South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

June 20, 2025

South Dakota Department of Social Services

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DEPARTMENT OF SOCIAL SERVICES
DIVISION OF MEDICAL SERVICES
700 GOVERNORS DRIVE
PIERRE, SD 57501-2291
PHONE: 605-773-3495
FAX: 605-773-5246
WEB: dss.sd.gov

South Dakota Department of Social Services

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA
https://sdm.pharmacy.optumrx.com

June 20, 2025
1:00 – 3:00 PM CT
12:00 – 2:00 PM MT

Meeting Link:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_ZDk4NDNiNTMtYTEzNS00YzVlLTg0ZWYtZjFhMjMwNTFiMTA2%40thread.v2/0?context=%7b%22Tid%22%3a%22db05faca-c82a-4b9d-b9c5-0f64b6755421%22%2c%22Oid%22%3a%22b6efd724-b34e-4a86-b34c-e34f07dd4ceb%22%7d

Join with a video conferencing device
teams@optum.onpexip.com
Video Conference ID: 247 837 622 607

Join by phone
+1 952-222-7450
Phone Conference ID: 631 491 909#

Call to order

Approval of previous meeting minutes

PA update
Review of top 15 therapeutic categories/top 50 drugs

Old business
- **Fleqsuvy review**
- **Opioid update**

New business
- **Calcitonin gene-related peptide (CGRP) review**
- **Antipsychotics review**
- **Journavx**
- **Ohtuvayre**

Public input accepted after individual topic discussion
Next meeting date June 20, 2025 & adjournment

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

Friday, March 21, 2025
1:00 – 3:00 pm CT

Members and DSS Staff

Michelle Baack, MD	-	Brandi Tackett, PharmD	X
Bill Ladwig, RPh	X	Deidra Van Gilder, PharmD, Chair	X
Kelley Oehlke, PharmD	-	Clarissa Barnes, MD, DSS Staff	X
Lenny Petrik, PharmD	-	Mike Jockheck, DSS Staff	X
Heather Preuss, MD	-	Taylor Koerner, DSS Staff	X
Matthew Stanley, DO	X		

Administrative Business

Van Gilder called the meeting to order at 1:02 pm. The minutes of the September meeting were presented since the December meeting was canceled. Stanley made a motion to approve. Ladwig seconded the motion. The motion to approve the minutes was approved unanimously.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from October 1, 2024, to December 21, 2024. A total of 3,837 PAs were reviewed of which 112 requests (2.9%) were received via telephone, 136 requests (3.5%) were received via fax, 1,434 requests (37.4%) were reviewed electronically, and 2,155 requests (56.2%) were received via ePA. There was a 2.7% increase in PAs received compared to the previous quarter. There was an 11% increase in the number of appeals.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from October 1, 2024, to December 21, 2024. The top five therapeutic classes based on paid amount were atypical antipsychotics, incretin mimetics, interleukin-mediated agents, tumor necrosis factor inhibitors, and antineoplastic agents. These top 15 therapeutic classes comprise 16.6 % 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 constitute 9% of total claims. Ladwig asked the significance of the bolded drug names. These are the combined total of different drug formulations which the committee had requested several years ago.

Old Business

Opioid Update

The committee reviewed opioid outcomes compared to the previous quarter from the opioid initiatives. There was an increase in opioid utilization and utilizers during 4Q2024 with corresponding increase in total eligibility and utilizers. The average MME/day/utilizer stayed steady. Ladwig commented if members labeled as “shoppers” within the poly-prescribers may be within same clinic/practice. Members could be labeled “shoppers” if seen by different prescribers in the same clinic/practice.

Review of PA forms & criteria
The committee reviewed all PA criteria currently in effect. Jockheck said he reviewed the current list of PAs and have some potential removals such as Viibryd since it is available as generic. Van Gilder and Stanley both agreed.

Van Gilder asked for public comment. Jasmin Inman, pharmacist at Teva Pharmaceuticals, provided public comment on new headache guidelines for CGRPs. Van Gilder provided comment on commercial plan criteria. Tackett inquired on the process of how clinical treatment/standard guidelines are made to PA criteria. Jockheck replied indications are updated timely. Some treatment guidelines are brought to the committee for review. The committee can also provide input if practice guidelines are outdated.

After discussion, Van Gilder motioned to accept the PAs with changes discussed. Van Gilder inquired if there was any public testimony. Jasmine Inman provided public comment. Committee approved PAs.

