Out With the Old, in With the New: Update on New Drugs and Indications

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Rivaroxaban *(Xarelto)*

Rivaroxaban

- ***Class:***
  - Factor Xa Inhibitor
- ***MOA:***
  - Selectively & reversibly inhibits factor Xa of coagulation cascade inhibiting platelet activation & fibrin formation
- ***Indications/Dosing:***
  - Thromboembolism prophylaxis post hip/knee replacement
    - Knee – 10 mg daily for 10-14 days
    - Hip – 10 mg daily for 35 days
  - Nonvalvular Atrial Fibrillation (for prevention of stroke/embolism): 20 mg daily
  - Treatment of DVT: 15 mg BID x 3 weeks then 20 mg daily (duration as per anticoagulant guidelines)
  - Treatment of recurrent PE (unlabeled): As per DVT

Evidence Supporting Use

- ***DVT/PE***
  - EINSTEIN-DVT & EINSTEIN-PE

P	Symptomatic confirmed DVT or PE
I	Rivaroxaban 15 mg BID x 3 weeks then 20 mg daily for 3,6, or 12 months
C	Enoxaparin 1 mg/kg BID and vitamin K antagonist 48 hours later dose adjusted to INR 2-3 for 3,6, 12 months
O	Symptomatic recurrent VTE and clinically relevant bleeding

  - Noninferior with similar bleeding risk (major bleeding higher with standard therapy in EINSTEIN-PE)

The EINSTEIN investigators. Oral rivaroxaban for symptomatic venous thromboembolism. NEJM. 2010; 363:2499-2510

•The EINSTEIN-PE investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. NEJM. 2012; 366:1287-1297

Atrial Fibrillation

- ROCKET-AF

P	Patients with nonvalvular atrial fibrillation (CHADS mean was 3-4)
I	Rivaroxaban 20 mg daily (15 mg if CrCl 30-59)
C	Warfarin dose adjusted for INR 2-3
O	Stroke/systemic embolism

- Rivaroxaban noninferior to warfarin with similar bleeding (ICH & fatal less) however INR only in range 55% (mean) of time for warfarin group

ROCKET-AF investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. NEJM. September 2011

Acute Coronary Syndrome

- ATLAS-ACS 2 TIMI

P	Patients with < 7 day history of ACS receiving standard therapy
I	Rivaroxaban 2.5 mg or 5 mg BID for maximum of 31 months (mean 13 months)
C	Placebo
O	Death from CV/MI/stroke

- Death from CV/MI/Stroke ↓ but ↑ risk of bleeding (currently not recommended)

ATLAS ACS 2–TIMI 51 investigators. Rivaroxaban in patients with a recent acute coronary syndrome. NEJM. 2012; 366:9-19

Rivaroxaban Continued

- ***Side Effects/Monitoring***
  - Bleeding
  - Headache

- ***Clinical Pearls/Tips***
  - Oral, no injections necessary, no waiting for therapeutic INRs.. But no simple antidote
  - Caution in elderly/renally impaired (Avoid if CrCL < 30 ml/min)
  - Use caution hepatically impaired (exclusion criteria)
  - Not recommended if prosthetic heart valves
  - 15 & 20mg tablets should be taken with food (↑ F)
  - CYP3A4 (GFJ okay) & PGP interactions
  - Hold 24 hours prior to surgery
  - *Covered* by NBPDP for post surgery prophylaxis & Atrial Fibrillation meeting criteria

Switching Agents

- ***Warfarin → Rivaroxaban:***
  - Stop warfarin, initiate rivaroxaban when INR ≤2.5
- ***Rivaroxaban → Warfarin:***
  - Continue both until INR ≥2.0 (INR testing 24 hours after last rivaroxaban and just prior to next rivaroxaban dose)
- ***Rivaroxaban → Parenteral AC:***
  - Start at next scheduled dose
- ***Parenteral AC → Rivaroxaban:***
  - Initiate rivaroxaban w/in 2 hours of next scheduled dose

