3:45 – 4:45 pm

**New Drugs for the Primary Care Clinician**

**SPEAKER**
**Gerald W. Smetana, MD**

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**The following relationships exist related to this presentation:**

► Gerald W. Smetana, MD: No financial relationships to disclose.

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# New Drugs for the Primary Care Provider: What You Need to Know

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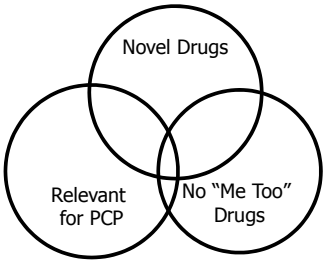
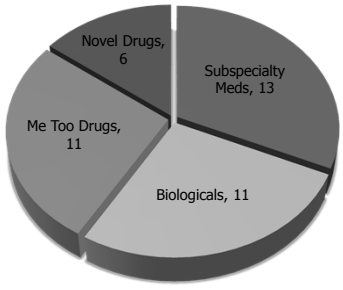
## Important New Drugs for 2015: What We Need to Know




# 2014: More Potentially Novel Drugs than Recent Years

## FDA New Drug Approvals in 2014: More Potentially Novel Drugs for Primary Care



## Four Novel Drugs for Primary Care Practice

- Vorapaxar for secondary prevention of cardiovascular events
- Alirocumab to reduce LDL cholesterol
- Canagliflozin for the treatment of type 2 diabetes
- Suvorexant for the treatment of insomnia

## Historical Perspective

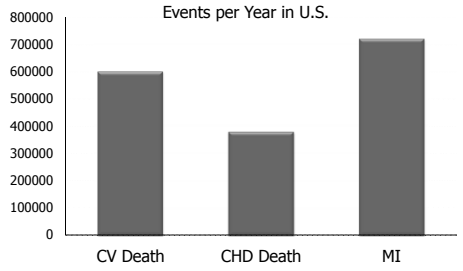
"Man has an inborn craving for medicine… The desire to take medicine is one feature which distinguishes man, the animal, from his fellow creatures… Even in minor ailments, which would yield to dieting or to simple home remedies, the doctor's visit is not thought to be complete without the prescription."

William Osler 1895

## Mr. Timi

- 56 year old man
- NSTEMI 3 mos. Ago
- On ASA, statin, beta blocker
- Should he add vorapaxar to prevent 2nd MI?

## Heart Disease is #1 Cause of Mortality and Morbidity in the U.S.




http://www.cdc.gov/heartdisease/facts.htm

## One in 4 Myocardial Infarctions Are Second Events

- Annual # of MI's in the U.S.:
  - 720,000
  - 515,000 are 1st MI's
  - 205,000 are 2nd MI's
- Secondary preventive strategies
  - ASA
  - Clopidogrel
  - Statins
  - ACE inhibitors
  - Beta blockers

## Meta-Analysis of 195 Trials: Aspirin for Secondary Prevention of CV Events

| Patient History | Anti-platelet, percent | Adjusted controls, percent | Odds reduction, percent |
|---|---|---|---|
| Prior MI | 13.5 | 17.0 | 25±4 |
| Acute MI | 10.4 | 14.2 | 30±4 |
| Prior stroke/TIA | 17.8 | 21.4 | 22±4 |
| Acute stroke | 8.2 | 9.1 | 11±3 |
| Unstable angina | 8.0 | 13.3 | 46±7 |
| Stable angina | 9.9 | 14.1 | 33±9 |
| Peripheral arterial disease | 5.8 | 7.1 | 23±8 |

Outcomes were nonfatal MI, nonfatal stroke, and vascular death

Antiplatelet Trialists' Collaboration, BMJ 1994; 308:81

## Vorapaxar is a Novel PAR-1 Antagonist

- Protease-activated receptor -1 (PAR-1)
- Primary thrombin receptor on platelets
- Vorapaxar blocks PAR-1 and inhibits thrombin mediated platelet aggregation
- Orally administered
- Half life 8 days

## TRACER: Vorapaxar in Acute Coronary Syndromes

- N=12,944
- ACS symptoms for < 24 hours
- At least one of:
  - Troponin or CK elevation, or
  - ST elevation or depression in ≥ 2 leads
- At least one of:
  - ≥ 55 years old
  - Prior MI, PCI, or CABG
  - Diabetes
  - PAD
- Randomly assigned
  - Vorapaxar 40 mg, then 2.5 mg qd
  - Or placebo

