Drug Update

Margaret A. Fitzgerald,
DNP, FNP-BC, NP-C, FAANP, CSP, FAAN, DCC
President,
Fitzgerald Health Education Associates, Inc.,
North Andover, MA
Family Nurse Practitioner,
Greater Lawrence (MA) Family Health Center
Editorial Board Member
The Nurse Practitioner Journal,
The Prescribers Letter, American Nurse Today
Member, Pharmacy and Therapeutics Committee
Neighborhood Health Plan, Boston, MA

Objectives

- Upon completion of the program, the participant will be able to:
  - Describe characteristics of and recommendations for the use of new medications.
  - Recognize new indications and cautions for established products.

What is hot? What is not?

- New products
- New warning

Drug Development: True or false?

- The average new drug developed by a major pharmaceutical company costs at least $4-11 billion to bring to market.
- Fewer than 1 drug or molecular entities that are considered to be therapeutic in 10 make it to market.

For Answers to Questions

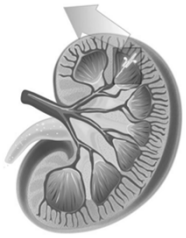
- Answers
  - http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs

New Treatment Options in T2DM

Prescribing information available at
www.invokanahcp.com/prescribing-information.pdf
www.azpicentral.com/farxiga/pi_farxiga.pdf#page=1

Canagliflozin (Invokana™) Dapagliflozin (Farxiga™)

- New class of drugs for treatment of T2DM
  - Sodium-glucose cotransporter 2 (SGLT2) inhibitor
  - Results in lowered renal glucose threshold, increased urinary glucose excretion



Canagliflozin (Invokana™) Dapagliflozin (Farxiga™) (continued)

- Indication
  - Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
  - Can be used as add-on with metformin and/or sulfonylurea

Canagliflozin (Invokana™) Dapagliflozin (Farxiga™) (continued)

- Canagliflozin dose
  - 100 mg daily taken with morning meal
  - Can increase to 300 mg in presence of GFR=>60 mL/min/1.73 m^2
- Dapagliflozin dose
  - Initially 5 mg PO once daily, can increase to 10 mg/day
  - Take with or without food

Canagliflozin (Invokana™)

- Dosing in presence of renal impairment
  - GFR=>60 mL/min/1.73 m^2= Standard dosing
  - GFR=45-59 mL/min/1.73 m^2, do not exceed 100 mg
  - GFR<45 mL/min/1.73 m^2, do not initiate or continue

Dapagliflozin (Farxiga™)

- Use in renal impairment
  - GFR≥60 mL/min/1.73 m^2: No dosage adjustment required (5-10 mg daily dependent on clinical response)
  - GFR<60 mL/min/1.73 m^2: Do not initiate
- Discontinue
  - GFR declines below 60 mL/min/1.73 m^2

Canagliflozin (Invokana™) Dapagliflozin (Farxiga™)

- A1c reductions (vs placebo)
  - 0.7-1% (0.007-0.01 proportion)
    - Higher doses=More reduction
- Weight reductions (vs placebo)
  - 4-7 lbs (1.8-3.2 kg)
    - Higher doses=More reduction

Teachable Moment:
Are most medication adverse effects specific to a given product or a class effect?

Canagliflozin (Invokana™) Dapagliflozin (Farxiga™) (continued)

- Hypoglycemia risk
  - Increased when used with insulin and insulin secretagogues
  - Anticipate need for lower dose of insulin or insulin secretagogue to minimize hypoglycemia risk when use in combination with either agent

Canagliflozin (Invokana™) Dapagliflozin (Farxiga™) (continued)

- Adverse effects in impaired renal function
  - Increases in K+, Mg+
  - Greater risk of volume constriction
    - Class effect=Osmotic diuretic
    - Potentially leading to hypotension
    - Also more an issue with elder, concomitant use of diuretic, ACEI, ARB
  - Less therapeutic effect on glucose/A1c

Canagliflozin (Invokana™) Dapagliflozin (Farxiga™) (continued)

- Additional adverse reactions≥5%
  - Female genital mycotic infection
    - 10-11% female, 4-5% male
  - Urinary tract infection, increased urination
  - Modest LDL increase
- Cost
  - $250-300 per month

Canagliflozin (Invokana™) Dapagliflozin (Farxiga™)

