMS)**
  - ***VMS assoc. with menopause***
- **Post-traumatic Stress Disorder (PTSD)**
- **Substance Use Disorders**
- **Eating Disorders**
- **Chronic Headache**
- **Chronic Pain Syndromes**
- **Impulse Control / Autism**

NSU Florida

The Available Antidepressants

- Amitriptyline
- Imipramine
- Doxepin
- Nortriptyline
- Desipramine
- Protriptyline
- Clomipramine
- Maprotiline
- Amoxapine
- Duloxetine
- Fluoxetine / Sertraline / Paroxetine
- Fluvoxamine / Citalopram / Escitalopram
- Trazodone / Nefazodone
- Bupropion / Mirtazepine
- Venlafaxine / Desvenlafaxine
- Selegiline / Phenelzine / Tranycypromine
- Vilazodone / Vortioxetine
- Levomilnacipran
- **Esketamine / Brexanolone**

NSU Florida

Antidepressant Selection Criteria

Primary Criteria:

- Patient's history of response
- Family history of response
- Patient's medical status / Age
- Side effect profile
- Patient's clinical presentation

- ***Other Secondary Criteria***

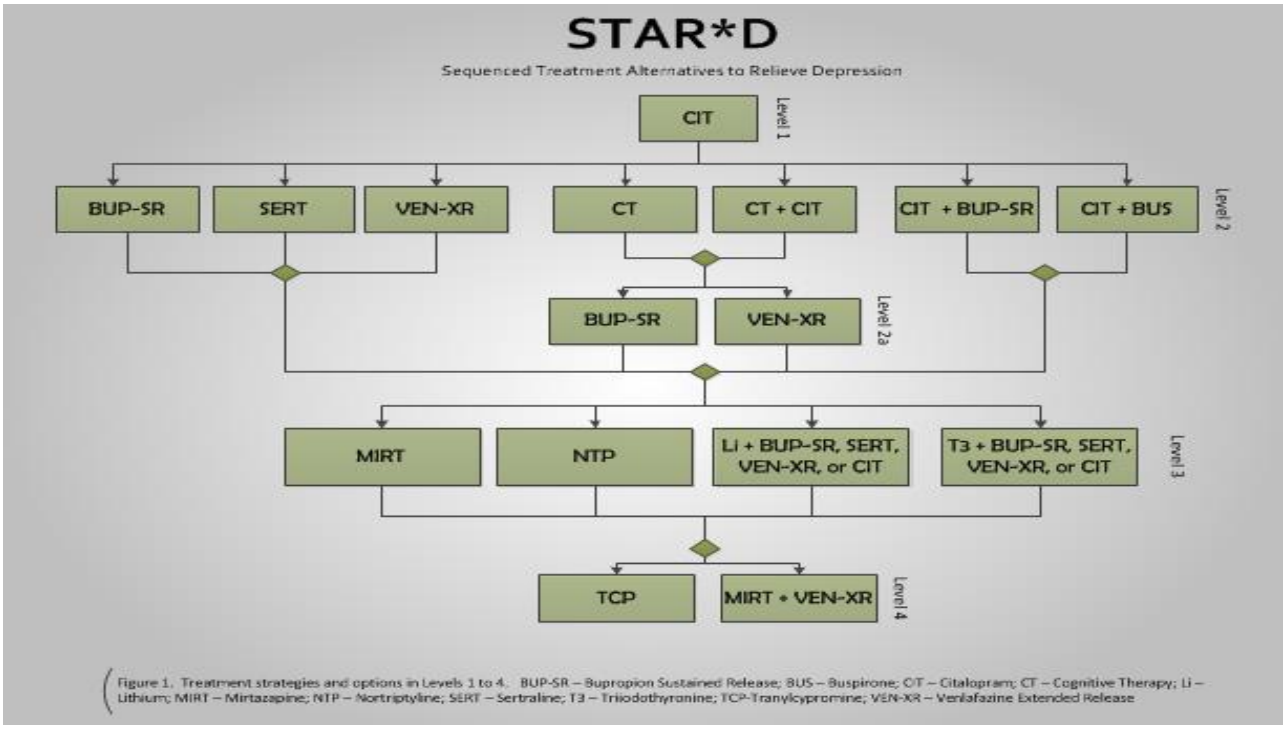
Antidepressant Selection Criteria

Secondary Criteria:

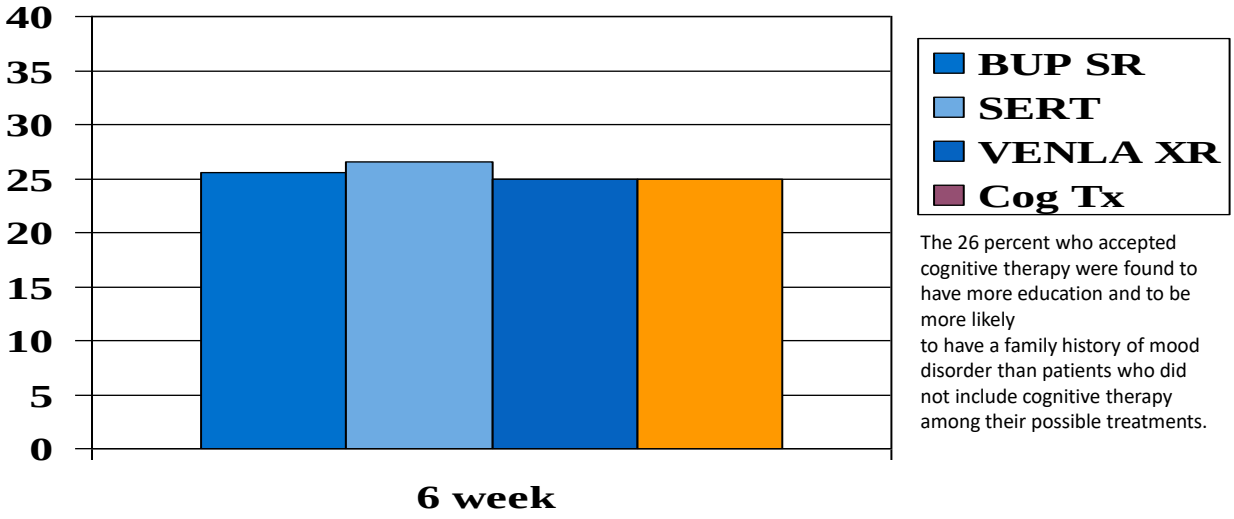
- Patient's concomitant medications
  - Drug-Drug / Drug-Food Interactions
- Cost
- Compliance / Adherence issues
- Dosing Regimen / Formulations
- Stigma, reputation of the drug, media

Challenges to Treatment

- Recognition of Depression
  - Worsening after treatment
- Co-Morbid Illnesses
  - Matching treatments
- Medication Compliance
- Side Effect Profiles of Antidepressants
- Direct and Indirect Costs of Treatment
- **Treatment Resistance / Partial Response**



