


New Practice Defining Drugs in Primary Care

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Objectives

At the end of this presentation, participants will be able to:

- Discuss recent data on medication approvals
- Identify medications approved in 2018 with potential to impact primary care practice
- Explain new uses for old medications in primary care services

New medications approved in 2018 with a significant potential impact on primary care services



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Disclosure

We have no real or potential conflicts or financial interest in any product or services mentioned in this presentation, including grants, equipment, medications, employment, gifts, and honoraria

Background

Many new medications are released each year

Providers may not be familiar with the new agents and may not even be aware of their release until patients ask



Year	Number of FDA Approved Novel Medications
2011	30
2012	39
2013	27
2014	41
2015	45
2016	22
2017	46
2018	55

U.S. Food & Drug Administration. Novel drug approvals for 2018. Updated December 7, 2018. <https://www.fda.gov/Drugs/DevelopmentandResearch/ProcessDrugs/newdrugs/ucm62464.htm>. Accessed December 12, 2018.

Patient Case 1

It is January and your patient, SK is a 58 year old male weighing 72kg comes to clinic complaining of flu-like symptoms for the last 24 hours. He has asthma, hypertension, and osteoporosis and has not received the influenza vaccine for this season. His CrCl is 55 mL/min. Your pharmacist completes a rapid influenza test point of care test in the clinic, which comes back positive for influenza B. Which of the following would be an appropriate treatment option for SK?

- amantadine 200mg daily x 5 days
- baloxavir 40mg once
- oseltamivir 75mg BID x 5 days
- zanamivir 10mg BID x 5 days

Baloxavir marboxil (Xoflouza™)

Indicated for treatment of acute, uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours

- Given as a single oral dose of 40mg or 80mg
 - Patients 40 – 80kg receive the 40mg dose
 - Patients ≥80kg receive the 80mg dose – as weight increases, exposure to baloxavir decreases
- Cost ~ \$90 per tablet
 - Available in 2x 20mg or 2x 40mg packets → cost ~\$180 per treatment
 - 5-day Tamiflu cost ~\$80 per treatment (adult)
- Added to formulary for Froedtert Health benefits plan (quantity limit of 4 tablets/6 months)

Baloxavir marboxil. In: Lexi-Comp, Hudson, OH: Lexi-Comp, Inc. [Updated November 16, 2018. A accessed November 27, 2018]. http://online.lexi.com/docaction/lookup/view/lookuppatch_8517774

Baloxavir marboxil (Xoflouza™)

Indicated for treatment of acute, uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours


- With or without food; avoid dairy, calcium, polyvalent cation laxatives/antacids/supplements (Ca, Fe, Mg, Se, Zn)
 - Baloxavir may chelate and decrease exposure
- Minimal side effects (diarrhea 2%)
- Avoid 48 hrs before and 2 weeks after influenza vaccine

Baloxavir marboxil. In: Lexi-Comp, Hudson, OH: Lexi-Comp, Inc. [Updated November 16, 2018. A accessed November 27, 2018]. http://online.lexi.com/docaction/lookup/view/lookuppatch_8517774

Fremanezumab-vfrm (Ajovy™)
Galcanezumab-gnlm (Emgality™)
Erenumab-aooe (Aimovig™)

Indicated for prevention of adult migraines

Pre-filled, subcutaneous injections of calcitonin gene-related peptide antagonist



AJOVY (fremanezumab-vfrm injection) [package insert] North Wales, PA: Teva Pharmaceuticals USA, Inc. Revised July 2018


Patient Case 1 (continued)

You recommend baloxavir 40mg as a single dose for your patient with influenza. Which of the following would be an important counseling point for SK's new medication?

