New Drug Update 2013

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Objectives

1. Identify new medications approved in the last year that may be useful in the clinical care of older adults
2. Identify characteristics, such as dosing, pharmacokinetics, side effects, and monitoring that may require special attention in older adults
3. Recognize patients who may be candidates for these medications, taking into consideration other patient characteristics

Methods

• The FDA website (www.fda.gov) was reviewed for new molecular entity approvals from January 2013 through December 2013
• Drugs were included according to the following criteria:
  1) they had potential to be prescribed in the elderly population
  2) they were expected to have a significant influence on the care of elderly patients

Selected New Molecular Entities (2013)

<table>
<thead>
<tr>
<th>Drug: Brand (generic)</th>
<th>Approval</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Invokana (canagliflozin)</td>
<td>March</td>
<td>Diabetes, type 2</td>
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<tr>
<td>Breo Ellipta (fluticasone/vilanterol)</td>
<td>May</td>
<td>COPD</td>
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<tr>
<td>Fetzima (levomilnacipran)</td>
<td>July</td>
<td>Depression</td>
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<tr>
<td>Brintellix (vortioxetine)</td>
<td>September</td>
<td>Depression</td>
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<tr>
<td>Anoro Ellipta (umeclidinium/vilanterol)</td>
<td>December</td>
<td>COPD</td>
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Canagliflozin (Invokana™)

- FDA-approved (March 29, 2013) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- Manufacturer: Janssen Pharmaceuticals, Inc.
- Mechanism of action:
  - The sodium-glucose co-transporter 2 (SGLT2) mediates reabsorption of approximately 90 percent of the filtered glucose load. Inhibition of SGLT2 promotes the renal excretion of glucose resulting in osmotic diuresis.

Approved dosing:
- 100mg, 300mg tablet
- Starting dose: 100 mg daily before 1st meal
- Renal adjustment:
  - GFR > 60 mL/min → Max of 300 mg once daily
  - GFR 45 to 60 mL/min → max of 100mg daily
  - GFR < 45 mL/min → do not use or discontinue

Warnings and Precautions:
- Hypotension:
  - Assess volume status and correct hypovolemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure or if on diuretics, ACEi, or ARB.
- Hypoglycemia with insulin or secretagogues:
  - Lower dose of insulin or secretagogue may be required
- Hyperkalemia:
  - Monitor potassium in those with renal dysfunction or those predisposed to increased K+
- Genital mycotic infections:
  - Monitor and treat if necessary
Canagliflozin (Invokana™)

- **Side effects (> 5%)**
  - Female genital mycotic infections, urinary tract infection, and increased urination

- **Drug interactions**
  - UGT inducers (e.g. rifampin, PHT, PHB) reduce canagliflozin exposure, consider increased dose
  - Digoxin: monitor dig level

- **Cost:** AWP = $346/mo (RedBook Online®)

- **Special populations**
  - Geriatrics: higher incidence of adverse reactions due to reduced intravascular volume
  - Renal impairment: higher incidence of adverse reactions due to reduced intravascular volume and renal function

Canagliflozin (Invokana™)

- **Use in Geriatric patients**
  - Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to canagliflozin
  - Patients > 65 years had more ADRs related to reduced intravascular volume (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), especially those 75 years or older

**Clinical Efficacy**

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Placebo + Metformin</th>
<th>Canagliflozin 100mg + Metformin</th>
<th>Canagliflozin 300mg + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HgbA1c change</td>
<td>-0.17%</td>
<td>-0.79%</td>
<td>-0.94%</td>
</tr>
<tr>
<td>A1c &lt; 7%</td>
<td>30%</td>
<td>46%</td>
<td>58%</td>
</tr>
<tr>
<td>Body wt (kg)</td>
<td>-1.2</td>
<td>-3.7</td>
<td>-4.2</td>
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</table>

- **Metformin + canagliflozin or glimepiride (52 wk)**
  - 0.8-0.9% A1c reduction
  - Weight loss with canagliflozin

- **Metformin/SU + canagliflozin 300mg or sitagliptin 100mg (52 wk)**
  - -1% vs. -0.66% A1c reduction
  - -2.5kg vs. 0.3kg weight loss

- **Metformin/pioglitazone +/- canagliflozin (26 wk)**
  - 0.7 to 0.8% more lowering as add-on vs. placebo
  - 3-5kg weight loss
Where does Invokana™ fit?

