New Drugs of 2016

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Objectives

- Describe the basic pharmacology of select new drugs of 2016, and how the pharmacological actions contribute to both therapeutic *and* adverse effects
- Discuss the appropriate dosing and monitoring parameters of these select new agents
- Review the therapeutic role of these new drugs and their place in therapy compared to previously available agents

Outline

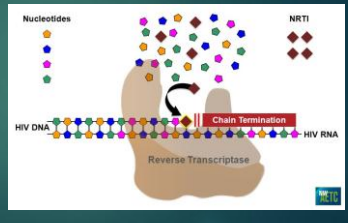
I. Will
   I. Descovy (emtricitabine/tenofovir alafenamide)
   II. Odefsey (rilpivirine/emtricitabine/tenofovir alafenamide)
II. Joy
   I. Taltz
   II. Vaxchora
III. Ian
   I. Briviact (Brivaracetam)
   II. Nuplazid (Pimavanserin)

Descovy[1] Dosage/Indications

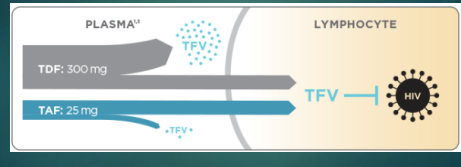
- Indication: Treatment of HIV-1 infection in pts ≥ 12yo in combination with other antiretroviral agents
- Dose: emtricitabine 200mg/tenofovir alafenamide (TAF) 25mg
  - 1 tablet po qd +/- food
- Renal adjustment: CrCl > 30 mL/min : none
  - CrCl < 30 mL/min: not recommended
- Hepatic adjustment: none

Descovy[1] MOA

- Combination NRTI
  - Emtricitabine 200mg
    - cytosine analogue
  - Tenofovir alafenamide 25mg
    - adenosine analogue



Descovy[1] MOA – TAF vs TDF



Descovy
Adverse Effects

- N/V/D
- Lactic acidosis
- Severe hepatomegaly with steatosis
- Worsening hepatitis B infection
- Body fat redistribution
- Nephrotoxicity
- Bone mineral density changes

Descovy
Monitoring

- Renal function
- Bone mineral density
- HIV viral load as indicated
- DDIs: Pgp substrate

Descovy[1]
Role in therapy

- NRT backbone in first-line ARV regimen
  - Dolutegravir + Descoby (AII)
  - Raltegravir + Descovy (AII)

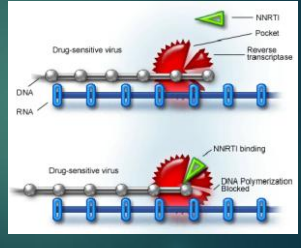
Odefsey[2]
Indications and dosing

Odefsey
emtricitabine 200mg/rilpivirine 25mg/
tenofovir alafenamide 25mg tablets

- Indication: Treatment of HIV-1 infection in pts ≥ 12yo
  - Treatment naïve and HIV viral load <100,000 copies/mL
  - Replacing current HIV-1 regimen with an undetectable viral load (<50 copies/mL) for ≥ 6 months
- Dose: 1 tablet po qd +/- food
- Renal adjustments: not recommended in CrCL <30 mL/min
- Hepatic adjustments: none

Odefsey[2]
MOA

- Dual NRTI + NNRTI (Rilpivirine)



Odefsey
Adverse Effects

- Descovy
  - Nausea
  - Lactic acidosis
  - Severe hepatomegaly with steatosis
  - Worsening hepatitis B infection
- Rilpivirine
  - Depression, insomnia, headache

Odefsey
Monitoring

- Descovy
  - Renal function
  - Bone mineral density
  - HIV viral load as indicated
  - DDIs: Pgp substrate
- Rilpivirine
  - DDIs: 3A4

Odefsey[2]
Role in therapy

- Indication: Treatment of HIV-1 infection in pts ≥ 12yo
  - Treatment naïve and HIV viral load <100,000 copies/mL (IA)
  - Replacing current HIV-1 regimen with an undetectable viral load (<50 copies/mL) for ≥ 6 months (IA)

