South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

September 18, 2020

DSS

Strong Families - South Dakota's Foundation and Our Future

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DEPARTMENT OF SOCIAL SERVICES
OFFICE OF THE SECRETARY
700 GOVERNORS DRIVE
PIERRE, SD 57501-2291
PHONE: 605-773-3165
FAX: 605-773-4855
WEB: dss.sd.gov

Strong Families - South Dakota's Foundation and Our Future

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

September 18, 2020
1:00 – 3:00 PM

Dial-in number: 866-410-8397
Conference Code: 8176972761

Call to order

Approval of previous meeting minutes

DSS Updates

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **Anti-migraine utilization**
- **Orilissa utilization**
- **Epidiolex utilization**
- **Atypical antipsychotic utilization in children**
- **Reyvow & Ubrelvy fax form**
- **Opioid update**

New business
- **Humira CF utilization**
- **Advair utilization**
- **Nurtec ODT**
- **Palforzia**
- **Nayzilam**
- **Valtoco**

Public comment accepted after individual topic discussion
Next meeting date December 2020 & adjournment

South Dakota Department of Social Services, Division of Medicaid Services
Pharmacy & Therapeutics (P&T) Committee Meeting Minutes

Friday, June 5, 2020
1:00 – 3:00 pm CT

Members and DSS Staff

Michelle Baack, MD	X	Matthew Stanley	X
Dana Darger, RPh, Chair	X	Deidre Van Gilder, PharmD	X
Mikal Holland, MD	X	Mike Jockheck, DSS Staff	X
Bill Ladwig, RPh	X	Sarah Akers, DSS Staff	X
Kelley Oehlke, PharmD	X	Bill Snyder, DSS Staff	X
Lenny Petrik, PharmD	-		

Administrative Business

Darger called the meeting to order at 1:05 PM. The minutes of the December meeting were presented. Baack made a motion to approve. Ladwig seconded the motion. The motion was unanimously approved via roll call vote.

Synder updated the committee on the committee's hepatitis C recommendations. In addition, Synder provided an update on the appointments for the two committee vacancies.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from January 1, 2020 to March 31, 2020. A total of 1,770 PAs were reviewed of which 193 requests (11%) were received via telephone and 1,063 requests (60%) were received via fax, and 514 (29%) were reviewed via electronically. Darger requested more information regarding the duloxetine PAs.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from January 1, 2020 to March 31, 2020. The top five therapeutic classes based on paid amount were atypical antipsychotics, disease-modifying anti-rheumatic agents, amphetamines, anticonvulsants, and respiratory/CNS stimulants. The top 15 therapeutic classes make up 24.83% of total claims. The committee also reviewed the top 50 drugs based on amount paid and number of claims. The top 50 drugs by amount paid make up 12.65% of total claims. New utilization for Strensiq was noted on the top 50 drugs list based on amount paid. Ladwig inquired about the number of patients utilizing Epidiolex. Committee discussed hemophilia utilization and appropriate level of management. Darger contemplated whether it was appropriate to try methylphenidate or amphetamine first before allowing Vyvanse. Darger requested information on how other states are managing Vyvanse. Darger also discussed adding PA to Humira CF and Advair. Jockheck recommended adding these items to the next agenda.

New Committee Member

Darger, Jockheck, and committee members welcomed new committee member, Dr. Matthew Stanley. Stanley expressed his wish to add value to the committee.

Old Business

CGRP & Orilissa utilization

The committee reviewed the calcitonin gene related peptide (CGRP) utilization comparing 3Q19 through 1Q20. Utilization increased each quarter, including new utilization of Ubrelvy. Committee requested to review CGRP and triptan utilization concurrently. The committee also reviewed utilization of Orilissa comparing 4Q19 through 1Q20. Committee requested to continue reviewing utilization of both classes at the next meeting.

PA criteria review

- After reviewing Lyrica and pregabalin utilization, the committee discussed removing PA. Van Gilder made a motion to remove PA on Lyrica and pregabalin. Baack seconded the motion. The motion was unanimously approved via roll call vote.
- The committee discussed Lidoderm PA. Ladwig made a motion to remove PA on Lidoderm. Baack seconded the motion. The motion was unanimously approved via roll call vote.
- The committee reviewed utilization for all topical ketoconazoles. Ladwig commented on the appropriate utilization achieved from management.
- The committee reviewed the triptan utilization. After discussion, Van Gilder made a motion to remove PA on rizatriptan ODT. Ladwig seconded the motion. The motion was unanimously approved via roll call vote. Ladwig made a motion to add PA to Zomig spray requiring failure of oral triptan, then failure of sumatriptan spray. Baack seconded the motion. The motion was unanimously approved via roll call vote.
- The committee reviewed utilization for GLP-1 receptor agonists. Ladwig was satisfied with the utilization.

Opioid update

The committee reviewed 1Q120 opioid outcomes compared to previous quarters from the opioid initiatives. Effective 1Q20, opioid utilization includes Indian Health System (IHS) where previously it had been excluded. Therefore, utilization appears to have increased.

New Business

Compound summary

The committee reviewed the utilization for all compounds for year 2019. Committee was satisfied with the review.

Review of maintenance mediation 90-day dispense fee savings

Committee reviewed the maintenance medication 90-day dispensing fee estimated savings. Jockheck explained the estimated savings based on federal share and state funds. Ladwig expressed pharmacies using synchronized programs, the use of monthly adherence calls, and adherence concerns in the Medicaid population. Baack commented that some targeted medications may have improved compliance in rural areas especially in the time of COVID. Oehlke provided the VA experience with 90-day fills which improved compliance. After discussion, Baack made a motion to allow 3, 30-day consecutive fills for maintenance medications and then authorizing 90-day fills. Holland seconded the motion. The motion carried via roll call vote with one dissent from Ladwig.

Atypical antipsychotic utilization in children

Committee reviewed atypical antipsychotic utilization in children. Stanley commented the potential call to action for children on multiple products. Stanley and Baack conversed on titration; with Stanley

providing his experience on titration, delay in follow up appointments and slow titrations generally taking 90 days or more. An in-depth analysis was requested for the 235 members taking two or more products concurrently for more than 90 days (i.e., review PAs, prescriber specialty, dosage titration, age).

Review of Baqsimi & Gvoke
Baqsimi and Gvoke clinical information were presented for review. Stevan Tomich from Xeris provided public comment on Gvoke. Committee to monitor utilization.

Review of Ubrelvy and Reyvow
Ubrelvy and Reyvow clinical information were presented for review. Josh Bishop with Allergan provided public comment on Ubrelvy. Committee recommended adding Reyvow to the triptan PA. Committee recommended developing a PA for Ubrelvy. Baack made the motion for one step of all triptans before allowing Ubrelvy and patients with cardiovascular disease would be exempt from the step therapy. Oehlke seconded the motion. The motion was unanimously approved via a roll call vote.

Adjournment
The next meeting is scheduled for September 18, 2020. Baack made a motion to adjourn the meeting and Holland seconded the motion. The motion passed unanimously and the meeting adjourned at 3:00 PM.

PA Report
4/1/2020 – 6/30/2020

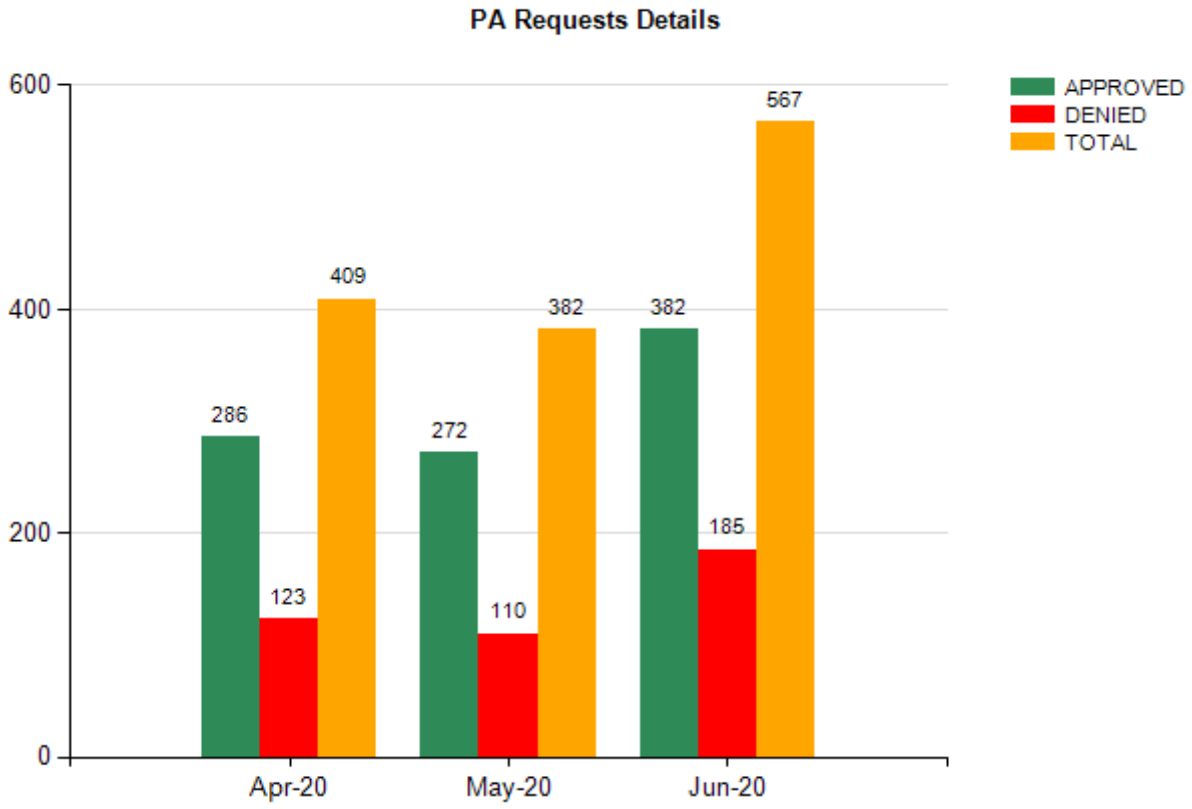
Compliance Summary

Priority	Total PAs	PAs Compliant (Standard - 72 Hrs Urgent - 24 Hrs)	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
STANDARD	1,329	1,329	0	100%	0%
URGENT	29	29	0	100%	0%
GRAND TOTAL	**1,358**	**1,358**	**0**		

	# of	Phone Requests		Fax Requests		Real-Time PA	
Drug Class	Requests	#	%	#	%	#	%
TOTAL	**1,358**	**147**	**11%**	**807**	**59%**	**404**	**30%**

PA Initial Requests Summary

Month	Approved	Denied	Total
Apr-20	286	123	409
May-20	272	110	382
Jun-20	382	185	567
2Q20	**940**	**418**	**1,358**
Percent of Total	**69.22%**	**30.78%**	



Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
59 - ANTIPSYCHOTICS/ANTIMANIC	189	27	216	87.50%	15.91%	, INVEGA SUSTENNA
49 - ULCER	154	14	168	91.67%	12.37%	, ESOMEPRAZOLE MAGNESIUM
90 - DERMATOLOGICALS	60	101	161	37.27%	11.86%	LIDOCAINE, MALATHION
58 - ANTIDEPRESSANTS	123	28	151	81.46%	11.12%	, DULOXETINE (PAs – quantity limit)
65 - ANALGESICS - OPIOID	84	60	144	58.33%	10.60%	HYDROCODONE/APAP, TRAMADOL
Others -	330	188	518	63.71%	38.14%	
	940	418	1358	69.22%	15.91%	
2Q20	189	27	216	87.50%	12.37%	

1Q-2Q PA Reviews	DULOXETINE HCL ENTERIC COATED CAP 20 MG	#68/ 34 days	4 per day – approved	
	DULOXETINE HCL ENTERIC COATED CAP 30 MG	#68/ 34 days	3 per day – approved	
	DULOXETINE HCL ENTERIC COATED CAP 60 MG	#34/ 34 days	2 per day – approved	4 per day – denied

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS	189	27	216	87.50%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	154	14	168	91.67%
58 - ANTIDEPRESSANTS	123	28	151	81.46%
65 - ANALGESICS - OPIOID	84	60	144	58.33%
72 - ANTICONVULSANTS	60	56	116	51.72%
90 - DERMATOLOGICALS	60	101	161	37.27%
27 - ANTIDIABETICS	55	3	58	94.83%
52 - GASTROINTESTINAL AGENTS - MISC.	41	9	50	82.00%
41 - ANTIHISTAMINES	22	5	27	81.48%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	21	11	32	65.63%
67 - MIGRAINE PRODUCTS	21	41	62	33.87%
75 - MUSCULOSKELETAL THERAPY AGENTS	16	4	20	80.00%
16 - ANTI-INFECTIVE AGENTS - MISC.	15	4	19	78.95%
54 - URINARY ANTISPASMODICS	15	7	22	68.18%
66 - ANALGESICS - ANTI-INFLAMMATORY	14	5	19	73.68%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	9	1	10	90.00%
50 - ANTIEMETICS	8	2	10	80.00%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	7	5	12	58.33%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.	4	1	5	80.00%
33 - BETA BLOCKERS	4	1	5	80.00%
39 - ANTIHYPERLIPIDEMICS	4	1	5	80.00%
36 - ANTIHYPERTENSIVES	3	4	7	42.86%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS	3	2	5	60.00%
83 - ANTICOAGULANTS	3	3	6	50.00%
05 - FLUOROQUINOLONES	1	0	1	100.00%
34 - CALCIUM CHANNEL BLOCKERS	1	0	1	100.00%
45 - RESPIRATORY AGENTS - MISC.	1	1	2	50.00%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	1	6	7	14.29%
82 - HEMATOPOIETIC AGENTS	1	0	1	100.00%
02 - CEPHALOSPORINS	0	2	2	0.00%
12 - ANTIVIRALS	0	11	11	0.00%
56 - GENITOURINARY AGENTS - MISCELLANEOUS	0	1	1	0.00%
85 - HEMATOLOGICAL AGENTS - MISC.	0	1	1	0.00%
93 - ANTIDOTES AND SPECIFIC ANTAGONISTS	0	1	1	0.00%
2Q20	**940**	**418**	**1,358**	
Percent of Total	**69.22%**	**30.78%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Apr-20	18	78.26%	5	21.74%	23
May-20	12	70.59%	5	29.41%	17
Jun-20	25	83.33%	5	16.67%	30
2Q20	55	78.57%	15	21.43%	70

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
PREGABALIN	9	1	10	90.00%
EMGALITY	4	2	6	66.67%
DUPIXENT	4	0	4	100.00%
AIMOVIG	2	0	2	100.00%
AJOVY	2	0	2	100.00%
AMITIZA	2	0	2	100.00%
OXYCONTIN	2	0	2	100.00%
TRAMADOL HCL	2	0	2	100.00%
ZOLPIDEM TARTRATE ER	2	0	2	100.00%
ARIPIPRAZOLE	1	1	2	50.00%
DESVENLAFAXINE ER	1	1	2	50.00%
ALTRENO	1	0	1	100.00%
AMPHETAMINE/DEXTROAMPHETAMINE	1	0	1	100.00%
ARMODAFINIL	1	0	1	100.00%
DULOXETINE HYDROCHLORIDE	1	0	1	100.00%
EPIDUO FORTE	1	0	1	100.00%
ESCITALOPRAM OXALATE	1	0	1	100.00%
ESOMEPRAZOLE MAGNESIUM	1	0	1	100.00%
ESZOPICLONE	1	0	1	100.00%
HEMLIBRA	1	0	1	100.00%
HYDROCODONE/ACETAMINOPHEN	1	0	1	100.00%
INGREZZA	1	0	1	100.00%
INVEGA SUSTENNA	1	0	1	100.00%
KINERET	1	0	1	100.00%
METRONIDAZOLE	1	0	1	100.00%
MORPHINE SULFATE ER	1	0	1	100.00%
NATROBA	1	0	1	100.00%
OXYCODONE/ACETAMINOPHEN	1	0	1	100.00%
PULMOZYME	1	0	1	100.00%
REPATHA SURECLICK	1	0	1	100.00%
REXULTI	1	0	1	100.00%
RISPERIDONE ODT	1	0	1	100.00%
SANCUSO	1	0	1	100.00%
VERZENIO	1	0	1	100.00%
XIFAXAN	1	0	1	100.00%
MAVYRET	0	5	5	0.00%
EPCLUSA	0	2	2	0.00%
HARVONI	0	1	1	0.00%
HUMIRA PEN	0	1	1	0.00%
LIDOCAINE	0	1	1	0.00%
2Q20	**48**	**21**	**69**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 4/1/2020 – 6/30/2020					
	AHFS Description	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	11,875	$158,913.23	$13.38	6.64%
2	MISCELLANEOUS ANTICONVULS	10,900	$1,014,244.20	$93.05	6.09%
3	ATYPICAL ANTIPSYCHOTICS	8,433	$2,394,860.35	$283.99	4.71%
4	SECOND GENERATION ANTIHIS	7,366	$84,818.04	$11.51	4.12%
5	PROTON-PUMP INHIBITORS	5,999	$205,433.56	$34.24	3.35%
6	RESPIRATORY AND CNS STIMULANTS	5,751	$651,984.81	$113.37	3.21%
7	SELECTIVE BETA-2-ADRENERGIC AGONISTS	5,711	$433,136.13	$75.84	3.19%
8	AMPHETAMINES	5,702	$1,025,940.38	$179.93	3.19%
9	OPIATE AGONISTS	5,211	$193,353.30	$37.10	2.91%
10	ADRENALS	3,913	$547,176.40	$139.84	2.19%
11	MISC. ANXIOLYTICS, SEDATIVE	3,539	$123,120.18	$34.79	1.98%
12	THYROID AGENTS	3,510	$69,273.78	$19.74	1.96%
13	SEROTONIN MODULATORS	3,419	$122,172.85	$35.73	1.91%
14	HMG-COA REDUCTASE INHIBIT	3,409	$44,928.59	$13.18	1.91%
15	LEUKOTRIENE MODIFIERS	3,236	$46,329.38	$14.32	1.81%
Total		**87,974**	**$ 7,115,685.18**	**$80.88**	**49.16%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 4/1/2020 – 6/30/2020					
	AHFS Description	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	ATYPICAL ANTIPSYCHOTICS	8,433	$2,394,860.35	$283.99	3.96%
2	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	212	$1,043,680.41	$4,923.02	0.11%
3	AMPHETAMINES	5,702	$1,025,940.38	$179.93	3.00%
4	MISCELLANEOUS ANTICONVULS	10,900	$1,014,244.20	$93.05	5.20%
5	CYSTIC FIBROSIS (CFTR) CORRECTORS	43	$838,211.90	$19,493.30	3.33%
6	SKIN AND MUCOUS MEMBRANE	355	$752,157.84	$2,118.75	0.20%
7	HEMOSTATICS	39	$722,145.57	$18,516.55	0.14%
8	ANTINEOPLASTIC AGENTS	280	$718,983.10	$2,567.80	0.02%
9	RESPIRATORY AND CNS STIMULANTS	5,751	$651,984.81	$113.37	0.02%
10	LONG-ACTING INSULINS	1,398	$595,117.58	$425.69	2.99%
11	RAPID-ACTING INSULINS	1,265	$579,111.34	$457.80	0.64%
12	ADRENALS	3,913	$547,176.40	$139.84	0.73%
13	SELECTIVE BETA-2-ADRENERGIC AGONISTS	5,711	$433,136.13	$75.84	4.23%
14	INCRETIN MIMETICS	494	$380,196.07	$769.63	0.22%
15	VASODILATING AGENTS (RESPIRATORY TRACT)	25	$286,438.51	$11,457.54	0.01%
Total		**44,521**	**$ 11,983,384.59**	**$269.16**	**24.88%**

Total Rx Claims from 4/1/2020 – 6/30/2020	**178,945**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 4/1/2020 – 6/30/2020						
	AHFS Description	**Drug Label Name**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE	4,170	$422,808.69	$101.39	2.33%
2	SECOND GENERATION ANTIHIS	CETIRIZINE	4,010	$41,912.48	$10.45	2.24%
3	PROTON-PUMP INHIBITORS	OMEPRAZOLE	3,571	$41,683.18	$11.67	2.00%
4	MISCELLANEOUS ANTICONVULS	GABAPENTIN	3,252	$57,411.92	$17.65	1.82%
5	LEUKOTRIENE MODIFIERS	MONTELUKAST	3,220	$44,570.43	$13.84	1.80%
6	SEROTONIN MODULATORS	TRAZODONE	3,112	$31,888.88	$10.25	1.74%
7	AMPHETAMINES	VYVANSE	3,055	$887,441.40	$290.49	1.71%
8	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE HFA	2,870	$124,158.65	$43.26	1.60%
9	THYROID AGENTS	LEVOTHYROXINE	2,861	$50,087.01	$17.51	1.60%
10	SELECTIVE-SEROTONIN REUPTAKE INHIB	FLUOXETINE	2,583	$37,184.73	$14.40	1.44%
11	AMPHETAMINES	AMPHETAMINE/DEXTROA	2,506	$119,948.55	$47.86	1.40%
12	SELECTIVE-SEROTONIN REUPTAKE INHIB	ESCITALOPRAM	2,336	$31,194.56	$13.35	1.31%
13	ANGIOTENSIN-CONVERTING EN	LISINOPRIL	2,232	$20,676.82	$9.26	1.25%
14	ATYPICAL ANTIPSYCHOTICS	ARIPIPRAZOLE	2,028	$41,204.62	$20.32	1.13%
15	SELECTIVE-SEROTONIN REUPTAKE INHIB	SERTRALINE HCL	1,943	$22,660.97	$11.66	1.09%
16	SECOND GENERATION ANTIHIS	LORATADINE	1,943	$21,705.51	$11.17	1.09%
17	HMG-COA REDUCTASE INHIBIT	ATORVASTATIN	1,933	$23,353.23	$12.08	1.08%
18	ANTIDEPRESSANTS, MISCELLANEOUS	BUPROPION	1,854	$40,037.23	$21.60	1.04%
19	AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN	1,756	$21,445.65	$12.21	0.98%
20	SELECTIVE-SEROTONIN REUPTAKE INHIB	SERTRALINE	1,750	$21,032.79	$12.02	0.98%
21	OPIATE AGONISTS	HYDROCODONE/APAP	1,744	$27,665.04	$15.86	0.97%
22	SELECTIVE-SEROTONIN REUPTAKE INHIB	FLUOXETINE HCL	1,735	$19,747.25	$11.38	0.97%
23	CENTRAL ALPHA-AGONISTS	CLONIDINE HCL	1,619	$17,177.43	$10.61	0.90%
24	BIGUANIDES	METFORMIN	1,581	$15,590.96	$9.86	0.88%
25	ATYPICAL ANTIPSYCHOTICS	RISPERIDONE	1,555	$19,813.36	$12.74	0.87%
26	MISCELLANEOUS ANTICONVULS	LAMOTRIGINE	1,492	$22,004.67	$14.75	0.83%
27	COMPOUNDS	-	1,480	$45,860.72	$30.99	0.83%
28	ATYPICAL ANTIPSYCHOTICS	QUETIAPINE	1,460	$19,142.26	$13.11	0.82%
29	BENZODIAZEPINES (ANTICONV	CLONAZEPAM	1,429	$15,503.98	$10.85	0.80%
30	CORTICOSTEROIDS	FLUTICASONE PROPIONATE	1,416	$21,877.46	$15.45	0.79%
31	SEL.SEROTONIN, NOREPI REUPTAKE INH	DULOXETINE	1,376	$21,228.48	$15.43	0.77%
32	MISCELLANEOUS ANTICONVULS	LEVETIRACETAM	1,300	$27,927.34	$21.48	0.73%
33	MISC. CENTRAL NERVOUS SYS	GUANFACINE ER	1,214	$25,012.19	$20.60	0.68%
34	MISCELLANEOUS ANTICONVULS	TOPIRAMATE	1,190	$17,669.74	$14.85	0.67%
35	DIHYDROPYRIDINES	AMLODIPINE	1,188	$11,501.30	$9.68	0.66%
36	1ST GENERATION CEPHALOSPORIN	CEPHALEXIN	1,135	$18,091.89	$15.94	0.63%
37	OPIATE AGONISTS	TRAMADOL HCL	1,135	$12,247.27	$10.79	0.63%
38	MISC. CENTRAL NERVOUS SYS	GUANFACINE	1,133	$22,529.84	$19.89	0.63%
39	CENTRALLY ACTING SKELETAL MUSCLE RELAX	CYCLOBENZAPRINE	1,128	$10,339.53	$9.17	0.63%
40	ANTIDEPRESSANTS, MISCELLANEOUS	MIRTAZAPINE	1,115	$16,011.58	$14.36	0.62%
41	CORTICOSTEROIDS (SKIN, MUCOUS ME)	TRIAMCINOLONE	1,111	$16,921.11	$15.23	0.62%
42	VITAMIN D	VITAMIN D	1,075	$10,935.13	$10.17	0.60%
43	BENZODIAZEPINES (ANXIOLYT	LORAZEPAM	1,056	$11,848.81	$11.22	0.59%
44	LOOP DIURETICS	FUROSEMIDE	1,041	$9,834.79	$9.45	0.58%
45	VITAMIN B COMPLEX	FOLIC ACID	974	$8,906.32	$9.14	0.54%
46	OTHER NONSTEROIDAL ANTI-INFLAM.	IBUPROFEN	973	$11,989.58	$12.32	0.54%
47	PROTON-PUMP INHIBITORS	PANTOPRAZOLE	969	$11,595.78	$11.97	0.54%
48	SELECTIVE-SEROTONIN REUPTAKE INHIB	CITALOPRAM	968	$8,264.81	$8.54	0.54%
49	GABA-DERIVATIVE SKELETAL MUSCLE RELAX	BACLOFEN	960	$19,564.62	$20.38	0.54%
50	ANGIOTENSIN II RECEPTOR ANTAGONIST	LOSARTAN	920	$11,916.34	$12.95	0.51%
	TOTAL TOP 50 DRUGS		**90,457**	**$2,631,126.88**	**$29.09**	**50.55%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 4/1/2020 – 6/30/2020						
	AHFS Description	**Drug Label Name**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	AMPHETAMINES	VYVANSE	3,055	$887,441.40	$290.49	1.71%
2	ATYPICAL ANTIPSYCHOTICS	INVEGA SUSTENNA	259	$580,537.30	$2,241.46	0.14%
3	CYSTIC FIBROSIS (CFTR) CORRECTORS	TRIKAFTA	23	$480,319.78	$20,883.47	0.01%
4	ATYPICAL ANTIPSYCHOTICS	LATUDA	381	$449,404.86	$1,179.54	0.21%
5	RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE	4,170	$422,808.69	$101.39	2.33%
6	DISEASE-MODIFYING ANTIRHEUMATIC	HUMIRA PEN	54	$368,655.93	$6,826.96	0.03%
7	CYSTIC FIBROSIS (CFTR) CORRECTORS	ORKAMBI	17	$355,805.41	$20,929.73	0.01%
8	ATYPICAL ANTIPSYCHOTICS	ARISTADA	124	$310,688.05	$2,505.55	0.07%
9	ATYPICAL ANTIPSYCHOTICS	VRAYLAR	274	$289,330.18	$1,055.95	0.15%
10	SKIN AND MUCOUS MEMBRANE	STELARA	14	$269,212.00	$19,229.43	0.01%
11	MOVEMENT DISORDER	INGREZZA	47	$264,317.08	$5,623.77	0.03%
12	MUCOLYTIC AGENTS	PULMOZYME	65	$240,575.46	$3,701.16	0.04%
13	LONG-ACTING INSULINS	LANTUS SOLOSTAR	563	$204,308.36	$362.89	0.31%
14	RAPID-ACTING INSULINS	NOVOLOG FLEXPEN	368	$201,967.19	$548.82	0.21%
15	SOMATOTROPIN AGONISTS	NORDITROPIN FLEXPRO	56	$197,858.30	$3,533.18	0.03%
16	MISCELLANEOUS ANTICONVULS	VIMPAT	226	$190,637.01	$843.53	0.13%
17	HEMOSTATICS	NOVOSEVEN RT	4	$186,442.00	$46,610.50	0.00%
18	ADRENALS	FLOVENT HFA	806	$185,458.18	$230.10	0.45%
19	ATYPICAL ANTIPSYCHOTICS	INVEGA TRINZA	24	$182,532.75	$7,605.53	0.01%
20	SKIN AND MUCOUS MEMBRANE	COSENTYX SENSOREADY PEN	26	$172,204.97	$6,623.27	0.01%
21	HEMOSTATICS	RECOMBINATE	3	$164,289.60	$54,763.20	0.00%
22	ATYPICAL ANTIPSYCHOTICS	REXULTI	165	$160,416.67	$972.22	0.09%
23	ATYPICAL ANTIPSYCHOTICS	ABILIFY MAINTENA	73	$152,366.18	$2,087.21	0.04%
24	MISCELLANEOUS ANTICONVULS	BANZEL	66	$149,330.86	$2,262.59	0.04%
25	CYSTIC FIBROSIS (CFTR) POTENTIATORS	KALYDECO	6	$143,436.48	$23,906.08	0.00%
26	INCRETIN MIMETICS	TRULICITY	183	$141,927.72	$775.56	0.10%
27	DISEASE-MODIFYING ANTIRHEUMATIC	ENBREL SURECLICK	26	$140,875.07	$5,418.27	0.01%
28	VASODILATING AGENTS (RESPIRATORY)	UPTRAVI	6	$137,679.41	$22,946.57	0.00%
29	ANTINEOPLASTIC AGENTS	IBRANCE	11	$137,048.67	$12,458.97	0.01%
30	MISCELLANEOUS ANTICONVULS	EPIDIOLEX	63	$135,977.93	$2,158.38	0.04%
31	LONG-ACTING INSULINS	LEVEMIR FLEXTOUCH	272	$124,770.40	$458.71	0.15%
32	SELECTIVE BETA-2-ADRENERGIC AGONIST	ALBUTEROL SULFATE HFA	2,870	$124,158.65	$43.26	1.60%
33	HEMOSTATICS	ADVATE	8	$122,947.00	$15,368.38	0.00%
34	AMPHETAMINES	AMPHETAMINE/DEXTROAM	2,506	$119,948.55	$47.86	1.40%
35	ANTINEOPLASTIC AGENTS	AFINITOR DISPERZ	4	$119,572.72	$29,893.18	0.00%
36	SODIUM-GLUC COTRANSPORT 2 (SGLT2)	JARDIANCE	235	$119,246.46	$507.43	0.13%
37	DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBIT	JANUVIA	264	$119,109.77	$451.17	0.15%
38	RIFAMYCIN ANTIBIOTICS	XIFAXAN	56	$114,976.83	$2,053.16	0.03%
39	LONG-ACTING INSULINS	TRESIBA FLEXTOUCH	247	$113,279.77	$458.62	0.14%
40	SERUMS	HIZENTRA	20	$112,648.50	$5,632.43	0.01%
41	SELECTIVE BETA-2-ADRENERGIC AGONIST	ADVAIR HFA	314	$112,357.95	$357.83	0.18%
42	DISEASE-MODIFYING ANTIRHEUMATIC	XELJANZ XR	24	$109,827.06	$4,576.13	0.01%
43	HIV INTEGRASE INHIBITORS	GENVOYA	35	$109,631.95	$3,132.34	0.02%
44	INCRETIN MIMETICS	OZEMPIC	139	$108,411.17	$779.94	0.08%
45	MISCELLANEOUS GI DRUGS	CHOLBAM	5	$107,852.50	$21,570.50	0.00%
46	IMMUNOMODULATORY AGENTS	TECFIDERA	13	$107,682.87	$8,283.30	0.01%
47	RESPIRATORY AND CNS STIMULANTS	DEXMETHYLPHENIDATE ER	905	$97,071.23	$107.26	0.51%
48	ANTINEOPLASTIC AGENTS	KISQALI	7	$92,763.96	$13,251.99	0.00%
49	SKIN AND MUCOUS MEMBRANE	DUPIXENT	30	$90,290.31	$3,009.68	0.02%
50	DIRECT FACTOR XA INHIBITORS	ELIQUIS	206	$90,188.26	$437.81	0.12%
	TOTAL TOP 50 DRUGS		**19,318**	**$10,120,589.40**	**$523.89**	**10.80%**