STAR-D Level 2 Results:
Remission = HAM-D ≤7 or QIDS-SR ≤5

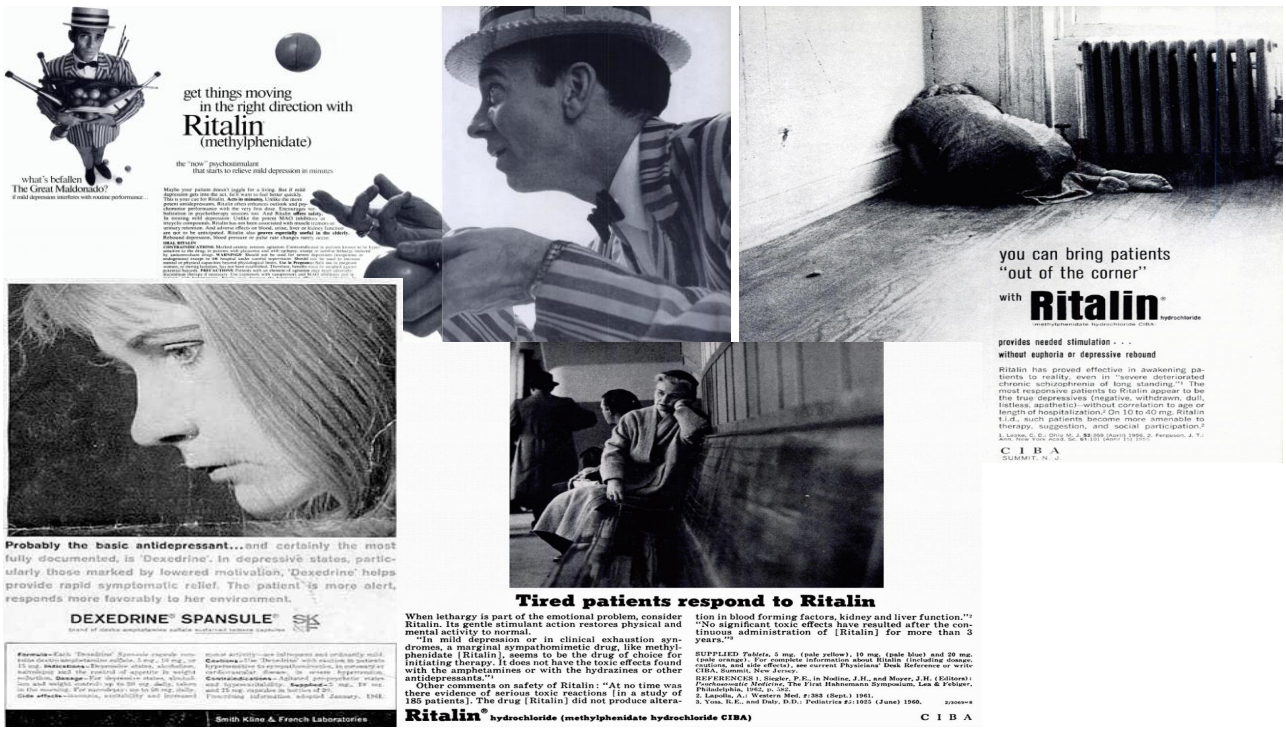


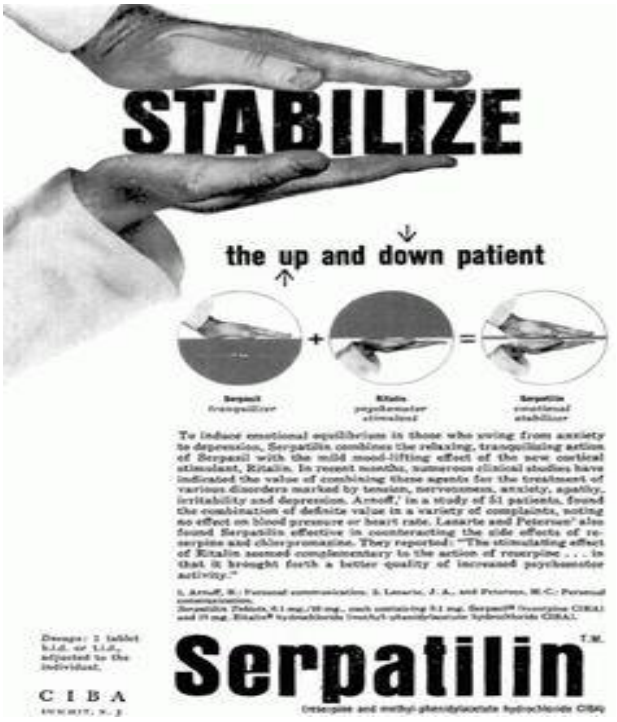
Quick Inventory of Depression Symptomotology - Self Rated

The 26 percent who accepted cognitive therapy were found to have more education and to be more likely
to have a family history of mood disorder than patients who did not include cognitive therapy among their possible treatments.

Options for the Treatment of the Severe or Refractory Patient

- **Combination of Antidepressants:**
  - Use agents having two (2) or more mechanism of actions
  - Use two different and selective acting antidepressants
  - Symbyax™ (Olanzapine+Fluoxetine) is FDA-approved for TRD
- **Adjunctive therapy:**
  - ***Atypical Antipsychotic Agents****
  - Mood Stabilizers?, Could it actually be a type of bipolar disorder?
  - Thyroid augmentation, Buspirone, Pindolol, Psychostimulants
  - ***Esketamine NS***





Bipolar-Depression

- **Difficult to diagnose**:
  - Often misdiagnosed as……
- **<u>Some features / indicators for BD</u>**:
  - Family hx. of bipolar disorder
  - Hx. of antidepressant-induced mania or hypomania
  - Early age of onset
  - Recurrent pattern of illness
  - Atypical sx: hypersomnia, hyperphagia
  - Psychotic sx
  - Lack of response to AD tx.
  - Abrupt onset and ending of sx.

Bipolar-Depression

Symptomatic Time:

- Spent in Depressed phase: **67.8%**
- Spent in Mania / hypomania: 19.7%
- Spent in Rapid cycling / mixed states: 12.5%

- ***Problem:***
  - ***Antidepressants are no more effective than Placebo in treating Bipolar Depression***

Sachs GS, et.al., NEJM. 2007; 356:1711-1722

Bipolar-Depression

The medications that are FDA-approved:

- _____
- _____
- _____
- _____

- _____ *actually indicated for…….
  "*manic-depressive illness, depressed type*", aka bipolar-depression

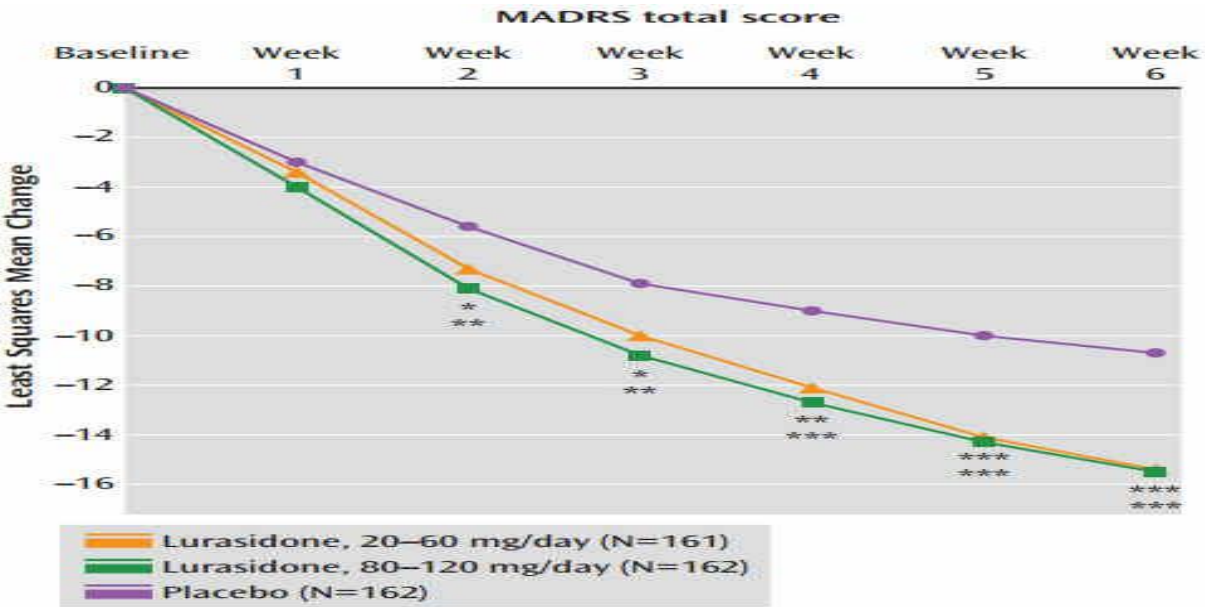
Lurasidone (Latuda™)