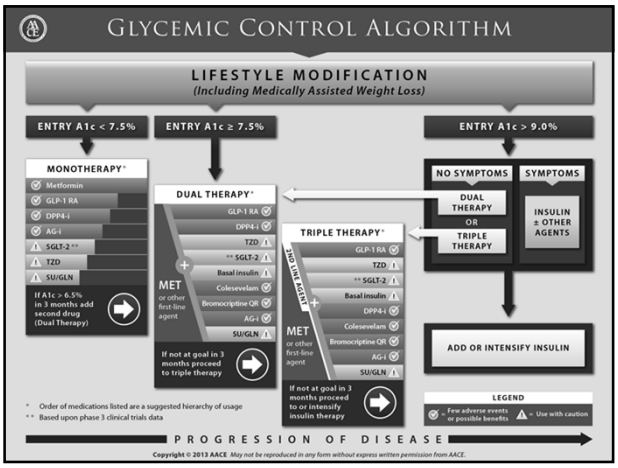
Where do the SGLT2 inhibitors fit in T2DM therapy?

AACE Algorithms: Allowable use for educational purposes

Available at

www.aace.com/publications/algorithm

"Clinicians have little experience with these agents, so the utility of the SGLT2 inhibitors and their place in the diabetes armamentarium remains undefined."



Therapeutic Option for Management of Postmenopausal Health Issues
Prescribing information available at
http://labeling.pfizer.com/ShowLabeling.aspx?id=1174

Conjugated Estrogens/ Bazedoxifene (DUAVEE®)

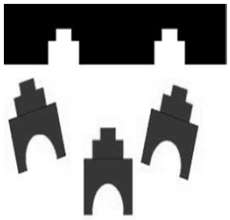
- What is it?
  - Conjugated estrogens with estrogen agonist/antagonist
- Indication
  - Treatment of moderate to severe vasomotor symptoms associated with menopause, prevention of postmenopausal osteoporosis in women with a uterus

Receptor Sites: Therapeutic Considerations

- Common point of drug action
  - Proteins that selectively allow medication, endogenous substance to bind and cause action
  - Medications designed to fit a specific receptor site in order to get select therapeutic effect

Receptor Sites: Therapeutic Considerations (continued)

- Receptor site characteristics
  - Electrical charge
  - Size
  - Shape
  - Binding affinity



Medications as Agonists

- Binds to a receptor, causes an effect similar to endogenous compound
- Name reflects receptor
  - Selective estrogen receptor agonist
    - Bazedoxifene does not activate all estrogen receptors but does work at bone estrogen receptors.
    - Estrogen is a nonselective estrogen receptor site agonist.

Medications as Agonists (continued)

- Endogenous regulatory compound action blocked by drug
- Name reflects receptor
  - Selective estrogen receptor antagonist
    - Bazedoxifene blocks action at select estrogen receptors including those in the uterus, likely breast.

Conjugated Estrogens/ Bazedoxifene (DUAVEE®)

- Dose
  - One tablet daily, taken with or without food
    - Conjugated estrogens 0.45 mg, bazedoxifene 20 mg
- Contraindications
  - Same as with any systemic estrogen, also allergy to any of tablets components

Conjugated Estrogens/ Bazedoxifene (DUAVEE®) (continued)

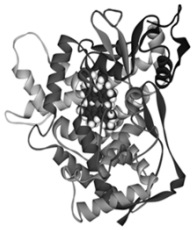
- Special populations
  - Not studied in women age=>75 y
- Only in woman with uterus
  - Estrogen antagonism not required in a woman who has undergone hysterectomy

Special Precautions: Specific to this Product?

- If feasible, discontinue conjugated estrogens/bazedoxifene (DUAVEE®)
  - =>4 to 6 weeks before surgery that is associated with thromboembolism risk, or during periods of prolonged immobilization

Conjugated Estrogens/ Bazedoxifene (DUAVEE®): Potential Drug Interactions

- Estrogen
  - Biotransformed (metabolized) partially by CYP P450 3A4
    - CYP3A4 substrate



Conjugated Estrogens/Bazedoxifene (DUAVEE®): CYP 450 3A4 Substrate Potential Drug Interactions

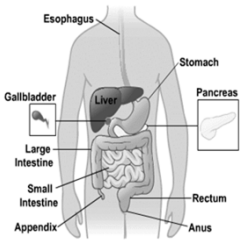
- Concomitant use CYP3A4 inducers
  - Examples- St. John's Wort (*Hypericum perforatum*), phenobarbital, carbamazepine, rifampin
- Result
  - Lower estrogen levels, decreased therapeutic effect

Conjugated Estrogens/Bazedoxifene (DUAVEE®): CYP 450 3A4 Substrate Potential Drug Interactions (continued)

