New Drug Update (2016)

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Objectives

- Identify new molecular entities approved in the last year which may be useful in the clinical care of older adults
- Identify characteristics, such as dosing, pharmacokinetics, side effects, and monitoring which may require special attention in older adults
- 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 2016 through December 2016.
- Drugs were included according to the following criteria:
  - They had potential to be prescribed in the elderly population.
  - They were expected to have a significant influence on the care of elderly patients.
Hot off the press!

- FDA approved 22 new medications…
  - Lowest number since 2010
  - Down from 2015’s 45 new medications
<table>
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<th>Drug: Brand (generic)</th>
<th>Indication</th>
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<td><strong>Toujeo</strong> (insulin glargine)</td>
<td>Long-acting insulin to improve glycemic control in adults with diabetes mellitus</td>
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<td><strong>Tresiba</strong> (insulin degludec)</td>
<td>Long-acting insulin to improve glycemic control in adults with diabetes mellitus</td>
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<td><strong>Zinplava</strong> (bezlotoxumab)</td>
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<td>Treatment of hallucinations &amp; delusions associated with Parkinson’s disease psychosis</td>
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Toujeo® (insulin glargine)

- FDA approved (February 2015) for diabetes mellitus
- MOA: Basal insulin, U-300 (300 units/mL)
  - Forms microprecipitate when injected—smaller volume leading to more consistent and prolonged insulin release than Lantus
  - Continuous activity beyond 24 hours
  - 10-15% higher doses of Toujeo are required to achieve similar levels of glucose control compared to Lantus
  - Steady-state concentrations reached by day 5

Toujeo® (insulin glargine)

- Approved dosing in Type 2 DM:
  - Insulin naïve: 0.2 u/kg once daily
  - Already on insulin:
    - Switching from Lantus or Levemir: initiate the same dose knowing the patient may eventually need a higher daily dose of Toujeo
    - Switching from BID NPH: initiate 80% of the total daily NPH dose
Warnings, Precautions, & Side Effects

- **Contraindications:** hypersensitivity

- **Warnings/Precautions:**
  - Do not share insulin pens with others
  - Hyperglycemia/hypoglycemia when changing insulin regimens
  - Medication errors
  - Hypokalemia
  - Fluid retention/heart failure when used with TZDs

- **Side effects:** hypoglycemia, hypersensitivity, hypokalemia
Evidence:

- In controlled clinical trials, 9.8% of patients with T1DM and 26.3% of patients with T2DM were ≥65 years of age
  - 2% and 3%, respectively, were ≥75 years of age
- No overall differences in effectiveness and safety were observed in the subgroup analysis based upon age
- The effects of renal impairment on Toujeo PK has not been studied

## Evidence: Edition 2

### Population (n=811)
- Mean age 58 years
- 94% Caucasian
- Mean A1c 8.24%
- Mean BMI 35 kg/m²
- Mean 12.5 yrs DM
- 94% taking metformin

### Open Label Intervention (6 mo study)
- Orals + U100
- Orals + U300

### Results
- ≈ 0.5% reduction in A1c in both groups
- 10% higher dose of U300
- Less hypoglycemia with U300 (RR 0.77, 95% CI 0.61-0.99, P=0.038)
- Lower weight gain with U300 (P=0.015)

Toujeo® (insulin glargine)

- **Cost:**
  - 1 box of 3 pens, 1.5mL each, 300 units/mL = 1350 units = $350
  - 1 box of 5 pens, 1.5mL each, 300 units/mL = 2250 units = $600
  - Lantus comparison: 1 box of 5 pens, 3mL each = 1500 units = $400
  - NPH comparison: 1 vial, 10 mL = 1000 units = $150

- **Insurance coverage:**
  - **Tricare and Buckley:** with PA, need to use > 100 units Lantus/day and have already split dose and getting hypoglycemic
  - **Humana:** covered, Tier 3
  - **Anthem:** covered, Tier 2
Where does Toujeo® fit?