New Business

Daybue review
Daybue clinical information was presented for review; including Baack's input on supporting State A's PA criteria with the inclusion of an endocrinologist and prescriber attestation that patient does not have other neurological problems. Mandi Champ, pharmacist with medical affairs from Acadia, provided public comment. Stanley supported Baack's input and made the motion to adopt the discussed PA to Daybue. Ladwig seconded the motion. The motion was approved unanimously.

Dupixent
Dupixent new indication information was presented for review. The committee discussed potential PA criteria for chronic obstructive pulmonary disease (COPD). Van Gilder inquired if there was any public comment. There were none. Stanley made the motion to adopt State A criteria with minor changes. Ladwig seconded the motion. The motion was approved unanimously.

Fintepla
Fintepla clinical information was presented for review. The committee discussed potential PA criteria. VanGilder was in favor of adding PA with trial of Epidiolex first. Kierra Brown, pharmacist with medical outcomes from UCB, provided public comment. Brent Fushimi, medical channel management from UCB, provided public comment. Van Gilder made a motion to adopt State C PA criteria with minor changes. Ladwig seconded the motion. The motion was approved unanimously.

Voquezna
Voquezna clinical information was presented for review. Van Gilder stated step therapy is warranted for this drug. Van Gilder inquired if there was any public comment. There were none. Van Gilder made a motion to adopt State C PA criteria for Voquenza. Tackett seconded the motion. The motion was approved unanimously. Ladwig requested to review Voquezna Dual and Triple pack utilization for H. Pylori in one year.

Adjournment
The next meeting is scheduled on June 20, 2025. The September meeting is tentatively scheduled for September 26, 2025. All motioned and were in favor of adjourning the meeting. The meeting adjourned at 2:18 pm CT.

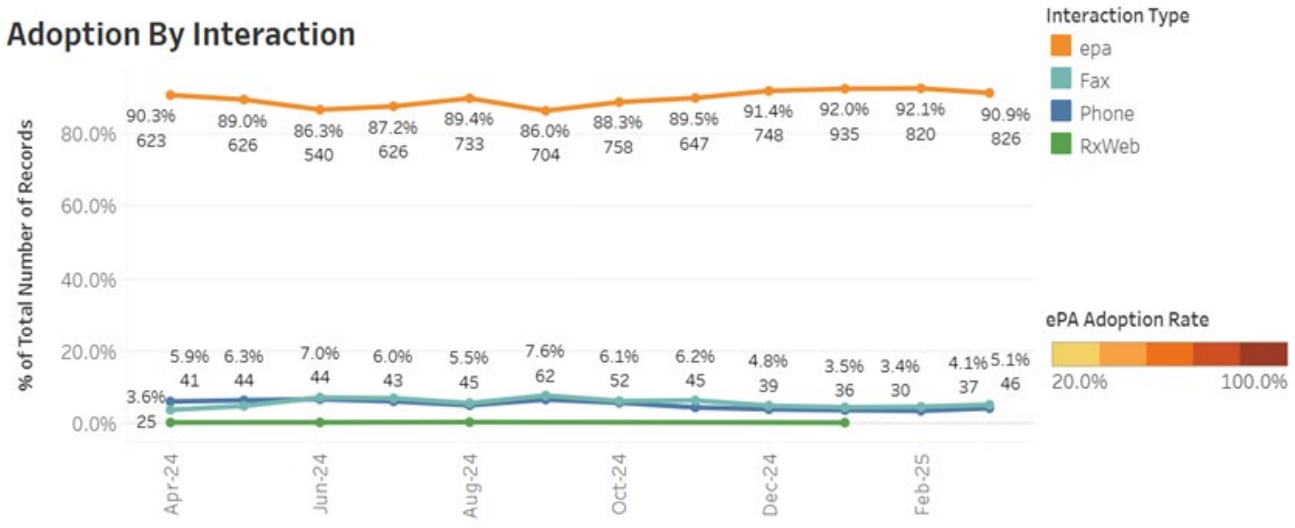
PA Report
1/1/2025 – 3/31/2025

Compliance Summary

Priority	Total PAs	PAs Compliant	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	3,988	3,988	0	100.00%	0.00%
Urgent	560	560	0	100.00%	0.00%
Grand Total	**4,548**	**4,548**	**0**		

Priority	Standard	Urgent
ePA	2,052	533
Fax	124	6
Phone	84	20
Real-Time	1,728	0
RxWeb	1	

Request Summary	Total # of Requests	Phone Requests		Fax Requests		Real-Time PA		ePA PA	
		#	%	#	%	#	%	#	%
Total	**4,548**	**104**	**2.3%**	**130**	**2.9%**	**1,728**	**38%**	**2,585**	**56.8%**



This graph shows the adoption of Interaction Types in percentage. This graph considers all resolved cases (Approved + Denied).