Dabigatran *(Pradax)*

Dabigatran

- ***Class:***
  - Direct Thrombin Inhibitor
- ***MOA:***
  - Reversible, direct inhibitor of free and fibrin bound thrombin
- ***Indications/Dosing:***
  - Atrial Fibrillation:
    - 150 mg BID
    - 110 mg twice daily (>75 years with at least one other risk factor for bleeding & all over 80)
  - Postoperative thromboprophylaxis:
    - *Knee Replacement:* 110 mg w/in 1-4 hours of surgery then 220 mg daily for 10 days
    - *Hip Replacement:* 110 mg w/in 1-4 hours of surgery then 220 mg daily for 28-35 days
    - Elderly >75: 75 mg w/in 1-4 hours then 150 mg daily (duration as above)

Evidence Supporting Use

Atrial Fibrillation

RE-LY

P	Patients with nonvalvular atrial fibrillation and 1 risk factor for stroke
I	Dabigatran 110 mg BID or 150 mg BID
C	Warfarin dose adjusted to INR 2-3
O	Stroke/systemic embolism

- Dabigatran 150 mg BID superior to warfarin
  - No difference in overall bleeding
  - Higher risk of GI bleed, lower risk of ICH
- Noninferior at 110 mg BID
  - Lower risk of bleeding overall

RE-LY steering committee and investigators. Dabigatran versus warfarin in patients with nonvalvular atrial fibrillation. NEJM. 2009; 361:1139-1151

Dabigatran Continued

- ***Side Effects/Monitoring:***
  - Bleeding
  - Dyspepsia/abdominal discomfort/epigastric pain
    - Antacids/PPIs not recommended (↓ F?)

Clinical Pearls/Tips

- Oral, no injections necessary, no waiting for therapeutic INRs…But no simple antidote
- Avoid use CrCl <30 ml/min (exclusion criteria RELY)
- Not recommended if prosthetic heart valves
- Caution antacids/PPIs
- Bioavailability increases 75% when pellets taken out of capsule
- Stop minimum 24 hours prior to elective surgery*
- NBPDP coverage for AF meeting criteria

* Based on bleeding risk/CrCl

Switching Agents

- ***Warfarin → Dabigatran***
  - Stop warfarin & initiate when INR <2
- ***Dabigatran → Warfarin:***
  - Initiate 1-3 days before D/C dabigatran (depends on CrCl)
- ***Parenteral AC → Dabigatran:***
  - Initiate within 2 hours of D/C or immediately if UFH
- ***Dabigatran → Parenteral AC:***
  - Initiate 24 hours (hip/knee surgery) or 12 hours (Atrial Fibrillation)

Apixaban (*Eliquis*)

Apixaban

- ***Class:***
  - Factor Xa inhibitor
- ***MOA:***
  - Selective reversible direct factor Xa inhibitor
- ***Indications/dosing:***
  - Postoperative venous thromboprophylaxis:
    - Knee Replacement: 2.5 mg BID for 10-14 days
    - Hip Replacement: 2.5 mg BID for 28-35 days
  - Atrial Fibrillation (unlabelled)
    - 5 mg twice daily
    - Dose reduced if ≥ 2 RF for bleeding - 2.5 mg twice daily

Evidence Supporting Use

Atrial Fibrillation

ARISTOTLE

P	Patients with atrial fibrillation at increased risk of stroke for mean 1.8 years
I	Apixaban 5 mg twice daily (2.5 mg twice daily in patients with 2 or more of the following: ≥80 years of age, ≤60 kg, or serum creatinine ≥133 umol/L)
C	Warfarin dose adjusted to INR 2-3
O	Stroke or systemic embolism

- Apixaban ↓ events compared to warfarin
- Apixaban↓ secondary outcome of mortality
- Apixaban lower risk for major bleeding (including GI bleeding)

ARISTOTLE committees and investigators. Apixaban versus warfarin in patients with atrial fibrillation. NEJM. 2011; 365:981-992

Apixaban Continued

- ***Side Effects/Monitoring***
  - Bleeding
- ***Clinical Pearls/Tips***
  - Avoid use in liver impairment (exclusion criteria)
  - Avoid use if CrCl <15 ml/min (dose ↓ may be considered for 15-30 ml/min although cautioned)
  - Many drug interactions (CYP3A4 and PGP; avoid GFJ)
  - Coming soon???