Test questions

1. Which of these agents is a guideline-recommended first-line treatment regimen for HIV in treatment-naïve adults?
   1. Rilpivirine
   2. Descovy
   3. Odesfey
   4. All of the above
2. What is the most common side effect of Descovy?
   1. Lactic acidosis
   2. Hepatic steatosis
   3. Nausea
3. What is the most common side effect of Rilpivirine?
   1. Worsening hepatitis B infection
   2. Depression
   3. Hypodontia
4. Which of these agents is indicated for HIV pre-exposure prophylaxis?
   1. Descovy
   2. Odesfey
   3. Both A and B
   4. None of the above

Taltz (ixekizumab)
Indication/MOA

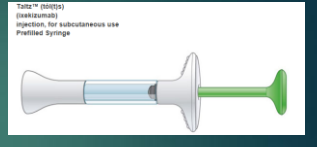
taltz® (ixekizumab) injection 80 mg/mL

- Indication
  - Treatment of adults with moderate-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
- MOA
  - A humanized IgG4 monoclonal antibody that selectively binds with interleukin 17A (IL-17A) cytokine and inhibits its interaction with IL-17 receptor.
  - Inhibiting the release of proinflammatory cytokines and chemokines.

Taltz (ixekizumab)
Dosage

- 80 mg (ixekizumab), SQ, prefilled syringe or auto injector
- Cost: $4469 per 80 mg (ixekizumab), prefilled syringe

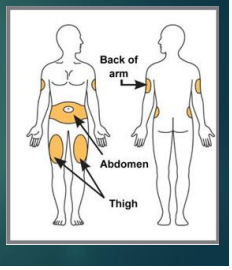
Taltz (ixekizumab)
Dosage



- Storage
  - 2°C to 8°C (36°F to 46°F)
  - Do not freeze
  - Protect from light
  - Discard any unused portion
  - Do not shake
- Warm to room temperature prior to injection
- Inspect prior to injection
  - Colorless to light yellow
  - No visible particles

Taltz (ixekizumab) Injections

- Rotate areas
- Do not give in areas with tissue damage
  - Tender
  - Bruised
  - Red, or hard
  - Affected by psoriasis
- Do not inject within 1 inch of navel



Taltz (ixekizumab) Adverse Effects

- Infections
  - Neutropenia
  - Thrombocytopenia
- Hypersensitive Reactions
  - Anaphylaxis
  - Injection site reactions
- Inflammatory Bowel Disease
  - Onset or exacerbations
  - Crohn's disease
  - Ulcerative colitis

Taltz (ixekizumab) Considerations

- Prior to starting treatment
  - Evaluate and treat for tuberculosis
  - Administer all age appropriate vaccinations
- Patients receiving treatment
  - Do not administer live vaccinations
  - Monitor for signs of infection
- No clinical trials
  - Pregnancy/nursing
  - < 18 years of age

Taltz (ixekizumab) Role in therapy

Moderate-to-severe psoriasis

- **5-10% of body surface area**
- **Involvement of face, palm, or sole**
- **Or disease is otherwise disabling**

Therapies

Photo therapy	Remicade (infliximab)	Cosentyx (secukinumab)
Methotrexate	Humira (adalimumab)	Taltz (ixekizumab)
Enbrel (etanercept)	Stelara (ustekinumab)	

Taltz (ixekizumab) Monitoring

Hypersensitive Reactions

Anaphylaxis
-Swelling; face, tongue
-Trouble breathing
-Skin rash

Injection site reactions
-Infection
-Redness
-Rash

Inflammatory Bowel Disease

Crohn's disease
Ulcerative colitis
-Stomach pain
-Diarrhea; with or without blood
-Weight loss

Infections

Tinea infections
Fungal infections
Upper respiratory infections
Neutropenia
Thrombocytopenia