Utilization

Time frame: 2Q 2020

Red font denotes drug is on Prior Authorization

CGRP Inhibitors

prevention	1Q 2020				2Q 2020			
Drug Name	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**
AIMOVIG	42	$24,456.28	$582.29	18	54	$31,270.39	$579.08	19
AJOVY	15	$7,656.56	$510.44	8	15	$8,245.05	$549.67	7
EMGALITY	38	$24,206.25	$637.01	17	72	$48,942.13	$679.75	29

PA criteria: Diagnosis of episodic or chronic migraines, 18 years or older, greater than X number of migraines per month, neurologist or pain specialist, trial of beta blocker & anti epileptics & antidepressants, not in combination with another CGRP inhibitor

treatment	1Q 2020				2Q 2020			
Drug Name	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**
UBRELVY	20	$17,225.74	$861.29	17	44	$38,460.72	$874.11	23
NURTEC ODT					7	$5,937.42	$848.20	6
REYVOW					1	$647.20	$647.20	1

PA criteria for Reyvow & Ubrelvy (cardiovascular disease): Trial of one triptan

Triptans

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/ Days Supply	Utilizing Members	Age Range
eletriptan tab	12	$811.14	$67.60	10/28 days	8	29 - 61
frovatriptan tab	5	$764.35	$15.27	9/30 days	4	34 - 35
naratriptan tab	9	$278.43	$30.94	9/27 days	6	14 - 63
rizatriptan tab	99	$1,608.19	$16.24	10/24 days	61	11 - 52
rizatriptan ODT	10	$194.31	$19.41	10/25 days	9	8 - 44
MAXALT MLT						
sumatriptan tab	434	$14,730.80	$33.94	9.5/24 days	257	11 - 64
sumatriptan inj	7	$1,294.73	$184.96	2/9 days	6	34 - 64
sumatriptan 5mg nasal spray	5	$1,044.42	$208.88	5/13 days	5	11 - 51
sumatriptan 20mg nasal spray	7	$1,445.08	$206.44	5/23 days	3	17 - 51
Tosymra sol 10mg nasal spray	1	$595.50	$595.50	6/30 days	1	11
IMITREX tab	0					
zomatriptan tab	13	$378.41	$29.11	10/29 days	8	10 - 59
ZOMIG spray	0					
ZOMIG ZMT	0					
TREXIMET	0					

PA criteria for triptan tablet: Trial of generic triptan

PA criteria for triptan ODT or nasal spray: Patient is less than 13 years old OR diagnosis of dysphagia

Orilissa

Drug Name	Quarter	Total Rx	Paid Amount	Paid/Rx	Utilizer
ORILISSA	4Q 2019	1	$828.06	$828.06	1
	1Q 2020	6	$3,357.62	$559.60	3
	2Q 2020	12	$10,450.48	$870.87	5
ORIAHNN	2Q 2020	0			

*Some states are watching utilization; other states added to PA
*1Q2020 – 2 Rxs at $13.78

Epidiolex

Drug Name	Quarter	Total Rx	Paid Amount	Paid/Rx	Utilizer
EPIDIOLEX	1Q 2019	18	$36,336.38	$2,018.69	7
	2Q 2019	49	$95,618.93	$1,951.41	18
	3Q 2019	55	$119,863.99	$2,179.35	18
	4Q 2019	46	$107,421.88	$2,335.26	16
	1Q 2020	59	$138,184.77	$2,342.11	20
	2Q 2020	63	$135,977.93	$2,158.38	21

Atypical Antipsychotic Utilization in Children (17 years old and younger)

	Year 2019		
Identifier	Unique Utilizers	% Per Utilizer	% Per Member <17
One Product Concurrent > 90 Days	793	59.8%	1.62%
One or More Products Concurrent < 90 Days	297	22.4%	0.61%
Two or More Products Concurrent > 90 Days	**235**	17.7%	0.48%
Grand Total	1,325	100.0%	
Members Age 17 or less - 4/2020	49,057		

Utilization Time Frame: 8/1/2019 to 7/31/2020 – Review of 235 Members

Member Demographics

Gender	Total Members
Female	83
Male	145
Total	**228**

*7 members – eligibility ended or no utilization after 7/31/2019

Age	Female	Male	Total Members	Misc Notes
4 years		1	**1**	Initial target age – 3 years old
5 years		2	**2**	
6 years	1	1	**2**	
7 years	2	10	**12**	
8 years	3	5	**8**	
9 years	1	13	**14**	
10 years	2	8	**10**	
11 years	1	8	**9**	
12 years	3	11	**14**	
13 years	11	8	**19**	
14 years	11	18	**29**	
15 years	17	16	**33**	
16 years	10	14	**24**	
17 years	12	17	**29**	
18 years	8	12	**20**	
19 years	1	1	**2**	
Total	**83**	**145**	**228**	

*195 members had birthdays during 8/1/2019 to 7/31/2020

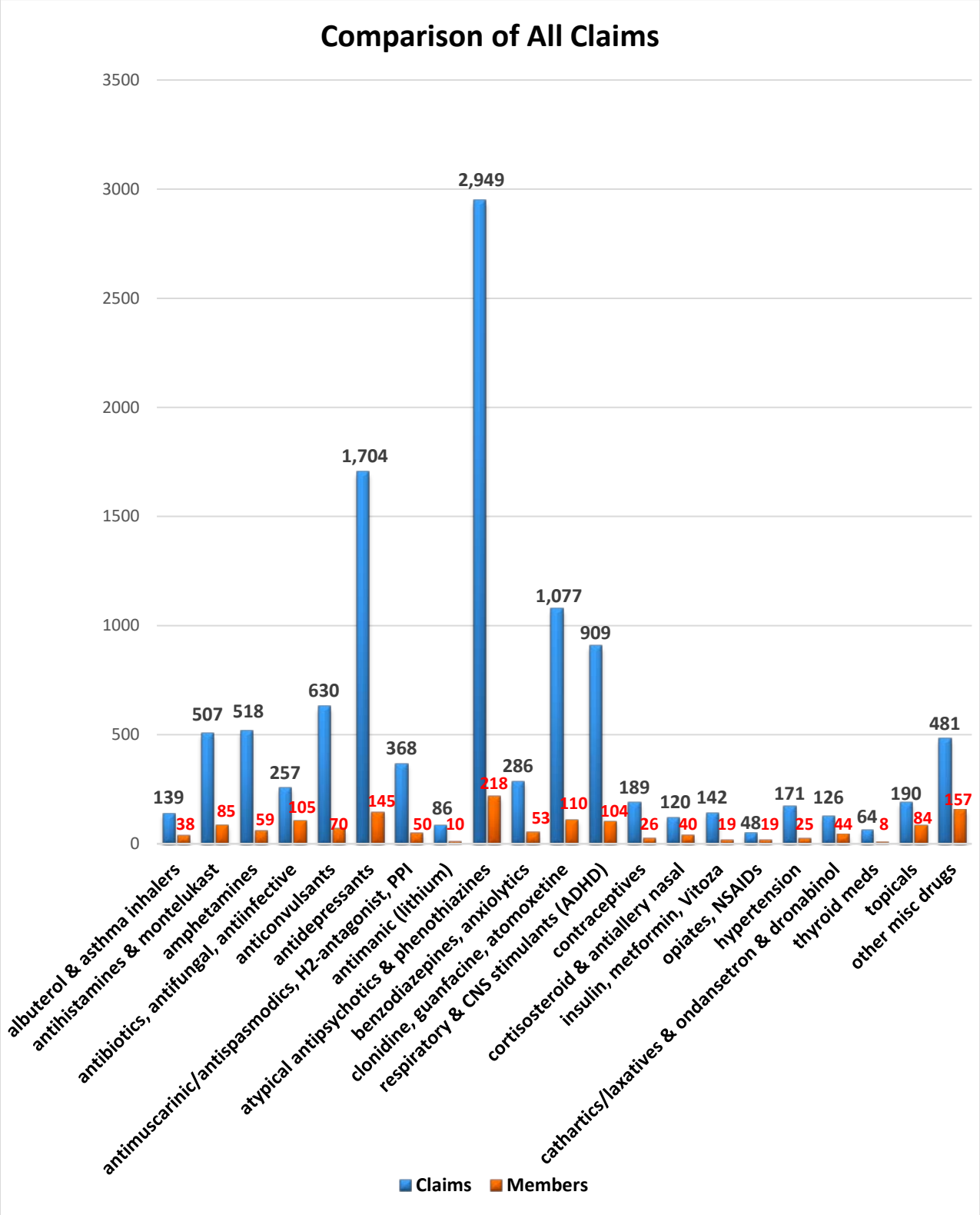
*33 members did not have birthdays yet or already had one

Plan Types	Female	Male	Total Members
Foster	28	36	64
IHS	10	13	23
NoCopay	35	69	104
Standard	19	46	65
Total	**92**	**164**	**256**

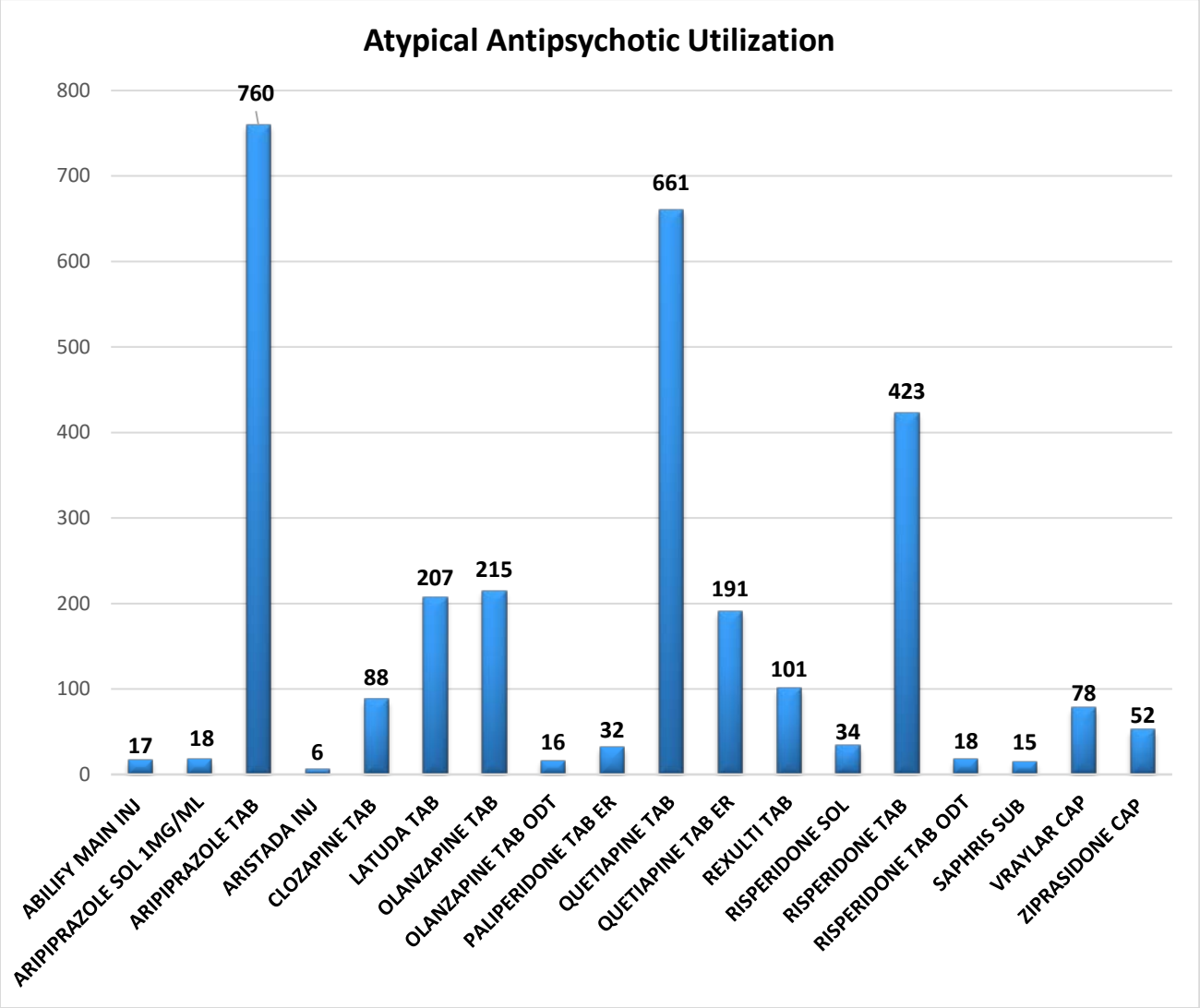
*28 members switched plan types

Drugs	Female	Male	Total Mbrs	Age Range
atypical antipsychotics (aripiprazole, Abilify, Aristada, Saphris, Rexulti, Vraylar, clozapine, Latuda, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone)	78	139	***217**	3-19
antidepressants (bupropion, mirtazapine)	8	26	**34**	6-19
SSRI (citalopram, escitalopram, fluvoxamine, fluoxetine, sertraline)	44	65	**109**	5-18
SNRI (duloxetine, venlafaxine ER)	7	1	**8**	12-18
serotonin modulators (trazodone)	23	29	**52**	6-18
antimanic agents (lithium/ER)	4	6	**10**	13-18
butyrophenones (haloperidol)	0	2	**2**	17
phenothiazines (chlopromazine, trifluperazine)	0	2	**2**	8-16
amphetamines (Vyvanse, Adderall XR, amphet-dextr/ER, dextroamphetamine/XR)	13	46	**59**	4-18
respiratory & CNS simulants (dexmethylphenidate, methylphenidate)	28	76	**104**	4-18
central alpha-agonists (clonidine, guanfacine)	12	38	**50**	3-18
central nervous system agents (atomoxetine, guanfacine)	22	53	**75**	5-19
anticonvulsants (divalproex, lamotrigine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproate, valproic acid)	22	43	**65**	6-19
anxiolytics, sedatives, hypnotics (buspirone, hydroxyzine hcl & pamoate)	18	30	**48**	6-19
benzodiazepines (anticonvulsant – clonazepam tab/ODT, clobazam susp)	6	4	**10**	6-19
benzodiazepines (anxiolytic – alprazolam, diazepam, lorazepam)	5	22	**27**	6-18
succinimides (ethosuximide)	0	1	**1**	15
opiate agonists (oxycodone, hydrocodone-APAP, codeine-APAP, tramadol)	11	5	**16**	8-18
opiate antagonist (naltrexone)	1	0	**1**	18
opiate partial agonist (buprenorphine, buprenorphine-naloxone)	0	1	**1**	17
anticholinergic agents (benztropine)	10	21	**31**	10-16
antimuscarinics (oxybutynin, tolterodine, tropsium)	2	1	**3**	9-16
antitussives (benzonatate, pseudoephed-bromphen DM, guaifenesin-codeine)		5	**5**	13-17
centrally acting skeletal muscle relaxant (cyclobenzaprine)	1	2	**3**	3-18
GABA-skeletal muscle relaxant (baclofen)	2	0	**2**	13-16
contraceptives	168	0	**168**	12-19

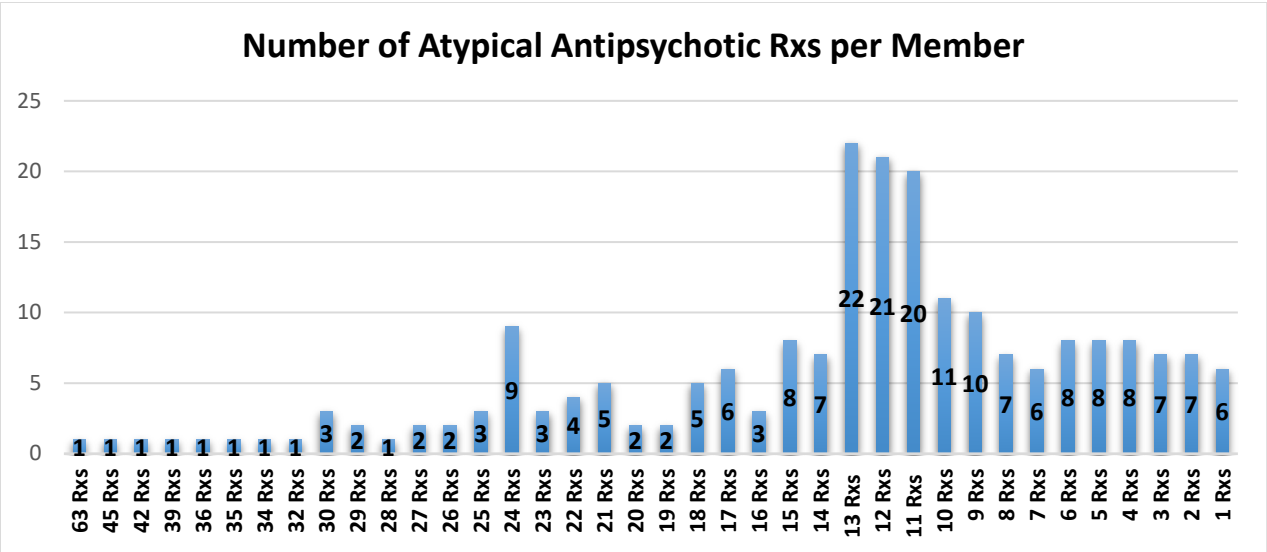
*11 members had no atypical antipsychotic utilization after 7/31/2019



*Total Number of Claims – 10,806
*Total Number of Drugs – 258 drugs (553 different strengths)
*Total Number of Atypical Antipsychotic Claims – 2,932 (27% of total number of claims)
*Total Number of Antidepressant Claims – 1,704 (15.8%)
*Total Number of ADHD (amphetamines, clonidine, guanfacine, atomoxetine, respiratory/CNS) – 2,504 (23%)