PA Initial Requests Summary

Month	Approved	Denied	Total
Jan-25	1,314	303	1,617
Feb-25	1,185	265	1,450
Mar-25	1,194	287	1,481
1Q25	**3,693**	**855**	**4,548**
Percent of Total	**81.2%**	**18.8%**	

Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
ANTIDIABETICS	638	106	744	85.75%	16.36%	, OZEMPIC
MEDICAL DEVICES & SUPPLIES	530	145	675	78.52%	14.84%	, DEXCOM G7 SENSOR
ANTIPSYCHOTICS/ANTIMANIC	614	43	657	93.46%	14.45%	, VRAYLAR
ANALGESICS - OPIOID	306	40	346	88.44%	7.61%	HYDROCODONE/APAP, TRAMADOL
DERMATOLOGICALS	245	56	301	81.40%	6.62%	DUPIXENT,
OTHERS -	1360	465	1825	74.52%	40.13%	
1Q25	**3693**	**855**	**4,548**	**81.2%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Jan-25	21	65.63%	11	34.38%	32
Feb-25	20	64.52%	11	35.48%	31
Mar-25	28	66.67%	14	33.33%	42
1Q25	**69**	**65.71%**	**36**	**34.29%**	**105**

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
27 - ANTIDIABETICS*	638	106	744	85.75%
97 - MEDICAL DEVICES AND SUPPLIES*	530	145	675	78.52%
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	614	43	657	93.46%
65 - ANALGESICS - OPIOID*	306	40	346	88.44%
90 - DERMATOLOGICALS*	245	56	301	81.40%
52 - GASTROINTESTINAL AGENTS - MISC.*	198	45	243	81.48%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	107	135	242	44.21%
58 - ANTIDEPRESSANTS*	187	47	234	79.91%
67 - MIGRAINE PRODUCTS*	187	31	218	85.78%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	152	10	162	93.83%
66 - ANALGESICS - ANTI-INFLAMMATORY*	102	14	116	87.93%
12 - ANTIVIRALS*	53	17	70	75.71%
54 - URINARY ANTISPASMODICS*	44	16	60	73.33%
16 - ANTI-INFECTIVE AGENTS - MISC.*	40	11	51	78.43%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	31	7	38	81.58%
72 - ANTICONVULSANTS*	28	9	37	75.68%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	13	23	36	36.11%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	27	5	32	84.38%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	22	3	25	88.00%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	17	8	25	68.00%
28 - THYROID AGENTS*	15	9	24	62.50%
41 - ANTIHISTAMINES*	18	4	22	81.82%
94 - DIAGNOSTIC PRODUCTS*	6	16	22	27.27%
50 - ANTIEMETICS*	14	4	18	77.78%
39 - ANTIHYPERLIPIDEMICS*	10	7	17	58.82%
83 - ANTICOAGULANTS*	14	2	16	87.50%
34 - CALCIUM CHANNEL BLOCKERS*	11	4	15	73.33%
36 - ANTIHYPERTENSIVES*	9	6	15	60.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	9	4	13	69.23%
75 - MUSCULOSKELETAL THERAPY AGENTS*	4	9	13	30.77%
33 - BETA BLOCKERS*	9	3	12	75.00%
02 - CEPHALOSPORINS*	4	2	6	66.67%
86 - OPHTHALMIC AGENTS*	5	1	6	83.33%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	2	3	5	40.00%
45 - RESPIRATORY AGENTS - MISC.*	3	2	5	60.00%
03 - MACROLIDES*	3	1	4	75.00%
01 - PENICILLINS*	2	1	3	66.67%
56 - GENITOURINARY AGENTS - MISCELLANEOUS*	3	0	3	100.00%
82 - HEMATOPOIETIC AGENTS*	2	1	3	66.67%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	3	0	3	100.00%
22 - CORTICOSTEROIDS*	1	1	2	50.00%
74 - NEUROMUSCULAR AGENTS*	1	1	2	50.00%
19 - PASSIVE IMMUNIZING AND TREATMENT AGENTS*	1	0	1	100.00%
25 - CONTRACEPTIVES*	0	1	1	0.00%
31 - CARDIOTONICS*	0	1	1	0.00%
64 - ANALGESICS - NONNARCOTIC*	1	0	1	100.00%
79 - MINERALS & ELECTROLYTES*	1	0	1	100.00%
85 - HEMATOLOGICAL AGENTS - MISC.*	1	0	1	100.00%
96 - CHEMICALS*	0	1	1	0.00%
1Q25	**3,693**	**855**	**4,548**	
Percent of Total	**81.2%**	**18.8%**		