- Due to lack of long-term efficacy and safety data, not recommended for routine use
- Could play a role as a third line agent if inadequate control on metformin/SU, but not a candidate for insulin
- Extra caution in the elderly and very elderly due to increased risk of side effects

Umeclidinium and Vilanterol
(Anoro Ellipta™)

Fluticasone furoate and Vilanterol
(Breo Ellipta™)

Breo Ellipta™
- Long-term, once-daily, maintenance treatment of airflow obstruction, and for reducing exacerbation in patients with COPD (May 10, 2013)
- Mechanism
  - Long-acting inhaled corticosteroid and beta₂ agonist
- Cost: AWP = $123/mo
  Manufacturer: GlaxoSmithKline

Anoro Ellipta™
- Mechanism
  - Long-acting anticholinergic and beta₂ agonist
- Cost: none available

Approved Dosing

- Breo Ellipta™: Fluticasone furoate 100mcg/Vilanterol 25mcg, one inhalation, once daily
- Anoro Ellipta™: Umeclidinium 62.5mcg/Vilanterol 25mcg, one inhalation, once daily
- Inhalation powder: Inhaler containing 2 double-foil blister strips of dry powder formulation for oral inhalation.
• **Contraindications**: Severe hypersensitivity to milk proteins or the active ingredients

• **Warnings and Precautions**
  – **Breo Ellipta™**
    • Localized infections, Pneumonia
    • Immunosuppression/Adrenal suppression
  – **Anoro Ellipta™**
    • Potential worsening of narrow angle glaucoma
    • Potential worsening of urinary retention
      – Exact bioavailability in healthy adults not reported
      – Use as indicated by guidelines; educate patients and monitor, especially in BPH/LUTS
  – **Both**:
    • Deterioration of disease or acute episode
    • Excessive dose or concomitant LABA

• **Drug interactions**
  – Inhibitors of CYP3A4
    • Vilanterol is a substrate of 3A4 and oral ketoconazole has been shown to increase vilanterol
  – MAOI’s, TCA’s, and other drugs known to prolong the QTc interval
  – Beta-blockers, Anticholinergic medications, corticosteroids

• **Adverse effects**
  – Anticipated to be minimal, but would be expected to be related to the beta agonist, anticholinergic, or corticosteroid properties

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**Where do Anoro Ellipta™ and Breo Ellipta™ fit?**

• The only available combinations of once daily inhaled beta-2 agonist/antimuscarinic and inhaled beta-2 agonist/inhaled corticosteroid

• Limited clinical evidence, no published head-to-head clinical comparison to other long-acting agents

• At this point, Anoro Ellipta™ and Breo Ellipta™ would be preferred if cost was substantially less, or if patient had a significant benefit with once daily dosing

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**Levomilnacipran**

(Fetzima™)

[Image of Levomilnacipran tablets]
Levomilnacipran (Fetzima™)

- FDA-approved July 25, 2013 for major depressive disorder
- Manufacturer:
  - Forest Laboratories, Inc.
  - Previously approved product: milnacipran (Savella™) for fibromyalgia (50mg BiD up to 200mg/d)
- Mechanism of action: SNRI
- Approved dosing: 40-120mg once daily
  - Availability: 20mg, 40mg, 80mg, 120mg XR capsules
  - Starting dose: 20mg once daily for 2 days, then increase to 40mg; increase by 40mg every ≥2 days
  - Renal adjustment:
    - Moderate impairment ➔ max of 80mg daily
    - Severe impairment ➔ max of 40mg daily

Warnings and Precautions

- Increased BP/HR
  - Measure at baseline and periodically and control HTN before treatment
- Urinary hesitancy/retention
  - Discontinue use if symptoms occur
- Seizures
  - Use with caution if hx seizures (1 case)
- Standard warnings:
  - Increased bleeding
  - Suicide
    - Medication guide and BBW
    - Reduced risk with adults aged 65 and older
  - Hyponatremia
  - Serotonin Syndrome
    - Avoid MAOIs and other drugs
  - Narrow-angle glaucoma
  - Activation of mania/hypomania
  - Discontinuation syndrome: taper dose

Levomilnacipran (Fetzima™)