- Patients using large amounts of Lantus (e.g. >80 units/dose)
  - More units overall but less fluid with Toujeo
- Patients getting hypoglycemic from split doses of basal insulin
- When it’s the only basal insulin on formulary
Toujeo® Case

1) 75 y/o man with an A1C 9% taking metformin, and with no hypoglycemia

2) 58 y/o man with an A1C 10% taking metformin and insulin detemir 90 units daily, and with no hypoglycemia

3) 62 y/o woman with an A1C 7.5% taking insulin glargine 60 units BID, and with no hypoglycemia

4) 89 y/o woman with an A1C 8% taking metformin, sitagliptan, and NPH insulin 10 units BID, and with hypoglycemia
Tresiba® (insulin degludec)

- FDA approved (September 2015) for DM
  - Approved in 2016 for patients > age 1 year with DM
- MOA: Ultra long-acting insulin, U-100 and U-200
  - Forms long, multi-hexamer chains when injected, resulting in a depot
  - Has a protracted, time action profile predominantly due to delayed absorption of insulin degludec from the subcutaneous tissue to the systemic circulation and to a lesser extent due to binding of insulin-degludec to circulating albumin.
Prolonged depot release: insulin monomers break off from hexamer chains

Release of Insulin Monomers into the Blood Stream
Tresiba® (insulin degludec)

- Unique PK profile
  - Half-life ≈ 25 hours
  - Glucose lowering effect: 42+ hours
  - Steady state: 3-4 days

- No dose “stacking”: trough concentrations increase over the first few days of treatment, before reaching a plateau; thereafter, the degludec concentration is unchanged from day to day

Tresiba® (insulin degludec)

- **Approved dosing in adults with Type 2 DM**
  - Insulin naïve: 10 units once daily
  - Already on insulin: initiate at the same total daily dose as the long or intermediate-acting insulin
  - 200 unit/mL pen allows up to 160 units in one dose

Tresiba® (insulin degludec): *Important Dosing Instructions*

- Dose at any time of the day
- Wait at least 8 hours between doses
- Adjust dose based upon patient’s metabolic needs, BG readings and A1c goal
- Recommended days between dose adjustments: 3-4 days
Warnings, Precautions, & Side Effects

- **Contraindications**: hypersensitivity

- **Warnings/Precautions**:
  - Do not share insulin pens with others
  - Hyperglycemia/hypoglycemia when changing insulin regimens
  - Medication errors
  - Hypokalemia
  - Fluid retention/heart failure when used with TZDs

- **Side effects**: hypoglycemia, hypersensitivity, hypokalemia
Tresiba® (insulin degludec)

- **Cost:**
  - 1 box of 5 pens, 3mL each, 100 units/mL = 1500 units = $470
  - 1 box of 3 pens, 3mL each, 200 units/mL = 1800 units = $560
  - Lantus comparison: 1 box of 5 pens, 3mL each = 1500 units = $400
  - Toujeo comparison: 1 box of 5 pens, 300 units/mL = 2250 units = $600

- **Insurance coverage:**
  - **Tricare and Buckley:** not on formulary, but medical necessity form if cannot take glargine or detemir
  - **Humana:** covered, Tier 3
  - **Anthem:** not covered
Evidence

- In controlled clinical trials, 7% of patients with T1DM and 25% of patients with T2DM were ≥65 years of age.
  - 1% and 3%, respectively, were ≥75 years of age.
- No overall differences in effectiveness and safety were observed in the subgroup analysis based upon age.
- No clinically relevant difference in PK was identified in a study comparing healthy subjects and subjects with renal impairment, including subjects with end stage renal disease.
Evidence: BEGIN Once Long

**Population (n=1030)**
- Type 2 DM pts
- Mean age 59 yrs
- 89% Caucasian
- Mean A1c 8.2%
- Mean BMI 31 kg/m²
- Mean 9 yrs DM

**Open Label Intervention (1 year study)**
- Metformin+ deglucdec
- Metformin+ glargine

<table>
<thead>
<tr>
<th>1°: Δ in A1c</th>
</tr>
</thead>
</table>

**Results**
- ≈ 1% reduction in A1c in both groups
- Overall rates of confirmed hypoglycemia similar
- Less nocturnal hypoglycemia with deglucdec (0.25 vs. 0.39 episodes/PYE; P = 0.038)

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Evidence: Variable Once Daily Dosing Study

<table>
<thead>
<tr>
<th>Population (n=946)</th>
<th>Open Label Intervention (6 mo study)</th>
<th>Results</th>
</tr>
</thead>
</table>

- Type 2 DM pts
- Mean age 57 yrs
- 67% Caucasian
- Mean A1c 8.4%
- Mean BMI 29 kg/m²
- Mean 11 yrs DM
- 58% previously on orals only
- Degludec QD
- Degludec QD flex dosing between 8-40 hrs
- Glargine QD
- ± Orals

≈ 1% reduction in A1c in each group (Deg Flex 1.28, Deg QD 1.07, Glar QD 1.26)

No difference in overall or nocturnal hypoglycemia in Deg Flex vs Glar QD

1°: Δ in A1c, non-inferiority

Safety: hypoglycemia

Where does Tresiba® fit?