- May cause bronchospasm
- Take both tablets with food
- Take both tablets 2 hours after calcium supplements
- Get the influenza vaccine before leaving clinic

Migraine Prophylaxis Medications

- Fremanezumab-vfrm (Ajovy™)
- Galcanezumab-gnlm (Emgality™)
- Erenumab-aooe (Aimovig™)



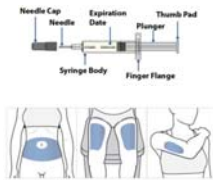
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Fremanezumab-vfrm (Ajovy™)
Galcanezumab-gnlm (Emgality™)
Erenumab-aooe (Aimovig™)

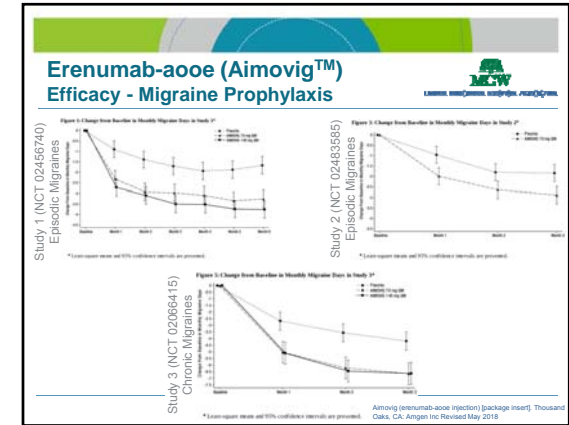
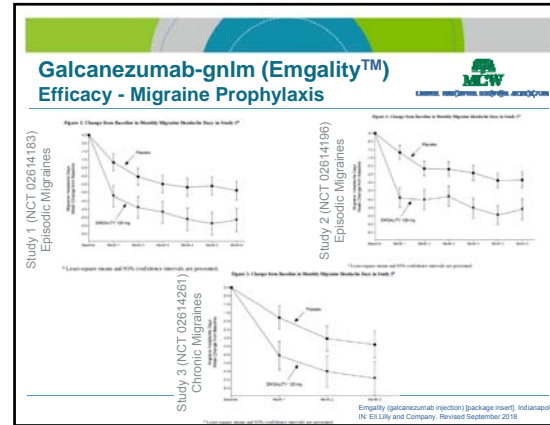
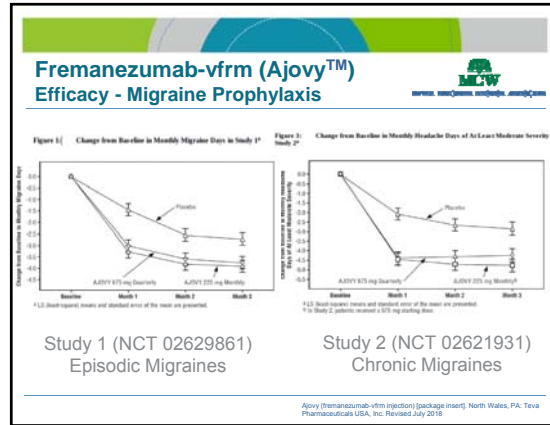
May be given by patient, caregiver, or healthcare professional

Refrigerated syringe must warm to room temperature prior to use (~30 minutes)

- Ajovy™
 - Pre-filled syringe
 - 225mg once monthly
 - 675mg once every 3 months
 - Given as 3 consecutive injections



AJOVY (fremanezumab-vfrm injection) [package insert] North Wales, PA: Teva Pharmaceuticals USA, Inc. Revised July 2018



Fremanezumab-vfrm (Ajovy™) Galcanezumab-gnlm (Emgality™) Erenumab-aooe (Aimovig™)

May be given by patient, caregiver, or healthcare professional
Refrigerated syringe must warm to room temperature prior to use (~30 minutes)

- Emgality™
 - Pre-filled syringe AND pre-filled pen
 - 240mg loading dose x 1
 - Given as 2 consecutive injections
 - 120mg once monthly

Emgality (galcanezumab injection) [package insert]. Indianapolis, IN: Eli Lilly and Company. Revised September 2018

Fremanezumab-vfrm (Ajovy™) Galcanezumab-gnlm (Emgality™) Erenumab-aooe (Aimovig™)

May be given by patient, caregiver, or healthcare professional
Refrigerated syringe must warm to room temperature prior to use (~30 minutes)