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
QELBREE	4	4	8	50.00%
DEXCOM G7	7	1	8	87.50%
BELSOMRA	4	2	6	66.67%
LINZESS	1	3	4	25.00%
MOUNJARO	2	2	4	50.00%
TIROSINT	3	1	4	75.00%
FREESTYLE LIBRE 3/SENSOR/GLUCOSE MONITORING	3	1	4	75.00%
MYRBETRIQ	2	1	3	66.67%
RINVOQ	2	1	3	66.67%
VRAYLAR	3	0	3	100.00%
WEGOVY	0	3	3	0.00%
AIMOVIG	2	0	2	100.00%
AZELASTINE/FLUTICASONE PROPIONATE	1	1	2	50.00%
GEMTESA	0	2	2	0.00%
MIRABEGRON ER	2	0	2	100.00%
QUVIVIQ	1	1	2	50.00%
REPATHA SURECLICK	2	0	2	100.00%
ACCU-CHEK GUIDE TEST STRIPS	1	0	1	100.00%
AMLODIPINE	1	0	1	100.00%
ARIPIPRAZOLE	1	0	1	100.00%
AUVELITY	1	0	1	100.00%
BIMZELX	0	1	1	0.00%
BRIVIACT	1	0	1	100.00%
BUPRENORPHINE	1	0	1	100.00%
DAPSONE	1	0	1	100.00%
DOBUTAMINE/DEXTROSE 5%	0	1	1	0.00%
DUPIXENT	1	0	1	100.00%
ESCITALOPRAM	1	0	1	100.00%
ESZOPICLONE	0	1	1	0.00%
EUCRISA	1	0	1	100.00%
EVRYSDI	0	1	1	0.00%
LEVOTHYROXINE CAPSULE	0	1	1	0.00%
LUBIPROSTONE	1	0	1	100.00%
LYBALVI	0	1	1	0.00%
MEKINIST	1	0	1	100.00%
NORDITROPIN FLEXPRO	1	0	1	100.00%
ONETOUCH VERIO TEST STRIPS	0	1	1	0.00%
OPSUMIT	1	0	1	100.00%
OTEZLA	1	0	1	100.00%
OXYCODONE	1	0	1	100.00%
OZEMPIC	1	0	1	100.00%
PRALUENT	1	0	1	100.00%
PREGABALIN	0	1	1	0.00%
REZDIFFRA	1	0	1	100.00%
RHOFADE	0	1	1	0.00%
RISPERIDONE	0	1	1	0.00%
SOFOSBUVIR/VELPATASVIR	1	0	1	100.00%
SOLU-CORTEF	1	0	1	100.00%
SOMATULINE DEPOT	1	0	1	100.00%
STELARA	1	0	1	100.00%
SYMPAZAN	1	0	1	100.00%
TAZAROTENE	0	1	1	0.00%
TRAMADOL	0	1	1	0.00%
VILAZODONE	1	0	1	100.00%
VTAMA	1	0	1	100.00%
WINREVAIR	1	0	1	100.00%
XELJANZ	1	0	1	100.00%
XIFAXAN	1	0	1	100.00%
XOLAIR	1	0	1	100.00%
ZEPBOUND	0	1	1	0.00%
1Q25	**69**	**36**	**105**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 1/1/2025 – 3/31/2025					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	ATYPICAL ANTIPSYCHOTICS	13,082	$4,866,802.18	$372.02	4.04%
2	INCRETIN MIMETICS	3,453	$3,379,610.89	$978.75	1.07%
3	INTERLEUKIN-MEDIATED AGENTS, MISC	221	$2,730,663.03	$12,355.94	0.07%
4	IMMUNOMODULATORY AGENTS	629	$2,638,343.88	$4,194.51	0.19%
5	TUMOR NECROSIS FACTOR INHIBITORS, MISC	311	$2,557,293.63	$8,222.81	0.10%
6	ANTINEOPLASTIC AGENTS	473	$2,048,020.83	$4,329.85	0.15%
7	CYSTIC FIBROSIS (CFTR) CORRECTORS	68	$1,604,028.73	$23,588.66	0.02%
8	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	350	$1,349,551.46	$3,855.86	0.11%
9	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	3,308	$1,218,120.79	$368.23	1.02%
10	HEMOSTATICS	54	$1,215,709.44	$22,513.14	0.02%
11	RESPIRATORY AND CNS STIMULANTS	10,401	$1,141,096.97	$109.71	3.21%
12	ADRENALS	9,605	$1,132,558.63	$117.91	2.97%
13	SODIUM-GLUC COTRANSPORT 2 (SGLT2) INHIB	1,940	$1,070,863.41	$551.99	0.60%
14	AMPHETAMINES	9,661	$1,050,050.70	$108.69	2.98%
15	ANTICONVULSANTS, MISCELLANEOUS	7,459	$916,617.92	$122.89	2.30%
Total		**61,015**	**$28,919,332.49**	**$473.97**	**18.85%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 1/1/2025 – 3/31/2025					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	ATYPICAL ANTIPSYCHOTICS	13,082	$4,866,802.18	$372.02	4.04%
2	INCRETIN MIMETICS	3,453	$3,379,610.89	$978.75	1.07%
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Total		**61,015**	**$28,919,332.49**	**$473.97**	**18.85%**