- Patients needing basal insulin but lacking ability to be adherent
- Patients with a caregiver who cannot administer insulin at the same time every day
- Patients with nocturnal hypoglycemia from basal insulin, possibly due to “peaks”
Tresiba® Case

1) 75 y/o man with an A1C 9% taking metformin, with no hypoglycemia, and with adherence difficulties

2) 58 y/o man with an A1C 10% taking metformin and insulin detemir 40 units daily, and with no hypoglycemia

3) 62 y/o woman with an A1C 7.5% taking insulin glargine 60 units BID, and with no hypoglycemia

4) 89 y/o woman with an A1C 8.5% taking metformin, sitagliptan, and NPH insulin 10 units BID, and with hypoglycemia
Ryzodeg® (insulin degludec/aspart 70/30)

- FDA approved in 2015
  - 100 units/mL prefilled pens
- Dosing based upon conversion from basal to degludec
  - I.e. do not account for the 30% aspart
- Dose once to twice daily with a meal
Other insulin news…

- FDA approved Basaglar® is moving to some formularies
  - “Follow-On” insulin glargine 100 units/mL made by Eli Lilly
    - Copy of biologic molecule that is already approved (e.g. has the same amino-acid sequence)
      - No clinically meaningful differences in safety/effectiveness
      - Approval process used data from Lantus®
    - Granted FDA approval through an abbreviated pathway under the Federal Food, Drug, and Cosmetic Act: a 505(b)(2) application
  - 1 box of 5 pens, 3mL each, 100 units/mL = 1500 units = $380
  - Lantus comparison: 1 box of 5 pens, 3mL each = 1500 units = $400

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm477734.htm; Goodrx.com
Zinplava™ (bezlotoxumab)

- FDA approved (Oct 2016) to reduce recurrence of Clostridium difficile infection (CDI) in patients > 18 years of age receiving antibacterial treatment of CDI

- MOA: humanized monoclonal antibody that binds to C. difficile toxin B and neutralizes its effects
  - Does not bind to C. difficile toxin A
Zinplava™ (bezlotoxumab)

- **Recommended dose:** 10 mg/kg IV
  - Vials include 1000 mg/40 mL (25 mg/mL)
  - Administer over 60 minutes
  - Administer during antibacterial drug treatment for CDI
  - Repeat administration has not been studied

- **No renal adjustment**
Warnings and Precautions

- **Contraindications:** none

- **Warnings/Precautions:** Heart failure
  - Heart failure was reported more commonly in two Phase 3 trials in Zinplava-treated individuals compared to placebo.
  - Patients with history of CHF should use Zinplava when benefit outweighs risk.
Zinplava™ (bezlotoxumab)

- **Side effects**: nausea (7%), pyrexia (5%), HA (4%)

- **Geriatric use**: 50% of patients >65 years of age in clinical trials; no differences observed

- **Cost**: not available—anticipated to be available 1st quarter of 2017
## Evidence: MODIFY I and II

<table>
<thead>
<tr>
<th>Population (n=1554)</th>
<th>Intervention</th>
<th>Definitions</th>
</tr>
</thead>
</table>
| **Inclusion:** 18 yrs +, confirmed CDI (3+ loose BMs in 24 hours), + stool test for toxigenic *C. difficile* | SoC* (vancomycin, metronidazole, fidaxomicin) x 10 - 14 days | **Clinical cure:** no diarrhea x 2 days after SoC  
**CDI recurrence:** new diarrhea episode associated with + stool test (*C. difficile*)  
**Sustained clinical response:** cure + no recurrence through 12 weeks after infusion |
| Median age: 65 yrs  
Oral metronidazole: 48%  
Oral vancomycin: 48% | SoC x 10 - 14 days + Zinplava x 1  
(median infusion: day 3) |  |

*Standard of Care*
## Results: MODIFY I and II

<table>
<thead>
<tr>
<th>Trial</th>
<th>Clinical response</th>
<th>SoC + Zinplava n (%)</th>
<th>SoC + placebo n (%)</th>
<th>Adj. diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sustained</td>
<td>n=386</td>
<td>n=395</td>
<td>4.8 (-2.1, 11.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>232 (60.1)</td>
<td>218 (55.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>87 (22.5)</td>
<td>68 (17.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrence</td>
<td>67 (17.4)</td>
<td>109 (27.6)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Sustained</td>
<td>n=395</td>
<td>n=378</td>
<td>14.6 (7.7, 21.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>264 (66.8)</td>
<td>197 (52.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>69 (17.5)</td>
<td>84 (22.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrence</td>
<td>62 (15.7)</td>
<td>97 (25.7)</td>
<td></td>
</tr>
</tbody>
</table>
Where does Zinplava™ fit?