Thromboembolism prophylaxis (MA, 2012)

P	Patients who underwent total hip or knee replacement, receiving approved daily doses of agents for VTE prophylaxis.
I	Dabigatran 220 mg or 150 mg per day
I2	Rivaroxaban 10 mg per day
I3	Apixaban 5 mg per day
C	Enoxaparin 40 mg daily 12 hours before surgery or 30 mg BID 12-24 hours after surgery
O	Symptomatic VTE and clinically relevant bleeding

- **Primary efficacy outcome**
  - Rivaroxaban ↓ outcomes, dabigatran & apixaban similar to enoxaparin
  - ***Overall new AC showed SS ↓***
- **Primary Safety Outcome**
  - Rivaroxaban increase in clinically relevant bleeding
  - Apixaban decrease in clinically relevant bleeding
  - Dabigatran similar
  - Overall combined, similar for new AC compared to enoxaparin

Gómez-Outes A., Terleira-Fernández AI., Suárez-Gea ML., Vargas-Castrillón E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. BMJ. 2012; 344e3675

Ticagrelor *(Brilinta)*

Ticagrelor

- ***Class:***
  - Antiplatelet Agent, Cyclopentyltriazolopyrimidine
- ***MOA:***
  - Reversible inhibitor of ADP mediated activity at the P2Y12 receptor
- ***Indications/Dosing***
  - ACS in combination with ASA: 180 mg LD then 90 mg BID x 12 months

Evidence Supporting Use

- PLATO

P	Patients hospitalized with ACS (sx in previous 24 hours)
I	Ticagrelor 180 mg LD then 90 mg BID for 12 months (w/ ASA)
C	Clopidogrel 300-600 mg LD then 75 mg daily for 12 months (w/ ASA)
O	Death from vascular causes/MI/stroke

- Primary outcome less frequent with ticagrelor
- Secondary endpoints (including death from any cause & stent thrombosis) ↓; stroke no difference
- ↑ risk non CABG related bleeding, but ~ major

PLATO investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. NEJM. 2009; 361:1045-1057

Ticagrelor Continued

- ***Side effects/Monitoring***
  - Bleeding
  - Dyspnea
  - Increased SCr & uric acid
  - Bradycardia

Ticagrelor Continued

- ***Clinical Pearls/Tips***
  - CYP3A4 interactions (moderate CYP2C9)
  - Hold 5 days prior to surgery
  - Caution in patients with gout history (although no difference in gout incidence in PLATO)
  - Avoid ASA doses >100 mg (↓ efficacy)
  - Can be used if clopidogrel allergy
  - NBPDP approved for patients w/ ACS undergoing PCI or NSTEMI high risk patients managed medically

- ***Switch from Clopidogrel:***
  - Initiate 24 hours after last clopidogrel dose (LD or maintenance)

Prasugrel *(Efient)*

Prasugrel

- ***Class:***
  - Thienopyridine
- ***MOA:***
  - Irreversible inhibition of the platelet P2Y12 adenosine diphosphate (ADP) receptor
- ***Indications/Dosing:***
  - ACS undergoing PCI: 60 mg LD then 10 mg daily x 12 months

Evidence Supporting Use

- TRITON-TIMI 38

P	Patients undergoing PCI for STEMI
I	Prasugrel 60 mg LD then 10 mg daily x 6-15 months
C	Clopidogrel 300 mg LD then 75 mg daily x 6-15 months
O	CV death/non fatal MI/non fatal stroke

- ↓ primary outcome and stent thrombosis (12% vs 10%) NNT=50
- Bleeding ↑ for prasugrel (including **fatal** bleeding)
- Net harm (i.e., increased major bleeding, including intracranial hemorrhage) if history stroke/TIA with *no net benefit*
- Those ≥75 years of age or weighing <60 kg had *no net benefit* for prasugrel over clopidogrel

TRITON-TIMI 38 investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. NEJM. 2007; 357:2001-2015