- Side effects
  - >5% and 2X PBO
    - N/V, constipation, sweating, ↑HR, ED, palpitations
- Drug interactions
  - Strong CYP3A4 inhibitors: max 80mg daily
- Alcohol interactions
  - Avoid E1OH due to an accelerated drug release that may occur if taken with alcohol
- Special populations
  - Geriatrics: slightly higher Cmax and AUC; higher risk for hyponatremia in general; no dose adjustments
  - Renal impairment: 76% of dose eliminated by renal excretion; lower maximum dose for moderate-severe renal impairment; t1/2 = 12 hrs
- Cost: $ 203/mo

Levomilnacipran (Fetzima™)

- Geriatric patients in RCTs: low!
  - 2.8% of patients were ≥65 yrs (N = 48)
  - Age range up to age 78 yrs
- RCTs were 8-wk DB, PBO-controlled
- Outcomes were the MADRS (Montgomery-Asberg Depression Rating Scale) and SDS (Sheehan Disability Scale)
**Levomilnacipran (Fetzima™)**

**Data with milnacipran in elderly with MDD**
  - Summary of 7 RCTs comparing milnacipran 50mg BID to imipramine/clomipramine 75mg BID
  - Response rate: 64% milnacipran, 67% TCAs
  - Milnacipran was better tolerated, only SE more common was dysuria (2.1%)
- Prog Neuropsychopharmacol Biol Psychiatry 2009;33:349–52
  - 14 patients with AD-MDD and 22 non-AD MDD patients, mean age 74, treated with milnacipran
  - Similar treatment benefits, no difference in MMSE

**Where does Fetzima™ fit?**
- Due to cost and relative lack of data, would not recommend it first-line in geriatric patients
- Could play a role as alternative agent, especially if patient has concomitant fibromyalgia
- Alternative to duloxetine and venlafaxine

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**Vortioxetine (Brintellix™)**

- FDA-approved Sept 30, 2013 for major depressive disorder
- Manufacturer
  - Takeda Pharmaceuticals America, Inc.
- Mechanism of action: SSRI
  - 5-HT3 antagonism (ondansetron)
  - 5-HT1A agonism (buspirone, trazodone)
Vortioxetine (Brintellix™)

- **Approved dosing**
  - 5mg, 10mg, 15mg and 20mg tablets
  - Starting dose: 10 mg once daily
  - Dose can be titrated from 5-20mg daily
- **Dose Adjustment**
  - Maximum 10mg/day in known CYP2D6 poor metabolizers
- **Discontinuation**
  - If dose is at 15-20mg/d, reduce to 10mg for 1 week before full discontinuation

- **Side effects**
  - >5% and 2X PBO
  - N/V, constipation
- **Drug interactions**
  - Strong CYP2D6 inhibitors
    - Reduce dose by half
  - Strong CYP inducers
    - Consider increasing the dose up to 3X the original dose
- **Cost:** $262/mo
- **Special populations**
  - Geriatrics:
    - No dose adjustment
    - PK is similar (t1/2 = 66hrs)
    - No increase in efficacy/toxicity
    - Higher risk for hyponatremia in general
- **Pharmacokinetics**
  - Highly dependent on CYP
  - Not dependent on kidney fxn

- **Cost:** $262/mo

Warnings and Precautions

- **Standard warnings:**
  - Increased bleeding
  - Suicide
    - Medication guide and BBW
    - Trend towards reduced risk with use in patients aged 65 and older
  - Hyponatremia
  - Serotonin Syndrome
    - Avoid MAOIs and other drugs
  - Activation of mania/hypomania

Vortioxetine (Brintellix™): Use in Geriatrics

- 8-wk DB, active & PBO controlled RCT
  - 453 patients, aged 64-88 (mean 71 yrs)
  - Recurrent MDD with at least one episode <60 yrs and with MMSE >24
- **Vortioxetine 5mg/d or duloxetine 60mg/d or PBO**
- **Endpoints**
  - HAM-D24 (mean 30 pts = mod/severe)
  - Some cognitive tests (DSST, RAVLT)

Vortioxetine (Brintellix™)

Where does Brintellix™ fit?

- Some positive data in the elderly, well tolerated, does not rely on renal function
- Expensive and new, so not first-line
- Alternative antidepressant if patient cannot tolerate or does not respond to standard generic SSRIs
Conclusions

- Canagliflozin (Invokana™)
- Umeclidinium and Vilanterol (Anero Ellipta™)
- Fluticasone furoate and Vilanterol (Breo Ellipta™)
- Levomilnacipran (Fetzima™)
- Vortioxetine (Brintellix™)