- Concomitant use CYP3A4 inhibitor
  - Examples- Erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice
- Result
  - Higher estrogen levels, risk of endometrial hyperplasia, especially with use >30 days, consider endometrial biopsy

Conjugated Estrogens/ Bazedoxifene (DUAVEE®): Bazedoxifene Component

- Uridine diphosphate glucuronosyltransferase (UGT)
  - Found in intestinal tract and liver
  - Bazedoxifene undergoes metabolism (biotransformation) by UGT enzymes in these locations



Conjugated Estrogens/ Bazedoxifene (DUAVEE®): Bazedoxifene Component (continued)

- UGT inducers
  - Rifampin, phenobarbital, carbamazepine, phenytoin
- Result of concomitant use bazedoxifene with UGT inducer
  - Reduction in bazedoxifene levels, possible risk for endometrial hyperplasia

Novel Treatment Option for
Vulvovaginal Atrophy
Prescribing information available at
www.shionogi.com/pdf/PI/Osphena-PI.pdf

Ospemifene (Osphena®)

- Indication
  - Moderate to severe post menopausal dyspareunia due to vulvovaginal atrophy
  - Per website, "only non-estrogen oral therapy" for this indication

Ospemifene (Osphena®) (continued)

- Dose
  - One, 60 mg tablet daily with food
  - When taken with food, Cmax, AUC 2.4 fold and 1.9 fold higher respectively, when compared to fasting state
- Length of therapy recommended
  - "For the shortest duration consistent with treatment goals and risks for individual woman"

Ospemifene (Osphena®) (continued)

- Mechanism of action
  - Selective estrogen receptor modulator
    - Same class as raloxifene, toremifene, tamoxifen, others
  - Estrogen agonist in vagina, ovary, bone
  - Mixed agonist/antagonism in uterus
  - Antagonism in mammary gland

Ospemifene (Osphena®) (continued)

- End result
  - Estrogen receptor agonist activity in the vagina results in cellular maturation and mucification and maturation of vaginal epithelium
  - Clinical effect=Decreased vaginal pH, and improvement in dyspareunia from vulvovaginal atrophy (VVA)

Ospemifene (Osphena®) (continued)

- Contraindications
  - Undiagnosed abnormal genital bleeding
  - Known or suspected estrogen-dependent neoplasia
  - Active or history of DVT, PE
  - Active or history of arterial thromboembolic disease (stroke, MI)
  - Known or suspected pregnancy

Boxed Warning with Ospemifene (Osphena®) Use

- Increased when compared to placebo
  - Incidence rates of thrombotic and hemorrhagic strokes (0.72 and 1.45 per 1000 women, respectively)
  - Incidence rate of deep vein thrombosis (1.45 per 1000 women)
  - Warning about endometrial hyperplasia due to estrogen agonism

Management of Symptomatic Vulvovaginal Atrophy: 2013 Position Statement of The North American Menopause Society. Menopause. 2013 Sep;20(9):888-902

Available at www.guideline.gov/content.aspx?id=47335

NAMS Recommendation for VVA

- First-line therapies for women with symptomatic vulvovaginal atrophy (VVA) include nonhormonal lubricants with intercourse and, if indicated, regular use of long-acting vaginal moisturizers. [**Level A**]

NAMS Recommendation for VVA (continued)

- For symptomatic women with moderate to severe VVA and for those with milder VVA who do not respond to lubricants and moisturizers, estrogen therapy (ET) either vaginally at low dose or systemically remains the therapeutic standard.

NAMS Recommendation for VVA (continued)

- Low-dose vaginal estrogen is preferred when VVA is the only menopausal symptom. [**Level A**]
- Ospemifene is another option for dyspareunia. [**Level A**]

Another Option for Hot Flash Management: Reformulation of Established Product

Prescribing information at www.brisdelle.com/brisdelle-pdf/Full-Prescribing-Information.pdf

Paroxetine Mesylate (Brisdelle®)

- What is it?
  - First nonhormonal FDA approved option for management of moderate to severe hot flashes
  - Dose: Paroxetine mesylate 7.5 mg tablet once a day taken at bedtime
    - Usually paroxetine hydrochloride dose for treatment of depression=10-40 mg

Paroxetine Mesylate (Brisdelle®): Clinical Efficacy

- RCT in postmenopausal women
  - Mean reduction in frequency and severity of hot flashes significantly greater with paroxetine than placebo at week 4 (-33.0 and -23.5 hot flashes, $p<0.001$) and week 12 (-43.5 and -37.3 hot flashes, $p=0.009$)

Since Brisdelle is a non-hormonal method of managing hot flashes, its use is acceptable in women with a history of breast cancer.