NEJM 2012;366:20-33

## Other Findings

- Intracranial hemorrhage: 1.1% vs. 0.2%
- TIMI major bleeding: 4.0% vs. 2.5%
- Conclusion: Vorapaxar did not reduce secondary CV events but did increase bleeding rates

## TRA 2°P-TIMI 50: Vorapaxar for Secondary Prevention

- N=26,449
- Prior history of:
  - MI
  - Ischemic Stroke
  - PAD
- Randomized to:
  - Vorapaxar 2.5 mg qd
  - Or Placebo
- Primary outcome
  - Composite of
  - CV death
  - MI
  - Stroke

NEJM 2012;366:1403

## Indirect Comparisons of Antiplatelet Agents for 2° Prevention

| Relative Risk Reduction * P <0.05 | Aspirin vs. Placebo | Clopidogrel plus ASA vs. ASA | Vorapaxar vs. Placebo |
|---|---|---|---|
| Study | ATC Meta analysis | CHARISMA | TRA 2°P |
| All CV Events | 19%* | 7% | 13%* |
| MI | 34%& | 6% | 17%* |
| Stroke | 22%* | 21%* | 3% |

NEJM 2006;354:16 Lancet 1996;348:1329

## Other Findings

- Most patients in trial also on ASA
- Lower MI rates: 6.1% vs. 5.1%
- No effect on mortality or CV mortality
- Intracranial bleeding high in patient with prior h/o stroke: 2.4% vs. 0.9%
- At 2 years, safety committee terminated trial for patient subset with prior stroke
- AE's other than bleeding uncommon

August 2015 RxPriceQuote.com

## Cost of Antiplatelet Agents

| Drug | 30 Day Supply AWP |
|---|---|
| Aspirin | < $5 |
| Clopidogrel 75 mg qd | $92 |
| Prasugrel 10 mg qd | $354 |
| Ticagrelor 90 mg bid | $252 |
| Vorapaxar 2.08 mg qd | $297 |

## Key Points

- Single daily dose 2.08 mg qd
- No dose adjustment for CKD
- Multiple drug interactions
- Do not use in patients with h/o prior stroke or TIA (black box warning)
- FDA indications: prior MI or PAD
- Modestly reduces CV risk but increases risk of bleeding
- Unknown if offers advantage over clopidogrel as add-on to ASA

## What to Advise Mr. Timi?

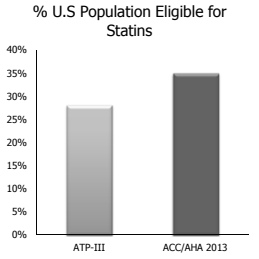
- Continue ASA, statin, beta blocker
- Shared decision making
- Does he fear recurrent MI or bleeding more?
- Vorapaxar discretionary

## Ms. Elle Dièlle

- 60 year old woman with PAD and type 2 diabetes
- LDL 140 mg/dl on atorvastatin 80 mg qd
- No CAD to date
- Should I begin a biologic Rx to lower LDL and reduce risk of MI?

## Prevalence of Hypercholesterolemia in the U.S.

- 32% of U.S adults have LDL levels > 130 mg/dl
- < One half are on treatment
- Fewer than 1/3 achieve target LDL
- ACC/AHA 2013 increases statin eligible patients by 25%




http://www.cdc.gov/cholesterol/facts.htm
Am Health Drug Ben 2014;7:430

## Not All Patients with High LDL are Able to Tolerate Statins

- 10-15% of statin treated patients develop myalgia
- 1-5% incidence of myopathy (weakness or significant CK elevation)
- In the "treat to goal LDL" approach (no longer recommended by ACC/AHA), not all patients achieve LDL target with statins

## PCSK9 Regulates LDL Metabolism

- Mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9) are a genetic cause of familial hypercholesterolemia
- PCSK9 is a negative regulator of LDL receptors (LDLR) and causes degradation of LDLR
- LDLR removes LDL from circulation
- PCSK9 reduces ability of liver to remove circulating LDL cholesterol

## Alirocumab

- Human recombinant Ig1 monoclonal antibody
- Binds and inhibits PCSK9
- Internalizes PCSK9/LDL complex
- Reduces serum PCSK9 levels
- Increases hepatic LDL receptors
- Results in increased LDL degradation
- Lowers serum LDL levels