- Aimovig™
 - Pre-filled syringe AND autoinjector
 - Syringe cap contains latex ⚠️
 - 70mg - 140mg once monthly
 - Give 140mg as 2 consecutive injections

Aimovig (erenumab-aooe injection) [package insert]. Thousand Oaks, CA: Amgen Inc. Revised May 2018

Fremanezumab-vfrm (Ajovy™) Galcanezumab-gnlm (Emgality™) Erenumab-aooe (Aimovig™)

Time to reach steady state range from after the first dose to 6 months
Half life of the medications ranges 27 days to 31 days

Most commonly reported side effects include injection site reactions and constipation



Not expected to require dose adjustments in renal or hepatic impairment

Not metabolized by cytochrome P450 enzymes

- Patients could use abortive headache medications in all studies

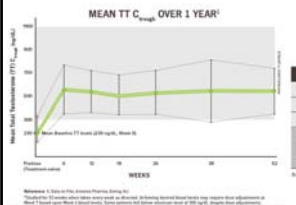
Updates and new applications of old medications

- Testosterone
- Metformin
- Mirabegron
- Epinephrine
- HPV vaccine (Gardasil 9™)
- Rivaroxaban

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Testosterone enanthate (Xyosted™)



Easy up-down titration

TT C _{trough} (n)	Done should
<350 ng/dL	Increase by 25 mg for 50 mg/weekly!
350-450 ng/dL	Be maintained
>450 ng/dL	Decrease by 25 mg for 50 mg/weekly!

Xyosted (testosterone enanthate injection) [package insert]. Easing, NJ: Antares Pharma. Revised Sept 2018.

Patient Case 2


A 67 YOM presenting to PCP for annual physical, reporting poorly controlled blood fasting blood sugars in the 180-210s and wonders how his insulin should be adjusted.

- PMH: T2DM, HTN, COPD, CKDIII
- Diabetes Medications:
 - Insulin NPH 30 Units BID
 - Insulin Regular 20 Units TID before meals
- Pertinent Labs:
 - Scr: 1.6 HgA1c: 9.1%
 - eGFR = 47 ml/min


How would you manage this veteran's diabetes?

Testosterone enanthate (Xyosted™)

FDA approval: October 2018
 Dosing: 50, 75, or 100 mg subcutaneous weekly
 Time to Peak: 12 hours
 Steady State: 6 weeks



When to check testosterone levels: Trough



Benefits: Convenient home administration
 Concerns: Clinically significant increase in blood pressure

Xyosted (testosterone enanthate injection) [package insert]. Easing, NJ: Antares Pharma. Revised Sept 2018.

Formulation	Dosing, Initial (Range)	Pharmacokinetic Profile	Advantages	Disadvantages	Cost in US (dollar/month)
Topical/Transdermal					
Gels 1%, 1.62%	40-50 mg daily (20-25, 100 mg)	Minimal fluctuations in concentration Duration: 24 hours Absorption: 100% Time to Peak: 8 hours	Flexible dosing; Easy application; Good tolerability; Less erythema than testosterone enanthate	Potential transfer to women/children; Variability in absorption; Skin irritation	\$100-\$200*
Thigh-put pumps: 2%	40 mg daily (10-20 mg)				\$290*
Aeris solution: 2%	60 mg daily (30-150 mg)				\$118*
Patch	4 mg daily (2-6 mg)				\$330 - \$660*
Rectal					
Rectal system	30 mg every 12 hours	Avoids first pass metabolism Time to Peak: 10-12 hours	Convenient and discreet route for administration	Gum irritation	\$720*
Intranasal					
Nasal gel	11 mg every 8 hours	Avoids first pass metabolism Time to Peak: 40 minutes	Quick onset of action	Multiple daily dosing; Nasal adverse effects	\$260*
Intramuscular Injections					
Testosterone cypionate	100 mg (50-100 mg every 1-2 weeks)	T peaks after injection; Mid-cycle T at goal; Prior to next 1 hypogonadal Duration: 3-2 weeks	Relatively inexpensive; Flexible dosing	Frequent IM injections; Peak and trough; Fluctuation in symptoms	\$11-\$30*
Testosterone enanthate	750 mg every 10 weeks	Duration: 10 weeks Time to Peak: 7 days			\$31*
Testosterone undecanoate	750 mg every 10 weeks thereafter				\$420*
Subcutaneous					
Testosterone implantable pellets	10 pellets 6-12 pellets every 3-6 months	Serum T peaks at 1 month then sustained for 3-6 months	Intramuscular administration	Surgical incision & manipulation; Pellet may extrude; local testosterone injection risk	\$120*
Testosterone enanthate subcutaneous	75 mg weekly (50-100 mg weekly)	Duration: 1 week Time to Peak: 12 hours	Convenient home administration	Increase in blood pressure (<4 mmHg)	Unknown