Decreased response to treatment
-Increased antibody production

Taltz (ixekizumab) Summary

- Treatment option in moderate-severe plaque psoriasis
- Requires 12 weeks of induction
- After 12 weeks it is a once a month SQ injection
- Decrease's immune response
  - TB
  - Tinea infections
  - No live vaccinations
- Causes/increases Irritable Bowl Syndrome, Crohn's
- May become ineffective due to antibody production

Review Questions

1. What is the most common adverse side effect of Taltz?
   A. Tinea infections
   B. Injection site reactions
   C. Upper respiratory infections
2. What is the most concerning infection for patients receiving Taltz?
   A. Tinea infections
   B. Injection site reactions
   C. Upper respiratory infections
3. Which disease state is not a contraindication of receiving Taltz but may be caused or exacerbated in patients receiving treatment?
   A. Tuberculosis
   B. Crohn's disease
   C. IBS
   D. Both A and B
   E. None of the above

Vaxchora (cholera vaccine) Indication/MOA

Vaxchora
Cholera Vaccine, Live, Oral
Never underestimate cholera

- Indication
  - Active immunization against disease caused by *Vibrio cholerae* serogroup O1 in adults 18 through 64 years of age traveling to cholera-affected areas
- MOA
  - Contains live attenuated cholera bacteria that replicate in the gastrointestinal tract of the recipient
  - Immune mechanism is unknown

Cholera

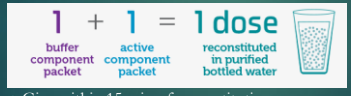
- Can cause death <24 hrs
- 80% of cases in US result from travel to Africa, Asia, Caribeean
- Non-vaccine prevention
  - Avoid contaminated water & food
  - 98 % of travels do not take precautions

Vaxchora (cholera vaccine) Dosage

- 1 single oral dose
- 10 days before potential exposure to *V. cholera*
- $191.25 per dose

Vaxchora (cholera vaccine) Administration

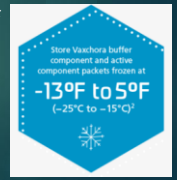
- Single dose carton
- 2 packets
- Reconstituted in purified bottled water



- Give within 15 min of reconstitution
- No eating or drinking for 60 minutes pre and post dose

Vaxchora (cholera vaccine) Storage

- Protect from light and moisture
- Thawing is not required prior to reconstitution
- Reconstitute within 15 min of removal from freezer
- Do not expose to temperatures above 80°F (27°C)
  - While thawing
  - Reconstituted



Vaxchora (cholera vaccine) Effectiveness

- Effectiveness has not been established in
  - Patients living in cholera-affected areas
  - Patients with pre-existing immunity due to previous exposure to V. Cholera
  - Previous exposure to a cholera vaccine
  - Age <18 or < 64
- Is not effect against V cholera serogroup 0139 or other non-01 sesrogroups

Vaxchora (cholera vaccine) Duration of Protection Comparison

Vaxchora formulation efficacy for protection against severe (>3L) diarrhea

Time post-vaccination	Vaccine	Placebo	VE (95% CI)
10 days	2/35 (5.7%)	39/66 (59.1%)	90.3% (62.7-100%)
3 months	4/33 (12.1%)		79.5% (49.9-100%)

- Vaxchora is currently not approved for use outside the US
- Further trials will evaluate use in areas of outbreaks
- Phase 3 trial > 3000 patients

Vaxchora (cholera vaccine) Adverse Effects

- Tiredness
- Headache
- Abdominal pain
- Nausea/emesis
- Diarrhea
- Vibrio cholerae can be shed in stool for ~ 7 days after vaccination

Vaxchora (cholera vaccine) Contraindications

- Do not take chloroquine within 10 days of immunization
- Age < 18
- Age > 64
- Immunocompromised individuals
- Pregnancy
- Nursing

Vaxchora (cholera vaccine) Role in Therapy

- Only FDA approved vaccination for cholera
- Only one-step cholera vaccination
- Internationally there are 2 two-step oral cholera vaccinations

Vaxchora (cholera vaccine) Monitoring

- Avoid spreading cholera during 14 days post dose
  - Immunocompromised household members
  - Infants
- Monitor for signs of infection
  - Diarrhea
  - Nausea/with emesis