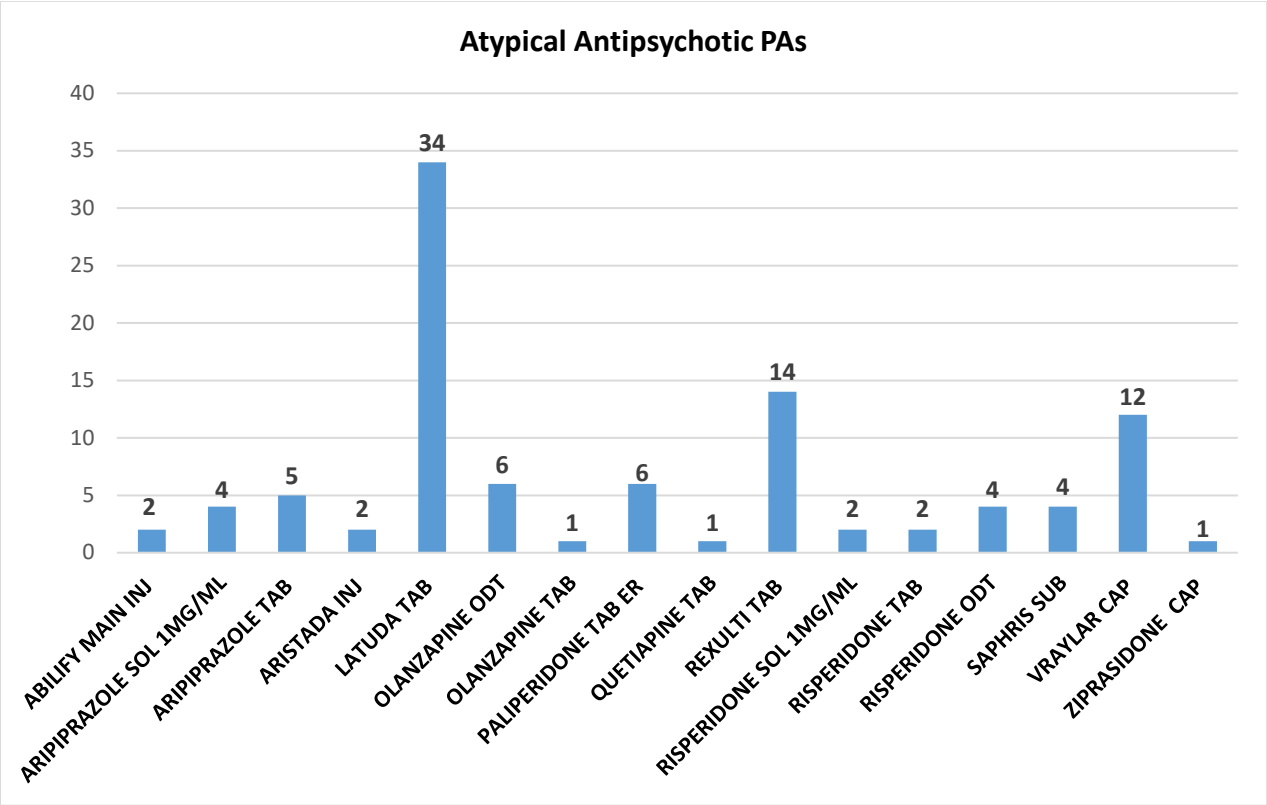


*Total Number of Atypical Antipsychotic Claims – 2,932
*Number of Members – 217

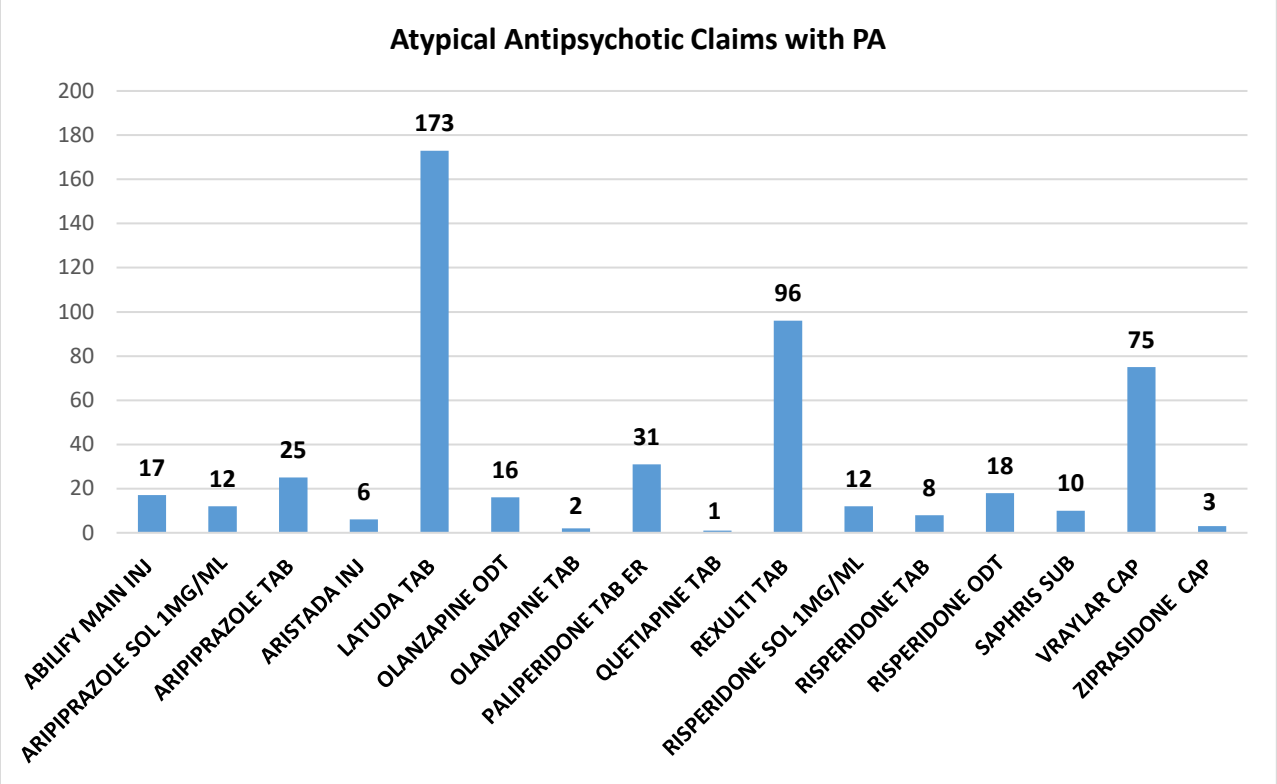


Prior Authorizations

Members: 74

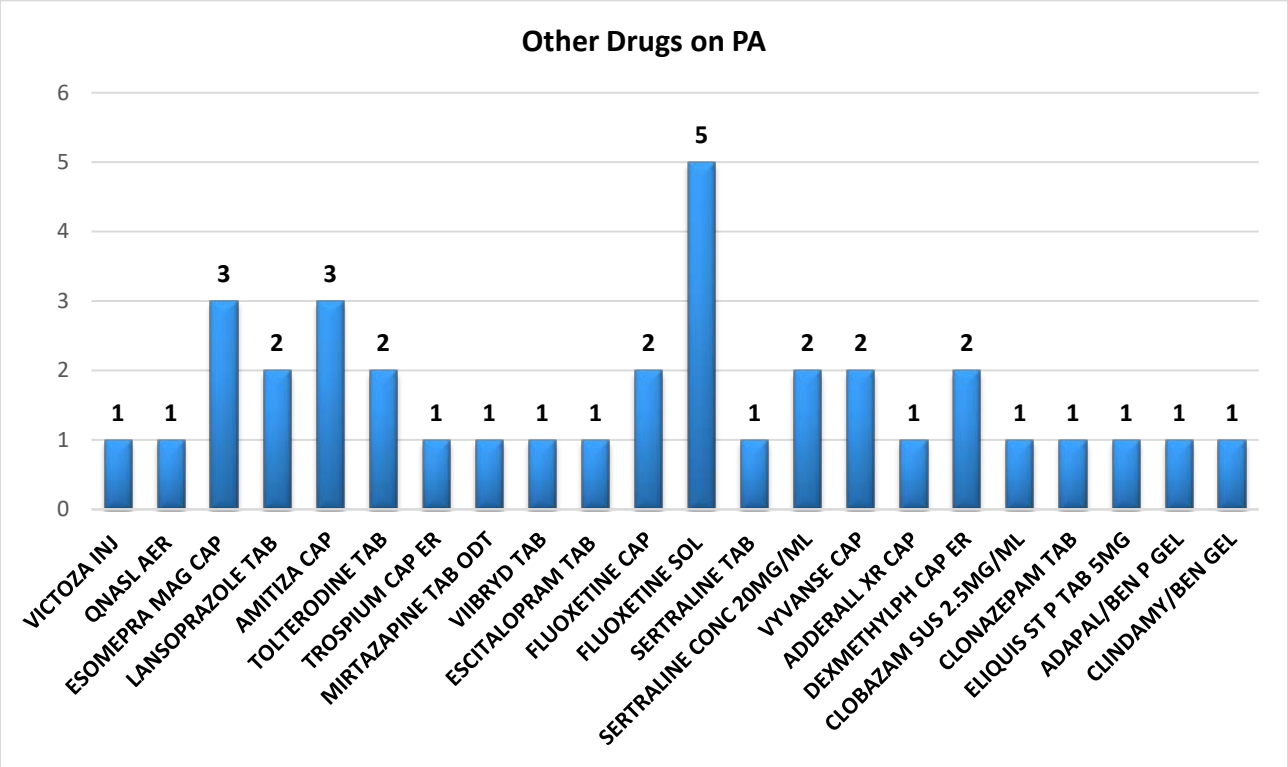


*Total Number of PAs – 100

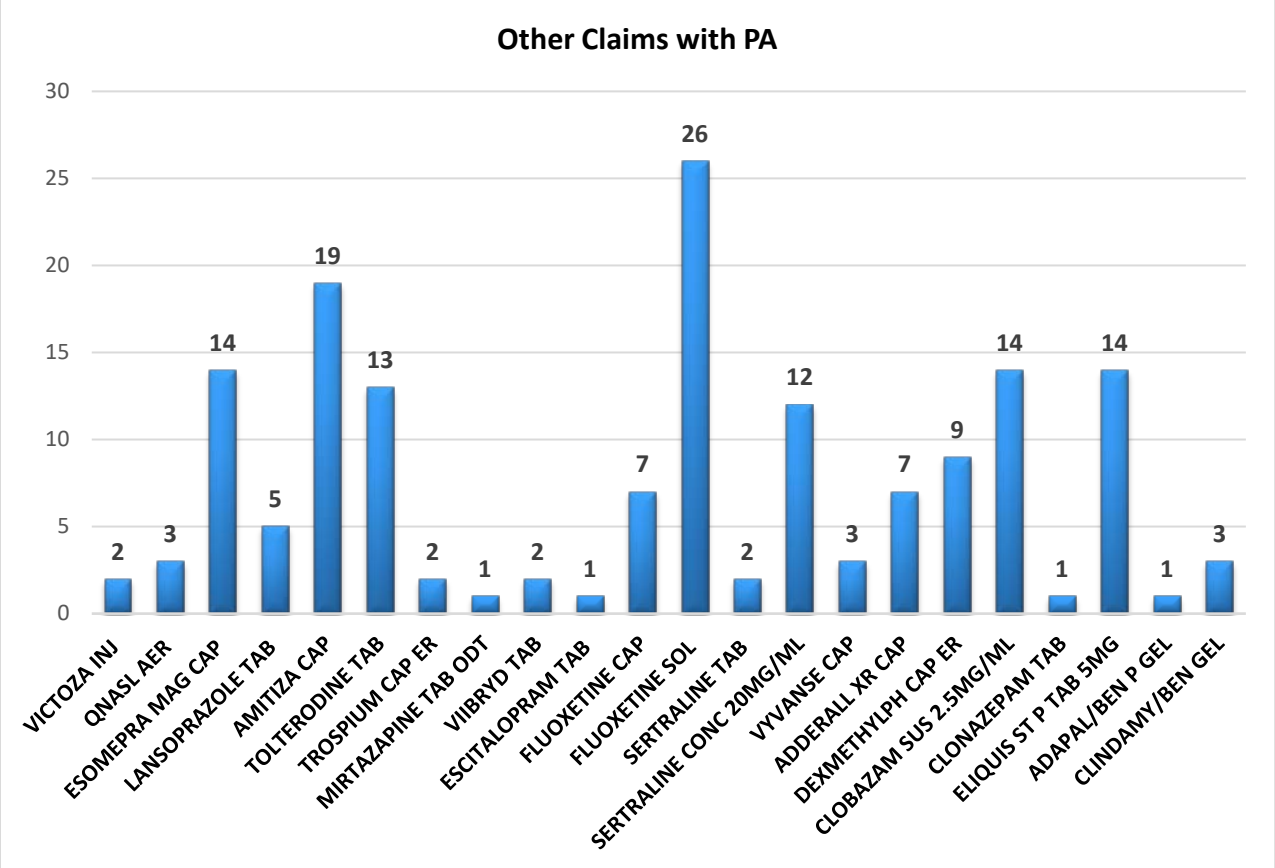


*Total Number of Claims with PA – 505

Members: 23

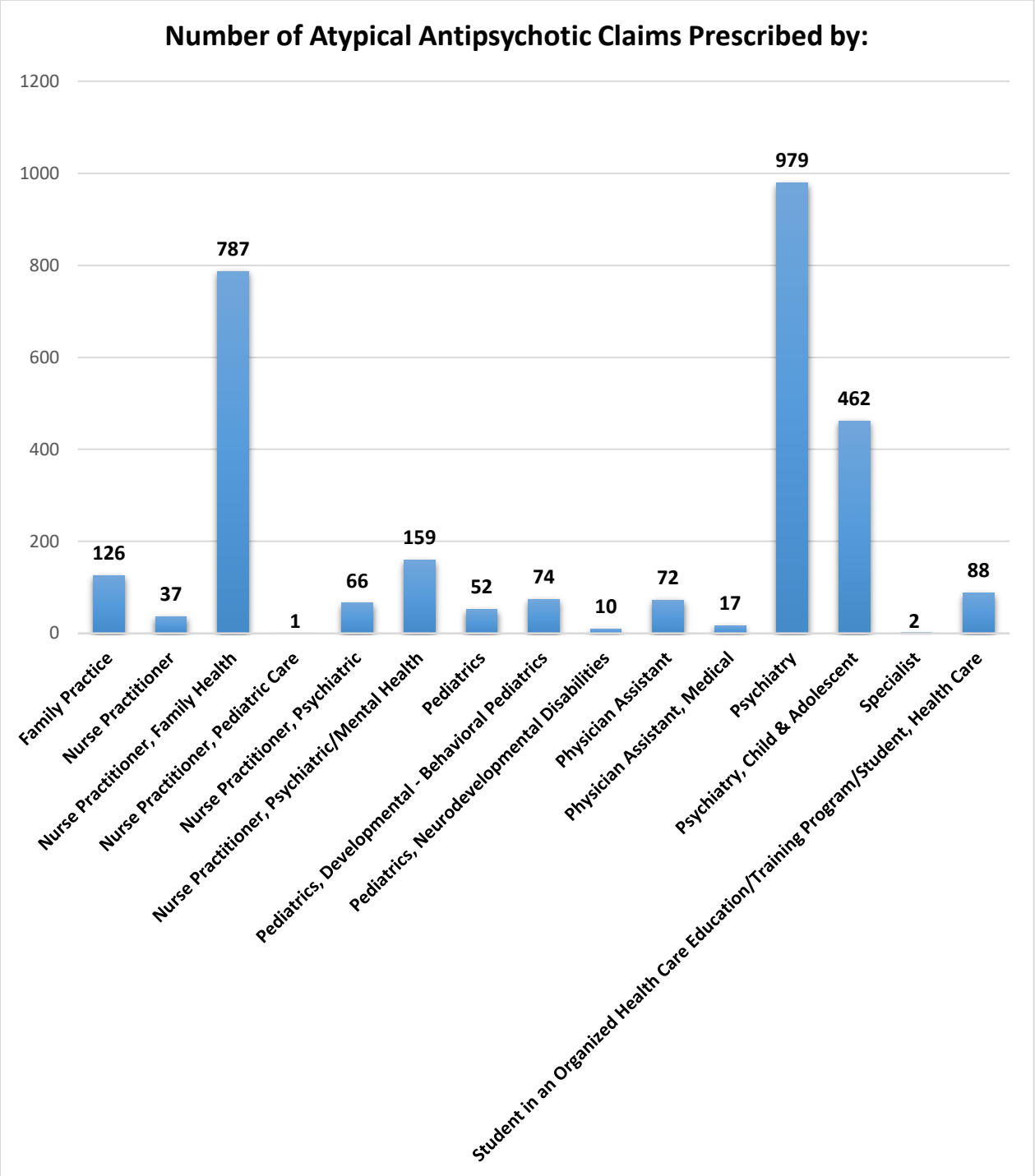


*Total Number of PAs – 36



*Total Number of Claims with PA – 151

Prescribers

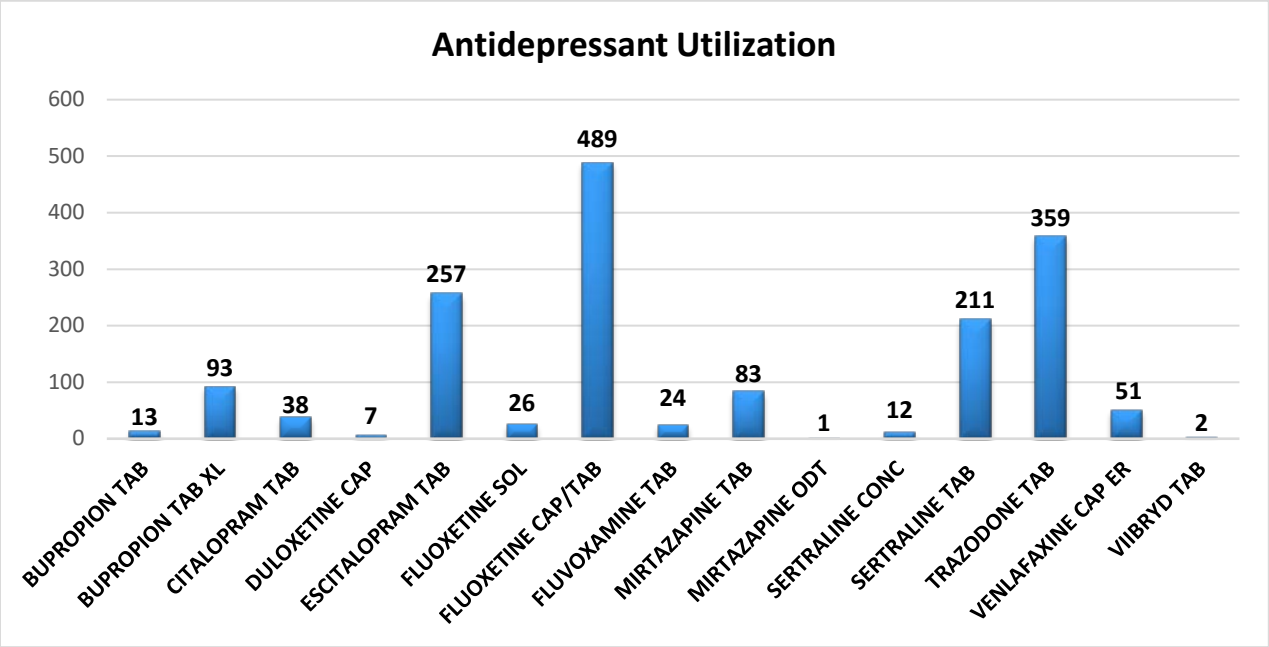


*Total Claims – 2,932
*Number of Members – 217
*Total Number of Prescribers of Atypical Antipsychotics – 106

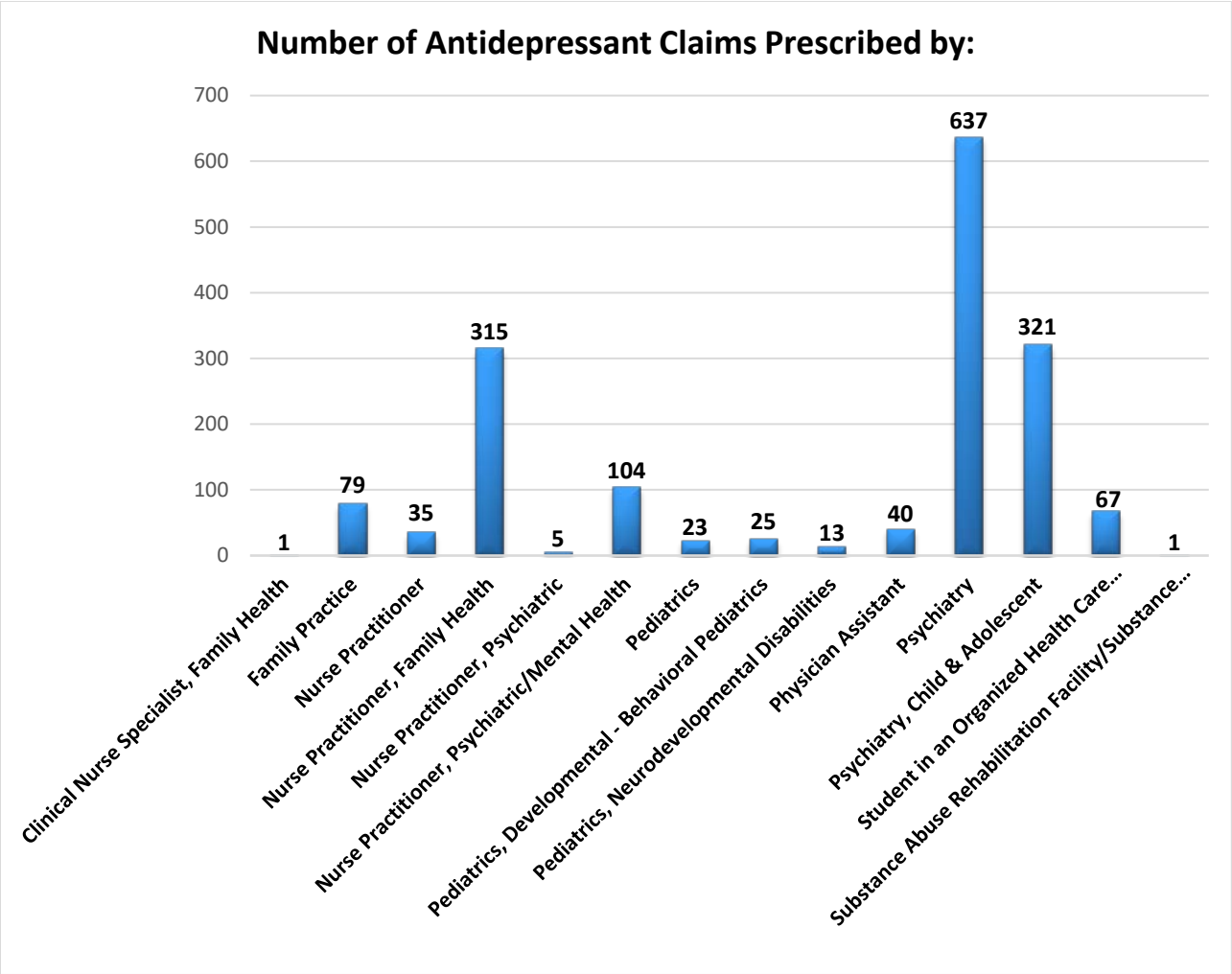
Top 30 Prescribers by Number of Total Atypical Antipsychotic Claims

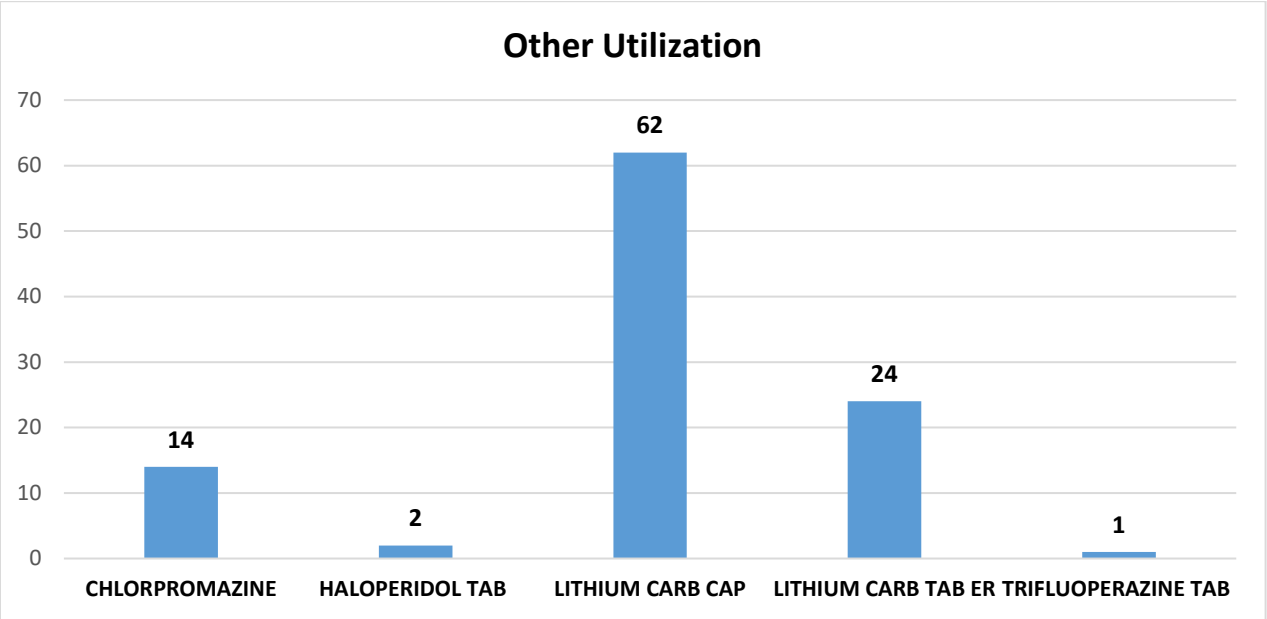
	Claims	Members	Prescriber Name	Taxonomy
1	642	40		Nurse Practitioner, Family Health
2	295	31		**Psychiatry**
3	266	26		**Psychiatry, Child & Adolescent**
4	200	18		**Psychiatry**
5	85	12		**Psychiatry**
6	84	8		**Psychiatry**
7	74	10		**Pediatrics, Developmental – Behavioral Pediatrics**
8	68	13		**Psychiatry**
9	64	8		**Nurse Practitioner, Psychiatric**
10	63	7		**Psychiatry, Child & Adolescent**
11	58	11		**Psychiatry, Child & Adolescent**
12	48	9		**Psychiatry**
13	48	9		Nurse Practitioner, Family Health
14	47	15		Student in an Organized Health Care Education/Training Program/Student, Health Care
15	46	10		Family Practice
16	43	10		**Psychiatry, Child & Adolescent**
17	41	8		Nurse Practitioner, Family Health
18	38	6		**Psychiatry**
19	38	4		**Nurse Practitioner, Psychiatric/Mental Health**
20	35	15		Physician Assistant
21	32	10		**Psychiatry, Child & Adolescent**
22	29	5		**Psychiatry**
23	27	12		Physician Assistant
24	25	1		**Nurse Practitioner, Psychiatric/Mental Health**
25	25	4		**Nurse Practitioner, Psychiatric/Mental Health**
26	24	1		**Psychiatry**
27	20	4		Family Practice
28	20	9		**Nurse Practitioner, Psychiatric/Mental Health**
29	19	6		**Psychiatry**
30	18	8		Student in an Organized Health Care Education/Training Program/Student, Health Care

*Total Number of Prescribers of Atypical Antipsychotics – 106

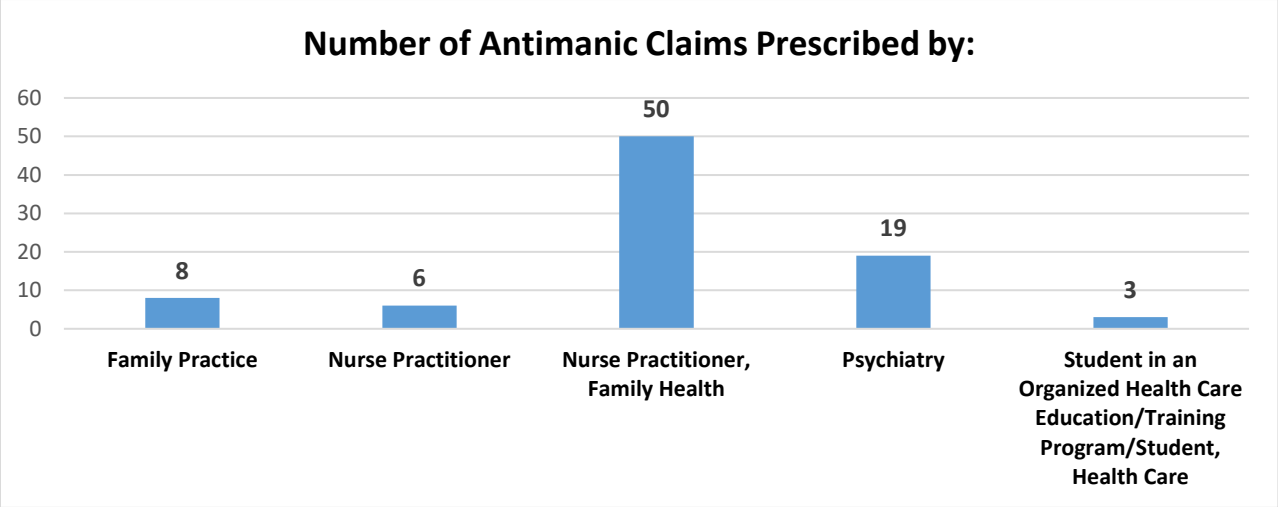


*Total Number of Claims – 1,666
*Total Number of Members – 144



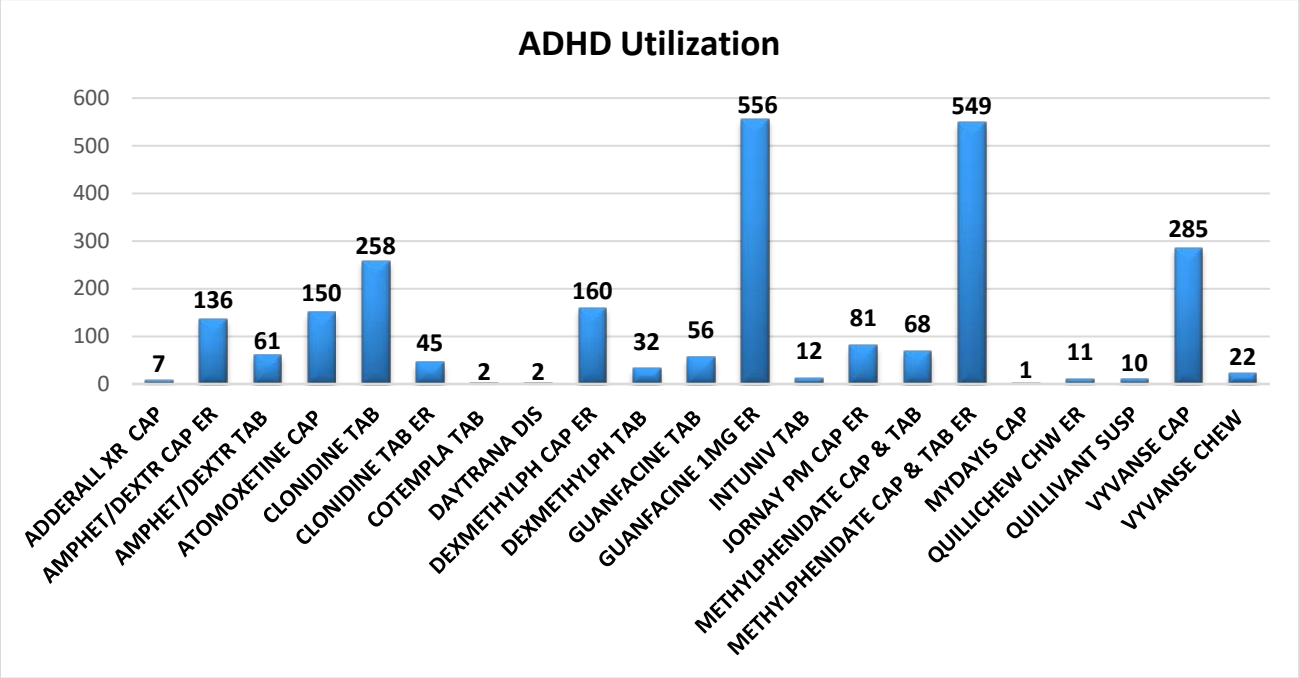


*Number of Claims

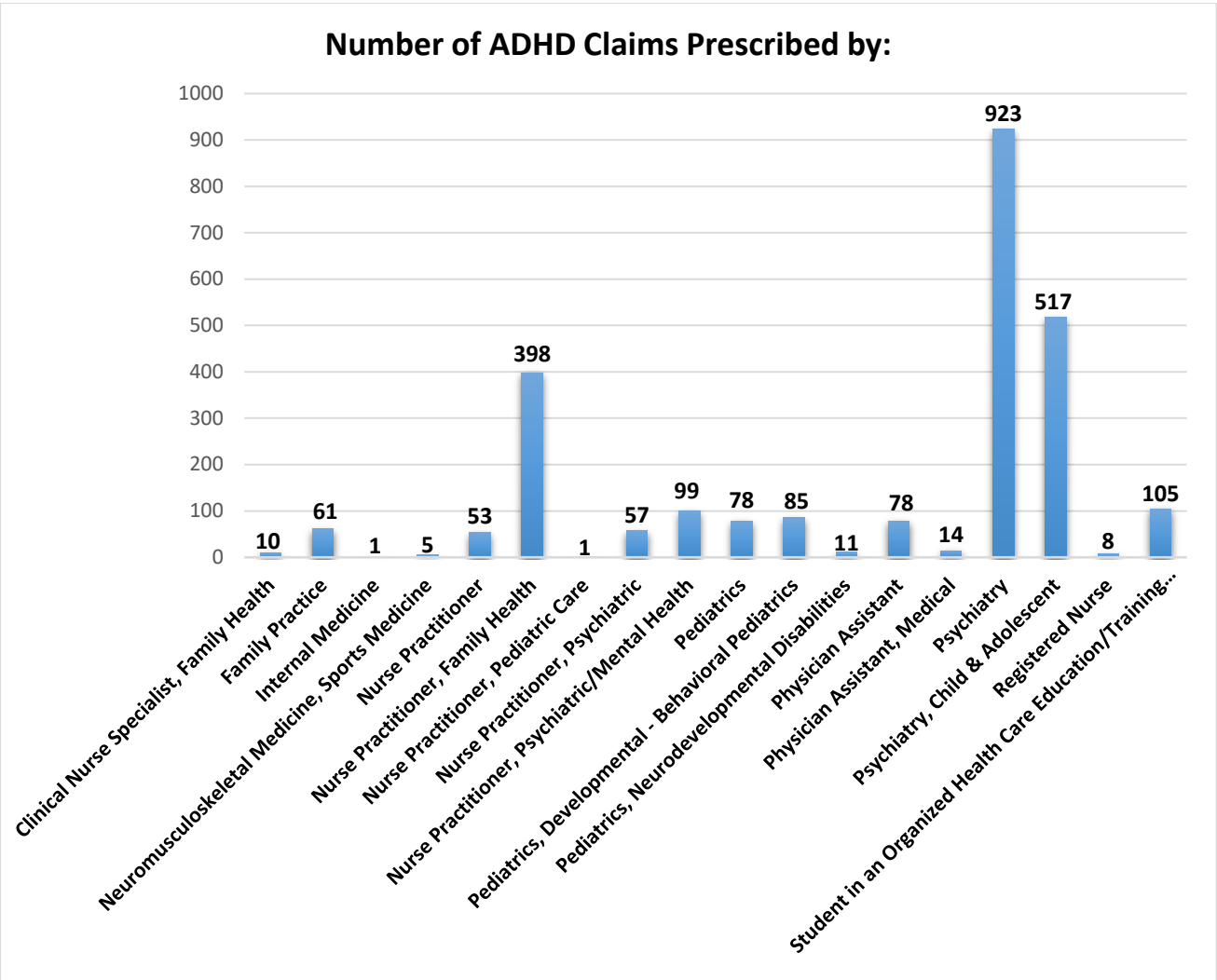


*Total Number of Claims – 86

Haloperidol – prescribed by nurse practitioner-family health (1 member, 1 prescriber)
Chlorpromazine – prescribed by NP, NP-family health, psychiatry, psychiatry-child & adol (1 member, 4 prescribers)
Trifluoperazine – prescribed by psychiatry (1 member, 1 prescriber)



*Total Number of Claims – 2,504
*Total Number of Members – 171



DSS
Strong Families - South Dakota's Foundation and Our Future

Please note: All information below is required to process this request.
Fax to 1-844-403-1029
Mon-Sat: 7am to 7pm Central

Reyvow (lasmiditan) & Ubrelvy (ubrogepant)
Prior Authorization Request Form

DO NOT COPY FOR FUTURE USE. FORMS ARE UPDATED FREQUENTLY AND MAY BE BARCODED

Member Information (required)			**Provider Information** (required)		
Member Name:			Provider Name:		
Insurance ID#:			NPI#:	Specialty:	
Date of Birth:			Office Phone:		
Street Address:			Office Fax:		
City:	State:	Zip:	Office Street Address:		
Phone:			City:	State:	Zip:

Medication Information (required)		
Medication Name:	Strength:	Dosage Form:
❑ Check if requesting **brand**	Directions for Use:	
❑ Check if request is for **continuation of therapy**		

Clinical Information (required)

Select the diagnosis below:
❑ Migraine with or without aura
❑ Other diagnosis: _____ ICD-10 Code(s): _____

Select the diagnosis below:
Has the patient had a trial and failure of a generic triptan within the last 120 days? ❑ **Yes** ❑ **No**

Quantity limit requests:
What is the quantity requested per MONTH? _____

What is the reason for exceeding the plan limitations?
❑ Titration or loading dose purposes
❑ Patient is on a dose-alternating schedule (e.g., one tablet in the morning and two tablets at night, one to two tablets at bedtime)
❑ Requested strength/dose is not commercially available
❑ Other: _____

Reauthorization:
If this is a reauthorization request, answer the following:

Are there any other comments, diagnoses, symptoms, medications tried or failed, and/or any other information the physician feels is important to this review?