- FDA approved for the acute treatment of schizophrenia in adults
  - Approved Oct. 28, 2010
  - ***Approved July, 2013 for Bipolar-Depression***

- Pharmacology
  - Exerts actions via combination blockade of D_2 & 5-HT_2 receptors (5-HT_2 > D_2)
  - Moderate receptor affinity for α_1 receptors
  - Low affinity for histamine receptors
  - No activity at cholinergic receptors
  - **40 – 160 mg/day**

Scott LJ. Iloperidone: in schizophrenia. *CNS Drugs.* 2009;23(10):867-80.

Bipolar-Depression Results



Adjunctive Treatments for Resistant or Partial Responders to Antidepressants for Unipolar Major Depression

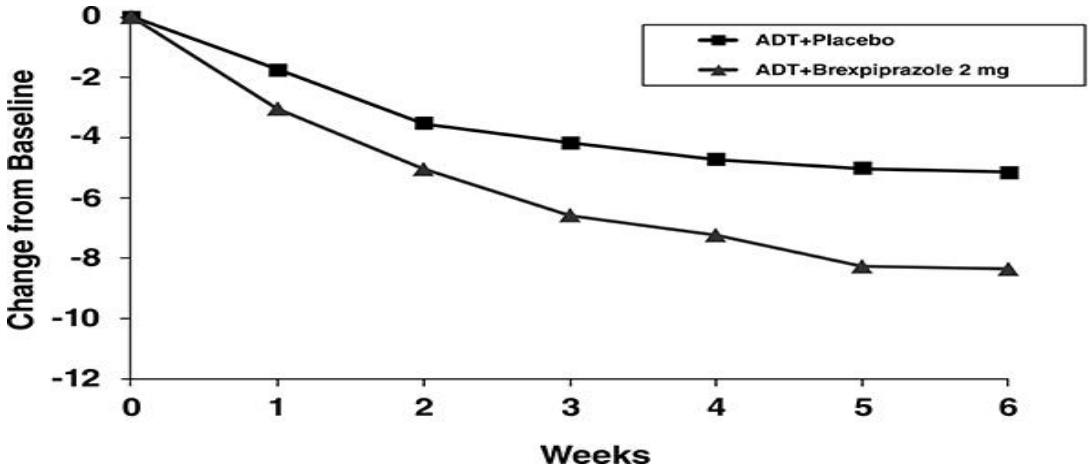
The medications that are FDA-approved:

- _____
- _____
- _____
- _____* (for TRD)
- _____* (for TRD)

Brexpiprazole (Rexulti™)

- MoA:
  - D2 partial agonist
  - 5-HT1a partial agonist
  - 5-HT2a antagonist
  - ?? influence of alpha-2 receptors
- Dosing: 1mg to 4mg/day
- ADRs: akathisia, weight gain, somnolence

Brexpiprazole (as Adjunct): MADRS score reduction



23.2% of the patients receiving brexpiprazole were responders, vs
14.5% for placebo, yielding a NNT of 12 (95% CI, 8-26);
14.4% of the brexpiprazole-treated patients met remission criteria, vs
9.6% for placebo, resulting in a NNT of 21 (95% CI, 12-138).[6]

Can we improve outcomes by improving our antidepressant selection?

Pharmacogenomics

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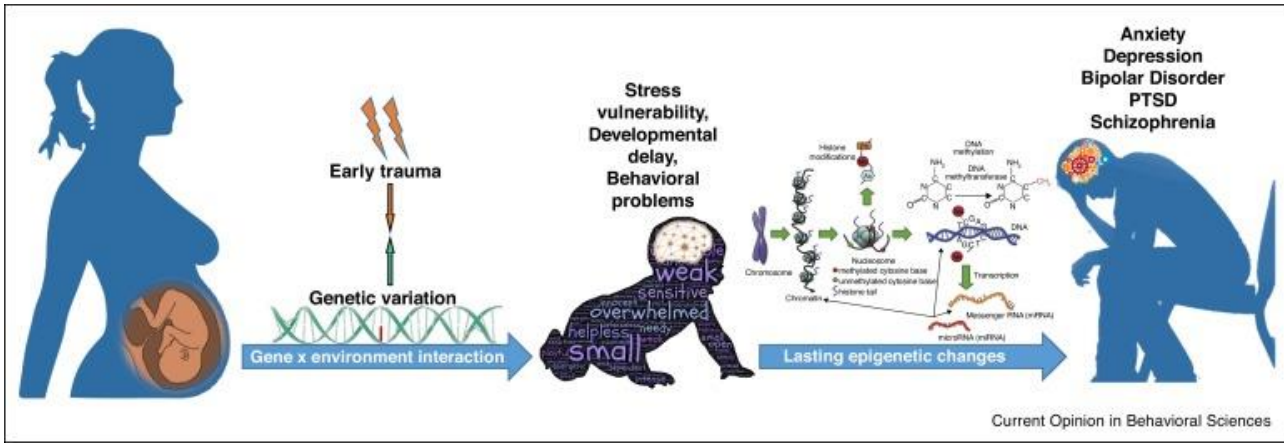
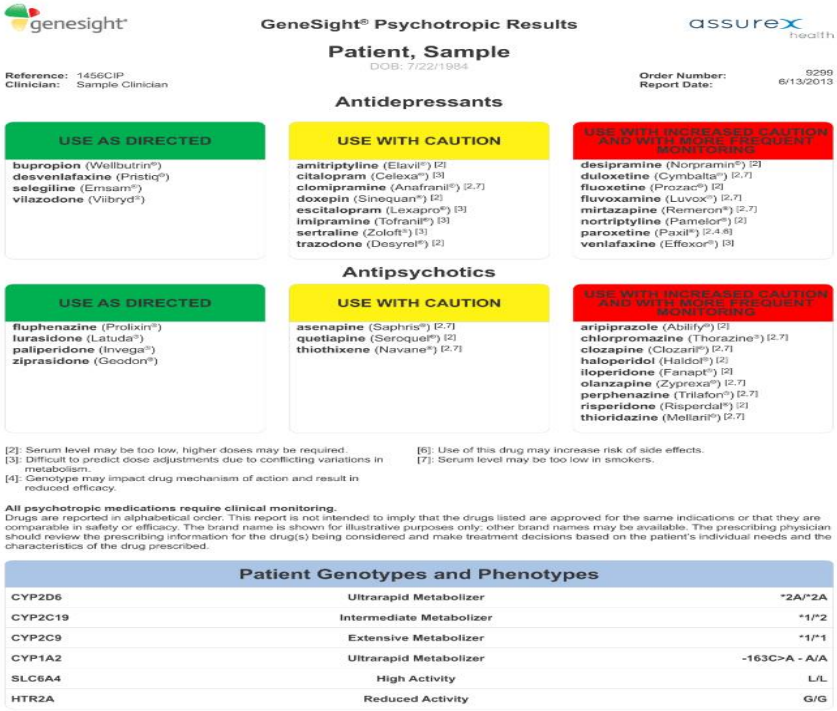


Current Opinion in Behavioral Sciences; Volume 14, April 2017, Pages 167-171

What is Pharmacogenomics?