Prasugrel Continued

- ***Side Effects/Monitoring***
  - Hypertension
  - Headache
  - Hypercholesteremia
  - Nausea
  - Back pain
  - Dyspnea
  - Bleeding

Prasugrel Continued

- ***Clinical Pearls/Tips***
  - Cross reactivity with clopidogrel
  - Avoid if ≥ 75 years old, <60 kg, history of TIA/stroke
  - Hold ***7 days*** prior to surgery
  - Recommended to be given no later then 1 hour after PCI and LD as soon as coronary anatomy known
- ***Clopidogrel → prasugrel***
  - Initiate 10 mg 24 hours after last clopidogrel dose

Liraglutide (*Victoza*)

Liraglutide (*Victoza*)

- **Class**

  - Glucagon-like peptide-1 (GLP-1) receptor agonist

- **MOA:**

  - Liraglutide is a long acting analog of GLP-1(incretin hormone) which causes insulin release in the presence of elevated glucose levels. Liraglutide also decreases inappropriate glucagon secretion and slows gastric emptying, resulting in decreased food intake.

- **Indications/dosing:**

  - T2DM with MF +/- SU

  - 0.6mg **SC** once daily, increase to 1.2mg, then to 1.8mg once daily as tolerated

Evidence Supporting Use

- The 6 LEAD (*Liraglutide Effect and Action in Diabetes*) studies and study 1860 investigated liraglutide in various dual and triple therapy combinations
- Overall, liraglutide demonstrated similar or greater reductions in A1C compared with antihyperglycemic agents from other drug classes, when added to metformin, or to metformin and a sulfonylurea
- ↓A1C by ~0.8-1.4%
- Statistically significant weight loss compared with other drug classes
- Costly- $4.89 to $7.34/day.
- Common drug review: do not list

Liraglutide (*Victoza*)

- **Side effects**

  - GI

  - Headache

  - Thyroid c-cell tumors and pancreatitis

  - Weight loss ~ 2.8kg

  - Rare hypoglycemia, however ↑ risk when combined with SU

- **Monitoring**

  - Improvement in A1C, blood glucose periodically

Liraglutide (*Victoza*)

- **Clinical pearls**

  - SC injection in abdomen, thigh or upper arm, once daily, independent of meals

  - Store in refrigerator. Once opened, is stable at room temperature for 30 days

  - Pre-filled multi-dose pen can deliver 30 doses of 0.6 mg, 15 doses of 1.2 mg or 10 doses of 1.8 mg

  - No dosage adjustment in mild renal insufficiency

  - Concomitant oral medications could theoretically be affected by delayed gastric emptying

Linagliptin (*Trajenta*)

Linagliptin (*Trajenta*)

- **Class:**

  - Dipeptidyl peptidase-4 inhibitors (DPP-4)

- **MOA:**

  - Reversible and selective inhibitor of DPP-4 which is responsible for inactivating GLP-1

- **Indications/dosing:**

  - Monotherapy when CI's to MF or MF not tolerated
  - Combination therapy with MF or SU or MF + SU
  - 5mg tablet daily

Evidence Supporting Use

Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study

P	T2DM patients with inadequate glycemic control on MF + SU
I	Linagliptin 5mg daily added to MF + SU
C	Placebo added to MF + SU
O	Reduction in A1C

- Statistically significantly greater reduction in A1C compared to placebo. ↓ A1C by 0.62%
- Common drug review: list as a third drug added to MF and SU when insulin is not an option

Linagliptin (*Trajenta*)

- **Side effects**
  - Nasopharyngitis
  - Pancreatitis
  - Weight neutral
  - Rare hypoglycemia, however ↑ risk when combined with SU
- **Monitoring**
  - Improvement in A1C, blood glucose periodically
- **Clinical pearls**
  - CYP3A4 and P-gp substrate
  - **No dosage adjustment required in impaired renal function**
  - Daily cost: less than Sitagliptin but higher than other drug classes

Future Place in Therapy?