_____

_____

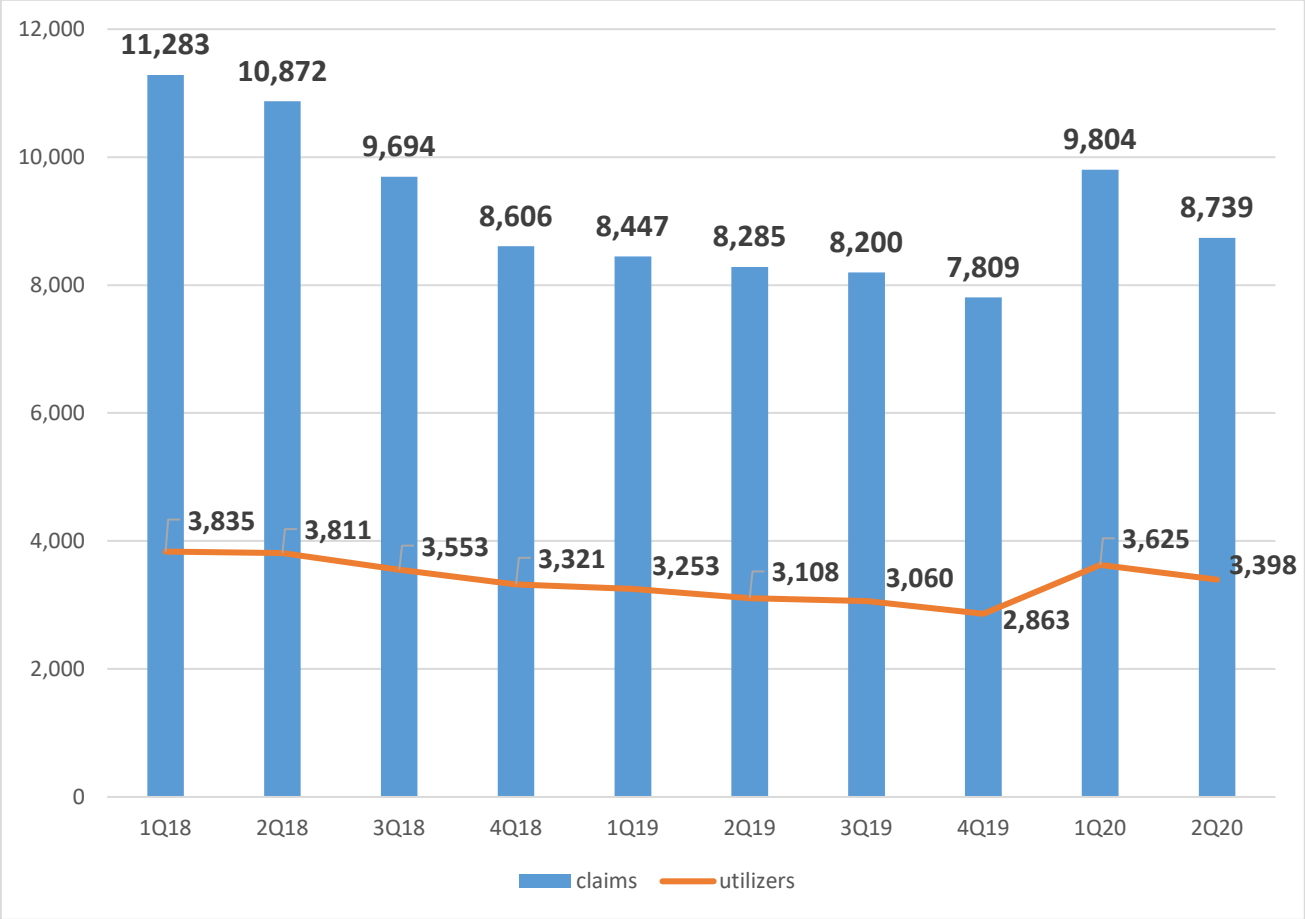
_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-844-403-1029.

Office use only: Reyvow & Ubrelvy_SouthDakotaMedicaid_2020July

Opioid Summary



-1Q2018 to 4Q2019 excludes IHS
-1Q2020 to current includes IHS

Opioid Utilization Snapshot

SDM 1Q2020

Dec 19 to Mar 20

Opioid Claims **9,804**

2.8% prescription claims filled for an opioid

0.7% lower than Medicaid FFS benchmark

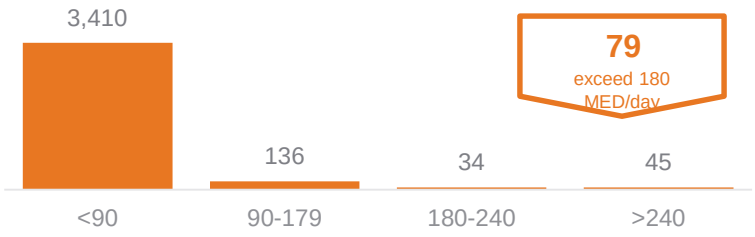
Utilizers **3,625**

30.7% are high utilizers [1]

18.9% lower than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]



Shoppers: Poly Pharmacy

54 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

236 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

2Q2020

Mar 20 to Jun 20

Opioid Claims **8,739**

3.0% prescription claims filled for an opioid

0.6% lower than Medicaid FFS benchmark

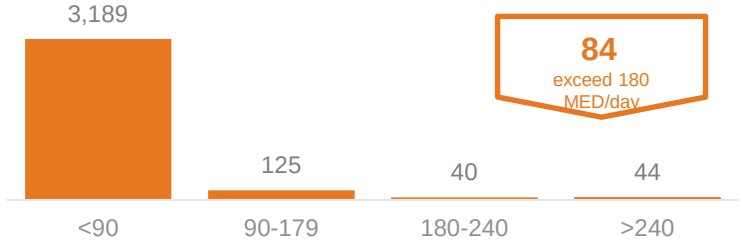
Utilizers **3,398**

32.7.0% are high utilizers [1]

-20% lower than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]



Shoppers: Poly Pharmacy

49 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

231 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

OPTUMRx®

[1]Defined as 3+ opioid scripts within 120 days period; [4]**MED** – Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period; [5]JAMA. 2016 Apr 19;315(15):1624-45. [6]MME – Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose.

Opioid Utilization

SDM
Viewing: Mar 2020 - Jun 2020
Benchmark: MEDICAID FEE FOR SERVICE

Utilizers: 3,398

3.0% of all Rx claims are filled for an Opioid

Opioid dependence can start in just a few days, and the risk of chronic opioid use increases with each additional day of opioid supplied, starting with the third day. Our Opioid Risk Management program, which includes point of sale, utilization management and retrospective drug utilization edits, are tightly aligned with CDC opioid prescribing guidelines which can help reduce exposure to excessive doses and prevent more members from transitioning from acute to chronic use.

- Opioid prescriptions account for 3.0% of all prescriptions this period, which is 0.6% lower than the benchmark
- 1,112 high opioid utilizers were identified this period, which is -20.0% lower than the benchmark

Opioid claims

8,739
TOTAL RXS

PERCENT NON-COMPLIANT
12.4%

Opioid utilizers

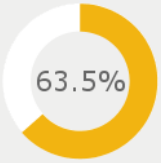
3,398
TOTAL UTILIZERS

HIGH UTILIZERS
32.7%
1,112 high utilizers

-20.0% under benchmark

High utilizers – view definition

Claim breakdown



short acting opioids

63.5% of all opioid Rxs were filled for short acting opioids. **788** Rxs were for medication assisted therapy (MAT) and **35** were for rescue therapy. CDC guidelines advise prescribers to manage pain with the lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day.

MAT – view definition
Overdose rescue therapy – view definition
MME – view definition

Utilizers by cumulative MED

84 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	3,189	125	40	44

MED – view definition

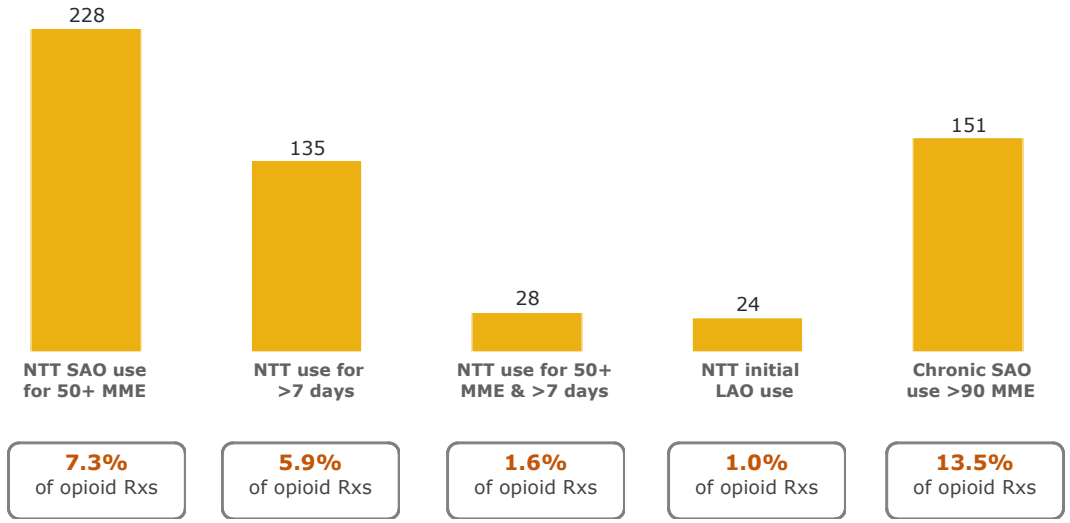
Opioid Opportunity Assessment

SDM
Viewing: Mar 2020 - Jun 2020
Benchmark: MEDICAID FEE FOR SERVICE

Percent non-compliant: 12.4%

Utilizers non-compliant to opioid Rx CDC guidelines

(new to therapy and chronic use)



NTT - view definition | SAO - view definition | LAO - view definition | MME - view definition

DID YOU KNOW?

49 opioid utilizing members use 3 or more pharmacies and 231 opioid utilizing members use 3 or more prescribers.

Identification, management and prevention of fraudulent or potential abuse of opioid medications are monitored and addressed by OptumRx through various means in pharmacy network audit capabilities and high touch clinical programs that include care coordination with opioid prescribers.

Opioid utilizers with potentially contraindicated medication use

SKELETAL MUSCLE RELAXANTS	BENZODIAZEPINES	ANTICONVULSANTS	MEDICATION ASSISTED THERAPY	PRENATAL
638	503	700	N/A	108

Anticonvulsants –view definition

Utilization

Time frame: 2Q 2020
Red font denotes drug is on Prior Authorization

Humira

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/ Days Supply	Utilizing Members	Age Range
Humira Inj 40 mg/0.4 ml	8	$54,217.50	$6,777.19	2.5/28 days	3	9 - 47
Humira Kit 40mg/0.8 ml	2	$16,252.70	$8,126.35	3/28 days	2	37 - 38
Humira Pen Inj 40mg/0.4 ml	37	$249,357.33	$6,739.39	2.5/27 days	14	13 - 61
Humira Pen Inj 40mg/0.8 ml	17	$119,298.60	$7,017.56	2.5/21 days	7	16 - 61
Humira Pen Inj CD/UC/HS	1	$16,214.99	$16,214.99	6/28 days	1	20
Humira Pen Kit CD/UC/HS	1	$16,681.47	$16,681.47	3/28 days	1	17
Humira Pen Kit PS/UV	1	$11,124.46	$11,124.46	3/28 days	1	18
TOTAL	**67**	**$483,147.05**			**27**	**9 - 61**

Advair

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/ Days Supply	Utilizing Members	Age Range
Advair HFA Aer 45/21	65	$19,008.58	$292.44	12/30 days	38	2 - 63
Advair HFA Aer 115/21	161	$54,098.30	$336.01	12/30 days	92	2 - 56
Advair HFA Aer 230/21	88	$39,251.07	$446.03	12/30 days	46	3 - 64
Advair Diskus Aer 100/50	3	$447.15	$0 $132.57 $314.58	60/30 days	3	16 - 59
Advair Diskus 250/50	8	$1,989.84	$248.73	54/27 days	6	50 - 63
Advair Diskus Aer 500/50	2	$422.24	$211.12	60/30 days	2	41 - 53
Wixela Inhub Aer 100/50	18	$2,429.76	$134.99	60/30 days	12	9 - 59
Wixela Inhub Aer 250/50	86	$14,246.38	$165.66	60/30 days	53	8 - 64
Wixela Inhub Aer 500/50	45	$9,466.61	$210.37	59/30 days	23	13 - 62
fluticasone-salmeterol 100/50	45	$6,114.11	$135.87	60/30 days	26	8 - 62
fluticasone-salmeterol 250/50	123	$20,385.94	$165.74	60/30 days	72	11 - 77
fluticasone-salmeterol 500/50	74	$15,646.57	$211.44	60/30 days	39	17 - 68
TOTAL	**718**	**$183,506.55**			**375**	**2 - 77**

Benzodiazepines – Anticonvulsants

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/ Days Supply	Utilizing Mbrs	Age Range	Prescriber Taxonomy
Nayzilam (midazolam)	2	$1,076.92	$538.46	2/1.5 days	2	19 - 32	Family Practice, Neurology
Valtoco nasal spray (diazepam)	0						
Diastat Acudial Rectal Gel	4	$1,178.31	$294.58	1/1.75 days	2	13 - 17	Neurology
diazepam rectal gel	50	$13,432.88	$268.66	1/4 days	38	1 - 23	NP, Neurology, Pediatrics, Clinical Neurophysiology, Pediatric Neurology, Student
diazepam tab	331	$3,347.02	$10.11	44/20 days	171	8 - 64	Various
diazepam con 5mg/5ml	6	$217.53	$36.26	30/23 days	3	14 - 31	FP, Neurology, Pediatric Neurology, Specialist
diazepam sol 5mg/5ml	11	$272.87	$24.81	135/25 days	6	2 - 33	NP, Hospitalist, Pediatrics, Physical Med & Rehab, Pediatric Physical Med & Rehab, Student
clobazam susp	121	$15,935.07	$131.69	198/28 days	45	1 - 23	NP, Neurology, Pediatric Neurology, Clinical Neurophysiology, Student
clobazam tab	137	$5,728.07	$41.81	77/30 days	48	2 - 35	NP, PA, FP, Pediatrics, Neurodevelopment Disabilities Pediatrics, Neurology, Pediatric Neurology, Specialist, Chiropractor, Student
Onfi susp (clobazam)	7	$7,111.86	$1,015.98	222/31 days	3	4 - 12	NP, Pediatrics, Pediatric Neurology
Onfi tab (clobazam)	6	$9,179.72	$1,529.95	45/30 days	2	16 -18	Pediatrics, Pediatric Neurology
Sympazan film (clobazam)	0						
clonazepam ODT	118	$3,541.68	$30.01	35/19 days	75	2 - 64	NP, PA, FP, Emergency Med, Psychiatric/Mental NP, Neurology, Pediatrics, Neurodevelopment Disabilities Pediatric, Forensic Psychiatry, Psychiatry, Chiropractor, Student,
clonazepam tab	1,429	$15,503.98	$10.85	53/25 days	505	3 - 64	Various
Klonopin tab	7	$939.92	$134.27	83/30 days	3	13 - 60	Psychiatry, Family Practice, Pediatric Neurology
TOTAL	**2,229**	**$77,465.83**					

PA criteria for Onfi: Diagnosis of seizures associated with Lennox-Gasutaut syndrome or intractable treatment-resistant seizure disorder

INTRODUCTION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period (*International Headache Society [IHS] 2018, Starling et al 2015).*
  - The goals for treatment of migraine are to reverse or stop the progression of a migraine attack. The goals for preventive treatment are to reduce the frequency, severity and duration of a migraine (*American Headache Society [AHS] 2019, Katsarava 2012*).
- The International Classification of Headache Disorders (ICHD) includes both cluster headache and migraine as part of a group of primary headache disorders (*IHS 2018*):
  - Chronic migraine is defined as ≥ 15 headache days per month for > 3 months with the features of migraine headache for at least 8 mean migraine days per month (MMD). The most common cause of symptoms suggestive of chronic migraine is medication overuse. According to the ICHD, around 50% of patients apparently with chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed with chronic migraine. In most clinical trials, migraine that is not chronic (ie, < 15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD.
  - Cluster headache is defined as ≥ 5 attacks lasting 15 to 180 minutes every other day to 8 times a day with severe unilateral orbital, supraorbital, and/or temporal pain. Episodic cluster headache attacks occur for a period of 7 days to 1 year and are separated by pain-free periods lasting at least 3 months. Common symptoms include nasal congestion, rhinorrhea, conjunctival injection and/or lacrimation, eyelid edema, sweating (forehead or face), miosis, ptosis, and/or a sense of restlessness or agitation.
- Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women. Migraines have a global prevalence of 15 to 18% and are a leading cause of disability worldwide. Chronic migraine is estimated to occur in 2 to 8% of patients with migraine, whereas episodic migraine occurs in more than 90% of patients. Cluster headache is rare compared to other primary headache disorders. It is estimated to have a prevalence of 0.1% within the general population (*Global Burden of Disease Study [GBD] 2016, Hoffman et al 2018, Lipton et al 2016, Ljubisavljevic et al 2019, Manack et al 2011*).
- Treatments for migraines and cluster headache are divided into acute and preventive therapies. Evidence and reputable guidelines clearly delineate appropriate therapies for episodic migraine treatment and prophylaxis; options stretch across a wide variety of therapeutic classes and are usually oral therapies. For the prevention of migraines, treatment options include oral prophylactic therapies, injectable prophylactic therapies, and neuromodulator devices. Oral prophylactic migraine therapies have modest efficacy, and certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. For the treatment of acute migraine, options include triptans, ergots, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, small molecule CGRP inhibitors, and a 5-hydroxytryptamine (5-HT)$_{1F}$ receptor agonist. For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy, and suboccipital steroid injections are most effective for prevention (*American Migraine Foundation [AMF] 2020, Marmura et al 2015, Robbins et al 2016, Silberstein et al 2012, Simpson et al 2016)*.
- The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation and the Food and Drug Administration (FDA) has approved 6 CGRP inhibitors for prevention or treatment of migraine/headache disorder(s). Erenumab-aooe is a fully human monoclonal antibody, which potently binds to the CGRP receptor in a competitive and reversible manner with greater selectivity than to other human calcitonin family receptors. Fremanezumab-vfrm, eptinezumab-jjmr, and galcanezumab-gnlm are humanized monoclonal antibodies that bind to the CGRP ligand and block its binding to the receptor. Rimegepant and ubrogepant are small molecule oral CGRP receptor antagonists (*Dodick et al 2018[b], Edvinsson 2017, Goadsby et al 2017, Sun et al 2016, Tepper et al 2017*).
  - Two CGRP inhibitors known as the “gepants,” telcagepant and olcegepant, were previously investigated. In 2009, Merck withdrew the FDA application for telcagepant because of elevated liver enzymes and potential liver toxicity

observed with chronic use, which was likely related to the chemical structure of the compound. The manufacturer of olcegepant also ceased pursuing FDA approval; however, the manufacturer did not explicitly state the rationale. It has been widely speculated that olcegepant development ceased due to limitations associated with administration as an intravenous (IV)-only product (*Edvinsson et al 2017, Walker et al 2013*). No substantial issues with liver toxicity have been observed in trials with the currently marketed CGRP inhibitors.
  - Additional CGRP inhibitors early in their development include vazegepant, the first intranasally administered CGRP inhibitor, and atogepant, another oral CGRP inhibitor (*Biohaven press release 2019*, *Staines 2019*).
  - In April 2019, Teva announced that it would not pursue development of fremanezumab-vfrm for an episodic cluster headache indication due to results from the ENFORCE trial (*Teva Pharmaceuticals press release 2019*). Erenumab-aooe and eptinezumab-jjmr are not currently under clinical investigation for the indication of cluster headache (*Clinicaltrials.gov 2020*).
- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene−related peptide (CGRP) receptor antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aimovig (erenumab−aooe)	–
Ajovy (fremanezumab-vfrm)	–
Nurtec ODT (rimegepant sulfate)	–
Emgality (galcanezumab-gnlm)	–
Ubrelvy (ubrogepant)	–
Vyepti (eptinezumab-jjmr)	–

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	**Aimovig** (erenumab−aooe)	**Ajovy** (fremanezumab-vfrm)	**Emgality** (galcanezumab-gnlm)	**Nurtec ODT** (rimegepant)	**Ubrelvy** (ubrogepant)	**Vyepti** (eptinezumab-jjmr)
Acute treatment of migraine with or without aura in adults	-	-	-	✔*	✔*	-
Preventive treatment of migraine in adults	✔	✔	✔	-	-	✔
Treatment of episodic cluster headache in adults	-	-	✔	-	-	-

* Limitation of use: Not indicated for the preventive treatment of migraine.

(*Prescribing information: Aimovig 2020, Ajovy 2020, Emgality 2019, Nurtec ODT, Ubrelvy 2019, Vyepti 2020*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Rimegepant ODT has been studied as acute therapy in approximately 1466 patients in 1 Phase 3 trial of episodic migraine (with or without aura) patients and in 1 unpublished long-term safety trial. Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet formulation were considered supportive for approval; 2 trials

included approximately 2348 patients with episodic migraine, and 1 dose-ranging study included 885 patients randomized to 6 dose groups of rimegepant, sumatriptan 100 mg, or placebo.

- Ubrogepant has been studied as acute therapy in approximately 3360 patients across 2 trials in patients with 2 to 8 migraines/month with moderate to severe pain intensity either with or without aura and in 1 unpublished, open-label extension (OLE) trial.
- Eptinezumab-jjmr has been studied in approximately 2019 patients across 2 trials in patients with episodic or chronic migraine subtypes for prevention, with data available in published formats.
- Erenumab-aooe has been studied as preventive therapy in approximately 2500 patients across 4 trials in patients with episodic or chronic migraine subtypes and 1 OLE trial, with data available in published and unpublished formats.
- Fremanezumab-vfrm has been studied as preventive therapy in approximately 2005 patients across 3 trials in patients with episodic or chronic migraine subtypes, with data available in published formats. In fremanezumab-vfrm trials, the definition of a headache or migraine day for the primary endpoint required a consecutive 2 hour (episodic) or 4 hour (chronic) duration of pain, compared to other CGRP inhibitor trials that required a duration of ≥ 30 minutes.
- Galcanezumab-gnlm has been studied as preventive therapy in approximately 2886 patients across 3 trials in patients with episodic or chronic migraine subtypes and 1 long-term safety trial with unpublished data to 1 year. The efficacy and safety of galcanezumab-gnlm was evaluated for treatment in one 8-week study with 106 adults with episodic cluster headache (maximum of 8 attacks/day).
- The definition of the primary and secondary endpoints differed in the prevention of episodic and chronic migraine trials. Additional differences included, but were not limited to, co-morbid conditions, concomitant medications, a requirement of stable doses of migraine prevention medication (if co-administered) for certain durations, and the definitions of headache, migraine headache, and migraine day. Some CGRP inhibitor trials allowed patients to receive concomitant preventive migraine medication during treatment. Also, some chronic migraine trials allowed for the inclusion of patients with medication overuse headache.

Prevention of episodic migraine

Eptinezumab-jjmr

- PROMISE-1 was a double-blind (DB), placebo-controlled (PC), multi-center (MC), Phase 3 trial in which adults with a history of episodic migraine were randomized to receive placebo (n = 222), eptinezumab-jjmr 100 mg (n = 221), or eptinezumab-jjmr 300 mg (n = 222) every 3 months for 12 months. The primary efficacy endpoint was the change in MMD from baseline to week 12. Eptinezumab-jjmr 100 mg and 300 mg significantly reduced MMDs across weeks 1 to 12 compared with placebo (placebo, −3.2; 100 mg, −3.9, p = 0.02; 300 mg, −4.3, p = 0.0001). The odds for a 50% reduction in MMD were approximately 1.7 to 2.2 times higher with eptinezumab-jjmr than placebo. Of note, the endpoints underwent a testing hierarchy and were not significant for 50% migraine responder rates in the 100 mg dose group (*Ashina et al 2020, Vyepti [dossier] 2020).*

Erenumab-aooe

- The STRIVE trial was a 6-month, DB, PC, MC, Phase 3 trial in which 955 patients with episodic migraine were randomized to placebo (n = 319), erenumab-aooe 70 mg (n = 317), or erenumab-aooe 140 mg (n = 319) once monthly. The primary endpoint was the change in mean MMD from baseline to months 4 to 6, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.4; 95% confidence interval [CI], −1.9 to −0.9; p < 0.001) and erenumab−aooe 140 mg (mean change vs placebo, −1.9; 95% CI, −2.3 to −1.4; p < 0.001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 16.7%; odds ratio [OR], 2.13; difference for 140 mg vs placebo, 23.4%; OR, 2.81). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 70 mg vs placebo, −0.9; difference for 140 mg vs placebo, −1.4) (*Goadsby et al 2017*).
- The ARISE trial was a 12-week, DB, PC, MC, Phase 3 trial in which 577 patients with episodic migraine were randomized to placebo (n = 291) or erenumab-aooe 70 mg (n = 286) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.0; 95% CI, −1.6 to −0.5; p < 0.001). Compared to placebo, erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference, 10.2%; OR, 1.59). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −0.6) (*Dodick et al 2018[a]*).