## ODYSSEY Trial of Alirocumab plus Statin vs. Statin Alone

- Phase 3 study (n=2341) at 320 sites
- CHD risk equivalent or
- Heterozygous hypercholesterolemia
  - Genotyping or
  - Clinical Criteria
- Maximum tolerated statin therapy
- Alirocumab 150 mg SC vs. placebo q 2 weeks for 78 weeks
- Primary endpoint change LDL at 24 weeks

NEJM 2015;372:1489

## Entry Criteria into Study

Simon Broome Clinical Criteria (adults)

- Total chol > 290
- LDL > 190
- Tendon xanthomas in patient or relative

CHD Equivalent

- PAD
- Stroke
- CKD moderate: GFR 30-60 ml/min
- Diabetes + 2 additional risk factors

## Meta-Analysis: All Outcomes

| Outcome | OR for Rx vs. Placebo | 95% CI |
|---|---|---|
| Mortality* | 0.45 | 0.23-0.86 |
| CV Mortality | 0.50 | 0.23-1.10 |
| Myocardial infarction* | 0.49 | 0.36-0.93 |
| Unstable angina* | 0.61 | 0.06-6.14 |
| Serious adverse events | 1.01 | 0.87-1.18 |
| % LDL reduction | 59% | |

## Safety Outcomes in ODYSSEY

| Event | Placebo % | Alirocumab % |
|---|---|---|
| Any adverse event | 82.5 | 81.0 |
| Serious adverse event | 19.5 | 18.7 |
| Study d/c | 5.8 | 7.2 |
| Major CV events | 5.1 | 4.6 |
| Nonfatal MI | 2.3 | 0.9 |
| Allergic reactions | 9.5 | 10.1 |
| Myalgia* | 2.9 | 5.4 |
| Neurocognitive events* | 0.5 | 1.2 |
| Ophthalmologic events* | 1.9 | 2.9 |

* $P < 0.05$. Only myalgia significant in pooled safety data

**Pooled Safety Data from 9 Trials: Significant Differences in Placebo Controlled Pools**

| Adverse Event | Placebo % | Alirocumab % |
|---|---|---|
| D/c due to adverse event | 5.1 | 5.3 |
| Myalgia | < 0.1 | 0.2 |
| Worsened glucose tolerance | 26.6 | 31.2 |
| Injection site reactions | 4.1 | 6.1 |
| Serious allergic reactions | 0.4 | 0.4 |
| Serious neurologic events | < 0.1 | 0.2 |
| Serious neurocognitive effects | 0.2 | 0.1 |
| Abnormal LFTs | 1.8 | 2.5 |

## FDA Prescribing Information

- Indications: heterozygous familial hypercholesterolemia or CVD who require additional LDL reduction
- 75 mg SC q 2 weeks (prefilled pens or syringes)
- Measure LDL 4-8 weeks after starting Rx
- If LDL response inadequate, increase to 150 mg SC q 2 weeks
- Injections safe at home, rotate injection site
- No data on pregnancy or breast feeding

## Key Points

- Alirocumab reduces LDL to a greater extent than all current drugs
- Reduces LDL by additional 50-60% beyond that on maximum dose statins
- Reduces mortality and possibly CV mortality in up to 2 years in post-hoc analyses
- Only minor safety issues to date
- No safety data beyond 2 years
- Studies of clinical outcomes over more prolonged Rx underway

## Recommendations

- Recommend alirocumab for patients with CAD or CAD equivalent if LDL above goal despite maximal tolerated statin therapy
- Consider for primary prevention if baseline LDL > 190 and total cholesterol > 290 and remain above target on maximal statin therapy
- Await longer term outcome and safety studies and post marketing surveillance
- Cost estimates (analysts) $6000 to $12,000 per year
- Manufacturer intends to offer cost assistance to selected patients

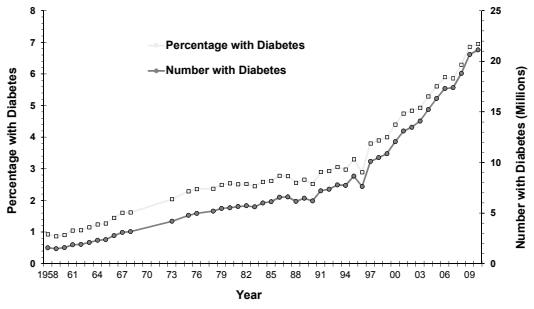
## Advice for Ms. Elle Dièlle?