- Liraglutide and Linagliptin not included in 2008 Canadian Diabetes Association Guidelines
- Watch for 2013 Guidelines!
- Long term safety data to come

Fidaxomicin (*Dificid*)

Fidaxomicin (*Dificid*)

- **Class:**

  -Macrolide antibacterial

- **MOA:**

  - Inhibits RNA synthesis by inhibiting RNA polymerases

- **Indications/dosing:**

  -Treatment of *Clostridium difficile*-associated diarrhea in adults ≥18 years of age

  - 200mg tablet po BID x 10 days

Evidence Supporting Use

Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011

P	Adults with acute sx. of c.diff and positive stool toxin
I	Fidaxomicin 200mg po BID x 10 days
C	Vancomycin 125mg po QID x 10 days
O	Primary: Clinical cure Secondary: Recurrence of c.diff

- Fidaxomicin was non-inferior to vancomycin for clinical cure, and rates of recurrence were significantly lower with fidaxomicin
- Adverse event profiles were similar between groups

Evidence Supporting Use

Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomized controlled trial. Lancet Infect Dis 2012

P	Patients >16 yo with acute, toxin positive c.diff infection
I	Fidaxomicin 200mg po q12h x 10 days
C	Vancomycin 125mg po q6h x 10 days
O	Primary: Clinical cure Secondary: Recurrence of c.diff

- Fidaxomicin was found to be non-inferior to vancomycin for clinical cure
- Adverse effects did not differ
- Common drug review: currently under review

Fidaxomicin (*Dificid*)

- **Side effects**

  - Common GI: abdominal pain, nausea, vomiting
  - Serious GI: bowel obstruction, hemorrhage
  - Anemia and neutropenia

- **Monitoring**

  - Resolution of symptoms

- **Clinical pearls**

  - Use with caution in severe renal and hepatic insufficiency
  - Can be taken with or without food
  - Acts locally and has minimal systemic absorption
  - Expensive: $2800 for 10 day treatment

DIFICID = DEFICIT?

Zolpidem (*Sublinox*)

Zolpidem (*Sublinox*)

- **Class:**

  -Imidazopyridine sedative-hypnotic

- **MOA:**

  - Enhances GABA activity by binding selectively to benzodiazepine-1 receptor

- **Indications/dosing:**

  -Short-term treatment and symptomatic relief of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakenings

  - 10mg ODT hs

Evidence Supporting Use

- Zolpidem (oral tablets) was found to be superior over placebo for sleep latency, efficiency and number of awakenings in chronic and transient insomnia.
- Zolpidem (ODT) was found to be superior to oral tablets in time to persistent sleep (20 mins vs. 30 mins)
- A meta-analysis suggested that Zolpidem may show greater improvements in sleep latency (85.5% vs. 77.5%), may have less side effects (31.3% vs. 45.3%), and less rebound insomnia (4.5%, 15.4%) compared to Zopiclone.
- Zolpidem half-life: 2.6 hrs, Tmax: 82 mins
- Zopiclone half life: 5 hrs, Tmax: 120 mins

Zolpidem (Sublinox)

- **Side effects**

  - Dizziness, diarrhea

  - Complex sleep behaviours

- **Monitoring**

  - Reevaluate use if symptoms persist beyond 7-10 days

  - Assess for worsening depression, suicidality or unusual changes in behavior

Zolpidem (Sublinox)

- **Clinical pearls**

  - CYP 3A4 substrate

  - No dosage adjustment in renal dysfunction

  - Only indicated for those ≤ 65 yrs (tablets cannot be split, so no smaller dose available)

  -Should not be taken with alcohol

  -Should not be taken by those who sleep walk

  -Only take if able to have a full night sleep (7-8hr)

  - Take on an empty stomach

Roflumilast (Daxys)

Roflumilast (*Daxas*)

- **Class:**

  - Phosphodiesterase 4 (PDE4) inhibitor

- **MOA:**

  - Roflumilast selectively blocks PDE4, which is a major cAMP metabolizing enzyme found in structural and inflammatory cells important to the pathogenesis of COPD. Levels of intracellular cAMP increase, thereby alleviating COPD-related malfunctions of leukocytes, airway and pulmonary vascular smooth muscle cells, endothelial and airway epithelial cells, and fibroblasts