- The LIBERTY trial was a 12-week, DB, PC, MC, Phase 3b trial in which 246 patients with episodic migraine who failed 2 to 4 prior preventive migraine treatments were randomized to placebo (n = 125) or erenumab-aooe 140 mg (n = 121) once monthly. The primary endpoint was the proportion of patients with ≥ 50% reduction in MMD from baseline to the last 4 weeks of DB treatment (weeks 9 to 12), which erenumab−aooe significantly increased over placebo (difference, 16.6%; OR, 2.73; 95% CI, 1.43 to 5.19; p = 0.002). Compared to placebo, 5.9% more patients treated with erenumab−aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab-aooe 140 mg/month compared with placebo significantly reduced the MMD (difference, −1.61; 95% CI, −2.70 to −0.52; p = 0.004). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −1.73) (*Reuter et al 2018*).

Fremanezumab-vfrm

- The HALO-EM trial was a 12-week, DB, PC, MC, Phase 3 trial in which 875 patients with episodic migraine were randomized to placebo (n = 294), fremanezumab-vfrm 225 mg once monthly (n = 290), or fremanezumab-vfrm 675 mg once quarterly (n = 291). The primary endpoint was the change in mean MMD, which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −1.5; 95% CI, −2.0 to −0.9; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.3; 95% CI, −1.8 to −0.7; p < 0.001). Of note, HALO-EM was powered to detect a 1.6-day difference in the MMD between the fremanezumab-vfrm and placebo groups, but effect sizes resulted in a 1.5-day reduction for the fremanezumab-vfrm monthly dosing group and a 1.3-day reduction for the fremanezumab-vfrm quarterly dosing group. Although the threshold was not reached, a minimal clinically important difference has not been established for this particular outcome. Compared to placebo, greater MMD reductions were also observed in patients who were prescribed fremanezumab-vfrm 225 mg (mean change vs placebo, −1.3) and 675 mg (mean change vs placebo, −1.1) as monotherapy. Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 225 mg vs placebo, 19.8%; OR, 2.36; difference for 675 mg vs placebo, 16.5%; OR, 2.06). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −1.4; difference for 675 mg vs placebo, −1.3) (*Dodick et al 2018[b]*).
- FOCUS was a DB, PC, Phase 3b trial that evaluated 838 patients with episodic (39%) or chronic migraine (61%) who had previously not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, approximately 40% were classified as having episodic migraines and randomized to fremanezumab-vfrm 225 mg administered monthly with no loading dose (n = 110/283), fremanezumab-vfrm 675 mg administered quarterly (n = 107/276), or placebo (n = 112/279) for 12 weeks. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment, discontinuation because of adverse events that made treatment intolerable, or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. At baseline, the MMD was approximately 14.2 days and the MMHD (of at least moderate severity) was 12.6 days. For the overall population, the MMD reduction over 12 weeks was 0.6 (standard error [SE], 0.3) days for placebo, 4.1 (SE, 0.34) days for the monthly fremanezumab-vfrm group (least squares mean difference [LSMD] vs placebo, -3.5; 95% CI, -4.2 to -2.8 days; p < 0.0001), and 3.7 (SE, 0.3) for days for the quarterly fremanezumab-vfrm group (LSMD vs placebo, -3.1; 95% CI, -3.8 to -2.4 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.1 days for both dose groups (fremanezumab-vfrm monthly: LSMD, -3.1; 95% CI, -4.0 to -2.3 days; fremanezumab-vfrm quarterly: LSMD, -3.1; 95% CI, -3.9 to -2.2 days; p < 0.0001 for both). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 34% in both the quarterly and monthly fremanezumab-vfrm groups vs 9% with placebo (p < 0.0001). Only the monthly fremanezumab-vfrm arm achieved a ≥ 75% sustained responder rate that was statistically different from placebo (OR, 8.6; 95% CI, 2.0 to 37.9; p = 0.0045). Adverse events were similar for placebo and fremanezumab-vfrm. Serious adverse events were reported in 4 (1%) of 277 patients with placebo, 4 (1%) of 285 with monthly fremanezumab-vfrm, and 2 (< 1%) of 276 with quarterly fremanezumab-vfrm (*Ferrari et al 2019*).

Galcanezumab-gnlm

- The EVOLVE-1 and EVOLVE-2 trials were 6-month, DB, PC, MC, Phase 3 trials in 858 and 915 patients with episodic migraine, respectively. Patients were randomized to placebo (EVOLVE-1, n = 433; EVOLVE-2, n = 461), galcanezumab-gnlm 120 mg once monthly (EVOLVE-1, n = 213; EVOLVE-2, n = 231), or galcanezumab-gnlm 240 mg once monthly (EVOLVE-1, n = 212; EVOLVE-2, n = 223). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The EVOLVE-1 trial included a North American population and the EVOLVE-2 trial included a global population. The primary endpoint was the change in mean monthly migraine headache days (MMHD) (*Stauffer et al 2018, Skljarevski et al 2018*).

- In EVOLVE-1, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −1.9; 95% CI, −2.5 to −1.4; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.8; 95% CI, −2.3 to −1.2; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.7%; OR, 2.64; difference for 240 mg vs placebo, 22.3%; OR, 2.50). Compared to placebo, 9.4% more patients treated with galcanezumab-gnlm 120 mg and 9.4% more treated with galcanezumab-gnlm 240 mg reported a 100% reduction in MMHD, or migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.6) (*Stauffer et al 2018*).
- In EVOLVE-2, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.0; 95% CI, −2.6 to −1.5; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.4 to −1.4; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.0%; OR, 2.54; difference for 240 mg vs placebo, 21.0%; OR, 2.34). Compared to placebo, 5.8% more patients treated with galcanezumab-gnlm 120 mg and 8.1% more treated with galcanezumab-gnlm 240 mg reported migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.7) (*Skljarevski et al 2018*).
- In an analysis of persistence for patients with episodic migraine, 41.5 and 41.1% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (21.4%; p < 0.001). Approximately 6% of galcanezumab-gnlm-treated patients maintained ≥ 75% response all 6 months vs 2% of placebo-treated patients. Few galcanezumab-gnlm-treated patients maintained 100% response for all 6 months (< 1.5%) (*Förderreuther et al 2018*).

Prevention of chronic migraine

Eptinezumab-jjmr

- The PROMISE-2 trial was a 12-week, DB, PC, MC, Phase 3 trial in which 1121 patients with chronic migraine were randomized to placebo (n = 366), eptinezumab-jjmr 100 mg (n = 356), or eptinezumab-jjmr 300 mg (n = 350) once every 12 weeks (or quarterly). The primary endpoint was the change in mean MMD. Treatment with eptinezumab 100 and 300 mg was associated with significant reductions in MMDs across weeks 1 to 12 compared with placebo (placebo −5.6; 100 mg −7.7, p < 0.0001; 300mg −8.2, p < 0.0001). The odds for a 50% reduction in MMD were approximately 2.1 to 2.4 times higher with eptinezumab-jjmr than placebo (*Lipton et al 2020*).

Erenumab-aooe

- Erenumab-aooe was studied in a 12−week, DB, PC, MC, Phase 2 trial in which 667 patients with chronic migraine were randomized to placebo (n = 286), erenumab−aooe 70 mg (n = 191), or erenumab−aooe 140 mg (n = 190) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg and erenumab−aooe 140 mg (mean change for both doses vs placebo, −2.5; 95% CI, −3.5 to −1.4; p < 0.0001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 17%; OR, 2.2; difference for 140 mg vs placebo, 18%; OR, 2.3). Both erenumab−aooe 70 mg (difference, −1.9) and erenumab−aooe 140 mg (difference, −2.6) significantly reduced the mean acute migraine−specific medication days; however, the higher 140 mg dose had a greater reduction numerically over placebo and reductions may be dose−dependent (*Tepper et al 2017*).
  - An analysis of patient reported outcomes found patients with chronic migraine had clinically relevant improvements across a range of measures. Improvements were observed at month 3 for all endpoints regardless of erenumab−aooe dose, and minimally important clinical differences were achieved for certain measures with the erenumab−aooe 140 mg dose (*Lipton et al 2019[b]*).

Fremanezumab-vfrm

- Fremanezumab-vfrm was studied in a 12-week, DB, PC, MC, Phase 3 trial, HALO-CM, in which 1130 patients with chronic migraine were randomized to placebo (n = 375), fremanezumab-vfrm 225 mg once monthly (n = 379), or fremanezumab-vfrm 675 mg once quarterly (n = 376). Patients in the fremanezumab-vfrm 225 mg group received a loading dose of 675 mg at the first injection only. The primary endpoint was the change in mean headache days (MHD), which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −2.1; SE, ± 0.3; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.8; SE, ± 0.3; p < 0.001). Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MHD (difference for 225 mg vs placebo, 22.7%; OR,

2.73; difference for 675 mg vs placebo, 19.5%; OR, 3.13). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −2.3; difference for 675 mg vs placebo, −1.8) (*Silberstein et al 2017*).

- FOCUS was previously described as including 838 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 61% were diagnosed with chronic migraine and were randomized to fremanezumab-vfrm 675 mg administered quarterly (n = 169/276), a fremanezumab-vfrm 675 mg loading dose followed by 225 mg administered monthly (n = 173/283), or placebo (n = 167/279). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.8 days for the fremanezumab-vfrm monthly group and 3.2 days for the fremanezumab-vfrm quarterly group (fremanezumab-vfrm monthly: LSMD, -3.8; 95% CI, -4.8 to -2.8 days; fremanezumab-vfrm quarterly: LSMD, -3.2; 95% CI, -4.2 to -2.2 days; p < 0.0001 for both) (*Ferrari et al 2019*).

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in a 12-week, DB, PC, MC, Phase 3 trial, REGAIN, in which 1113 patients with chronic migraine were randomized to placebo (n = 558), galcanezumab-gnlm 120 mg once monthly (n = 278), or galcanezumab-gnlm 240 mg once monthly (n = 277). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The primary endpoint was the change in MMHD, which favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.1; 95% CI, −2.9 to −1.3; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.7 to −1.1; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 12.2%; OR, 2.10; difference for 240 mg vs placebo, 12.1%; OR, 2.10). Compared to placebo, 0.2% more patients treated with galcanezumab-gnlm 120 mg and 0.8% more treated with galcanezumab-gnlm 240 mg reported migraine cessation; this was not statistically different for either dose group. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −2.5; difference for 240 mg vs placebo, −2.1) (*Detke et al 2018*).
  - In an analysis of persistence for patients with chronic migraine, 29% of galcanezumab-gnlm-treated patients maintained ≥ 30% response all 3 months compared to 16% of placebo-treated patients. A total of 16.8 and 14.6% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (6.3%; p < 0.001). Few patients maintained ≥ 75% response (< 3%) (*Förderreuther et al 2018*).

Treatment of episodic cluster headache

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in an 8-week, DB trial, in which 106 patients with episodic cluster headache were randomized to placebo (n = 57) or galcanezumab-gnlm 300 mg once monthly (n = 49). A total of 90 (85%) patients completed the DB phase. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen (APAP), and NSAIDs during the study. At baseline, patients had a mean of 17.5 headache attacks/week, maximum of 8 attacks/day, minimum of 1 attack every other day, and at least 4 attacks during the prospective 7-day baseline period. For the primary endpoint, galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency during weeks 1 to 3 vs placebo (-8.7 vs -5.2 attacks; p = 0.036). Galcanezumab-gnlm was also associated with a significantly greater proportion of responders (≥ 50% reduction in weekly cluster headache attack frequency) at week 3 (71.4 vs 52.6%; p = 0.046). Adverse events did not differ between groups, except for a significant increase in the incidence of injection-site pain with galcanezumab-gnlm treated patients (8 vs 0%; p = 0.04) (*Clinicaltrials.gov [NCT02397473] 2020, Emgality prescribing information 2019, Goadsby et al 2019*).

Treatment of acute migraine (with or without aura)

Rimegepant ODT

- Rimegepant ODT was evaluated in a Phase 3, DB, MC, PC, randomized controlled trial (RCT) in 1466 patients (modified intention to treat, n = 1351) with migraine with or without aura. Patients were randomized to placebo (n = 682) or rimegepant ODT 75 mg (n = 669) and were not allowed a second dose of study treatment. Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Approximately 14% of patients were taking

preventive medications for migraine at baseline. The co-primary endpoints were pain freedom and most bothersome symptom (MBS) freedom at 2 hours post-dose. Among patients randomized, 92.2% were included in the efficacy analysis and 93.8% in the safety analysis (*Croop et al 2019, Nurtec ODT [dossier] 2020, Nurtec ODT prescribing information 2020*).
  - The percentage of patients achieving headache pain freedom and MBS freedom 2 hours after a single dose was statistically significantly greater in patients who received rimegepant ODT compared to those who received placebo.
    - *Pain-free at 2 hours*: 21.2% for rimegepant ODT 75 mg vs 10.9% for placebo ($p < 0.0001$)
    - *MBS-free at 2 hours*: 35.1% for rimegepant ODT 75 mg vs 26.8% for placebo ($p = 0.0009$)
  - Out of the 21 secondary endpoints tested hierarchically, significant results were achieved for the first 19 endpoints. Those endpoints that were considered not significant included freedom from nausea at 2 hours post-dose, and pain relapse from 2 to 48 hours.
  - The most common adverse events were nausea and urinary tract infection. No serious adverse events were reported.
- Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet (non-ODT) formulation were considered supportive for approval.
  - A MC, DB, dose-ranging trial using an adaptive design was conducted to determine an effective and tolerable dose range of rimegepant for the acute treatment of migraine. A total of 885 adults with migraine with or without aura were randomized to 1 of 6 rimegepant dose groups (10, 25, 75, 150, 300, or 600 mg), sumatriptan 100 mg, or placebo. It was found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (31.4% [n = 27/86] vs 15.3% [n = 31/203]; $p = 0.002$). The most common adverse events were nausea, vomiting, and dizziness. No treatment-related serious AEs were reported (*Marcus et al 2014*).
  - A MC, DB, PC, Phase 3 trial (n = 1072 in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.6 vs 12.0%; absolute difference, 7.6%; 95% CI, 3.3 to 11.9; $p < 0.001$). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (37.6 vs 25.2%; absolute difference, 12.4%; 95% CI, 6.9 to 17.9; $p < 0.001$). Nausea and urinary tract infection were the only AEs reported in > 1% of the patients in the rimegepant and placebo groups. A serious adverse event associated with rimegepant was back pain (n = 1) (*Lipton et al 2019[c]*, *Nurtec ODT [dossier] 2020*).
  - A MC, DB, PC, Phase 3 trial (n = 1084 in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.2 vs 14.2%; $p = 0.03$). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (36.6 vs 27.7%; $p = 0.002$). Nausea and dizziness were the most common adverse events reported in the rimegepant and placebo treatment groups, respectively. Serious adverse events were reported in 2 patients treated with rimegepant and 1 patient treated with placebo (*Lipton et al 2018 [poster], Nurtec ODT [dossier] 2020*).

Ubrogepant

- Ubrogepant was evaluated in 2 Phase 3, PC, DB trials (ACHIEVE I and II), in which 3358 patients (ACHIEVE I, n = 1672; ACHIEVE II, n =1686) were randomized to take 1 dose of placebo (n = 1122), ubrogepant 50 mg (n = 1118), or ubrogepant 100 mg (n = 557) (100 mg was evaluated in the ACHIEVE I trial only, and a 25 mg group was included in the ACHIEVE II trial only [n = 561]). Patients had 2 to 8 migraines/month with moderate to severe pain intensity in the past 3 months either with or without aura and had a history of migraine for ≥ 1 year. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. At baseline, 23% of patients were taking preventive medications for migraine, and approximately 23 to 27% were insufficient triptan responders. In ACHIEVE I, 79% were included in the efficacy analysis and 86% in the safety analysis, and in ACHIEVE II, 91.7% had a qualifying migraine event and 88% were included in the analysis (*Dodick et al 2019, Lipton et al 2019[a], Ubrelvy prescribing information 2019*).
  - Compared to placebo, significant improvements were demonstrated for the co-primary endpoints of pain freedom and the MBS freedom at 2 hours post-dose in the ubrogepant arms. MBS was a collection of selective, self-identified symptoms (ie, photophobia, phonophobia, or nausea). The following differences from placebo were demonstrated:

  - *Pain-free at 2 hours*: 7.4% (p = 0.002) and 7.5% (p = 0.007) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.4% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
  - *MBS-free at 2 hours*: 10.8% and 11.5% (p < 0.001 for both) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.9% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
- The incidence of photo- and phonophobia was reduced following administration. Significantly more patients maintained pain freedom for 2 to 24 hours post-dose in the ubrogepant 100 mg arm (difference from placebo, 6.8%; p = 0.002) and the 50 mg arm for ACHIEVE II only (6.2%; p = 0.005).
- In ACHIEVE I, the most common adverse events included nausea (1.5 to 4.7%), somnolence (0.6 to 2.5%), and dry mouth (0.6 to 2.1%). In ACHIEVE II, the most common adverse events within 48 hours were nausea (≤ 2.5% for all arms) and dizziness (≤ 2.1% for all arms). No serious adverse events or adverse events leading to discontinuation were reported 48 hours after the initial dose. In ACHIEVE II, the serious adverse events at 30 days included appendicitis, spontaneous abortion, pericardial effusion, and seizure.

Open-label extensions (OLE) and long-term safety studies

- One published OLE with data to 1 year and 1 unpublished abstract with data to ≥ 3 years evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) in patients with episodic migraine. Of 472 patients in the parent study, 308 patients completed 1 year of open-label (OL) treatment. For the ≥ 3 year assessment, of the 383 patients enrolled in the OLE, 250 continued into the 140 mg once monthly dosing. At the time of interim analysis, 236 patients remained in the OLE (*Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018*).
  - There may be greater improvements with sustained therapy based on a 1-year OLE interim analysis of episodic migraine patients treated with erenumab-aooe 70 mg once monthly. Patients had a mean value of 8.8 MMDs at parent study baseline. After 3 months of treatment in the parent study, the number of MMDs was reduced to 6.3 days (mean change of 2.5 days). After a total of 16 months of treatment, the number of MMDs was reduced to 3.7 days (mean change of 5.1 days). After 64 weeks, 65% (n = 184) of episodic migraine patients achieved a ≥ 50% reduction in MMDs and 26% (n = 73) had achieved a migraine-free status. The most frequently reported adverse events (≥ 4.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, influenza, and back pain.
- One unpublished OLE evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) with data to 1 year in patients with chronic migraine. A total of 609 patients with chronic migraine enrolled in the OLE. A total of 199 increased their dose from 70 mg to 140 mg by week 28 (*Amgen [data on file] 2018, Tepper et al 2018*).
  - Patients with chronic migraine had a mean value of 18.8 MMDs at parent study baseline. After a total of 1 year of treatment, the number of MMDs was reduced to 8.5 in the erenumab-aooe 70 mg group and 10.5 in the erenumab-aooe 140 mg group. After 1 year of erenumab-aooe 70 mg and 140 mg monthly dosing, a total of 53% and 67% of chronic migraine patients achieved a ≥ 50% reduction in MMDs and 6% and 13% had achieved a migraine-free status, respectively. The most frequently reported adverse events (≥ 2.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, and arthralgia.
- Another unpublished safety study, the CGAJ study, evaluated galcanezumab-gnlm 120 mg (plus 240 mg loading dose) and 240 mg monthly dosing to 1 year in patients with episodic or chronic migraine. At baseline, 80.7% of patients in the galcanezumab-gnlm 120 mg arm and 77.0% in the galcanezumab-gnlm 240 mg arm had episodic migraine. A total of 270 patients who had a history of ≥ 4 MMHDs and ≥ 1 headache-free day/month for the past 3 months continued galcanezumab-gnlm treatment (*Eli Lilly and Company [data on file] 2018, Emgality [dossier] 2018, Stauffer et al 2017*).
  - At baseline, patients had a mean value of 9.7 to 11.4 (standard deviation [SD], 6.0 to 6.6) MMHDs. After a total of 1 year of treatment, the number of MMHDs was reduced to 5.6 days in the galcanezumab-gnlm 120 mg group and 6.5 days in the galcanezumab-gnlm 240 mg group. After ≥ 12 consecutive months of treatment, 24.2% of patients treated with galcanezumab-gnlm 120 mg and 34.8% of patients treated with galcanezumab-gnlm 240 mg maintained response. The most frequently reported adverse events (incidence ≥ 15.0%) were injection site pain, nasopharyngitis, and upper respiratory tract infections. One patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. There were no overall concerns regarding safety or tolerability.
- The long-term safety of ubrogepant was evaluated in 813 patients with intermittent dosing administered for up to 1 year in an OLE. Of the 813 patients, 421 patients were exposed to ubrogepant 50 mg or 100 mg for ≥ 6 months, and 364 patients were exposed for ≥ 1 year. All patients were treated for ≥ 2 migraine attacks/month, on average. In the OLE, 2.5% of patients withdrew from ubrogepant treatment because of an adverse reaction. The most common adverse

reaction resulting in discontinuation in the OLE was nausea (*Clinicaltrials.gov [NCT02873221] 2020, Ubrelvy prescribing information 2019*).

- Rimegepant 75 mg was evaluated in an unpublished interim analysis of a long-term safety study which evaluated 1784 patients for up to 52 weeks. The most frequently reported adverse events were upper respiratory tract infection (8.5%) and nasopharyngitis (6.4%). There were no deaths, and the rates of serious adverse events and adverse events leading to discontinuation of rimegepant were low (2.5% and 2.7%, respectively). No clinically relevant trends in laboratory abnormalities were observed on-treatment or during follow up (*Nurtec ODT dossier 2020*).
- Caution should be exercised in applying results from extension trials. The OL design may contribute to biased reports. Extension trials may have biased outcomes because those experiencing benefit are included in extension trials; results are useful for reporting trends in treatment. Additionally, there is no comparator to account for placebo effects.

CLINICAL GUIDELINES

Acute treatment of migraine

- The American Headache Society (AHS) published updated consensus statement guidelines for migraine in 2018. The AHS recommends the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans, but recommend that non-oral routes be used when severe nausea or vomiting is present. Overall, the AHS designated the following drugs as having efficacy (*AHS 2019*):
  - Established efficacy:
    - Triptans
    - Ergotamine derivatives
    - NSAIDs (aspirin, diclofenac, ibuprofen, naproxen)
    - Opioids (butorphanol, although use is not recommended)
    - Combination medications
  - Probably effective
    - Ergotamine or other forms of DHE
    - NSAIDs (ketoprofen, ketorolac intramuscular or IV, flurbiprofen)
    - Magnesium IV
    - Isometheptene compounds
    - Combination medications (codeine/APAP, tramadol/APAP)
    - Antiemetics (prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
  - The AHS recommends that rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire or healthcare provider attestation. Coverage should be provided until ≥ 2 attacks are treated to determine efficacy and tolerability.
    - Other agents have had more established efficacy and safety relative to the newly FDA-approved migraine agents.
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan or therapy (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]*).
- In 2019, the American Academy of Neurology (AAN) and the AHS published a guideline on the acute treatment of migraine in children and adolescents. The guideline states that there is evidence to support the efficacy of ibuprofen, APAP (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents (*Oskoui et al 2019[a]*).
  - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Prevention of migraine

- According to the AAN/AHS evidence−based guideline update on the pharmacologic treatment for episodic migraine prevention in adults, the following medications are effective preventive treatment options (see Appendix A for a definition of classifications) (*Silberstein et al 2012*):
  - Level A (established efficacy and > 2 Class I trials):
    - Antiepileptic drugs: divalproex sodium, sodium valproate, and topiramate

    - Beta blockers: metoprolol, propranolol, and timolol
    - Triptans (for menstrual related migraine [MRM]): for short−term prophylaxis, frovatriptan
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Antidepressants: amitriptyline and venlafaxine
    - Beta blockers: atenolol and nadolol
    - Triptans (for MRM): for short−term prophylaxis, naratriptan and zolmitriptan
  - Level C (possibly effective and 1 Class II trial):
    - Angiotensin−converting enzyme (ACE) inhibitors: lisinopril
    - Angiotensin II receptor blockers (ARBs): candesartan
    - Alpha agonists: clonidine and guanfacine
    - Antiepileptic drugs: carbamazepine
    - Beta blockers: nebivolol and pindolol
    - Antihistamines: cyproheptadine
- The AAN recommends onabotulinumtoxin A as an effective treatment option that should be offered for chronic migraine. However, onabotulinumtoxin A is considered ineffective for the treatment of episodic migraines and should not be offered. There is insufficient evidence to compare the effectiveness of botulinum neurotoxin A with that of oral prophylactic topiramate (*Simpson et al 2016*).
- In 2019, the AAN/AHS published a guideline on the preventive treatment of migraine in pediatric patients. The guideline states that the majority of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. The guidelines make the following statements and recommendations for initial therapy (see Appendix B for a definition of classifications) (*Oskoui et al 2019[b]*):
  - It is possible that cognitive behavioral therapy (CBT) alone is effective in migraine prevention.
  - There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents.
  - Acknowledging the limitations of currently available evidence, use of short-term treatment trials (a minimum of 2 months) may be warranted in those who could benefit from preventive treatment (Level B).
  - Consider amitriptyline combined with cognitive behavioral therapy (CBT) (inform of the potential adverse events, including risk of suicide) (Level B).
  - Consider topiramate (Level B). Inform of side effects including decreased efficacy when combined with oral contraceptives and the teratogenic effect in patients of childbearing potential (Level A). In patients of childbearing potential, daily folic acid is recommended (Level A).
  - Consider propranolol (Level B).
    - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Cluster headache

- According to the AHS evidence-based guidelines for the treatment of cluster headache, there are a number of effective treatment options (AAN classifications were used for grading; see Appendix A for definitions) (*Robbins et al 2016*).
- For acute therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Certain triptans: sumatriptan subcutaneous and zolmitriptan nasal spray
    - Oxygen
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Certain triptans: sumatriptan nasal spray and zolmitriptan oral
    - Sphenopalatine ganglion stimulation
  - Level C (possibly effective and 1 Class II trial):
    - Cocaine/lidocaine nasal spray
    - Octreotide subcutaneous
- For preventive therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Suboccipital steroid injection
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Civamide nasal spray (not marketed in the US)

- Level C (possibly effective and 1 Class II trial):
  - Lithium
  - Verapamil
  - Warfarin
  - Melatonin

SAFETY SUMMARY

- Ubrogepant is contraindicated with concomitant use of strong CYP3A4 inhibitors.
- Eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, and rimegepant are contraindicated in patients with serious hypersensitivity to the active ingredient or any of the excipients. Mild to moderate hypersensitivity reactions (eg, rash, dyspnea, pruritus, urticaria) were reported in trials. Cases of anaphylaxis and angioedema have been reported post-marketing. Delayed serious hypersensitivity has occurred with rimegepant. In cases of serious or severe reactions, treatment should be discontinued.
- Warnings and precautions associated with the CGRP inhibitors include hypersensitivity reactions. Erenumab-aooe has additional warnings and precautions associated with the following:
  - Constipation with serious complications: Constipation with serious complications has been reported post-marketing. Some cases have required hospitalization, including surgery. Constipation was a common adverse event reported in up to 3% of patients. Concurrent use of medication associated with decreased gastrointestinal motility may increase the risk for severe constipation.
  - Hypertension: Post-marketing reports of the development or worsening of hypertension have emerged. Some cases required pharmacological treatment to manage or, in other cases, hospitalization. Incidences of hypertension were most frequently reported within 7 days of treatment, and most cases were reported after the first dose.
- The CGRP inhibitors generally have a similar incidence of adverse events as placebo. Very few severe adverse events and treatment discontinuations due to adverse events were reported. Across studies, adverse events were generally mild and/or similar to placebo. The most common adverse events observed in studies of injectable CGRP inhibitors included injection site reactions (subcutaneous CGRP inhibitors), constipation (erenumab-aooe only), and nasopharyngitis and hypersensitivity (eptinezumab-jjmr only). For the oral CGRP inhibitors, ubrogepant was associated with somnolence, and both ubrogepant and rimegepant were associated with nausea.
- CGRP is a vasodilator and is found at higher concentrations during a migraine attack. In the 1-year interim analysis of an OLE study with erenumab-aooe, 2 patients had severe adverse events (a fatal arteriosclerosis event and a myocardial ischemia event confounded by sumatriptan administration). No additional concerns were raised within the OLE at ≥ 3 years, including any CV events. In a long-term safety study of patients treated with galcanezumab-gnlm for 1 year, 1 patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. In a safety study of eptinezumab-jjmr in which 90.2% of patients were exposed to the drug for ≥ 6 months and 47.7% were exposed for ≥ 12 months, the most common adverse events observed were nasopharyngitis and hypersensitivity. A total of 9 patients reported serious adverse events with ubrogepant 50 mg (sinus tachycardia, intestinal obstruction, gait disturbance, cholelithiasis, acute cholecystitis, allergy, pneumonia, pelvic inflammatory disease, post-procedure infection, hypertensive crisis, and a substance-induced mood disorder) and 12 with ubrogepant 100 mg (colitis, hiatus hernia, acute pancreatitis, non-cardiac chest pain, cholelithiasis, acute cholecystitis, gastroenteritis, pneumonia, sepsis, subdural hematoma, ketoacidosis, hemiparesis, abortion, ectopic pregnancy, suicidal ideation, and acute respiratory failure); however, not all events may be related to treatment. In an interim analysis of an OL, 52-week safety study of rimegepant, the most frequently reported adverse events were upper respiratory tract infection and nasopharyngitis. There were no deaths, and the rates of serious adverse events and adverse events leading to discontinuation of rimegepant were low. The long-term implications of prolonged CGRP inhibition are not fully established and safety has not been fully characterized *(Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018, Clinicaltrials.gov [NCT02873221] 2020, Eli Lilly and Company [data on file] 2018, Nurtec ODT [dossier] 2020,Stauffer et al 2017, Tepper et al 2018, Vyepti prescribing information 2020)*.
- There are no adequate data on the risks associated in patients who are pregnant or nursing, or in adolescent or pediatric populations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aimovig (erenumab−aooe)	Auto-injector (70 mg/mL or 140 mg/mL)	SC	Once monthly (70 or 140 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. Latex−sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, erenumab-aooe has a limited stability of 7 days.
Ajovy (fremanezumab−vfrm)	Prefilled syringe (225 mg/1.5 mL)	SC	Once monthly (225 mg) or once every 3 months (675 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. The prefilled syringe cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, fremanezumab-vfrm has a limited stability of 24 hours.
Emgality (galcanezumab−gnlm)	Auto-injector (120 mg/mL) Prefilled syringe (100 mg/mL or 120 mg/mL)	SC	*Prevention of migraine*: 2 consecutive injections (120 mg each) as a loading dose, then once monthly *Episodic cluster headache*: 3 consecutive injections (100 mg each) at onset, and then once monthly until the end of the cluster period	May be self−administered by patients in the abdomen, thigh, back of upper arm or buttocks. The cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, galcanezumab-gnlm has a limited stability of 7 days.
Nurtec ODT (rimegepant sulfate)	ODT (75 mg)	PO	*Acute migraine treatment:* As needed. Maximum dose: 75 mg in 24 hours.	The safety of treating > 15 migraines in a 30-day period has not been established. Avoid concomitant administration with strong inhibitors of CYP3A4, moderate or strong inducers of CYP3A, or P-gp or BCRP inhibitors.
Ubrelvy (ubrogepant)	Oral tablets (50 and 100 mg)	PO	*Acute migraine treatment:* As needed. A second dose may be taken at least 2 hours after the	The safety of treating > 8 migraines in a 30 day period has not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			initial dose. Maximum dose: 200 mg in 24 hours.	Dose adjustments are warranted with certain concomitant drugs or in cases of metabolic impairment. Avoid use in patients with end stage renal disease (CrCL < 15 mL/min). Take with or without food
Vyepti (eptinezumab-jjmr)	Single-dose vial (100 mg/mL)	IV	Once every 3 months (100 or 300 mg) The recommended dosage is 100 mg every 3 months; some patients may benefit from a dosage of 300 mg every 3 months.	Dilute with 0.9% sodium chloride injection. Following dilution, eptinezumab-jjmr must be infused within 8 hours. Infuse over approximately 30 minutes. Administered by a healthcare provider in a healthcare setting. Must be refrigerated and protected from light until time of use.