*Drug pricing from GoodRx.com cash price accessed 08/07/2018. * Pricing from Up-to-Date accessed 08/07/2018. † = subcutaneous; IM = intramuscular

Patient Case 2 (Continued)

Based on the prior case, which of the following statements is most appropriate.

- Patient is insulin dependent, therefore metformin is not efficacious
- Patient has CKD with serum creatinine above 1.5, therefore metformin is contraindicated
- Patient is a viable candidate for metformin, however it should be limited to 1000 mg daily
- Patient is a viable candidate for maximum dose metformin (i.e. 2000 mg daily)

Updated Metformin Renal Impairment Dosing Recommendations

EGFR (mL/minute/m2)	Initial Dose (mg/day)	Maximum Dose (mg/day)	Frequency of Renal Monitoring
> 60	500	2,500	Annually
45 to 60	500	2,000	3-6 months
30 to 45	250	1,000	3 months
< 30	Use is contraindicated		

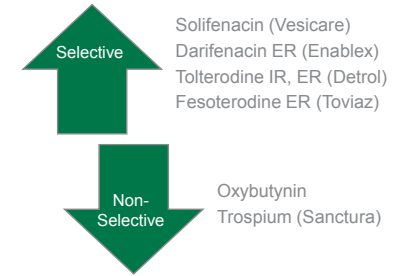
Accessed 1/6/2019: <https://www.fda.gov/Drugs/DrugSafety/ucm433244.htm>

Epinephrine Device Comparison

Epinephrine Products	Photo	MPK	AMP	Product Size	Notes
Auvi-Q® Auto-Injector		Kalco	\$2,940	0.15 mg/0.15 mL, 0.3 mg/0.3 mL	Recall in 2015, returned to market 2017
EpiPen® Auto-Injector		Mylan	\$600	0.15 mg/0.15 mL, 0.3 mg/0.3 mL	Original product released 30 years ago
Generic Epinephrine Auto-Injector (EpiPen® Generic)		Mylan	\$365	0.15 mg/0.15 mL, 0.3 mg/0.3 mL	
Adrenaclick® Auto-Injector		Amindra Pharmaceuticals LLC	\$500	0.15 mg/0.15 mL, 0.3 mg/0.3 mL	
Generic Epinephrine Auto-Injector (Adrenaclick® Generic)		Lineage Therapeutics	\$110	0.15 mg/0.15 mL, 0.3 mg/0.3 mL	Heavily promoted by CVS + coupons available
Symjepi® Prefilled Injection		Novartis	TBA	0.3 mg/0.3 mL	Availability in US is TBA
Generic Epinephrine Injection Vial + Syringe		Various	\$15-20	1 mg/1 mL vial	Patient safety concerns

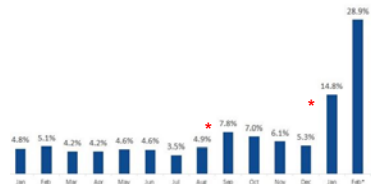
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Antimuscarinic Bladder Selectivity



Epinephrine Updates

Share of epinephrine auto-injector prescriptions that are not EpiPen, Jan 2016-Feb 2017*



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Mirabegron (Myrbetriq™)

FDA new indication approved: 4/27/2018
 "Use in combination with solifenacin succinate for treatment of overactive bladder"

Category	Mirabegron (%)	Solifenacin (%)	Combination (%)
Response Rates	40-46	43-45	50-53
Adverse Effects			
Urinary Retention	0	0.7	0.9-1.2
Dry Mouth	3.3-4.0	5.9	7.2-8.7
Constipation	1.4-2.6	1.4	3.7-4.5
Dyspepsia	0.2	0.2	1.2-1.9

Herschorn, et al. *BJU Int* 2017;120:562-575.