- **Indications/dosing**

  - Add-on treatment of severe COPD associated with chronic bronchitis and frequent exacerbations.
  - 500 mcg tablet po daily

Evidence supporting use

Roflumilast in Symptomatic Chronic Obstructive Pulmonary Disease: Two Randomised Clinical Trials," *Lancet*, 2009

P	Patients with COPD older than 40 years with severe airflow limitation, bronchitis symptoms and a history of exacerbations (LABA, SAACs and SABAs were allowed)
I	Roflumilast 500mcg po daily x 52 weeks
C	Placebo x 52 weeks
O	Primary: Change in FEV1 and rate of moderate or severe exacerbations

-Roflumilast group showed a modest increase (48mL) in prebronchodilator FEV1

-Rate of exacerbation in Roflumilast group was lower (1.14/yr) than placebo group (1.37/yr)

-Common drug review: do not list

Roflumilast (*Daxas*)

- **Side effects**

  - GI: nausea, diarrhea, ↓ appetite, wt loss
  - Headache
  - Anxiety and depression have been reported

- **Monitoring**
  - Improved PFTs, ↓ exacerbations, ↓ sx
  - Suicidal thoughts, body weight

Roflumilast (*Daxas*)

- **Clinical pearls**

  - CYP 3A4 substrate: caution with strong inducers and inhibitors

  - CI: moderate or severe hepatic impairment

  - No dosage adjustment is required in elderly patients, or in patients with renal impairment.

  - Major pharmacodynamically active metabolite: roflumilast N-oxide

References

- Xarelto product monograph. eCPS. February 13, 2012
- The EINSTEIN investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *NEJM.* 2010; 363:2499-2510
- The EINSTEIN-PE investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *NEJM.* 2012; 366:1287-1297
- ROCKET-AF investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *NEJM.* 2011; 365:883-891
- ATLAS ACS 2–TIMI 51 investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *NEJM.* 2012; 366:9-19
- Pradax product monograph. eCPS. February 13, 2012.
- RE-LY steering committee and investigators. Dabigatran versus warfarin in patients with nonvalvular atrial fibrillation. *NEJM.* 2009; 361:1139-1151
- Eliquis product monograph. eCPS. December 13, 2011.
- ARISTOTLE committees and investigators. Apixaban versus warfarin in patients with atrial fibrillation. *NEJM.* 2011; 365:981-992
- Gómez-Outes A., Terleira-Fernández AI., Suárez-Gea ML., Vargas-Castrillón E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *BMJ.* 2012; 344e3675
- Brillinta product monograph. eCPS. May 26, 2011.
- PLATO investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *NEJM.* 2009; 361:1045-1057
- Effient product monograph. eCPS. September 20, 2011.
- TRITON-TIMI 38 investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *NEJM.* 2007; 357:2001-2015
- Lexi drugs
- e-CPS
- Dynamed
- Micromedex
- Cadth.ca- Common drug review, 2012
- Rx files- Drug Chart Comparison, 9th edition, Aug 2012
- LEAD-1, LEAD-2, study 1860, study 1796, LEAD-5, LEAD-6
- Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study
- 2008 Canadian Diabetes Association Guidelines- http://diabetes.ca/files/cpg2008/cpg-2008.pdf
- Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012; 12:281–9.
- Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011;364:422–31. Dockhorn RJ, Dockhorn DW. Zolpidem in the treatment of short-term insomnia: a randomized, double-blind, placebo-controlled clinical trial. *Clin Neuropharmacol* 1996;19(4):333-40.v
- Comparative efficacy of newer hypnotic drugs for the short-term management of insomnia: a systematic review and meta-analysis, Yenal Du¨ndar1*, Susanna Dodd2, Judith Strobl1, Angela Boland1, Rumona Dickson1 and Tom Walley1
- Calverley PM, Rabe KF, Goehring UM, et al, “Roflumilast in Symptomatic Chronic Obstructive Pulmonary Disease: Two Randomised Clinical Trials,” *Lancet*, 2009, 374(9691):685-94

Thank you!

Questions?