- *Pharmacogenomics is the study of* ***how genes affect a person's response to drugs.*** *This field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.*

https://ghr.nlm.nih.gov/primer/genomicresearch/pharmacogenomics



genesight

GeneSight® Psychotropic Results

assurex health

Patient, Sample

DOB: 7/22/1984

Reference: 1456CIP
Clinician: Sample Clinician

Order Number: 9299
Report Date: 6/13/2013

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
bupropion (Wellbutrin®) **desvenlafaxine** (Pristiq®) **selegiline** (Emsam®) **vilazodone** (Viibryd®)	**amitriptyline** (Elavil®) [2] **citalopram** (Celexa®) [3] **clomipramine** (Anafranil®) [2,7] **doxepin** (Sinequan®) [2] **escitalopram** (Lexapro®) [3] **imipramine** (Tofranil®) [3] **sertraline** (Zoloft®) [3] **trazodone** (Desyrel®) [2]	**desipramine** (Norpramin®) [2] **duloxetine** (Cymbalta®) [2,7] **fluoxetine** (Prozac®) [2] **fluvoxamine** (Luvox®) [2,7] **mirtazapine** (Remeron®) [2,7] **nortriptyline** (Pamelor®) [2] **paroxetine** (Paxil®) [2,4,6] **venlafaxine** (Effexor®) [3]

Antipsychotics

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[2]: Serum level may be too low, higher doses may be required.
[3]: Difficult to predict dose adjustments due to conflicting variations in metabolism.
[4]: Genotype may impact drug mechanism of action and result in reduced efficacy.
[6]: Use of this drug may increase risk of side effects.
[7]: Serum level may be too low in smokers.

All psychotropic medications require clinical monitoring.
Drugs are reported in alphabetical order. This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient's individual needs and the characteristics of the drug prescribed.

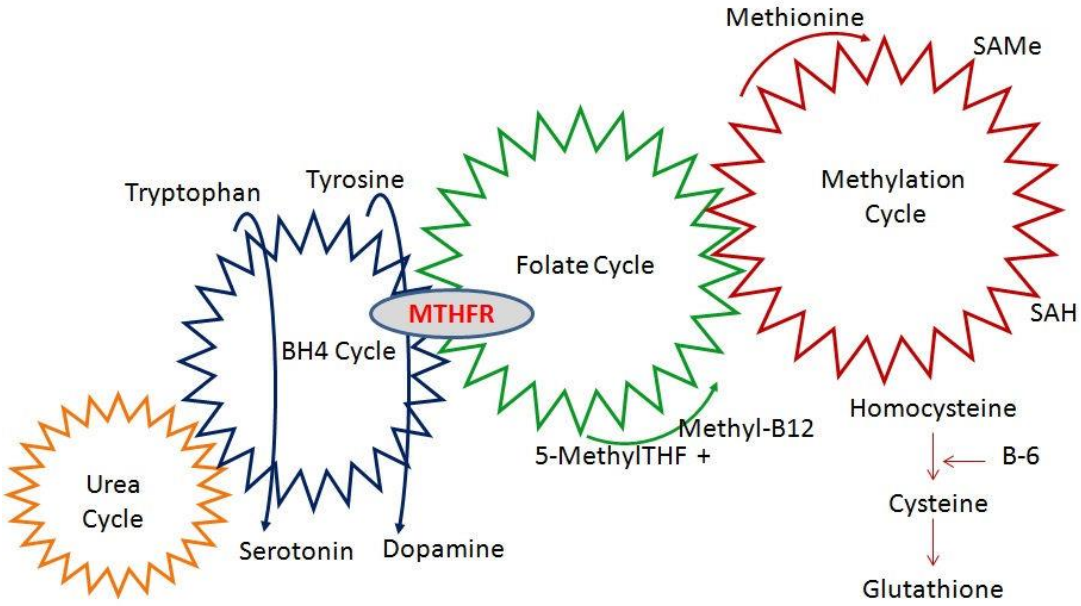
Patient Genotypes and Phenotypes

CYP2D6	Ultrarapid Metabolizer	*2A/*2A
CYP2C19	Intermediate Metabolizer	*1/*2
CYP2C9	Extensive Metabolizer	*1/*1
CYP1A2	Ultrarapid Metabolizer	-163C>A - A/A
SLC6A4	High Activity	L/L
HTR2A	Reduced Activity	G/G

Psychotropics and Pharmcogenomics

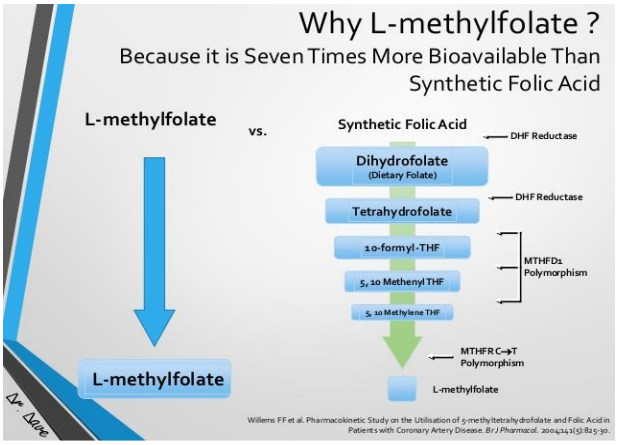
- **Tricyclic Antidepressants (TCAs):**
  - Amitriptyline (CYP2D6)
  - Imipramine (CYP2D6, 2C19)
- **Selective Serotonin Reuptake Inhibitors (SSRIs):**
  - Fluoxetine, Fluvoxamine, Paroxetine
    - CYP2D6
  - Citalopram, Escitalopram, Sertraline
    - CYP2C9, CYP2C19
  - ***Serotonin Transport polymorphism may reduce SSRI response (SLC6A4)***
- **MTHFR enzyme dysfunction:**
  - **L-methylfolate (Deplin)**
  - **5-20 % of depressed individuals may have this polymorphism**
- **Carbamazapine (HLA-B-1502)**
  - SJS / TEN risk (increased with Asian decent)
  - Oxcarbazepine

CPIC®
Clinical Pharmacogenetics Implementation Consortium



Methylfolate

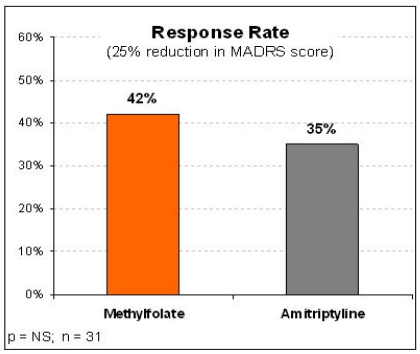
- To be used as an adjunct to Antidepressants.