Vaxchora (cholera vaccine) Summary

- Only FDA approved oral vaccine for cholera
- Live vaccination
- Individual should take precautions for 14 days to prevent transfer of bacteria
- Must be taken 10 days prior to expected exposure
- Effective for

Vaxchora (cholera vaccine) Review questions

1. When is Vaxchora most effective?
   - A. 10 days post dose
   - B. 90 days post dose
   - C. 180 days post dose
2. What is the most critical counseling point to patient who receive Vaxchora?
   - A. Taking precautions to avoid transferring cholera to others
   - B. Avoiding food and drink for two hours pre and post dose
   - C. That if patients develop diarrhea they should seek medical care
3. Which disease state is not a contraindication for receiving Vaxchora?
   - A. Age <18
   - B. Pregnancy
   - C. Previous exposure to cholera
   - D. Both A and B and D
   - E. None of the above

Brivaracetam (Briviact)

BRIVIACT

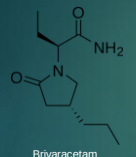
Indication

- Adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.

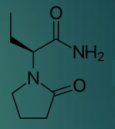
Mechanism of Action:

- Unknown; high affinity for synaptic vesicle protein 2A (SV2A) in brain which may contribute to the anticonvulsant effect

Chemical Structure



Brivaracetam



Levitiracetam

Pharmacokinetics

- Absorption
  - Nearly 100% bioavailable; high-fat meal delays absorption, AUC unchanged.
  - Time to peak: 1 hour
- Distribution
  - 0.5 L/kg; <20% protein-bound
- Metabolism
  - Primarily by CYP2C19
  - Half-life ~9 hr
- Excretion
  - >95% Urine (<10% unchanged); feces <1%

Dosing

- Recommended starting dose 50 mg BID
- May be adjusted down to 25 mg BID or up to 100 mg BID as tolerated

Dose Adjustments:

- Hepatic impairment
  - Start at 25 mg BID, max 75 mg BID
- Concurrent administration with rifampin
  - Increase dose by 100% (double)

Formulations

- Oral tablet: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg
  - Tablets should not be crushed
- Oral solution: 10 mg/mL
- Injectable: 50 mg/5mL single dose vial
  - Clinical study experience limited to 4 consecutive days of treatment
    - Only used temporarily when oral administration not feasible

Efficacy

Table 4: Percent Reduction in Partial-Onset Seizure Frequency over Placebo (Studies 1, 2, and 3)

	Percent Reduction Over Placebo (%)
STUDY 1[a]	
Placebo (n=100)	--------
50 mg/day (n=99)	9.5
100 mg/day (n=100)	17.0
STUDY 2[a]	
Placebo (n=98)	--------
50 mg/day (n=101)	16.9*
STUDY 3[b]	
Placebo (n=259)	--------
100 mg/day (n=252)	25.2*
200 mg/day (n= 249)	25.7*

* Statistically significant based on testing procedure with alpha = 0.05
[a] Based upon 7-day seizure frequency
[b] Based upon 28-day seizure frequency

Adverse Effects

- Fatigue (20-27%)
- Dizziness (12-16%)
- Psychiatric/Behavioral disturbance (13%)
- N/V (5%)

Comparison

Category	Brivaracetam	Levitiracetam
Indication	Partial onset only	Partial onset, myoclonic, tonic-clonic
Age	≥16 years	≥4 years (partial onset)
Efficacy vs. Placebo	Reduce seizure frequency 16.9-25.7%	Reduce seizure frequency 17-26.8%
Adverse Effects	Similar to levitiracetam; Higher rates of somnolence	Similar to brivaracetam
Cost	100 mg (60): $1092.00 copay assistance available	1000 mg (60): $422.18
Abuse potential	Schedule V Controlled Substance	Legend Drug

Summary

- No head-to-head efficacy studies between brivaracetam and levitracetam
- Similar efficacy compared to placebo
- Similar adverse effect profiles
- Currently only approved for persons ≥16 yo w/ partial onset seizures
  - Clinicaltrials.gov: No clinical trials underway for other indications
  - Some trials in pediatric populations