- Continue high dose atorvastatin
- Aspirin
- Submit prior authorization request or win the lottery
- Begin alirocumab 75 mg SC q 2 weeks

## Mr. Sugarman

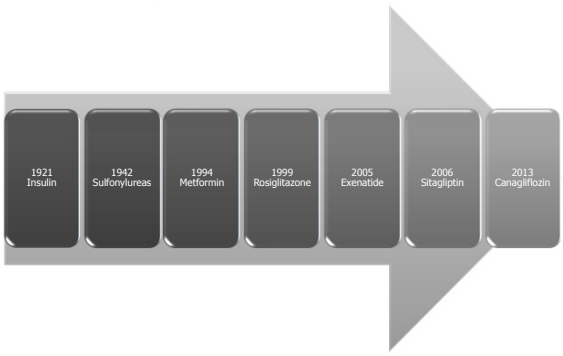
- 15 year of history of type 2 diabetes
- PMHx hypertension, obesity
- A1c 8.5% on metformin alone
- What about this adding this new medication canagliflozin?
- Is this better than adding glyburide?

## Number and Percentage of U.S. Population with Diagnosed Diabetes




CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

## History of Diabetes Medications




## Canagliflozin is a Novel SGL2 Inhibitor

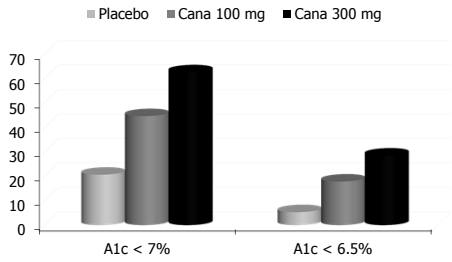
- Sodium-glucose co-transporter 2 = SGL2
- Selective membrane protein expressed in in kidney
- Transports glucose from proximal tubular lumen to epithelial cells
- Canagliflozin blocks SGL2, prevents glucose reabsorption, and causes glucosuria
- Decreases blood glucose

## Effect of Canagliflozin Monotherapy in Type 2 Diabetes

- N=584
- A1c 7-10% at baseline
- Randomly assigned to:
  - Canagliflozin 100 mg qd
  - Canagliflozin 300 mg qd
  - Placebo
- 26 week follow up
- Primary endpoint = change in A1c

Diabetes Obes Metab 2013;15:3725

## Most Patients Achieved A1c Goal at 300 mg qd Dose




## Adverse Effects Among Pooled Studies

| Event | Placebo | Canagliflozin 100 mg qd % | Canagliflozin 300 mg qd % |
|---|---|---|---|
| Any | 75.8 | 76.6 | 77.0 |
| Rx discontinuation | 5.0 | 5.6 | 7.3 |
| Constipation | 0.9 | 2.8 | 2.3 |
| UTI | 4.0 | 5.9 | 4.3 |
| Polyuria | 0.8 | 5.3 | 4.6 |
| Balanitis | 0.6 | 4.2 | 3.7 |
| Vaginal candidiasis | 3.2 | 10.4 | 11.4 |
| Orthostasis | < 0.1 | 0.3 | 0.9 |
| Rash / urticaria | NA | < 2 | < 2 |

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| Rash / urticaria | NA | < 2 | < 2 |

## Mean Change in A1c and Weight for Approved Drugs for Diabetes

| Agent | A1c↓ (%) | Δ Weight (kg) |
|---|---|---|
| Insulin DCCT conventional | 0.2 | + 2.4 |
| Insulin DCCT intensive | 1.5 | + 9.8 |
| Sulfonylureas | 1.1-1.9 | + 2.8 to + 3.6 |
| Metformin | 0.9-1.4 | -0.6 to -0.8 |
| Thiazolidinediones | 0.-1.5 | +2.6 to +3.5 |
| GLP-1 agonists | 0.4 to 0.9 | -0.9 to -2.8 |
| DPP-4 inhibitors | 0.6-0.9 | 0 to -1.0 |
| Canagliflozin | 0.9-1.1 | -2.2 to 3.3 |