See the current prescribing information for full details
Abbreviations: CrCL = creatinine clearance; CYP = cytochrome P450; BCRP = breast cancer resistance protein; IV = intravenous; ODT = orally disintegrating tablet; P-gp = P-glycoprotein; PO = oral; SC = subcutaneous
Note: With all of the CGRP inhibitors, there are no data in pregnant women or breastfed infants. A benefit/risk assessment should be taken into consideration prior to administering.

CONCLUSION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Migraines have a spectrum of frequency and severity that can significantly affect the quality of life of patients. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period. Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women.
- Rimegepant and ubrogepant are oral CGRP inhibitors indicated for acute treatment of migraine with or without aura. The injectable CGRP inhibitors eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm are indicated for the prevention of migraine. Galcanezumab-gnlm has an additional indication for the treatment of episodic cluster headache. No CGRP inhibitor is FDA-approved for use in patients aged < 18 years. Eptinezumab-jjmr is the only IV formulation and requires administration in a healthcare setting.
- Guidelines divide treatment recommendations according to age, prevention or treatment, and migraine type:
  - Current evidence−based prophylactic migraine treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used for the preventive treatment of chronic migraine. Prophylactic migraine treatment options include oral agents (mainly anti−seizure agents, antidepressants, and beta blockers), injectable agents (onabotulinumtoxin A for chronic subtypes only), or neuromodulation devices for migraine or headache attacks. Certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. There is no optimal prophylactic migraine therapy and head-to-head trials are lacking.
  - For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy according to the AHS guidelines. To date, only subcutaneous sumatriptan is FDA-approved for the acute treatment of cluster headache. Additionally, sumatriptan nasal spray, zolmitriptan oral formulations, and sphenopalatine ganglion stimulation are probably effective for acute treatment per guidelines. For prevention of cluster headaches, suboccipital steroid injections are most effective according to the guidelines; however, there is no preventive medication currently FDA-approved for cluster headache.

- For acute treatment of migraine in adults, guidelines generally recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or DHE are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. Recent AHS guidelines state that rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans.

- There are no head-to-head studies with the CGRP inhibitors and no agent is clearly superior to others. Evidence for the CGRP inhibitors have demonstrated efficacy for the respective indications:
  - Like other preventive medications for migraine, the CGRP inhibitors are not likely to render patients migraine-free. Based on 3 to 6 month data, primary endpoint reductions are similar to many oral prophylactic therapies; however, comparisons are limited as endpoints have been inconsistently defined. There are limited analyses and trials examining efficacy in patients who failed ≥ 2 prior preventive therapies; however, available data suggest that these patients may achieve greater reductions in migraine/headache frequency. Further research is warranted.
    - Compared to placebo, the CGRP inhibitors when prescribed for prophylactic migraine therapy consistently demonstrated modest but statistically significant reductions in primary endpoint measures (eg, MMD, MMH, or MMHD) ranging from 0.7 to 3.5 days after 3 to 6 months of treatment. Overall, the odds for a 50% reduction in MM(H)D were approximately 1.6 to 5.8 times higher with the CGRP inhibitors than placebo with numbers-needed to treat (NNTs) ranging from 3 to 10.
  - For the treatment of cluster headaches, galcanezumab-gnlm demonstrated efficacy compared to placebo in an 8-week trial, which allowed for acute/abortive treatments during therapy. Galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency by 3.5 during weeks 1 to 3 vs placebo. Additionally, 18.8% more patients were classified as responders (≥ 50% reduction in weekly cluster headache attack frequency) with galcanezumab-gnlm at week 3 vs placebo (p = 0.046).
  - Ubrogepant and rimegepant are oral CGRP inhibitors FDA-approved for acute treatment of migraine with or without aura in adults. One differing characteristic is that ubrogepant allows for a second dose within 24 hours whereas rimegepant does not.
    - Rimegepant ODT demonstrated efficacy compared to placebo in a Phase 3, DB, RCT which evaluated acute response to migraine treatment after 2 hours. Patients were not allowed a second dose of study treatment (placebo or rimegepant). Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Compared to placebo, significantly more patients treated with rimegepant 75 mg were pain-free at 2 hours (difference vs placebo, 10.3%). For the co-primary endpoint of MBS, significantly more rimegepant-treated patients reported being MBS-free at 2 hours post-dose (difference vs placebo, 8.3%). Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet formulation were considered supportive for approval.
    - Ubrogepant demonstrated efficacy compared to placebo in 2 DB, RCTs, which reported acute response to migraine treatment after 2 hours. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. Compared to placebo, significantly more patients treated with ubrogepant were pain-free at 2 hours when administered the 50 mg (difference vs placebo, 7.4 to 7.5%) or 100 mg (difference vs placebo, 9.4%) dose. For the co-primary endpoint of MBS, significantly more ubrogepant-treated patients reported being MBS-free at 2 hours post dose for the 50 mg (difference vs placebo, 10.8 to 11.5%) and 100 mg (difference vs placebo, 9.9%) dose.

- Lack of information during pregnancy and breastfeeding is a consideration as many migraine patients are women of childbearing potential. The unknown risks of monoclonal antibodies and the effects on certain conditions are not fully characterized. Furthermore, rimegepant and ubrogepant have a number of drug interactions, and may not be appropriate with other medications. Important co-morbid populations were excluded from trials (eg, anxiety, depression, hypertension, and fibromyalgia), which also limits the generalizability to broader groups. There are no data in adolescents and children.

- The safety profiles of the subcutaneous CGRP inhibitors are generally mild with the most common adverse events observed being injection site reactions. Hypersensitivity and nasopharyngitis were the most commonly reported adverse events for the IV-administered agent, eptinezumab-jjmr. Mild to moderate hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported with all CGRP inhibitors. Post-marketing reports with erenumab-aooe have included hypertension and constipation with serious complications; some cases of constipation have required hospitalization and surgery. The oral CGRP inhibitors, ubrogepant and rimegepant, were associated with nausea; ubrogepant was additionally associated with somnolence.

- Overall, ubrogepant and rimegepant are alternatives to triptans and/or DHE in patients who are unable to tolerate or have an inadequate response or contraindication to established pharmacologic abortive migraine treatments. The injectable CGRP inhibitors represent another therapy option in the prevention of episodic or chronic migraine. Eptinezumab-jjmr and fremanezumab-vfrm are the only agents in the class that may be administered quarterly, which may fulfill a niche in patients who are non-adherent with treatment. Galcanezumab-gnlm is the only CGRP inhibitor indicated for the treatment of episodic cluster headaches. Dosage and administration vary by product and indication. Further long-term study is warranted.

APPENDICES

- **Appendix A. AAN levels of evidence classification** *(AAN 2017, Gronseth et al 2011)*

Rating of recommendation	
A	Established as effective, ineffective, or harmful for the given condition in the specified population
B	Probably effective, ineffective, or harmful for the given condition in the specified population
C	Possibly effective, ineffective, or harmful for the given condition in the specified population
U	Data inadequate or conflicting; given current knowledge, treatment is unproven.
Rating of therapeutic article	
Class I	RCT in representative population with masked outcome assessment. The following are required: a) concealed allocation; b) primary outcome(s) is/are clearly defined; c) exclusion/inclusion criteria are clearly defined; d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; e) certain requirements are needed for noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs.
Class II	Cohort study that meets a–e (Class I) or RCT that lacks 1 criterion from above (b−e).
Class III	Controlled trials (including well−defined natural history controls or patients serving as own controls), a description of major confounding differences between groups, and where outcome assessment is independent of patient treatment.
Class IV	Does not include patients with the disease, different interventions, undefined/unaccepted interventions or outcomes measures, and/or no measures of effectiveness or statistical precision presented or calculable.

- **Appendix B. AAN/AHS levels of evidence classification** *(Oskoui et al 2019[b])*

Level of obligation; magnitude of benefit	
A	Must; large benefit relative to harm
B	Should; moderate benefit relative to harm
C	May; small benefit relative to harm
U	No recommendation supported; too close to call

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INTRODUCTION

- The United States (U.S.) National Institutes of Allergy and Infectious Disease (NIAID) defines food allergy as an "adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" (*Boyce et al 2010*).
  - Food allergy reactions may include symptoms ranging from oral pruritus and gastrointestinal (GI), ocular, oropharynx, respiratory, and cardiovascular/neurological effects to acute urticaria/angioedema which can progress to more serious sequelae such as anaphylaxis, hypotension, and multiple organ dysfunction syndrome (*Burks et al 2012, Food and Drug Administration [FDA] Allergenic Products Advisory Committee [APAC] briefing document 2019, Pajno et el 2018*).
- Peanut allergy is the most common food allergy in children in the U.S. It affects approximately 1.6 million children with an estimated prevalence of 2.2%; this has increased from 0.4% in 1997 (*FDA summary basis for regulatory action 2020, Gupta et al 2018, Sicherer and Sampson 2014*).
  - Some food allergies (eg, milk, egg, wheat, soy) have a high rate of resolving with age, whereas others (eg, peanut, tree nut, seeds, shellfish) typically persist over time. It is estimated that only 20% of children with peanut allergy outgrow the condition (*FDA summary basis for regulatory action 2020, Muraro et al 2014, Sicherer and Sampson 2018*).
  - Peanut allergy is the leading cause of food-induced anaphylaxis; one study estimated an annual 12.4% incidence of accidental exposures in peanut-allergic children (*Cherkaoui et al 2015, FDA summary basis for regulatory action 2020*). Peanut has been reported to be associated with food allergy death in 35 of 91 persons from 2010 to 2019 (*Pepper et al 2020*).
- The primary approach to managing food allergies is allergen avoidance (*Boyce et al 2010*). However, despite avoidance, accidental exposure may occur and can potentially be serious and life-threatening due to anaphylaxis (*Cherkaoui et al 2015*).
  - To manage symptoms after accidental exposure, epinephrine is used first-line for suspected or confirmed anaphylaxis, while antihistamines can be used for mild symptoms (*Boyce et al 2010*).
- Another approach for managing peanut allergy involves preventive measures. The Learning Early about Peanut Allergy (LEAP) trial demonstrated that introduction of peanut-containing foods to infants at high risk for developing peanut allergy was safe and led to an 81% relative reduction in the subsequent development of peanut allergy (*Du Toit et al 2015, Togias et al 2017*).
- Immunotherapy, including oral immunotherapy (OIT), has also been investigated for treatment of food allergy and involves the delivery of increasing doses of a specific allergen to increase the threshold of reaction while on therapy (also known as desensitization) (*Chinthrajah et al 2019, Institute for Clinical and Economic Review [ICER] 2019, Pajno et al 2018*).
  - The goal of immunotherapy is to decrease the likelihood of life-threatening reactions to accidental exposures rather than induce full tolerance (*FDA APAC briefing document 2019*).
  - Clinical trials have found substantial benefit for patients with peanut allergy undergoing OIT with respect to efficacy during treatment, although adverse events have been frequently reported (*Pajno et al 2018, Pepper et al 2020*).
  - In general, guidelines do not indicate an established place in therapy for oral food allergen immunotherapy (FA-AIT) and emphasize the risk vs benefit with OIT. Of note, the majority of current guidelines were published before the FDA-approval of OIT for food allergy (*Boyce et al 2010, Cox et al 2011, Jutel et al 2015, Muraro et al 2014, Pajno et al 2018, Pepper et al 2020, Sampson et al 2020, Togias et al 2017*).
- Palforzia (peanut [*Arachis hypogaea*] allergen powder-dnfp) is the first standardized FDA-approved OIT for the treatment of peanut allergy in children; it was approved in January 2020. Palforzia is a peanut powder manufactured from defatted peanut flour and evaluated for quantities of specific allergenic peanut proteins (*Aimmune 2020, FDA summary basis for regulatory action 2020, FDA Vaccines, Blood & Biologics 2020*).
- Medispan class: Allergenic Extracts

INDICATIONS

- Palforzia is an OIT indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Palforzia is approved for use in patients with a confirmed diagnosis of peanut allergy.
  - Initial Dose Escalation may be administered to patients 4 through 17 years of age, and Up-Dosing and Maintenance may be continued in patients ≥ 4 years of age.
  - Palforzia is to be used in conjunction with a peanut-avoidant diet.
- Limitation of use: Palforzia is not indicated for the emergency treatment of allergic reactions, including anaphylaxis.
- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization (PALISADE), a Phase 3, double-blind, placebo-controlled, multi-center randomized controlled trial evaluated the efficacy and safety of Palforzia for the mitigation of allergic reactions, including anaphylaxis in 551 patients 4 to 55 years of age with peanut allergy (*FDA APAC briefing document 2019, Vickery et al 2018*).
  - Palforzia was administered orally for 52 weeks through 3 dosing phases: a 1-day supervised Initial Dose Escalation phase, an Up-Dosing phase during which the dose was gradually increased every 2 weeks, and a 24-week Maintenance phase with a daily dose of Palforzia 300 mg.
  - For the primary outcome in patients 4 to 17 years of age in the intention-to-treat population, 67.2% (250/372) of patients in the Palforzia group vs 4.0% (5/124) in the placebo group were able to ingest a single dose of 600 mg peanut protein, the equivalent of approximately 2 peanut kernels, during the exit double-blind placebo-controlled food challenge (DBPCFC; which involves ingesting gradually increasing amounts of peanut protein to determine if the patient has become desensitized or tolerant to peanuts) with no more than mild symptoms (see Table 1). This yielded a between-group treatment difference of 63.2% (95% confidence interval, 53.0 to 73.3; $p < 0.001$).
    - For secondary endpoints, significantly more patients 4 to 17 years of age in the Palforzia group tolerated peanut protein doses of 300 mg and 1000 mg during the exit DBPCFC vs placebo (76.6% vs 8.1% and 50.3% vs 2.4%, respectively; $p < 0.001$ for both comparisons), and less patients experienced moderate and severe symptoms (see Table 1) as the maximum severity of symptoms vs placebo ($p < 0.001$).
  - The proportion of patients 18 to 55 years of age who tolerated 600 mg of peanut protein at the exit DBPCFC in the intention-to-treat population (n = 55) did not demonstrate a significant treatment difference with Palforzia vs placebo; data were limited due to the small sample size and the failure to meet the specified success criterion in adults.

Table 1. Assessment of severity of acute allergic reaction to Palforzia, based on the American Academy of Allergy, Asthma and Immunology (AAAAI)-European Academy of Allergy and Clinical Immunology (EAACI) Practical Allergy (PRACTALL) consensus report on DBPCFC (*Sampson et al 2012, Vickery et al 2018*)

Symptom Severity	Description
Mild	• Skin: Limited (few) or localized hives, swelling (eg, mild lip edema), skin flushing (eg, few areas of faint erythema), pruritus (mild, eg, causing occasional scratching) • Respiratory: Rhinorrhea (eg, occasional sniffling or sneezing), nasal congestion, occasional cough, throat discomfort • GI: Mild abdominal discomfort (including mild nausea), minor vomiting (typically a single episode), single episode of diarrhea
Moderate	• Skin: Systemic hives (eg, numerous or widespread hives), swelling (eg, significant lip or face edema), pruritus causing protracted scratching, more than a few areas of erythema or pronounced erythema • Respiratory: Throat tightness without hoarseness, persistent cough, wheezing without dyspnea • GI: Persistent moderate abdominal pain/cramping/nausea, more than a single episode of vomiting and/or diarrhea
Severe	• Skin: Severe generalized urticaria/angioedema/erythema • Respiratory: Laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea, stridor

	• GI: Severe abdominal pain/cramping/repetitive vomiting and/or diarrhea • Neurological: Change in mental status • Circulatory: Clinically significant hypotension

- An ICER final evidence report evaluated the effectiveness and value of Palforzia, Viaskin Peanut (not FDA-approved), and non-commercialized OIT to desensitize patients with peanut allergies (*ICER 2019*). The substantial increase in Palforzia-treated patients who tolerated peanut protein vs placebo was balanced by a significant increase in GI symptoms, systemic allergic reactions, and epinephrine use. The benefit of Palforzia was rated as Promising but Inconclusive (P/I), with only moderate certainty of a comparable, small, or substantial net health benefit and a small (but nonzero) likelihood of a negative net health benefit for Palforzia compared with strict avoidance and rapid use of epinephrine.
  - The primary benefit of desensitization to peanuts in patients with peanut allergy is likely to be improvements in quality of life (QOL) for both the patient and caregivers. However, QoL outcomes from clinical trials have not been published (*ICER 2019*).

CLINICAL GUIDELINES

Food Allergy Research and Education (FARE) 2019 Oral Immunotherapy for Food Allergy Summit. Consensus report (*Pepper et al 2020*)

- OIT is an emerging option for the treatment of food allergy, but it is not appropriate for all patients with a history of allergic reactions to food. While the EAACI food allergy guidelines (*Pajno et el 2018*) have recommended the use of OIT in “highly specialized clinical centers with expertise and facilities to safely deliver this therapy" for milk, egg or peanut, older U.S. practice guidelines recommend against its use and need to be updated, especially with the approval of Palforzia.
- OIT is most beneficial for fully informed, motivated patients and families who desire enhanced normalcy and a reduced influence of food allergy in their lives, and who are willing to accept the added potential harms and burdens of the treatment.
- The impact of OIT on patient-centered outcomes such as QOL and enhanced normalcy in food-allergic patients are needed in research studies. While studies have demonstrated significant improvement in QOL after OIT, more robust data are needed.
- OIT is a treatment for food allergy but it is not a cure. OIT induces desensitization and may, in a subset of patients, induce sustained unresponsiveness. There is limited evidence that OIT provides long-lasting unresponsiveness after discontinuation in only a subset of patients.

National Institute of Allergy and Infectious Diseases (NIAID)/(AAAAI). Guidelines for the diagnosis and management of food allergy in the U.S. (*Boyce et al 2010*)

- Allergen avoidance is recommended as the first-line treatment for patients with documented immunoglobulin E (IgE)-mediated food allergy.
- Allergen-specific immunotherapy to treat food allergies is not recommended.
- To treat anaphylaxis, epinephrine is the first-line treatment, which may be re-administered every 5 to 15 minutes.

NIAID/AAAAI. Addendum guidelines for the prevention of peanut allergy in the U.S. (*Togias et al 2017*)

- The guidelines recommend early introduction of peanut-containing food at 4 to 6 months of age in infants with severe eczema, egg allergy, or both, based on the evidence of the single randomized, open-label LEAP trial (*Togias et al 2017*).

International Collaboration in Asthma, Allergy and Immunology (formed by the EAACI; AAAAI; the American College of Allergy, Asthma & Immunology; and the World Allergy Organization). International consensus statement on allergen immunotherapy (AIT) (*Jutel et al 2015*)

- Guidelines did not recommend food immunotherapy for clinical use due to the risk of adverse events, including anaphylaxis.
- Studies using OIT for peanut, milk, and egg allergies have shown positive results.

- After 1 to 4 years of OIT of high maintenance doses (300 to 4000 mg) of food protein, a high proportion of patients were able to pass an oral food challenge. However, the rates of epinephrine use due to systemic reactions were up to 25% of the patients, which is too high to recommend OIT for daily practice.
- Food immunotherapy can result in desensitization requiring continuous therapy; however, whether food immunotherapy can result in long-term tolerance in which therapy can be discontinued indefinitely is unknown.

AAAAI. Food allergy: a practice parameter update (*Sampson et al 2014*)
- The primary therapy for food allergy is strict avoidance of the causal food or foods.
- Epinephrine should be used as first-line management for the treatment of anaphylaxis
- Although immunotherapeutic approaches, such as OIT, have shown promise in treating food allergy, they are not ready for implementation in clinical practice at the present time due to inadequate evidence for therapeutic benefit over risks of therapy.
- Experts recommend that introduction of solid foods, including potentially allergenic foods, should not be delayed beyond 4 to 6 months of age.

AAAAI. Allergen immunotherapy practice parameter update (*Cox et al 2011*)
- Several clinical trials with OIT and sublingual immunotherapy have demonstrated an increased tolerance to oral food challenge in patients with food hypersensitivity while receiving therapy.
- Allergen immunotherapy is recommended to be administered by trained staff with on-hand medical equipment for treating anaphylaxis.

EAACI. Guidelines on AIT: IgE-mediated food allergy (*Pajno et el 2018*)
- AIT is potentially indicated for patients with evidence of an IgE-mediated food allergy and in whom avoidance measures are ineffective, undesirable, or cause severe limitations to a patient's QOL.
  - The downside of the adverse events associated with treatment, including risk of mild systemic reactions and anaphylaxis, is outweighed by both the achievement of desensitization and reduced risk of a serious allergic reaction by accidental exposure.
  - FA-AIT is logistically demanding, time-consuming, and most patients are affected by adverse events. Only patients and families who understand the aim of the intervention and its risks and are motivated and adherent should be considered for treatment.

EAACI. Food allergy and anaphylaxis guidelines: diagnosis and management of food allergy (*Muraro et al 2014*)
- Dietary avoidance is the key treatment in the management of food allergy, with the use of epinephrine for emergency management of anaphylaxis.
  - Food allergen-specific immunotherapy for primary food allergy is a promising treatment approach, but it is associated with risk of adverse events including anaphylaxis and is therefore not currently recommended for routine clinical use.

SAFETY SUMMARY

- Key contraindications include use in patients with uncontrolled asthma, and those with a history of eosinophilic esophagitis (EoE) or other eosinophilic GI disease.
- Boxed warnings include the following:
  - Anaphylaxis, which may be life-threatening and can occur at any time during therapy with Palforzia.
  - Injectable epinephrine should be prescribed, and patients should be trained on its appropriate use and instructed to seek immediate care upon its use.
  - Dose modifications may be necessary following an anaphylactic reaction.
  - Palforzia should not be administered in patients with uncontrolled asthma.
  - Patients should be observed for ≥ 60 minutes during and after Initial Dose Escalation and the first dose of each Up-Dosing level with Palforzia administration.
- Other warnings and precautions include risk of EoE and GI reactions.
- Most common adverse events (incidence ≥ 5% and ≥ 5% higher than placebo) were GI, respiratory, and skin symptoms commonly associated with allergic reaction, including abdominal pain, vomiting, nausea, oral pruritus, oral paresthesia, throat irritation, cough, rhinorrhea, sneezing, throat tightness, wheezing, dyspnea, pruritus, urticaria, anaphylactic reaction, and ear pruritus. The highest proportion of adverse events occurred during the Up-Dosing phase of therapy.

- Palforzia will only be available through health care providers, health care settings, pharmacies, and patients who are enrolled and certified in the Palforzia Risk Evaluation and Mitigation Strategy (REMS) program due to anaphylaxis risk.
  - Health care providers and pharmacies must be educated on the risk of anaphylaxis, and health care settings must have on-site access to equipment and trained personnel to manage anaphylaxis and monitor patients during and after Initial Dose Escalation and Up-Dosing of Palforzia.
  - Patients and/or caregivers must be counseled on the need to have injectable epinephrine available for immediate use at all times, continued dietary peanut avoidance, and how to recognize anaphylaxis signs/symptoms.
  - Palforzia may only be dispensed by certified pharmacies to certified health care settings or enrolled patients.

DOSING AND ADMINISTRATION

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Palforzia (peanut [Arachis hypogaea] allergen powder-dnfp)	Powder administered in: • Capsules (0.5 to 100 mg) • Foil-laminate sachet (300 mg)	Oral	Once daily

See the current prescribing information for full details

- The powder from the Palforzia capsule(s) or sachet should be emptied and mixed with a small amount to semisolid food (eg, applesauce, yogurt, pudding) to be consumed by the patient.
- Treatment with Palforzia is administered in 3 sequential phases: Initial Dose Escalation (4 to 5 doses of 0.5 mg up to 6 mg administered at 20 to 30 minute intervals over 1 day), Up-Dosing (dose increases from 3 mg to 300 mg daily at 2 week intervals, over approximately 6 months), and Maintenance (300 mg daily).
  - As part of the REMS program, Initial Dose Escalation and the first dose of each Up-Dosing level must be administered in a certified health care setting equipped to monitor patients and to identify and manage anaphylaxis.
  - Dose modifications are not appropriate during Initial Dose Escalation; however, temporary dose modification of Palforzia may be required for patients who experience allergic reactions during Up-Dosing or Maintenance, for patients who miss doses, or for practical reasons of patient management.
- Daily maintenance is required to maintain the effect of Palforzia.
  - Patients who miss ≥ 3 consecutive days of Palforzia should consult their health care providers and resumption of Palforzia should be done under medical supervision.

CONCLUSION

- Palforzia is only FDA-approved OIT indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut in patients with peanut allergy.
  - Phase 3 data demonstrated a significant reduction of symptom severity due to peanut exposure vs placebo in children 4 to 17 years of age. However, treatment with Palforzia resulted in an increased risk of systemic allergic reactions and use of epinephrine vs placebo.
- Palforzia may cause anaphylaxis, EoE, and GI reactions; it is contraindicated in patients with uncontrolled asthma or a history of other eosinophilic GI disease. The most common adverse events were associated with allergic reaction. Palforzia is only available through a REMS program due to anaphylaxis risk.
- Palforzia is administered in 3 sequential phases; the Initial Dose Escalation and the first dose of each Up-Dosing level must be administered in a certified health care setting equipped to monitor patients and manage anaphylaxis. Patient adherence is critical to ensure the safety and efficacy of treatment with Palforzia.
- OIT with Palforzia is an option for the treatment of peanut allergy; it is efficacious in inducing desensitization but is not without potential harms and burdens, and it is not curative.
  - Treatment with Palforzia does not preclude a peanut-avoidant diet and injectable epinephrine must be available for immediate use at all times due to the risk of anaphylaxis.
- Treatment with Palforzia may be logistically demanding and time-consuming, with most patients affected by adverse events, including the risk of anaphylaxis. Use of Palforzia may be appropriate in patients and families who understand the goal of the intervention and its risks and are motivated and compliant to treatment; adherence is an important consideration to ensure both the efficacy and safety of Palforzia.