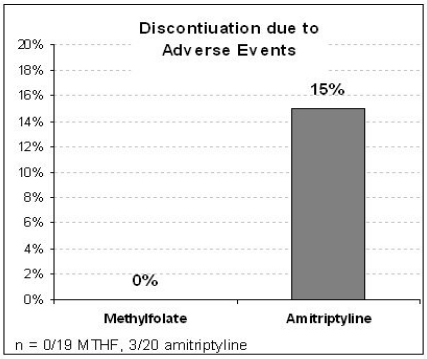


https://www.deplin.com/hcp

Methylfolate Monotherapy vs. Amitriptyline in Depression*

- After a 2-week placebo run-in period, this double-blind trial randomized 31 depressed outpatients to 50mg methylfolate (25mg L-methylfolate) or 150mg amitriptyline each in monotherapy for 6 weeks. All but 3 patients had normal folate levels (90%).
- MADRS response rate was similar with methylfolate and amitriptyline (42%, 35% respectively).
- No side effects were reported with methylfolate, whereas 3 patients (15%) were withdrawn due to unacceptable side effects with amitriptypline.





* Crellin R, Bottiglieri T et al. Drugs 45(5):623-636, 1993.

https://slideplayer.com/slide/6984802/

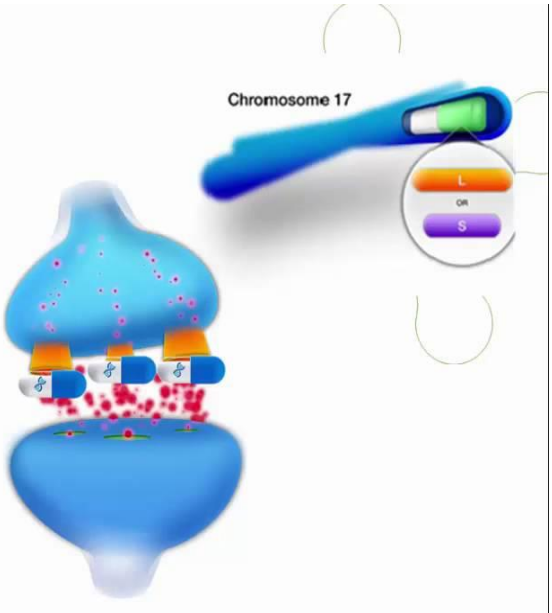
What is SLC6A4?

Serotonin Transporter (SLC6A4)

The SLC6A4 promoter has two main variants: L and S

The S allele makes fewer serotonin transporters, providing less active sites for SSRIs

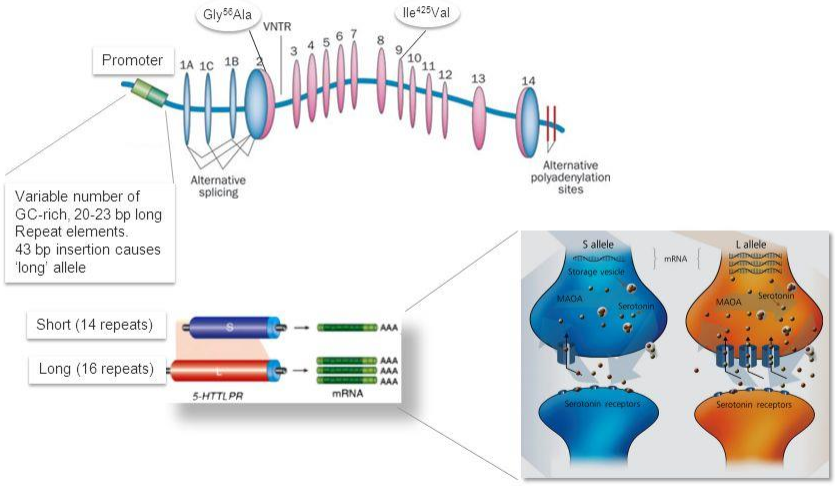
This results in lower rates of response with SSRIs.[1]



1. Lesch KP, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*. 1996;274:1527-1531.

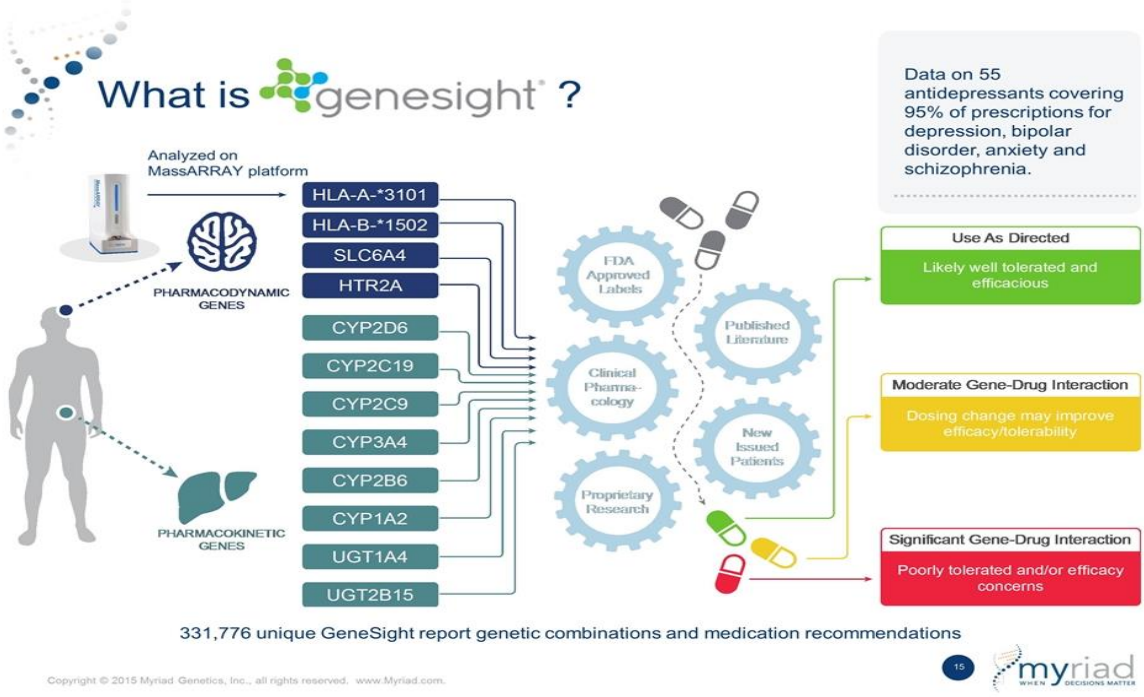
genesight

SLC6A4



Murphy et al (2008) Neuropharmacol 55:932-60
De Neve (2011) J Hum Genet 56:456-59

18/25



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SLC6A4	High Activity	L/L
HTR2A	Reduced Activity	G/G

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www.genomind.com

Drug Interaction Summary:

This summary provides a listing of implications for psychotropic and pain medications specific to your patient's genetic profile