Perhaps….

Tamoxifen

- Selective estrogen receptor agonist/antagonist
  - Antiestrogen therapy in breast cancer
- Prodrug metabolized CYP450 2D6
  - Metabolites as much as 100-fold more potent as antiestrogen form than tamoxifen

Drug Interaction Consideration

- Tamoxifen and CYP 2D6 inhibitors
  - For SSRI class, paroxetine, fluoxetine strongest 2D6 inhibition
  - Yield higher rate of breast cancer recurrence
    - Source: Stearns V, Johnson MD, Rae JM, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J Natl Cancer Inst 2003;95:1758-64.

New Treatment Option in Major Depressive Disorder (MDD)

Prescribing information at http://us.brintellix.com/?gclid=CLG5_a6T4b8CFSpo7AodHFkAkA

Vortioxetine (Brintellix®)

- What is it?
  - Selective serotonin norepinephrine reuptake inhibitor
    - Same class as venlafaxine, desvenlafaxine, duloxetine
      - While in this class, novel mechanism of action

Vortioxetine (Brintellix®) (continued)

- Mechanism of action
  - "Serotonin modulator and stimulator"
- Agonist at the following receptors
  - 5-HT1A receptors
    - Antidepressive effect
  - Partial agonist at 5-HT1B receptors
    - Antidepressive effect

Vortioxetine (Brintellix®) (continued)

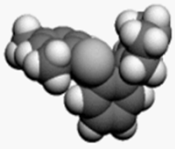
- Antagonist at the following receptors
  - 5-HT3
    - When activated, GI symptoms including nausea
  - 5-HT7, 5-HT1D
    - Blockade noted with use many of the SGAs

Vortioxetine (Brintellix®) (continued)

- Available in a variety of doses
  - 5 mg, 10 mg, 15 mg and 20 mg tablets
  - Standard starting dose=10 mg with increase to 20 mg daily, with/without food
- Common adverse events
  - Incidence ≥5% and =>2 X rate of placebo)=Nausea, constipation, vomiting
  - 5-8% discontinuation rate

Vortioxetine (Brintellix®) (continued)

- Results
  - Enhanced levels of serotonin, noradrenaline, dopamine, acetylcholine and histamine in specific areas of the brain



Vortioxetine Clinical Trials

- Double-blind, randomized, placebo-controlled clinical trial
  - Venlafaxine as an active reference
  - Superior to placebo
  - Fewer adverse effects than venlafaxine

Vortioxetine Potential Drug Interactions

- Reduce vortioxetine dose by 50%
  - With concomitant use of CYP450 2D6 inhibitors
    - Examples: Bupropion, fluoxetine, paroxetine, quinidine
- Consider increasing dose
  - With concomitant use of strong CYP 2D6 inducer
    - Rifampicin, carbamazepine, phenytoin

Vortioxetine (Brintellix®) (continued)

- Boxed warning and medication guide
  - With all antidepressants
  - Increased risk of suicidal thoughts and behavior in children, adolescents and adults ages 18 to 24 years during initial treatment
  - >Age 24 y risk not noted

New Adult Immunization Recommendation in Select Population

Reference at http://www.cdc.gov/diabetes/pubs/pdf/hepb_vaccination.pdf

Hepatitis B Vaccination

- In unvaccinated adults with diabetes mellitus age 19–59 years
  - Provide hepatitis B series
- In unvaccinated adults with diabetes mellitus age=>60 years
  - Consider administering hepatitis B

Why the recommendation?

- Outbreaks of HBV in long-term care facilities
  - At least 29 HBV outbreaks of HBV with the majority involving adults with diabetes receiving assisted blood glucose monitoring by healthcare professional with responsibility for more than one patient

Why the recommendation? (continued)

- Where is HBV found?
  - Stable for long periods lancing devices, blood glucose meters, even when no blood is visible
  - Found in reservoirs of insulin pens

Branded-only to Generic Status

Going Generic

- Esomeprazole magnesium (Nexium®)
  - Also a lower dose branded OTC slated to be available this year
- Donepezil (Aricept®): 23 mg tablet
  - Highest recommended dose
- Duloxetine (Cymbalta®)
- Zolmitriptan (Zomig®)

End of Presentation
Thank you for your time and attention.

Margaret A. Fitzgerald,
DNP, FNP-BC, NP-C, FAANP, CSP, FAAN, DCC

www.fhea.com E-mail: cs@fhea.com

All websites listed active at the time of publication.