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INTRODUCTION

- Epilepsy is a disease of the brain defined by any of the following (*Fisher et al 2014*):
  - At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart;
  - 1 unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years;
  - Diagnosis of an epilepsy syndrome.
- Types of seizures include generalized seizures, focal (partial) seizures, and status epilepticus (*Centers for Disease Control and Prevention [CDC] 2018, Epilepsy Foundation 2016*).
  - Generalized seizures affect both sides of the brain and include:
    - Tonic-clonic (grand mal): begin with stiffening of the limbs, followed by jerking of the limbs and face
    - Myoclonic: characterized by rapid, brief contractions of body muscles, usually on both sides of the body at the same time
    - Atonic: characterized by abrupt loss of muscle tone; they are also called drop attacks or akinetic seizures and can result in injury due to falls
    - Absence (petit mal): characterized by brief lapses of awareness, sometimes with staring, that begin and end abruptly; they are more common in children than adults and may be accompanied by brief myoclonic jerking of the eyelids or facial muscles, a loss of muscle tone, or automatisms.
  - Focal seizures are located in just 1 area of the brain and include:
    - Simple: affect a small part of the brain; can affect movement, sensations, and emotion, without a loss of consciousness
    - Complex: affect a larger area of the brain than simple focal seizures and the patient loses awareness; episodes typically begin with a blank stare, followed by chewing movements, picking at or fumbling with clothing, mumbling, and performing repeated unorganized movements or wandering; they may also be called “temporal lobe epilepsy” or “psychomotor epilepsy”
    - Secondarily generalized seizures: begin in 1 part of the brain and spread to both sides
  - Status epilepticus is characterized by prolonged, uninterrupted seizure activity.
- Seizure classifications from the International League against Epilepsy (ILAE) were updated in 2017. The ILAE classification of seizure types is based on whether the seizure has a focal, generalized, or unknown onset; has a motor or non-motor onset; and whether the patient is aware or has impaired awareness during the event (for focal seizures). Additional classification details may also be used (*Fisher et al 2017A, Fisher et al 2017B*).
  - There is variation between the ILAE classifications and many of the Food and Drug Administration (FDA)-approved indications for antiepileptic drugs (AEDs). For example, a “focal aware” seizure corresponds to the prior term “simple partial seizure,” and a “focal impaired awareness” seizure corresponds to the prior term “complex partial seizure.”
- A number of epilepsy syndromes have also been described; these are defined by groups of features that tend to occur together such as having a similar seizure type, age of onset, part of the brain involved, and electroencephalogram (EEG) pattern (*Epilepsy Foundation 2013*). An example is a childhood epilepsy syndrome called Lennox-Gastaut syndrome (LGS), which is characterized by several seizure types including tonic (stiffening) and atonic (drop) seizures. In LGS, there is a classic EEG pattern seen and intellectual development is usually impaired (*Epilepsy Foundation 2020*).
- Epilepsy management is focused on the goals of 1) controlling seizures, 2) avoiding treatment-related adverse effects (AEs), and 3) maintaining or restoring quality of life. Management options vary based on the seizure type. It is usually appropriate to refer patients to a neurologist to establish the epilepsy diagnosis and formulate the management strategy (*Schachter 2019*).
  - A correct diagnosis is essential to proper treatment selection. For example, absence seizures are commonly confused with complex partial seizures. However, drugs that reduce absence seizures are generally ineffective for complex partial seizures, and the most effective drugs for complex partial seizures may be ineffective against or even increase the frequency of absence seizures (*Epilepsy Foundation 2016*).

- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. When combination therapy is needed, it is recommended to select products with different mechanisms of action and AE profiles. There is little comparative clinical data to support the use of specific combinations (*Schachter et al 2019*).
- Several broad classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents (see Table 1).
- Cannibidiol (Epidiolex) was FDA-approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Cannabidiol is a schedule V controlled substance (*Epidiolex prescribing information 2018*).
- Stiripentol (Diacomit) capsules and powder for oral suspension were FDA-approved in August 2018 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication in April 2018 for use in partial-onset seizures associated with tuberous sclerosis complex (TSC). This product is a kinase inhibitor that also has several oncology indications.
- Midazolam nasal spray (Nayzilam) was approved in May 2019 for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age (*Nayzilam prescribing information 2019*). In January 2020, diazepam nasal spray (Valtoco) was approved for the same indication in patients as young as 6 years of age (*Valtoco prescribing information 2020*).
- Several of the AEDs are used for additional indications beyond the management of epilepsy, including (but not limited to) bipolar disorder, migraine prophylaxis, and several types of neuropathic pain. These additional indications are listed in Table 2; however, this review primarily focuses on the use of AEDs for the management of epilepsy. Additionally, brands and formulations FDA-approved and marketed only for non-epilepsy indications are not included within this review; these include gabapentin tablets (Gralise), FDA-approved only for the management of postherpetic neuralgia, gabapentin enacarbil extended-release tablets (Horizant), FDA-approved only for management of postherpetic neuralgia and treatment of moderate-to-severe restless leg syndrome, and pregabalin extended-release tablets (Lyrica CR), FDA-approved only for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.
- Medispan class: Antianxiety agents, benzodiazepines; Anticonvulsants, AMPA glutamate receptor antagonists; Anticonvulsants, anticonvulsants – misc; Anticonvulsants, carbamates; Anticonvulsants, GABA modulators; Anticonvulsants, hydantoins; Anticonvulsants, succinimides; Anticonvulsants, valproic acid; Hypnotics/Sedatives/Sleep Disorder Agents, barbiturate hypnotics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Barbiturates	
Pentobarbital (Nembutal)	✔
Phenobarbital* (Luminal†, Solfoton†)	✔
Primidone (Mysoline)	✔
Benzodiazepines	
Clobazam (Onfi; Sympazan)	✔ ***
Clonazepam (Klonopin§)	✔
Clorazepate (Tranxene T-Tab§)	✔
Diazepam (Diastat¶, Valium,§ Valtoco)	✔ ‖
Midazolam (Nayzilam)	-
Hydantoins	
Ethotoin (Peganone)	-
Fosphenytoin (Cerebyx)	✔
Phenytoin (Dilantin§, Phenytek)	✔ ‖
Miscellaneous	
Brivaracetam (Briviact)	-
Cenobamate (Xcopri¶¶)	-

Drug	Generic Availability
Cannabidiol (Epidiolex)	-
Carbamazepine (Carbatrol, Epitol**, Equetro, Tegretol§, Tegretol-XR)	✔
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✔
Eslicarbazepine (Aptiom)	-
Ethosuximide (Zarontin)	✔
Everolimus (Afinitor Disperz)	-
Felbamate (Felbatol)	✔
Gabapentin (Neurontin)	✔
Lacosamide (Vimpat)	-
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite**)	✔
Levetiracetam (Keppra, Keppra XR, Roweepra**, Roweepra XR**, Spritam, Elepsia XR)	✔ ‖
Methsuximide (Celontin)	-
Oxcarbazepine (Oxtellar XR, Trileptal)	✔ ‖
Perampanel (Fycompa)	-
Pregabalin (Lyrica)	✔
Rufinamide (Banzel)	-
Stiripentol (Diacomit)	-
Tiagabine (Gabitril)	✔ ‖
Topiramate (Topamax, Topamax Sprinkle, Topiragen††, Trokendi XR, Qudexy XR¶)	✔ ‖
Valproic acid/valproate sodium (Depacon, Depakene)	✔ ‖
Vigabatrin (Sabril, Vigadrone**)	✔ ‖
Zonisamide (Zonegran§)	✔

* Not FDA approved
† Brand product not currently marketed; generic is available
§ Brand marketing status may vary by strength and/or formulation
‖ Generic availability may vary by strength and/or formulation
¶ Authorized generic available; no A-rated generics approved via abbreviated new drug application
** Branded generic
†† Branded generic; not currently marketed
***Generic available for Onfi tablets and oral suspension; only brand name available for Sympazan oral film.
¶¶ FDA-approved product, but not yet marketed.
(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

- Tables 2A and 2B provide an overview of anticonvulsant indications. Except where noted, only FDA-approved products and indications are included. For items marked with an asterisk, there is additional information about the indication provided in the box following the tables.
- Acute-care indications that are not related to convulsive disorders (for example, pre-procedural use of benzodiazepines in hospital settings) are not included.

Table 2A. Indications for anticonvulsants (Part 1 of 2)

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Cenobamate	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Partial seizures (simple partial, complex partial and/or secondarily generalized)	✔ *		✔ *	✔ *			A		✔, A*	✔, A*		✔ *		✔, A*		A*	✔ *	✔, A*	✔ *
Primary generalized tonic-clonic seizure (grand mal)			✔									✔			✔ *			A*	A*
Absence seizure (petit mal)						✔ *			✔, A*		✔								
Multiple seizure types that include absence seizures									A										
Seizures of Lennox-Gastaut syndrome (LGS)		✔ *			A*	✔, A								A*				A*	
Seizures of Dravet syndrome		✔ *																	
Juvenile myoclonic epilepsy (JME)																			A*
Emergency/acute/short-term use for seizure control (see notes)								✔ *							✔ *				
Akinetic and myoclonic seizures						✔, A													
Convulsive disorders (see notes)								A*											
Certain mixed seizure patterns or other partial or generalized seizures			✔ *																
Migraine prophylaxis									✔ *										
Trigeminal neuralgia			✔ *																
Postherpetic neuralgia																✔ *			
Bipolar disorder			✔ *						✔ *									✔ *	
Panic disorder, with or without agoraphobia						✔													
Anxiety disorder; short-term relief of anxiety symptoms							✔	✔											
Symptomatic relief of acute alcohol withdrawal							✔	✔											

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Cenobamate	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Relief of skeletal muscle spasm, spasticity, athetosis, and stiff-man syndrome								A											
Partial-onset seizures associated with tuberous sclerosis complex (TSC)													A*						

✓ = monotherapy (or not specified); A = adjunctive therapy

Table 2B. Indications for Anticonvulsants (Part 2 of 2)

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Partial seizures (simple partial, complex partial and/or secondarily generalized)			✔, A*		✔*		✔*	A*	✔, A*			A*	✔, A*	✔, A*	A*	A*
Primary generalized tonic-clonic seizure (grand mal)					A*		✔*		✔, A*				✔, A*			
Absence seizure (petit mal)		✔*												✔, A*		
Multiple seizure types which include absence seizures														A*		
Seizures of LGS										A*			A*			
Seizures of Dravet syndrome											A*					
Emergency/acute/ short-term use for seizure control (see notes)	✔*			✔*			✔*									
Infantile spasms															✔*	
Convulsive disorders (see notes)						✔*										
Migraine prophylaxis													✔*	✔*		

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Postherpetic neuralgia								✔								
Bipolar disorder														✔ *		
Sedative for anxiety, tension, and apprehension																
Neuropathic pain associated with diabetic peripheral neuropathy								✔								
Neuropathic pain associated with spinal cord injury								✔								
Fibromyalgia								✔								

✓ = monotherapy (or not specified); A = adjunctive therapy
†Phenobarbital is not approved by the FDA.

***Notes: Additional Detail on Selected Anticonvulsant Indications**

- Brivaracetam:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (oral formulations); ≥ 16 years of age (IV formulation)
- Cannabidiol:
  - Treatment of seizures associated with LGS or Dravet syndrome in patients ≥ 2 years of age
- Carbamazepine:
  - Partial seizures with complex symptomatology (psychomotor, temporal lobe); patients with these seizures appear to show greater improvement than those with other types; generalized tonic-clonic seizures (grand mal); mixed seizure patterns which include the above, or other partial or generalized seizures
  - Absence seizures do not appear to be controlled; carbamazepine has been associated with increased frequency of generalized convulsions in these patients
  - Treatment of pain associated with true trigeminal neuralgia; beneficial results also reported in glossopharyngeal neuralgia
  - Bipolar indication is for an extended-release capsule formulation (Equetro) only: treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
- Cenobamate:
  - Partial-onset seizures in adult patients
- Clobazam:
  - Seizures associated with LGS in patients ≥ 2 years of age
- Clonazepam:
  - In patients with absence seizures who have failed to respond to succinimides, clonazepam may be useful
- Diazepam:
  - Oral diazepam may be used adjunctively in convulsive disorders; it has not proved useful as sole therapy.
  - Rectal diazepam is indicated in the management of selected, refractory patients with epilepsy on stable regimens of AEDs who require intermittent use of diazepam to control bouts of increased seizure activity
  - Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures

- Diazepam nasal spray is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 6 years of age

- Divalproex sodium:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures (≥ 10 years of age for all formulations)
  - Monotherapy and adjunctive therapy in the treatment of simple and complex absence seizures (≥ 10 years of age for extended-release tablets; age not specified for tablets/sprinkle capsules)
  - The tablets and extended-release tablets have indications in bipolar disorder and migraine prophylaxis; the sprinkle capsule formulation does not. For bipolar disorder, safety and effectiveness for long-term use (> 3 weeks) has not been demonstrated in controlled clinical trials. Bipolar disorder indications are as follows:
    - Treatment of the manic episodes associated with bipolar disorder (tablets)
    - Treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features (extended-release tablets)
- Eslicarbazepine:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age
- Ethotoin:
  - Complex partial (psychomotor) seizures
- Everolimus:
  - Adjunctive treatment of adult and pediatric patients ≥ 2 years of age with TSC-associated partial-onset seizures (tablets for oral suspension only)
- Felbamate:
  - Not first-line; recommended only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or renal failure is deemed acceptable
  - Monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy
  - Adjunctive therapy of partial and generalized seizures associated with LGS in children (age not specified)
- Fosphenytoin:
  - Treatment of generalized tonic-clonic status epilepticus
  - Prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted short-term for oral phenytoin when oral phenytoin administration is not possible
- Gabapentin:
  - Adjunctive therapy in the treatment of partial-onset seizures, with and without secondary generalization, in adults and pediatric patients ≥ 3 years of age with epilepsy.
  - Management of postherpetic neuralgia in adults
- Lacosamide:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (tablet and oral solution)
  - Treatment of partial-onset seizures in patients ≥ 17 years of age (injection)
- Lamotrigine immediate-release formulations:
  - Age ≥ 2 years for adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of LGS
  - Age ≥ 16 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED
  - Maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (treatment of acute manic or mixed episodes is not recommended)
- Lamotrigine extended-release tablets:
  - Age ≥ 13 years for adjunctive therapy for primary generalized tonic-clonic seizures and partial-onset seizures with or without secondary generalization, and age ≥13 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with a single AED
  - The extended-release formulation is not FDA-approved for bipolar disorder
- Levetiracetam:
  - Tablets, oral solution, injection, and tablets for oral suspension:

        - Treatment of partial-onset seizures in patients ≥ 1 month of age (tablets, oral solution, and injection [Keppra]); adjunctive treatment for partial-onset seizures in patients ≥ 4 years of age and weighing > 20 kg (tablets for oral suspension [Spritam])
        - Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents ≥ 12 years of age with JME
        - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children ≥ 6 years of age with idiopathic generalized epilepsy
    - The extended-release tablets are only indicated for the treatment of partial-onset seizures in patients ≥ 12 years of age
- Methsuximide:
    - Control of absence (petit mal) seizures that are refractory to other drugs
- Midazolam nasal spray:
    - Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age.
- Oxcarbazepine immediate-release formulations:
    - Monotherapy in the treatment of partial seizures in adults and children 4 to 16 years of age
    - Adjunctive therapy in the treatment of partial seizures in adults and children 2 to 16 years of age
- Oxcarbazepine extended-release tablets:
    - Treatment of partial-onset seizures in adults and children ≥ 6 years of age
- Pentobarbital:
    - In anesthetic doses in the emergency control of certain acute convulsive episodes, eg, those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics
- Perampanel:
    - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ≥ 4 years of age
    - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy ≥ 12 years of age
- Phenobarbital (not FDA-approved):
    - Phenobarbital tablets are indicated for use as an anticonvulsant; the elixir is indicated for the treatment of generalized and partial seizures; the injection is indicated as an anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures, in the emergency control of certain acute convulsive episodes, and in pediatric patients as an anticonvulsant
- Phenytoin oral formulations:
    - Treatment of tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery (the oral suspension does not have the neurosurgery indication)
- Phenytoin injection:
    - Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery
    - Can be substituted as short-term use for oral phenytoin when oral phenytoin administration is not possible
- Pregabalin:
    - Adjunctive therapy for treatment of partial-onset seizures in patients ≥ 1 month of age
- Primidone:
    - Control of grand mal, psychomotor, and focal epileptic seizures; may control grand mal seizures refractory to other anticonvulsant therapy
- Rufinamide:
    - Adults and pediatric patients ≥ 1 year of age
- Stiripentol:
    - Treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age taking clobazam; no clinical data to support its use as monotherapy
- Tiagabine:
    - Adjunctive therapy in adults and children ≥ 12 years of age in the treatment of partial seizures

- Topiramate:
  - Initial monotherapy in patients with partial-onset or primary generalized tonic-clonic seizures (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Adjunctive therapy for adults and pediatric patients with partial-onset seizures or primary generalized tonic-clonic seizures and in patients with seizures associated with LGS (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Prophylaxis of migraine headache in patients ≥ 12 years of age
- Valproic acid/valproate sodium:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures; sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures
- Vigabatrin:
  - Adjunctive therapy for patients ≥ 2 years of age with refractory complex partial seizures who have responded inadequately to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss
  - Monotherapy for patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
- Zonisamide:
  - Adjunctive therapy in the treatment of partial seizures in adults with epilepsy

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. Clinical trial data demonstrating efficacy of the anticonvulsants for the treatment of epilepsy is described in the prescribing information for the individual products, particularly for anticonvulsants more recently approved by the FDA. However, the prescribing information for some older, conventional products (eg, benzodiazepines, carbamazepine, ethotoin, ethosuximide, methsuximide, phenytoin, and primidone) and non-FDA approved products (eg, phenobarbital) do not contain efficacy data in their prescribing information.
- No single AED is clearly the most effective. Comparative efficacy data for the management of epilepsy are limited, and trials have generally not shown significant differences among drugs in terms of efficacy. However, the quality of the data is limited and generally derived from short-term trials (*Karceski 2019*).
- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. (*Schachter et al 2019*). Most patients with epilepsy are treated with anticonvulsant monotherapy (*Nevitt et al 2017*).
- An evidence review summarized AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (*Glauser et al 2013*). This publication provides conclusions based on a review of 64 randomized trials and 11 meta-analyses. Conclusions include the following:
  - As initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures:
    - Carbamazepine, levetiracetam, phenytoin, and zonisamide are established as efficacious/effective.
    - Valproate is probably efficacious/effective.
    - Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin are possibly efficacious/effective.
    - Clonazepam and primidone are potentially efficacious/effective.
  - As initial monotherapy for children with newly diagnosed or untreated partial-onset seizures:
    - Oxcarbazepine is established as efficacious/effective.
    - Carbamazepine, phenobarbital, phenytoin, topiramate, valproate, and vigabatrin are possibly efficacious/effective.
    - Clobazam, carbamazepine, lamotrigine, and zonisamide are potentially efficacious/effective.
  - As initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures:
    - Gabapentin and lamotrigine are established as efficacious/effective.

        - Carbamazepine is possibly efficacious/effective.
        - Topiramate and valproate are potentially efficacious/effective.
    - As initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
        - Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
        - Gabapentin, levetiracetam, and vigabatrin are potentially efficacious/effective.
        - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
    - For children with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
        - Carbamazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
        - Oxcarbazepine is potentially efficacious/effective.
        - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
    - As initial monotherapy for children with newly diagnosed or untreated absence seizures:
        - Ethosuximide and valproate are established as efficacious/effective.
        - Lamotrigine is possibly efficacious/effective.
        - Gabapentin is established as inefficacious/ineffective.
        - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence seizures (based on scattered reports).
    - As initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes (BECTS):
        - Carbamazepine and valproate are possibly efficacious/effective.
        - Gabapentin, levetiracetam, oxcarbazepine, and sulthiame (not available in the United States) are potentially efficacious/effective.
    - For patients with newly diagnosed JME:
        - Topiramate and valproate are potentially efficacious/effective.
        - Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence, myoclonic, and in some cases generalized tonic-clonic seizures. There has also been a report that lamotrigine may exacerbate seizures in JME.
    - There is a lack of well-designed randomized trials in epilepsy, particularly for generalized seizures and in the pediatric population.
- A Cochrane systematic review evaluated the efficacy of AED monotherapy for epilepsy (*Nevitt et al 2017*). The review included the use of carbamazepine, phenytoin, valproate, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide for the treatment of partial-onset seizures (simple partial, complex partial or secondarily generalized) or generalized tonic-clonic seizures with or without other generalized seizure types.
    - This network meta-analysis showed that for the primary outcome, the time to withdrawal of allocated treatment:
        - For individuals with partial seizures, levetiracetam performed better than carbamazepine and lamotrigine; lamotrigine performed better than all other treatments (aside from levetiracetam); and carbamazepine performed better than gabapentin and phenobarbital.
        - For individuals with generalized onset seizures, valproate performed better than carbamazepine, topiramate and phenobarbital.
        - For both partial and generalized onset seizures, phenobarbital seems to perform worse than all other treatments.
    - For the secondary outcome, time to first seizure:
        - For individuals with partial seizures, phenobarbital performed better than both carbamazepine and lamotrigine; carbamazepine performed better than valproate, gabapentin, and lamotrigine; and phenytoin performed better than lamotrigine.
        - For both partial and generalized seizure types, phenytoin and phenobarbital generally performed better than other treatments.
    - Few notable differences were shown for either partial or generalized seizure types for the secondary outcomes of time to 6-month or 12-month remission of seizures.
    - Overall, direct evidence and network meta-analysis estimates were numerically similar, and effect sizes had overlapping confidence intervals.
    - Data for individuals with generalized seizures are still limited and additional randomized trials are needed.
- The relative efficacy among valproate, lamotrigine, phenytoin, carbamazepine, ethosuximide, topiramate, levetiracetam, and phenobarbital as monotherapy for generalized (n = 7 studies) or absence seizures (n = 3 studies) was evaluated in

a systematic review and network meta-analysis (*Campos et al 2018*). The outcomes analyzed were seizure freedom and withdrawal due to inefficacy. Compared to valproate, phenytoin had a lower odds of seizure freedom (odds ratio, 0.50; 95% credible Interval [CrI] 0.27 to 0.87) in patients with generalized tonic-clonic seizures. Lamotrigine had the highest probability of seizure freedom and valproate had the highest probability of withdrawal due to inefficacy in these patients. For absence seizures, ethosuximide and valproate were found to have a higher probability of seizure freedom compared to lamotrigine.

- A meta-analysis estimated the comparative efficacy of achieving seizure freedom with 22 antiepileptic drugs and placebo in children and adolescents (*Rosati et al 2018*). For the treatment of newly diagnosed focal epilepsy (n = 4 studies), point estimates suggested superiority of carbamazepine and lamotrigine; however, this was not statistically significant. For refractory focal epilepsy (n = 9 studies), levetiracetam and perampanel were more effective than placebo in mixed comparisons. Ethosuximide and valproic acid were more effective than lamotrigine for absence seizures. The authors concluded that better designed comparative studies with appropriate length of follow-up, well-defined outcomes, and reliable inclusion criteria are needed to validate these results.
- A meta-analysis compared monotherapy with carbamazepine or phenytoin in children and adults with focal onset seizures (simple or complex focal and secondarily generalized), or generalized onset tonic-clonic seizures (with or without other generalized seizure types). Results demonstrated that the time to treatment failure (primary outcome) did not significantly differ between treatment groups. The time to first seizure after randomization and 6-month and 12-month remission were also similar between groups (*Nevitt et al 2019).*
- Approximately 20% to 40% of patients with epilepsy can be considered refractory to drug treatment, referred to as drug-resistant epilepsy. Treatment of drug-resistant epilepsy may include additional anticonvulsant drug trials, epilepsy surgery, vagal nerve stimulation, and dietary changes (the ketogenic diet) (*Sirven 2018*).
  - Combination AED regimens are an option for the treatment of drug-resistant epilepsy. However, robust clinical evidence of suitable combinations of AEDs has been difficult to generate due to the large number of possible combinations of drugs and doses. Examples of combinations for which there is some evidence of efficacy include valproate plus lamotrigine for partial-onset and generalized seizures, valproate plus ethosuximide for absence seizures, and lamotrigine plus topiramate for various seizure types; however, even this evidence is fairly limited. In general, when considering combination therapy, it is recommended to combine medications with different mechanisms of action, and to be mindful of the overall drug load to minimize AEs. Two-drug therapy should be attempted before considering addition of a third drug, and higher numbers of drugs should be avoided as they are associated with a very low likelihood of additional seizure reduction (*Kwan et al 2011*).
  - A meta-analysis examined the efficacy of newer AEDs (eslicarbazepine, brivaracetam, perampanel, and lacosamide) versus levetiracetam as adjunctive therapy for uncontrolled partial-onset seizures. Most patients in this meta-analysis were on at least 2 other AEDs at the time of treatment. In this analysis, eslicarbazepine, lacosamide, and brivaracetam were non-inferior to levetiracetam in terms of efficacy, but all newer AEDs except brivaracetam had worse tolerability profiles than levetiracetam at high doses (*Zhu et al 2017*).
  - A network meta-analysis examined the efficacy of AEDs (including brivaracetam, eslicarbazepine acetate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, perampanel, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide) for adjunctive use in patients with refractory partial-onset seizures while using monotherapy (*Zhao et al 2017*). The efficacy outcomes studied were 50% responder rate and state of seizure freedom. The authors concluded that topiramate, levetiracetam, pregabalin, and oxcarbazepine were preferable for their relatively high efficacy and low risk of AEs. Rufinamide was the least preferable medication due to its low efficacy and high risk of AEs.
  - A network meta-analysis was conducted to evaluate the efficacy of 17 newer AEDs for treatment of refractory partial-onset epilepsy with or without secondary generalization (*Hu et al 2018*). The primary outcome was seizure freedom, which was defined as a 100% seizure reduction in the maintenance or double-blind treatment period of the trial. Safety was assessed by the withdrawal rate due to treatment-emergent AEs. Based on results of 54 studies that evaluated the efficacy outcome, the most effective agents included tiagabine, brivaracetam, and valproic acid, and the least effective agents included rufinamide, lamotrigine, and zonisamide. Products with favorable safety included levetiracetam, brivaracetam, and perampanel, while those with the least favorable safety included retigabine (not available in the United States), oxcarbazepine, and rufinamide. The authors stated that agents with the best outcomes in terms of efficacy and safety included levetiracetam, vigabatrin, valproic acid, and brivaracetam.
  - Cannabidiol (Epidiolex) was approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet

syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Its approval for these 2 indications was based on 3 placebo-controlled trials in patients refractory to other treatments. Epidiolex, along with use of other agents, demonstrated a significant reduction in seizure frequency compared to placebo (*Thiele et al 2018*; *Devinsky et al* 2018; *Devinsky et al* 2017). To date, no comparative trials have been published.

- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication for adjunctive use in TSC-associated partial-onset seizures in April 2018. Results of a randomized, double-blind, placebo-controlled study of 366 patients with inadequately controlled seizures on 2 or more AEDs demonstrated a significant reduction in seizure frequency compared to placebo (*French et al 2016*).
- In August 2018, the FDA approved a second drug, stiripentol (Diacomit), for use in the treatment of seizures associated with Dravet syndrome. Two multicenter placebo-controlled studies evaluated the addition of stiripentol to clobazam and valproate therapy in patients 3 years to less than 18 years of age with Dravet syndrome. Responder rates (seizure frequency reduced by 50%) with respect to generalized tonic-clonic seizures were significantly lower with stiripentol compared to placebo (*Diacomit prescribing information 2018).*
- In May 2019, a nasal spray formulation of midazolam (Nayzilam) was approved for the acute treatment of cluster seizures in adults and adolescents. In one randomized controlled trial in patients with seizure clusters while receiving a stable AED regimen, the proportion of patients who experienced treatment success (seizure termination within 10 minutes and no recurrence for the next 6 hours) was significantly higher with midazolam nasal spray compared to placebo (53.7% vs 34.4%, p = 0.0109) with similar tolerability (*Detyniecki et al 2019*).
- Cenobamate was approved in late 2019 and its efficacy has yet to be compared to other AEDs. The approval of this agent was based on 2 multicenter, randomized, double-blind, placebo-controlled studies that enrolled 655 adults with partial-onset seizures with or without generalization who were not adequately controlled with 1 to 3 other AEDs. The results of these trials demonstrated that cenobamate significantly reduced the frequency of seizures occurring in a 28-day period. In the first trial, the median percent change in seizure frequency from baseline was -55.6% with cenobamate and -21.5% with placebo. In the second trial, the median percent change ranged from -36.3% to -55.3% with cenobamate and was -24.3% with placebo (*Xcopri package insert 2019, Krauss et al 2020*).
- A 2019 randomized controlled trial of children and adults with benzodiazepine-refractory convulsive status epilepticus compared the efficacy of intravenous levetiracetam (n = 145 patients), fosphenytoin (n = 118), or valproate (n = 121) in this setting. Results demonstrated that each agent led to seizure cessation and improved alertness by 1 hour in approximately 50% of patients, with no significant differences between groups (*Kapur et al 2019*).

CLINICAL GUIDELINES

- **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy**. American Academy of Neurology and American Epilepsy Society (*French et al 2004A, Kanner et al, 2018A*).
  - A 2018 update to the 2004 guideline focuses on treatment of new-onset epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with newly diagnosed partial and generalized epilepsies.
  - The recommendations from the 2004 guideline include the following:
    - Patients with newly diagnosed epilepsy who require treatment can be initially treated with standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital, or on the newer AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice will depend on individual patient characteristics.
    - Lamotrigine can be included in the options for children with newly diagnosed absence seizures.
  - The 2018 recommendations include the following:
    - As monotherapy in adult patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures:
      - Lamotrigine use should be considered to decrease seizure frequency.
      - Lamotrigine use should be considered and gabapentin use may be considered to decrease seizure frequency in patients aged ≥ 60 years.
      - Levetiracetam and zonisamide use may be considered to decrease seizure frequency.
      - Vigabatrin appears to be less efficacious than carbamazepine immediate-release and may not be offered; furthermore, the toxicity profile precludes vigabatrin use as first-line therapy.
      - Pregabalin 150 mg per day is possibly less efficacious than lamotrigine 100 mg per day.

        - There is insufficient evidence to consider use of gabapentin, oxcarbazepine, or topiramate over carbamazepine.
        - There is insufficient evidence to consider use of topiramate instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures.
        - Data are lacking to support or refute use of third-generation AEDs (eslicarbazepine, ezogabine [no longer marketed], lacosamide, perampanel, pregabalin, and rufinamide), clobazam, felbamate, or vigabatrin for new-onset epilepsy.
        - Data are lacking to support or refute use of newer AEDs in treating unclassified generalized tonic-clonic seizures.
    - Ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency in children with absence epilepsy. An exception would be if there are compelling AE-related concerns with use of ethosuximide or valproic acid.
    - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy**. American Academy of Neurology and American Epilepsy Society (*Kanner et al 2018B*, *French et al 2004B*).
    - A 2018 update to the 2004 guideline focuses on management of treatment-resistant epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with refractory partial and generalized epilepsies.
    - Recommendations from the 2004 guideline include the following:
        - It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy.
        - Oxcarbazepine, topiramate, and lamotrigine can be used as monotherapy in patients with refractory partial epilepsy.
        - Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children.
        - Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures.
        - Topiramate and lamotrigine may be used to treat drop attacks associated with LGS in adults and children.
    - Recommendations from the 2018 guideline include the following:
        - As adjunctive therapy in patients with treatment-resistant adult focal epilepsy (TRAFE):
            - Immediate-release pregabalin and perampanel are established as effective to reduce seizure frequency.
            - Lacosamide, eslicarbazepine, and extended-release topiramate should be considered to decrease seizure frequency.
            - Vigabatrin and rufinamide are effective for decreasing seizure frequency, but are not first-line agents.
            - Ezogabine (no longer marketed) use should be considered to reduce seizure frequency, but carries a serious risk of skin and retinal discoloration.
            - Clobazam and extended-release oxcarbazepine may be considered to decrease seizure frequency.
        - As monotherapy in patients with TRAFE:
            - Eslicarbazepine use may be considered to decrease seizure frequency.
            - Data are insufficient to recommend use of second- and the other third-generation AEDs.
        - For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine should be considered as add-on therapy to decrease seizure frequency in adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy.
        - Rufinamide is effective to reduce seizure frequency as add-on therapy for LGS. Clobazam use should be considered as add-on therapy for LGS.
        - For add-on therapy in pediatric patients with treatment-resistant focal epilepsy:
            - Levetiracetam use should be considered to decrease seizure frequency (ages 1 month to 16 years).
            - Zonisamide use should be considered to decrease seizure frequency (age 6 to 17 years).
            - Oxcarbazepine use should be considered to decrease seizure frequency (age 1 month to 4 years).

- Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, rufinamide, tiagabine, or vigabatrin.
- The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.

- **Evidence-based guideline: management of an unprovoked first seizure in adults.** Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (*Krumholz et al 2015; reaffirmed in 2018*).
  - This practice guideline makes recommendations based on a consideration of the evidence for prognosis and treatment of adults with an unprovoked first seizure.
  - Recommendations include the following:
    - Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21% to 45%).
    - Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, or a nocturnal seizure.
    - Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure, it may not improve quality of life.
    - Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.
    - Patients should be advised that their risk for AED AEs ranges from 7% to 31% and that these AEs are predominantly mild and reversible.
  - Immediate AED therapy after an unprovoked first seizure is likely to reduce seizure recurrence risk. A reduction in risk may be important, particularly for adults, for whom seizure recurrences may cause serious psychological and social consequences such as loss of driving privileges and limitations on employment. However, immediate AED treatment is not well accepted and is debated. Decisions should be based on weighing the risk of recurrence against the AEs of AED therapy, and should take patient preferences into account.
  - It is accepted that when a patient has a second or additional seizures, an AED should be initiated because the risk of subsequent seizures is very high.
- **Evidence-based guideline: treatment of convulsive status epilepticus in children and adults.** Guideline Committee of the American Epilepsy Society (*Glauser et al 2016*).
  - This publication provides conclusions and a treatment algorithm based on a structured literature review of randomized trials of anticonvulsant treatments for seizures lasting longer than 5 minutes. A total of 38 trials were included.
  - For treatment in the adult population, conclusions included the following:
    - Intramuscular (IM) midazolam, intravenous (IV) lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes.
    - IV lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes.
    - There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin.
    - IV valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine.
    - Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy.
    - In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam.
    - No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus.
  - For treatment in the pediatric population, conclusions included the following:
    - IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes.
    - Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes.
    - Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy.
    - IV valproic acid has similar efficacy but better tolerability than IV phenobarbital as second therapy after failure of a benzodiazepine.

        - Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine.
        - In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam.
        - In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal).
    - Conclusions included the following (age not specified):
        - Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. Fosphenytoin is better tolerated compared with phenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative.
    - The overall treatment algorithm directs that:
        - A benzodiazepine (IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice in the first phase of treatment (5 to 20 minutes after the beginning of the seizure). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration positions it as an alternative initial therapy. For prehospital settings or where first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.
        - In the second phase of treatment (from 20 to 40 minutes after the beginning of the seizure), reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any of these options is better than the others. Because of AEs, IV phenobarbital is a reasonable second-therapy alternative if none of the 3 recommended therapies are available.
        - There is no clear evidence to guide therapy in the third phase of therapy (≥ 40 minutes after the beginning of the seizure).
- **Evidence-based guideline update: medical treatment of infantile spasms.** Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Go et al 2012*; reaffirmed in 2018)
    - This publication provides updated recommendations for the treatment of infantile spasms. The literature review included an evaluation of 26 published articles on this topic.
    - Recommendations include the following:
        - Evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as adrenocorticotropic hormone (ACTH) for short-term treatment of infantile spasms.
        - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.
        - ACTH or vigabatrin may be offered for short-term treatment of infantile spasms; evidence suggests that ACTH may be offered over vigabatrin.
        - Evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam [not available in the United States], levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms.
        - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
        - A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
    - There is a lack of sufficient randomized trials to provide definitive answers to key questions related to treatment of infantile spasms.
- **Practice parameter: treatment of the child with a first unprovoked seizure.** Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Hirtz et al 2003*; reaffirmed in 2018)
    - This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Treatment during the neonatal period is not addressed.
    - Recommendations include the following:
        - Treatment with AEDs is not indicated for the prevention of the development of epilepsy.
        - Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial AEs.

- The majority of children who experience a first unprovoked seizure will have few or no recurrences. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission.
- Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence; however, there is a relative paucity of data from studies involving only children after a first seizure.

- **Summary of recommendations for the management of infantile seizures**. Task force report for the ILAE Commission of Pediatrics (*Wilmshurst et al 2015*).
  - This publication recommends an approach to the standard and optimal management of infants with seizures. When possible, recommendations are evidence-based; however, when no evidence was available, recommendations are based on expert opinion and standard practice.
  - Recommendations/findings include the following:
    - There is no indication for initiation of chronic AEDs for simple febrile seizures. However, in the acute treatment of febrile seizures, it is important to treat seizures lasting 10 minutes or longer.
    - In an otherwise healthy infant, a policy of "wait and see" is reasonable after the first afebrile seizure. However, this is a rare event and close monitoring is essential.
    - Treatment options with established or probable efficacy include the following:
      - Focal seizures: levetiracetam
      - Epileptic spasms: High-dose or low-dose ACTH
      - Dravet syndrome: stiripentol
    - Treatment options with possible efficacy include the following:
      - Generalized seizures: levetiracetam, valproate, lamotrigine, topiramate, clobazam
      - Epileptic spasms: prednisone, vigabatrin
      - Benign infantile convulsions: carbamazepine, phenobarbital, valproate
      - Dravet syndrome: topiramate, zonisamide, valproate
      - Benign myoclonic epilepsy of infancy: valproate, topiramate, lamotrigine, clonazepam
      - Provoked or situational seizures: carbamazepine
    - There is no clear evidence supporting an optimal duration of treatment; this is dependent on seizure type.
- **Guidelines on neonatal seizures**. World Health Organization (WHO) (*WHO 2011*).
  - This document was prepared based on a systematic review of the literature and involved cooperation between the WHO, the ILAE, and the International Bureau of Epilepsy (IBE).
  - Recommendations include the following:
    - Phenobarbital should be used as the first-line agent for treatment of neonatal seizures and should be made readily available in all settings.
    - In neonates who continue to have seizures despite administering the maximum tolerated dose of phenobarbital, either a benzodiazepine, phenytoin, or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring).
    - In neonates with a normal neurological examination and/or normal EEG, stopping AEDs may be considered if the neonate has been seizure-free for > 72 hours; the drug(s) should be reinstituted if seizures recur.
    - In neonates in whom seizure control is achieved with a single AED, the drug can be discontinued abruptly without tapering the dose. In neonates requiring > 1 AED for seizure control, the drugs may be stopped one at a time, with phenobarbital being the last drug to be withdrawn.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009A*; reaffirmed in 2013; Update in progress)
  - This publication summarizes evidence for selected issues regarding the clinical management of women with epilepsy (WWE) who are pregnant or planning to be pregnant.
  - Recommendations include the following:
    - If possible, avoidance of the use of valproate as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (MCMs).
    - If possible, avoidance of the use of valproate monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs.

        - To reduce the risk of MCMs, the use of valproate during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine.
        - To reduce the risk of MCMs, avoidance of the use of polytherapy with valproate during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without valproate.
        - To reduce the risk of MCMs, avoidance of the use of valproate during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin or lamotrigine.
        - To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered.
        - Limiting the dosage of valproate or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of MCMs.
        - Avoidance of the use of valproate, if possible, should be considered to reduce the risk of neural tube defects and facial clefts, and may be considered to reduce the risk of hypospadias.
        - Avoidance of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for phenytoin use, posterior cleft palate for carbamazepine use, and cardiac malformations for phenobarbital use.
        - Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE.
        - Avoiding valproate in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes.
        - Avoiding phenytoin and phenobarbital in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes.
        - Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, may be considered compared to phenytoin to reduce the risk of poor cognitive outcomes.
    - Valproate has the most data showing an association with risk from in utero exposure. If a change from valproate to another AED is planned, it is prudent to make this change well before pregnancy.
    - Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Discontinuing AEDs may expose the mother and fetus to physical injury from accidents due to seizure activity.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009B*; reaffirmed in 2013; Update in progress)
    - This publication summarizes evidence for selected issues regarding the clinical management of WWE who are pregnant or planning to be pregnant.
    - Recommendations include the following:
        - The fact that phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, valproate, gabapentin, lamotrigine, oxcarbazepine, and topiramate cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy.
        - Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered.
        - Monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels during pregnancy may be considered.
        - There is insufficient evidence to support or refute a change in phenobarbital, valproate, primidone, or ethosuximide levels related to pregnancy, but this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.
        - Valproate, phenobarbital, phenytoin, and carbamazepine may not transfer into breast milk to as great an extent as primidone, levetiracetam, gabapentin, lamotrigine, and topiramate.
    - Although many of the AEDs were shown to cross the placenta or enter breast milk, studies were limited in duration and did not systematically evaluate neonatal symptoms.

- Guidelines also support the use of AEDs for several common non-epilepsy indications:
  - The American Academy of Neurology and American Headache Society state that AEDs with established efficacy for migraine prevention include valproate, divalproex sodium, and topiramate; carbamazepine is noted to be possibly effective (*Silberstein et al 2012;* reaffirmed in 2015; Update in progress). An American Academy of Neurology guideline for pediatric migraine prevention noted that children and adolescents with migraine receiving topiramate are probably more likely than those receiving placebo to have a reduction in migraine or headache day frequency, whereas there was insufficient evidence to support the efficacy of extended-release divalproex sodium for reducing frequency (*Oskoui et al 2019*).
  - The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation state that, for relief of painful diabetic neuropathy, pregabalin is established as effective, and gabapentin and valproate are probably effective (*Bril et al 2011*; Update in progress).
  - A retired guideline from The American Academy of Neurology states that gabapentin and pregabalin are of benefit in reducing pain from postherpetic neuralgia (*Dubinsky et al 2004; retired February 27, 2018*).
  - American Psychiatric Association guidelines describe the key role of AEDs in the management of bipolar disorder, including the following (*Hirschfeld et al 2002*):
    - First-line pharmacological treatment for more severe manic or mixed episodes is either lithium plus an antipsychotic or valproate plus an antipsychotic; for less ill patients, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. For mixed episodes, valproate may be preferred over lithium. Carbamazepine and oxcarbazepine are alternatives.
    - First-line pharmacological treatment for bipolar depression is either lithium or lamotrigine. When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment, the next steps include adding lamotrigine, bupropion, or paroxetine.
    - The initial treatment for patients who experience rapid cycling should include lithium or valproate; an alternative is lamotrigine.
    - The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine.
    - Note: This guideline was published in 2002 and cannot be assumed to be current; however, AEDs continue to be recommended for both acute (mania or hypomania) and maintenance phases of bipolar disorder *(Post 2017, Stovall 2018).*

SAFETY SUMMARY

- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment (*Schachter 2019*).
- Common AEs among AEDs include the following (*Schachter 2019*).
  - Systemic AEs:
    - nausea, vomiting, constipation, diarrhea, anorexia
    - rash
    - hyponatremia (carbamazepine, eslicarbazepine, oxcarbazepine)
    - weight gain (pregabalin, perampanel, valproate), weight loss (felbamate, topiramate, stiripentol)
  - Neurologic AEs:
    - headache
    - somnolence, sedation, drowsiness, lethargy, fatigue
    - dizziness, vertigo
    - tremor, anxiety, nervousness, insomnia
    - aggression, irritability, hyperactivity
    - depression, mood alteration
    - confusion
    - ataxia
    - blurred or double vision
- Examples of rare but serious AEs include the following (*Schachter 2019, individual package inserts*):
  - suicidal ideation and behavior (AEDs as a class, except everolimus)

- neutropenia, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, and/or aplastic anemia (brivaracetam, carbamazepine, ethosuximide, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, stiripentol, valproate, vigabatrin, zonisamide)
- anaphylaxis or angioedema (brivaracetam, fosphenytoin, gabapentin, levetiracetam, phenytoin, pregabalin)
- severe skin rashes, Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN) (carbamazepine, clobazam, eslicarbazepine, fosphenytoin, ethosuximide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, rufinamide, tiagabine, valproate, zonisamide)
- hepatic failure (carbamazepine, ethosuximide, felbamate, phenytoin, phenobarbital, primidone, valproate)
- hepatocellular injury (cannabidiol)
- prolonged PR interval, atrioventricular block, and/or changes in QT interval (cenobamate, eslicarbazepine, lacosamide, rufinamide)
- serum sickness (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate)
- multiorgan hypersensitivity (carbamazepine, cenobamate, ethosuximide, gabapentin, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, valproate, zonisamide)
- severe neuropsychiatric effects/hostility/aggression (brivaracetam, levetiracetam, perampanel)
- hemophagocytic lymphohistiocytosis (HLH) (lamotrigine)
- Cardiac AEs, including bradycardia and cardiac arrest (phenytoin)
- Abnormal magnetic resonance imaging signals in infants (vigabatrin)
- Intramyelinic edema (vigabatrin)

- A number of AEDs carry boxed warnings related to potentially serious AEs; these include the following:
  - Carbamazepine:
    - Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Patients with ancestry in genetically at-risk populations (across broad areas of Asia) should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
    - Aplastic anemia and agranulocytosis have been reported. If a patient exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely, and discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.
  - Clobazam, clonazepam, clorazepate, diazepam, and midazolam:
    - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing should be reserved for use in patients for whom alternative treatment options are inadequate, and patients should be followed for signs and symptoms of respiratory depression and sedation.
  - Felbamate:
    - Use is associated with a marked increase in the incidence of aplastic anemia. Felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but it will in some cases allow detection of hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.
    - Cases of acute liver failure have been reported. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction. Treatment should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proven that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Serum transaminases should be monitored at baseline and periodically thereafter. Felbamate should be discontinued if either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) become increased to ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure, and should not be considered for retreatment.
  - Fosphenytoin and phenytoin:
    - There is a cardiovascular risk associated with rapid IV infusion rates. The rate of administration should not exceed recommendations, and careful cardiac monitoring is required.

- Lamotrigine:
  - Cases of life-threatening serious skin rashes, including SJS and TEN, and/or rash-related death have been caused by lamotrigine. Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious. Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.
- Perampanel:
  - Serious or life-threatening psychiatric and behavioral AEs including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported. Patients should be monitored for these reactions and for changes in mood, behavior, or personality. The dose should be reduced if these symptoms occur, and it should be discontinued if symptoms are severe or worsening.
- Valproic acid and divalproex sodium:
  - Hepatotoxicity, including fatalities, have been reported, usually during the first 6 months of treatment. Serum liver tests are required and patients should be monitored closely. There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with mitochondrial disease. Valproic acid and divalproex sodium are contraindicated in patients known to have mitochondrial disorders caused by polymerase gamma (POLG) gene mutations, and in children < 2 years of age who are suspected of having a mitochondrial disorder.
  - There is a risk to fetuses exposed in utero, particularly neural tube defects, other major malformations, and decreased intelligence quotient (IQ). Valproate should not be given to a woman of childbearing potential unless the drug is essential to the management of her medical condition, and women should use effective contraception while using valproate.
  - Pancreatitis, including fatal hemorrhagic cases, has occurred. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.
- Vigabatrin:
  - Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also damage the central retina and may decrease visual acuity. Baseline and periodic vision assessment are recommended. However, this assessment cannot always prevent vision damage, and once detected, vision loss due to vigabatrin is not reversible. Vigabatrin should be withdrawn from patients who fail to show substantial clinical benefit.
  - Due to the risks of vision loss, vigabatrin is available only through a risk evaluation and mitigation strategy (REMS) program (*FDA REMS 2020*). Healthcare providers who prescribe vigabatrin and pharmacies that dispense the product must be specially certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic visual monitoring is performed and report any AE suggestive of vision loss to the vigabatrin REMS program.

- Everolimus is an antineoplastic, immunosuppressant agent associated with several adverse reactions.
  - The most common AE that occurred in trials for TSC-associated partial-onset seizures was stomatitis.
  - More serious AEs include:
    - non-infectious pneumonitis
    - infections
    - hypersensitivity reactions
    - angioedema (when taken with an angiotensin-converting enzyme inhibitor)
    - renal failure
    - impaired wound healing
    - myelosuppression
    - reduced immune response with vaccination
    - hyperglycemia
    - hyperlipidemia
    - embryo-fetal toxicity

DOSING AND ADMINISTRATION

- General dosing information is provided in Table 3. Dosing may vary based on the specific indication, interacting medications, and the patient's age and renal and hepatic function. Additionally, some medications are recommended to be titrated during initial treatment. Please refer to the prescribing information of the individual products for more detailed information.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Barbiturates				
Pentobarbital (Nembutal)	injection	IV, IM	Single dose	Acute use only. If needed, additional small increments may be given after the initial dose.
Phenobarbital* (Luminal†, Solfoton†)	tablets, elixir, injection	oral, IV, IM	2 to 3 times per day	
Primidone (Mysoline)	tablets	oral	3 to 4 times per day	
Benzodiazepines				
Clobazam (Onfi, Sympazan)	tablets, oral suspension, oral film	oral	1 or 2 times per day	Daily doses > 5 mg should be given in divided doses 2 times per day. Sympazan should be applied on top of the tongue where it adheres and dissolves.
Clonazepam (Klonopin)	tablets, orally disintegrating tablets (wafers)	oral	3 times per day	
Clorazepate (Tranxene T-Tab)	tablets	oral	2 to 3 times per day	
Diazepam (Diastat, Valium, Valtoco)	tablets, oral solution, oral concentrate, rectal gel, injection, nasal spray	oral, rectal, IV, IM, intranasal	2 to 4 times per day	For the rectal gel (for acute use), a second dose may be given 4 to 12 hours after the initial dose when required. The injection and nasal spray are also for short-term acute use. For the nasal spray, a second dose may be given 4 hours after the initial dose when required. The product should be used to treat no more than 1 episode every 5 days and no more than 5 episodes per month.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Midazolam (Nayzilam)	nasal spray	intranasal	Up to 2 doses per seizure cluster, with the second dose given at least 10 minutes after the first dose	Should be used to treat no more than 1 episode every 3 days and no more than 5 episodes per month.
Hydantoins				
Ethotoin (Peganone)	tablets	oral	4 to 6 times per day	
Fosphenytoin (Cerebyx)	injection	IV, IM	2 times per day or other divided doses based on drug levels	Generally used in acute situations as a loading dose; may be given in divided doses when substituted for oral phenytoin.
Phenytoin (Dilantin, Phenytek)	extended-release capsules, chewable tablets, oral suspension, injection	oral, IV, IM	2 to 4 times per day	Capsules are extended-release and may be suitable for once-daily dosing in some adults.
Miscellaneous				
Brivaracetam (Briviact)	tablets, oral solution, injection	oral, IV	2 times per day	The injection may be used when oral administration is temporarily not feasible.
Cannabidiol (Epidiolex)	oral solution	oral	2 times per day	The provided oral syringe should be used to measure an accurate dose.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	tablets, chewable tablets, oral suspension, extended-release tablets, extended-release capsules	oral	2 to 4 times per day	Immediate-release tablets are given 2 to 3 times per day and the suspension is given 4 times per day. Carbatrol and Equetro are twice-daily extended-release capsule formulations; these capsules may be opened and sprinkled on soft food. Tegretol-XR is a twice-daily extended-release tablet formulation; these tablets must be swallowed whole.
Cenobamate (Xcopri)¶	tablets	oral	once daily	The recommended titration schedule should not be exceeded.
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	delayed-release tablets, delayed-release sprinkle capsules, extended-release tablets	oral	2 to 3 times per day (once daily for extended-release tablets)	Delayed-release tablets and extended-release tablets should be swallowed whole. Sprinkle capsules may be opened and sprinkled on soft food. Delayed-release tablet and capsule doses > 250 mg per day should be given in divided doses.
Eslicarbazepine (Aptiom)	tablets	oral	once daily	Tablets may be crushed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ethosuximide (Zarontin)	capsules, oral solution/syrup	oral	once daily or in divided doses	
Everolimus (Afinitor Disperz)	tablets for oral suspension	oral	once daily	Should be taken at the same time each day with or without food. Suspension should be prepared using water only and administered immediately after preparation. The suspension should be discarded if not taken within 60 minutes of preparation. Dose adjustments are made based on trough drug concentration.
Felbamate (Felbatol)	tablets, oral suspension	oral	3 or 4 times per day	
Gabapentin (Neurontin)	tablets, capsules, oral solution	oral	3 times per day	Capsules should be swallowed whole.
Lacosamide (Vimpat)	tablets, oral solution, injection	oral, IV	2 times per day	
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite)	tablets, chewable dispersible tablets, orally disintegrating tablets, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	Only whole tablets should be administered. Extended-release tablets must not be chewed or crushed.
Levetiracetam (Keppra, Keppra XR, Roweepra, Roweepra XR, Spritam, Elepsia XR)	tablets, tablets for oral suspension, oral solution, extended-release tablets, injection	oral, IV	2 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should not be chewed or crushed. Tablets for oral suspension (Spritam) can be dissolved in liquid and swallowed or allowed to disintegrate in the mouth.
Methsuximide (Celontin)	capsules	oral	3 to 4 times per day (*Lexicomp 2020*)	
Oxcarbazepine (Oxtellar XR, Trileptal)	tablets, oral suspension, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary. Extended-release tablets must not be chewed or crushed.
Perampanel (Fycompa)	tablets, oral suspension	oral	once daily at bedtime	
Pregabalin (Lyrica)	capsules, oral solution	oral	2 to 3 times per day	
Rufinamide (Banzel)	tablets, oral suspension	oral	2 times per day	Tablets can be administered whole, as half tablets, or crushed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Stiripentol (Diacomit)	capsules, powder for oral suspension	oral	2 to 3 times per day	Capsules must be swallowed whole with a glass of water during a meal. Powder should be mixed with water and taken immediately after mixing during a meal.
Tiagabine (Gabitril)	tablets	oral	2 to 4 times per day	
Topiramate (Topamax, Topamax Sprinkle, Topiragen, Trokendi XR, Qudexy XR)	tablets, sprinkle capsules, extended-release capsules, extended-release sprinkle capsules	oral	2 times per day (once daily for extended-release capsule formulations)	Sprinkle capsules may be opened and sprinkled on soft food. Extended-release capsules (Trokendi XR) must not be chewed or crushed, but extended release sprinkle capsules (Qudexy XR) may be sprinkled on soft food.
Valproic acid/ valproate sodium (Depakene, Depacon)	capsules, oral solution/ syrup, injection	oral, IV	1 to 3 times per day (*Lexicomp 2020*)	Capsules should be swallowed whole without chewing to avoid local irritation of the mouth and throat. If the total dose exceeds 250 mg, it should be given in divided doses.
Vigabatrin (Sabril, Vigadrone)	tablets, powder for oral solution	oral	2 times per day	Powder for oral solution is supplied in individual dose packets to be mixed with water before administration.
Zonisamide (Zonegran)	capsules	oral	1 or 2 times per day	Capsules must be swallowed whole.

* Not FDA approved
† Brand product not currently marketed; generic is available
¶ FDA-approved product, but not yet marketed

CONCLUSION

- Several classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents. These products vary in terms of their indications for specific seizure types and indications other than epilepsy.
- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. When possible, monotherapy with a single AED is the preferred treatment approach.
- Patients who are refractory to monotherapy may be treated with combination therapy. When considering combination therapy, it is recommended to combine medications with different mechanisms of action and AE profiles.
- Comparative efficacy data for the management of epilepsy are limited.
- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment. Both systemic AEs and neurologic AEs commonly occur. Some AEDs are associated with rare but serious AEs, and careful patient selection and monitoring are required.
- Epilepsy management can be complex and is often performed by neurologists. A variety of AEDs should be available to allow clinicians to select the most clinically appropriate agent for individual patients.
- Anticonvulsants are also established as effective for several non-epilepsy indications, including (but not limited to) bipolar disorder, migraine prophylaxis, and neuropathic pain.

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