	Medication	Primary metabolizing enzyme(s)	Use as Directed: No known gene-drug interactions	Therapeutic Options: Options which may be used if clinically indicated	Use with Caution: CYP450 Serum levels may be ↑ [reduced dose may be required]	Use with Caution: CYP450 Serum levels may be ↓ [increased dose may be required]	Use with Caution: Increased risk for adverse events or poor response
	Antidepressants			SLC6A4			SLC6A4
SSRIs	Citalopram (Celexa®) (R)	2C19, 3A4/5, 2D6					✓
SSRIs	Escitalopram (Lexapro®)	2C19, 2D6					✓
SSRIs	Fluoxetine (Prozac®)	2D6, 2C9					✓
SSRIs	Fluvoxamine (Luvox®)	2D6, 1A2				With Inducers[6]	✓
SSRIs	Paroxetine (Paxil®)	2D6					✓
SSRIs	Sertraline (Zoloft®)	MultiCYP [11]					✓
SNRIs	Desvenlafaxine (Pristiq®)	--	✓	✓			
SNRIs	Duloxetine (Cymbalta®)	1A2, 2D6		✓		With Inducers[6]	
SNRIs	Levomilnacipran (Fetzima®)	3A4/5	✓	✓			
SNRIs	Milnacipran (Savella®)	--	✓	✓			
SNRIs	Venlafaxine (Effexor®) [1]	2D6, 2C19	✓	✓			
Other	Bupropion (Wellbutrin®) [1]	2B6		✓	Prodrug [1]		
Other	Mirtazapine (Remeron®)	2D6, 3A4/5, 1A2		✓		With Inducers[6]	
Other	Nefazodone	3A4/5, 2D6	✓	✓			
Other	Trazodone (Desyrel®, Oleptro®)	3A4/5	✓	✓			
Other	Vilazodone (Viibryd®)	3A4/5	✓	✓			
Other	Vortioxetine (Trintellix®) (R)	2D6	✓	✓			

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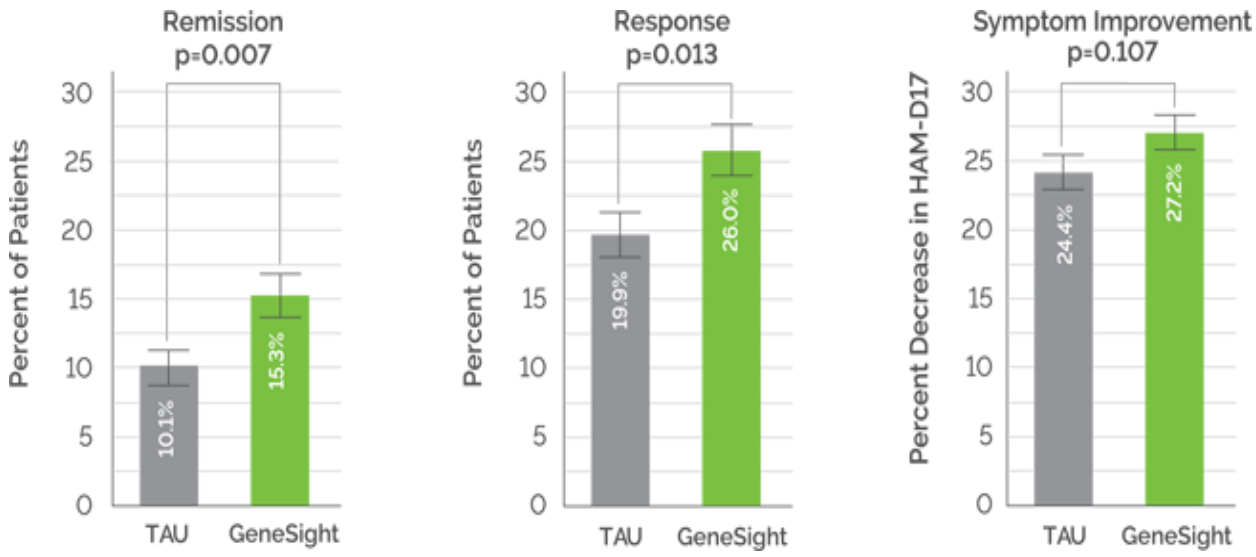
Brain Science to Better Lives

Clinical Study from Genesight™



https://genesight.com/product/ Depression and improvement vs Treatment as Usual

Formulations & Adherence & Outcomes

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Historical, Research & Clinical Applications of *Antipsychotics*

- ***Schizophrenia***
- Parkinson's Disease
- Alzheimer's Disease
- Drug-induced psychosis
- Affective Disorders
  - ***Bipolar Disorder***
    Acute Mania
    Bipolar Depression
  - Major Depression
    Psychotic or
    Refractory Depression
- Eating Disorders
- Developmental Disorders
  - ***Autism***
- Personality Disorders
- Anxiety Disorders
  - ***GAD***, OCD, PTSD
- Aggression in Children
- Other Dementias
  - Vascular, Lewy Body

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Conventional / Older / Typical
First Generation Antipsychotics (FGAs)

Chlorpromazine	Thorazine	1958
Trifluoperazine	Stelazine	1958
Perphenazine	Trilafon	1958
Thioridazine	Mellaril	1959
Fluphenazine	Prolixin	1959
Thiothixene	Navane	1967
Haloperidol	Haldol	1967
Loxapine*	Loxitane	1973
Molindone*	Moban	1974

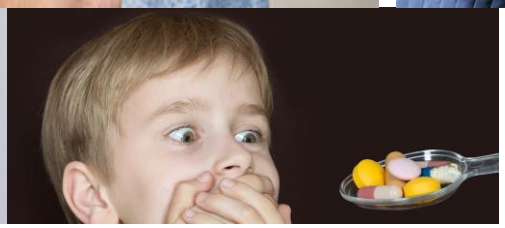
Tenth FGA, practically never used for schizophrenia despite FDA-approval?

Atypical Antipsychotics (SGAs)

Clozapine	Clozaril	Novartis	1990
Risperidone	Risperdal	Janssen	1994
Olanzapine	Zyprexa	Lilly	1995
Quetiapine	Seroquel	Zeneca	1997
Ziprasidone	Geodon	Pfizer	2001
Aripiprazole	Abilify	BMS/Otsuka	2002
Paliperidone	Invega	Janssen	2007
Illoperidone	Fanapt	Novartis	2009
Asenapine	Saphris	Merck	2009
Lurasidone	Latuda	Sunovion	2010
Brexpiprazole	Rexulti	Otsuka	2015
Cariprazine	Vraylar	Allergan	2015
Lumateperone	Caplyta	ITCI	2019

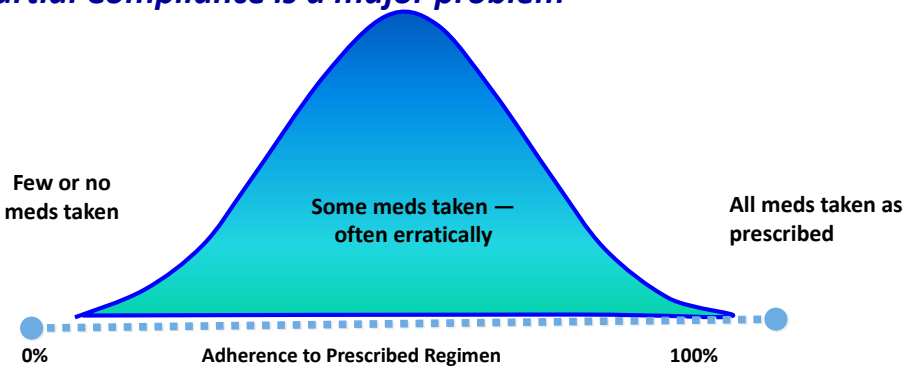
Problem:

A good drug doesn't work if you don't take it



Partial Adherence: A *(probably THE)* Primary Treatment Challenge in Severe Mental Illness

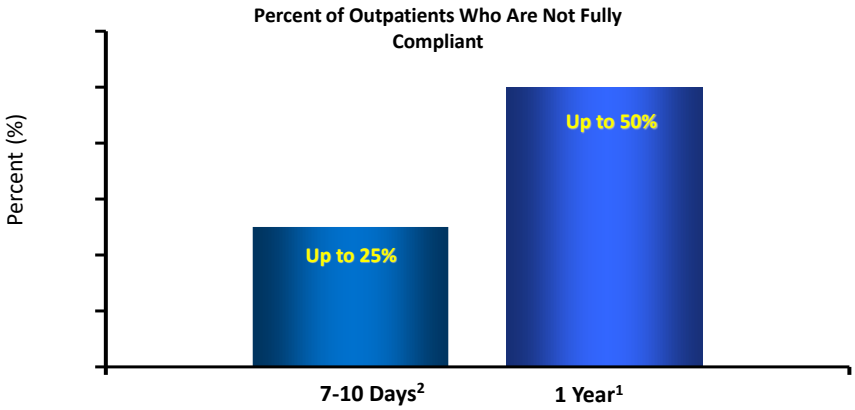
- ***Even Partial Compliance is a major problem***



1. Weiden PJ et al. *Psych Serv.* 2004;55:886-891; 2. Weiden PJ et al. *J Pract Psych Behav Health*. 1997;3:106-110;

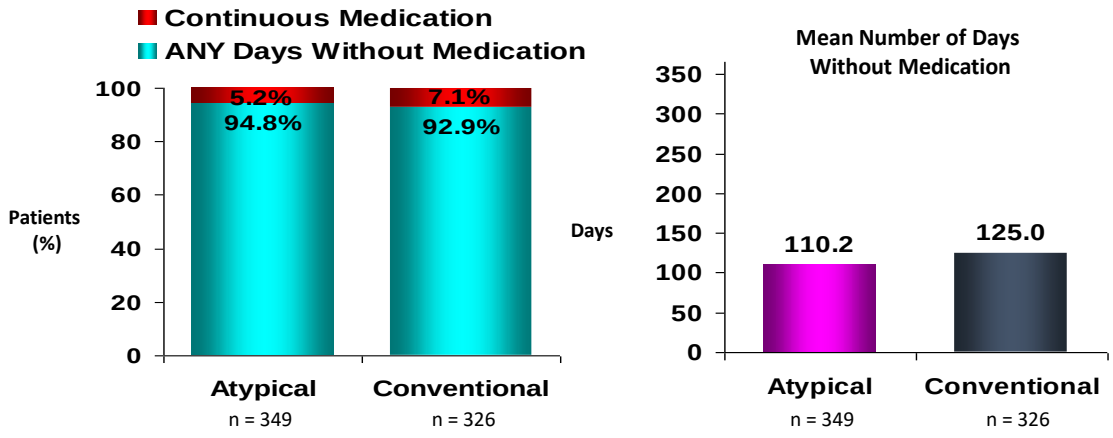
Partial Adherence Begins Shortly After Discharge and Increases Over Time

- Partial compliance may begin within days of discharge from the hospital and may increase over time[1,2]



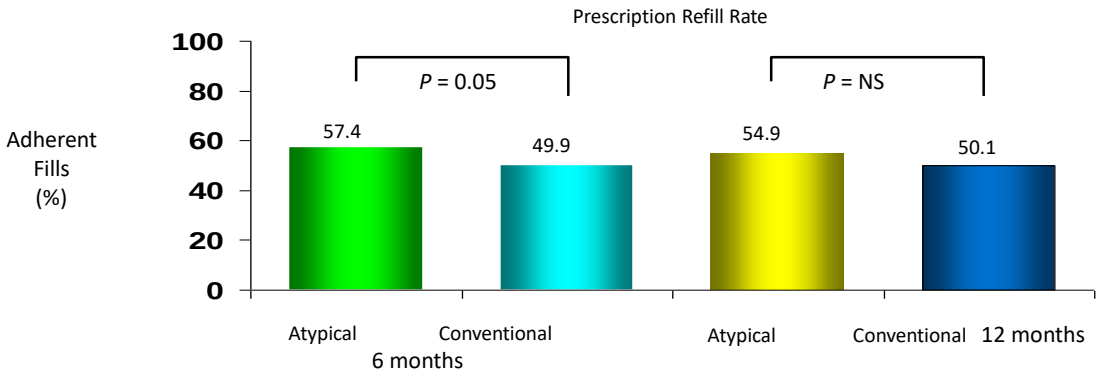
1. Weiden PJ et al. *J Pract Psych Behav Health*. 1997;3:106-110; 2. Lam F et al. Poster presented at: 42nd Annual New Clinical Drug Evaluation Unit Meeting: June 10-13, 2002; Boca Raton, Florida.

Compliance Challenges Affect Almost ALL Patients



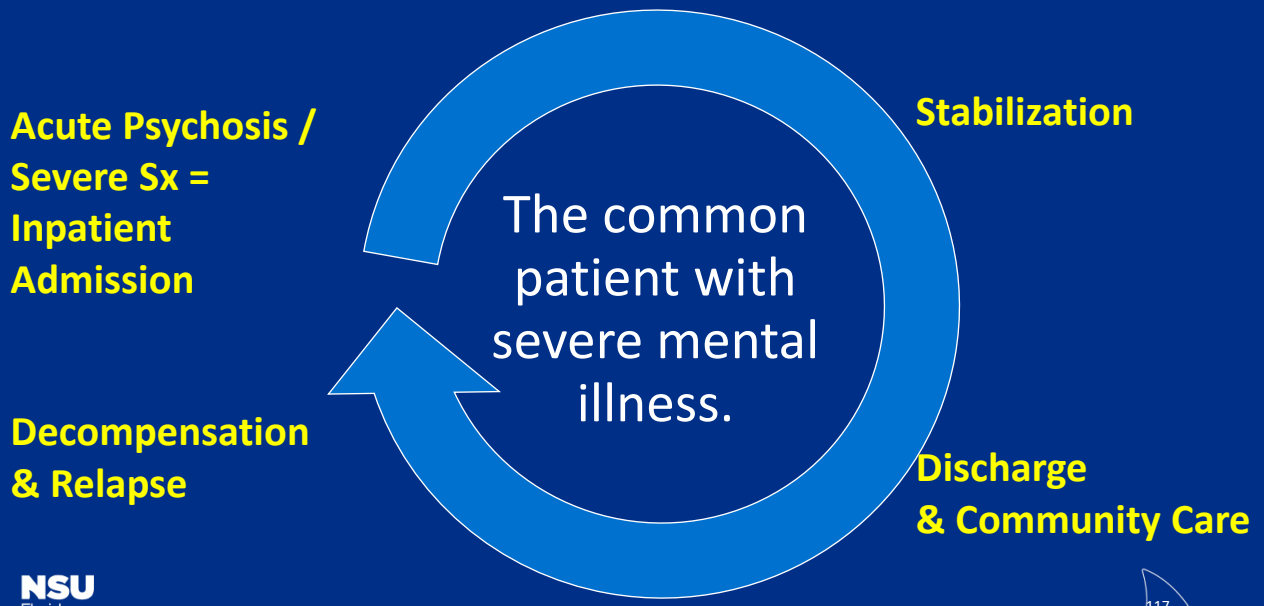
Mahmoud RA et al. Poster. 1997 ACNP Meeting; Kamuela, HI.