- High risk for CDI recurrence
  - Age ≥ 65 years
  - History of CDI in past 6 months
  - Immunocompromised
  - Severe CDI presentation
Zinplava™ Case

1) 75 y/o man taking vancomycin for CDI

2) 58 y/o man taking vancomycin for CDI and EF ~ 25%

3) 62 y/o woman *C. difficile* toxin A +

4) 89 y/o woman *C. difficile* toxin B +
Nuplazid® (pimavanserin)

- FDA approved (April 2016) for treatment of hallucinations & delusions associated with Parkinson’s disease psychosis

- MOA: unknown
  - Possibly a combination of inverse agonist and antagonist activity at serotonin 5-HT\textsubscript{2A} receptors and a lesser extent at serotonin 5-HT\textsubscript{2C} receptors
Nuplazid® (pimavanserin)

- **Recommended dose: 34 mg**
  - Taken orally as two 17 mg tablets once daily, without titration
  - Taken with or without food

- **No renal adjustments**
  - Not studied CrCl < 30 ml/min

- **Hepatic impairment: not recommended**
Warnings and Precautions

- **BBW**: elderly pts with dementia-related psychosis treated with antipsychotics are at increased risk of death

- **Warnings/Precautions**: QTc prolongation

- **Drug-drug interactions**: CYP3A4 substrate
  - CYP3A4 inhibitors: reduce dose by half
Nuplazid® (pimavanserin)

- **Side effects:** nausea, peripheral edema, confusion

- **Geriatric Use:** No differences

- **Cost:** $2340/month
# Evidence

## 6 week randomized, placebo-controlled, parallel-group

<table>
<thead>
<tr>
<th>Population (n=185)</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion:</strong> 40+ years (80% &gt;65 yrs), MMSE ≥ 21, PD + psychotic symptoms Mean age: 72 yrs</td>
<td>Placebo daily x 6 weeks</td>
<td><strong>Primary:</strong> change in baseline to 6 weeks in SAPS-PD score</td>
</tr>
<tr>
<td>Mean SAPS-PD score (0-45) Placebo: 14.7 Nuplazid: 15.9</td>
<td>Nuplazid 34 mg daily x 6 weeks</td>
<td>Placebo: - 2.73 Nuplazid: - 5.79</td>
</tr>
</tbody>
</table>
SAPS-PD (Scale for the Assessment of Positive Symptoms)

<table>
<thead>
<tr>
<th>Auditory hallucinations</th>
<th>Persecutory delusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voices conversing</td>
<td>Delusions of jealousy</td>
</tr>
<tr>
<td>Somatic or tactile</td>
<td>Delusions of reference</td>
</tr>
<tr>
<td>hallucinations</td>
<td></td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td>Global rating of</td>
</tr>
<tr>
<td></td>
<td>severity of delusions</td>
</tr>
<tr>
<td>Global rating of</td>
<td></td>
</tr>
<tr>
<td>severity of hallucinations</td>
<td></td>
</tr>
</tbody>
</table>

*Each item rated 0 (absent) to 5 (severe)
Results

**Figure 2** SAPS-PD Change from Baseline through 6 Weeks Total Study Treatment

- **34 mg NUPLAZID**
- Placebo

**Diff:** -3.1 (-4.9, -1.2)

**p=0.001**
Where does Nuplazid® fit?

- Patient with PD + delusions and/or hallucinations
- Patients with a normal baseline QTc
- Patients who fail antipsychotic therapy
Nuplazid® Case

1) 75 y/o man with MMSE 18

2) 58 y/o man taking sotalol

3) 62 y/o woman with dementia taking olanzapine

4) 89 y/o woman with dementia and CrCl ~45 ml/min
Conclusions

- Nuplazid
- Toujeo
- Zinplava