Human Papillomavirus 9-valent Vaccine, Recombinant (Gardasil 9™)

Expanded ages approved for Gardasil 9 to include men and women 27 through 45 years of age

The 3-dose series (0, 2, 6 months) is used to prevent up to 90% of specific diseases and cancers that can be caused by 9 common human papilloma virus types

- This approval is based on a long term follow up study on the efficacy of Gardasil 9, including 3,200 female patients
 - Women: approved for prevention of cervical, vulvar, vaginal and anal cancers
 - Men: approved for prevention of anal cancer

* U.S. Food & Drug Administration. FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old. <https://www.fda.gov/news-events/press-announcements/ucm622716.htm>
 Updated October 9, 2018. Accessed November 27, 2018.
 • Gardasil 9 Vaccine (Human Papillomavirus 9-valent Vaccine, Recombinant) (package insert). Whitehouse Station, NJ: Merck & Co., Inc. Revised October 2018.

Rivaroxaban (Xarelto™)

New approval for reducing the risks for major cardiovascular events in patients with chronic coronary or peripheral artery diseases (CAD/PAD)

Previously approved for treatment and prophylaxis of venous thromboembolism and stroke

- Factor Xa inhibitor
- The 2.5mg dose when combined with aspirin
- Approval based on findings from the COMPASS trial
 - Stopped early due to efficacy

Rivaroxaban. In: Lexi-Comp, Hudson, OH: Lexi-Comp, Inc. Updated November 26, 2018. Accessed November 27, 2018. <https://www.lexi.com/lookup/monograph/monograph.aspx?monograph=1322296>

U.S. FDA Approves XARELTO (Rivaroxaban) to Reduce the Risk of Major Cardiovascular Events in Patients with Chronic Coronary Artery Disease (CAD) or Peripheral Artery Disease (PAD) (news release). Teaneck, NJ: Janssen Pharmaceuticals; Updated October 11, 2018. Accessed November 27, 2018. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/018123Orig1s010.pdf

Take home points

- New option to treat influenza infections
- Three new injectables approved for migraine prevention in adults
- New formulation of testosterone with new risks
- Updated dosing criteria for metformin
- New indications for mirabegron and rivaroxaban
- New age range for Gardasil 9 vaccine

Cumulative Risk of Cardiovascular Death, Stroke, or Myocardial Infarction

No. at Risk	0	1	2	3	4	5
Rivaroxaban plus aspirin	9126	7908	6867	5887	4957	4057
Aspirin alone	9126	7924	6882	5892	4957	4057
Rivaroxaban alone	9126	7924	6882	5892	4957	4057
Rivaroxaban plus aspirin (expanded y-axis)	9126	7924	6882	5892	4957	4057

Figure 1. Cumulative Incidence of the Primary Efficacy Outcome among Participants Receiving Rivaroxaban plus Aspirin, Rivaroxaban Alone, or Aspirin Alone.

Participants in the rivaroxaban plus aspirin group received 2.5 mg of rivaroxaban twice daily and 300 mg of aspirin once daily. Participants in the rivaroxaban alone group received 5 mg of rivaroxaban twice daily and an aspirin-matched placebo once daily. Participants in the aspirin alone group received 100 mg of aspirin once daily and a rivaroxaban-matched placebo twice daily. The inset shows the same data on an expanded y axis.

Eastburn JM, Connolly SJ, Braun J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377(14):1319-30. doi: 10.1056/NEJMoa1709118

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