## Cost: AWP for Selected Agents

| *Oral* | Monthly Cost (USD) |
|---|---|
| Glipizide 10 mg qd | 4 |
| Metformin 1000 mg qd | 8 |
| Pioglitazone 15 mg qd | 8 |
| Sitagliptin 50 mg qd | 365 |
| Canagliflozin 100 mg qd | 379 |
| *Injectable* | |
| Exenatide 10 mcg bid | 471 |
| Insulin Glargine 2 pens | 170 |

August 2015 RxPriceQuote.com

## What To Add After Metformin?

| | Advantages | Disadvantages |
|---|---|---|
| Sulfonylurea | ▪Most A1c reduction | ▪Hypoglycemia |
| Glitazones | ▪No hypoglycemia | ▪Weight gain<br>▪Fluid retention |
| GLP-1 Agonists | ▪No hypoglycemia<br>▪Weight loss | ▪Injections<br>▪Nausea |
| DPP-4 Inhibitors | ▪No hypoglycemia | ▪Less effective<br>▪Long term side effects? |
| Insulin | ▪Effective | ▪Injections<br>▪Hypoglycemia |
| Canagliflozin | ▪Weight loss<br>▪BP reduction | ▪Yeast infections<br>▪UTIs |

## Other Considerations

- Less A1c reduction (0.6%) for patients with CKD
- Reduces systolic bp by 4-8 mm Hg
- LDL increase 8 mg/dl
- Small increase in serum $PO_4$ and Mg
- Rarely may cause hyperkalemia, hypotension
- Does not cause hypoglycemia in monotherapy
- Small reduction in BMD
- FDA requiring post marketing surveillance due to possible increased risk of breast and bladder cancer

## FDA July 2015: Risk of DKA with SGLT-2 Inhibitors

- Case reports of DKA in patients with type 2 diabetes treated with canagliflozin and other SGLT-2 inhibitors
- Blood sugar may be < 250 mg/dl
- Consider if nausea, abdominal pain, confusion, unexplained fatigue
- May be triggered by acute infection, low PO caloric or fluid intake, reduced insulin dose

## Key Points

- Dose 100 to 300 mg qd
- Adjust for CKD; contraindicated for GFR < 45
- A1c reduction comparable to other agents
- Glucosuria causes weight loss
- More weight loss than any other Rx
- May cause polyuria and orthostasis
- Yeast and urinary tract infections
- ? Potential for long term CA risk
- Very expensive

## Mr. Rip Van Winkle

- Had no trouble sleeping when younger
- Now 55 years old and lays in bed for an hour or two before falling asleep
- Has tried lorazepam, zolpidem, and vodka with no benefit
- Wants to know if this new medication will help him

## Background

- 35-50% of adults have occasional insomnia
- 10-20% have insomnia disorders
- Subtypes
  - Poor sleep maintenance (50-70%)
  - Difficulty initiating sleep (35-60%)
  - Nonrestorative sleep (20-25%)
  - Often more than one feature present
- Primary or secondary (caused by another medical problem or substance use)

JAMA 2013;309:706 Sleep 2011;34:997

## Sleep Hygiene Advice for All Patients

- Sleep only as much as you need to feel rested
- Keep a regular sleep schedule
- Avoid forcing sleep
- Exercise regularly at least 4 to 5 hours before bedtime
- Avoid caffeinated beverages after lunch
- Avoid alcohol near bedtime: no "night cap"
- Avoid smoking, especially in the evening
- Do not go to bed hungry
- Adjust bedroom environment
- Deal with your worries before bedtime

UpToDate 2015

## Attributes of an Ideal Hypnotic

- Rapid absorption and action
- Works through full night
- No morning hangover
- Safe in overdose
- No dependence
- No tolerance
- No memory impairment
- No rebound insomnia or withdrawal

## Suvorexant is a Novel Orexin Receptor Antagonist

- Orexin is a neurotransmitter in the lateral hypothalamus
- Regulates wakefulness
- Active while awake and inactive during sleep
- Blocking orexin receptors promotes sleep
- Suvorexant blocks both orexin-1 and orexin-2 receptor sites (OX1R and OX2R)

## Two RCTs of Suvorexant vs. Placebo for 3 Months

- Two identical trials, total n = 2040
- Suvorexant 40 mg (30 mg for elderly) vs. placebo
- 1 week randomized wash out at end of trial
- Evaluated time to sleep onset and total sleep time

Biol Psychiatry 2014 (epub ahead of press)