Review Questions

1. What is the proper dose adjustment for brivaracetam for a patient on concurrent rifampin?

A) Increase dose by 50%
B) Increase dose by 100%
C) Decrease dose by 50%
D) Decrease dose by 100%

2. Which patient would be an appropriate candidate for adjunct treatment with brivaracetam?

A) 15 year old with partial onset seizures
B) 54 year old with myoclonic seizures
C) 19 year old with partial onset seizures
D) 4 year old with partial onset seizures

Parkinson's Disease Psychosis

- Dopamine therapy- ↓ motor symptoms, ↑hallucinations/delusions
- Up to 50% of patients with Parkinson's experience some degree of psychosis:
  - Visual hallucinations
  - Paranoia
  - False Beliefs
  - Out of touch with reality
- Current treatments include low-dose olanzapine, quetiapine and clozapine
  - Clozapine most efficacious, but can worsen motor symptoms and requires frequent monitoring

Pimavanserin (Nuplazid)

NUPLAZID™ (pimavanserin) tablets

Indication

- Treatment of Parkinson's Disease Psychosis

Mechanism of Action

- 5HT2a receptor inverse agonist
- No affinity for 5HT2b, dopaminergic, muscarinic, histaminergic, adrenergic receptors or calcium channels

Dosing

- 34 mg PO once daily
- Strong CYP3A4 inhibitors: 17 mg PO once daily
- Strong CYP3A4 inducers: No dose adjustment, monitor for reduced efficacy, may require dose increase

Formulation:

- 17 mg tablets (60): $2340

Pharmacokinetics

- Absorption: Not affected by high fat meals. Tmax=6 hr
- Distribution: Vd= 2173 L
- Metabolism: CYP3A4 and CYP3A5. Forms active metabolite AC-279
- Excretion: Half-life pimavanserin 57 hours. Active metabolite (AC-279) 200 hours
  - <2% excreted unchanged in urine

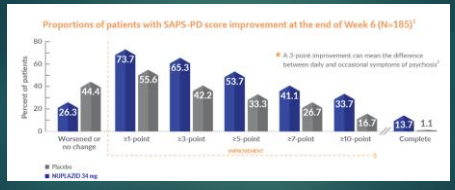
Efficacy

- Scale for Assessment of Positive Symptoms (SAPS-PD)
  - 9 items, scored 0 to 5 (never present to always present)

Table 3 Primary Efficacy Analysis Result Based on SAPS-PD (N=185)

Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
SAPS-PD	NUPLAZID	15.9 (6.12)	-5.79 (0.66)	-3.06* (-4.91, -1.20)
	Placebo	14.7 (5.55)	-2.73 (0.67)	--
SAPS-PD Hallucinations[b]	NUPLAZID	11.1 (4.58)	-3.81 (0.46)	-2.01 (-3.29, -0.72)
	Placebo	10.0 (3.80)	-1.80 (0.46)	--
SAPS-PD Delusions[b]	NUPLAZID	4.8 (3.59)	-1.95 (0.32)	-0.94 (-1.83, -0.04)
	Placebo	4.8 (3.82)	-1.01 (0.32)	--

Efficacy



Adverse Effects

Table 1 Adverse Reactions in Placebo-Controlled Studies of 6-Week Treatment Duration and Reported in ≥2% and >Placebo

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

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

Summary

- Pimavanserin is an improvement over existing treatments for Parkinson's Disease Psychosis
  - No affinity for dopamine receptors
- Minimal adverse effect profile
- Efficacious compared to placebo
  - Not compared to other treatments like clozapine or quetiapine
- Cost benefit ratio?

Review Questions

Which of the following is a true regarding pimavanserin?

a) It reduces frequency of partial onset seizures by about 20%
b) It has no affinity for dopamine receptors, so it improves positive symptoms of PDP without a decrease in motor function.
c) It improves positive symptoms of PDP, at the expense of decreasing motor function
d) It is also approved for use in patients with schizophrenia

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