Long-Term Medication Compliance: Similar for Atypical vs Conventional Antipsychotics



Prescription refill rate = (# adherent fills / total # of fills) x 100.
Dolder CR et al. *Am J Psychiatry.* 2002;159:103-108.

A Terrible Cycle of Multiple Relapses



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How can this cycle be overcome?

Address the Reasons for Non-Adherence and Relapse

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Think about the Most Common Reason
Or
The Most Memorable Reason your patient provided on why they stopped taking their medication
Or
Why do patients with chronic and/or severe mental health issues not take their medications?

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"They come around three or four times a day and try to poison me. . . ."

The suspiciousness and hostility inherent in paranoid schizophrenia can cause many patients to avoid taking medication.

'Stelazine' Concentrate can be ideal for these patients. The concentrate dosage form enables the administering nurse to insure that the medication has been taken. And the potent antipsychotic activity of 'Stelazine' can exert a profound effect on the patient's paranoid thought patterns. It can help him realize that the hospital personnel are not menacing individuals who are "out to get him," but instead that they are genuinely interested in his well-being.

STELAZINE®
brand of
TRIFLUOPERAZINE
CONCENTRATE

Before prescribing, please see the complete prescribing information, including adverse effects reported with phenothiazines and symptoms and treatment of overdosage, in SK&F literature or *PDR*. The following is a brief precautionary statement.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias, bone marrow depression, and liver damage.

Precautions: Use with caution in angina patients and in patients with impaired cardiovascular systems. Antiemetic effect may mask signs of overdosage of other drugs or symptoms of other disorders. An additive depressant effect is possible when used with other C.N.S. depressants. Prolonged administration of high doses may result in accumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. In pregnancy, use only when necessary.

Adverse Reactions: Mild drowsiness, dizziness, mild skin reactions, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, rash, lactation, blurred vision, and hypotension. Extrapyramidal reactions (restlessness, dystonias, and pseudo-parkinsonism) may occur and, in rare instances, may persist. Blood dyscrasias and jaundice have been extremely rare.

Available: Tablets, 1 mg., 2 mg., 5 mg. and 10 mg.; Injection, 2 mg./cc.; and Concentrate, 10 mg./cc.

Smith Kline & French Laboratories

WARNING!

MENTAL PATIENTS ARE NOTORIOUS

DRUG EVADERS*

Many mental patients "cheek" or hide their tablets and then dispose of them. Unless this practice is stopped, they deprive themselves of opportunities for improvement or remission . . . deceive their doctors into thinking that their drugs have failed . . . and impose a needless drain on their hospital's finances.

When drug evaders jeopardize the effectiveness of your treatment program—

SPECIFY LIQUID CONCENTRATE†

THORAZINE® brand of chlorpromazine
STELAZINE® brand of trifluoperazine
COMPAZINE® brand of prochlorperazine

Liquid Concentrate is the practical dosage form for any patient who resists the usual forms of oral medication. It can easily be mixed with other liquids or semisolid foods to assure ingestion of the drug.

*According to Goldman, from 25% to 40% of hospitalized mental patients attempt to evade oral medication. (In Trifluoperazine: Clinical and Pharmacological Aspects. Philadelphia, Lea & Febiger, 1958, p. 14.)
†For hospital use

Smith Kline & French Laboratories, Philadelphia
leaders in psychopharmaceutical research

Watch Clara
She's hiding another 'Stelazine' tablet

She's got quite a collection in her secret place. And as her hoard increases, her condition deteriorates.

'STELAZINE' CONCENTRATE can help patients like Clara. She might even forget about her secret place.

Stelazine **Concentrate**
trifluoperazine
10 mg./cc. in 2 fl. oz. bottles

The following is a brief precautionary statement. Before prescribing, the physician should refer to SK&F literature or the complete prescribing information in the *PDR*. *Contraindications:* Comatose or greatly depressed states due to C.N.S. depressants and in cases of existing blood dyscrasias, bone marrow depression and liver damage. *Precautions:* Use with caution in angina patients and in patients with impaired cardiovascular systems. Antiemetic effect may mask symptoms of other disorders. An additive depressant effect is possible when used with other C.N.S. depressants. Prolonged administration of high doses may result in accumulative effects with severe C.N.S. or vasomotor symptoms. Use in pregnant patients only when necessary for the patient's welfare. *Side Effects:* Occasional drowsiness, dizziness, dry mouth, skin reactions, GI disturbances, insomnia and amenorrhea. Neuromuscular (extrapyramidal) reactions (motor restlessness, dystonias, pseudo-parkinsonism) may occur and, in rare instances, may persist. In addition, muscular weakness, anorexia, rash, lactation, hypotension, and blurred vision have been observed. Blood dyscrasias and cholestatic jaundice have been extremely rare.

For a comprehensive presentation of 'Stelazine' prescribing information and side effects reported with phenothiazine derivatives, please refer to SK&F literature or *PDR*.

Smith Kline & French Laboratories, Philadelphia

Photograph professionally posed

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Techniques to Improve Adherence

- Counseling at time of Dispensing
- Motivational Interviewing to discover and address barriers to Adherence
- ***Offering Alternative Formulations***
- Follow-up via Telephone (Virtual Meetings?)
- Cell Phone APPs for Alarms / Adherence / Monitoring
- Patient Self-Monitoring
- Education, Education, Education…… Health Literacy
- Incentives?

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Long-Acting Injectable Antipsychotics

GENERIC	BRAND	DOSE	Relapse Rates
Fluphenazine	**Prolixin Decanoate**	25-75 mg q 2 weeks IM / SQ	30%
Haloperidol	**Haldol Decanoate**	50-450 mg q 4 weeks	25-30%
Risperidone	**Risperdal Consta**	25-50 mg q 2 weeks	15%
Olanzapine	**Zyprexa Relprevv**	150-300 mg q 2-4 weeks	10%
Paliperidone	**Invega Sustenna**	39-234 mg q 4 weeks	10%
Aripiprazole	**Abilify Maintena**	400 mg q 4 weeks	10%
Paliperidone	**Invega Trinza**	273 – 819 mg q 12 weeks	7%
Aripiprazole	**Aristada** **Aristada Initio (675 mg)**	441 – 882 mg q 4 weeks 882 mg q 6 weeks 1064 mg q 8 weeks	3% open-label
Risperidone	**Perseris**	90-120 mg q 4 weeks SQ	??

Summary on Psychotropic Review

- **Plethora of pharmacological treatments to choose from…… but no cures yet.**
- **We rarely see an agent that is proven consistently superior to the other agents in the same class.**
- **Monotherapy is still the Gold Standard**
  - **Evidence-based medicine rarely supports combination tx.**
- **Innovative / Alternative delivery systems have been dominating the drug development arena for psychotropics**