## RCT: Safety and Efficacy of Suvorexant over One Year

- Multicenter trial n = 781
- Patients with primary (idiopathic) insomnia
- Randomly assigned to 40 mg suvorexant (30 mg if ≥ 65 y.o) vs. placebo
- Rx for one year, 2 month discontinuation phase
- Primary outcomes:
  - Change in total sleep time
  - Time to sleep onset

Lancet Neurol 2014;13:461

## Suvorexant: Other Findings in One Year RCT

- Benefit began by week 1 and persisted without change for 1 year
- No effect on mood or rates of depression
- MVA or traffic citation during trial: 6% vs. 4%
- No withdrawal symptoms after abrupt d/c
- No rebound insomnia (returned to pre-Rx levels)
- Drug interactions with CYP3A inhibitors

* = statistically significant

## RCT of 1 Year Rx: Adverse Events Were Expected and Infrequent

| Event | Suvorexant % | Placebo % |
|---|---|---|
| Study d/c due to event | 11.7 | 8.5 |
| Somnolence* | 13.2 | 2.7 |
| Fatigue* | 6.5 | 1.9 |
| Dry mouth* | 5.0 | 1.6 |
| Suicidal ideation | 0.8 | 0 |
| Drug abuse potential | 3.5 | 3.9 |
| Hallucinations | 0.6 | 0 |
| Falls | 2.3 | 3.1 |
| Sleep paralysis | 0.4 | 0 |

* = statistically significant

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| Falls | 2.3 | 3.1 |
| Sleep paralysis | 0.4 | 0 |

## Unpublished RCT Data Submitted to FDA on Driving Safety

- 28 healthy subjects undergoing driving safety tests (lane deviation or weaving) day after bedtime suvorexant
- Next day impairment with 40 mg dose (but not 20 mg)
- 24 elderly patients (65-74 y.o.)
- Impairment on higher dose (30 mg) on some but not all measures of driving safety

## FDA: Conditions of Approval

- Recommended lower dose of 10 mg
- At least 7 hours expected before wakeup time
- Maximum dose 20 mg
- No driving or activities requiring full alertness next day after 20 mg dose
- Do not drink alcohol
- Potential for increased depression or SI
- Reports of amnesia for events next a.m.
- Schedule IV controlled substance

## Indirect Comparison of Efficacy of Hypnotics

| Drug | Sleep onset (min) | Faster than placebo by (min) | Increase in total sleep time (min) | Morning drowsiness % |
|---|---|---|---|---|
| Zolpidem | 33-45 | 20 | 34 | 2-3% |
| Zaleplon | 35-55 | 15 | 19 | 5-6% |
| Eszopiclone | 50 | 20 | 46 | 8-10% |
| Benzodiazepines | | 10-20 | 35 | 10-15% |
| TCA's | | 10-12 | 50 | |
| Ramelteon | 75 | 8 | 3 | 5% |
| Suvorexant | 34 | 10 | 41 | 13% |

Consumer Reports Jan. 2012; Package Inserts
CMAJ 2000;162:225 JGIM 2007;22:1335

Rx PriceQuotes.com August 2015

## Monthly Retail Cost of Commonly Use Hypnotics

| Drug | Cost for 30 Tablets |
|---|---|
| *BDZ Receptor Agonists* | |
| Eszopiclone 2 mg | $310 |
| Zaleplon 5 mg | $20 |
| Zolpidem 5 mg | $11 |
| *Benzodiazepines* | |
| Temazepam 15 mg | $14 |
| Lorazepam 1 mg | $9 |
| *Novel drugs* | |
| Ramelteon (Rozerem) 8mg | $309 |
| Suvorexant (Belsomra) 10 mg | $293 |

## Key Points

- Improvement in total sleep time and sleep latency similar to benzos and zolpidem
- Morning somnolence may be more common
- Caution with driving
- Do not use if < 7 hours before wakeup time
- Expensive compared to generic options
- A reasonable option for patients who have not responded to older, less expensive drugs or have had side effects

## Summary

- Vorapaxar reduces risk of second CV event but increases risk of bleeding
- Alirocumab reduces LDL by 50-60% beyond that achieved with statin and reduces mortality
- Canagliflozin reduces A1c and weight; though long term safety is unknown
- Suvorexant promotes sleep comparably to existing drugs but is expensive

## A Final Thought...

"For some patients, though conscious that their condition is perilous, recover their health simply through contentment with the goodness of their physician."

Hippocrates

(460-375 BC)