Total Rx Claims from 1/1/2025 – 3/31/2025	**323,663**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 1/1/2025 – 3/31/2025						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Penicillins	AMOXICILLIN	8,057	$109,950.37	$13.65	2.49%
2	Antidepressants	FLUOXETINE	6,543	$77,494.70	$11.84	2.02%
3	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	5,992	$197,460.36	$32.95	1.85%
4	Antidepressants	**SERTRALINE**	**5,914**	**$76,064.81**	**$12.86**	**1.83%**
5	Anticonvulsants - 2nd Generation	GABAPENTIN	5,837	$87,466.39	$14.98	1.80%
6	Proton Pump Inhibitors	**OMEPRAZOLE**	**5,795**	**$66,262.86**	**$11.43**	**1.79%**
7	ADHD & Narcolepsy Medications	METHYLPHENIDATE	5,540	$273,022.70	$49.28	1.71%
8	Antidepressants	TRAZODONE	5,270	$59,217.93	$11.24	1.63%
9	ADHD & Narcolepsy Medications	AMPHETAMINE/DEXTROAMP	4,989	$153,172.21	$30.70	1.54%
10	Antidepressants	ESCITALOPRAM	4,660	$58,100.40	$12.47	1.44%
11	Thyroid Hormones	LEVOTHYROXINE	4,627	$52,327.01	$11.31	1.43%
12	Antidepressants	**BUPROPION**	**4,455**	**$82,164.23**	**$18.44**	**1.38%**
13	Antihistamines	**CETIRIZINE**	**4,225**	**$43,538.79**	**$10.31**	**1.31%**
14	Biguanides & Combos	**METFORMIN**	**4,190**	**$50,522.46**	**$12.06**	**1.29%**
15	Statins & Combos	ATORVASTATIN CALCIUM	3,952	$46,763.40	$11.83	1.22%
16	ACE Inhibitors & Combos	LISINOPRIL	3,707	$36,733.37	$9.91	1.15%
17	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE	3,506	$531,632.96	$151.64	1.08%
18↑	Antianxiety Agents	**HYDROXYZINE**	**3,278**	**$40,712.12**	**$12.42**	**1.01%**
19	Antidepressants	**DULOXETINE**	**3,271**	**$49,984.25**	**$15.28**	**1.01%**
20	ADHD & Narcolepsy Medications	GUANFACINE	3,186	$49,244.85	$15.46	0.98%
21	Antiemetics	ONDANSETRON ODT	3,171	$43,920.91	$13.85	0.98%
22	Opioid Agonists & Combos	HYDROCODONE BIT/AC	3,074	$51,562.38	$16.77	0.95%
23	Leukotriene Modulators	MONTELUKAST	3,050	$38,283.31	$12.55	0.94%
24	Antiadrenergic Antihypertensives	CLONIDINE	3,010	$27,982.02	$9.30	0.93%
25↓	Macrolides	AZITHROMYCIN	2,981	$42,813.75	$14.36	0.92%
26	Glucocorticosteroids	PREDNISONE	2,929	$28,736.68	$9.81	0.90%
27	Penicillins	AMOXICILLIN/CLAVULANATE	2,916	$52,257.09	$17.92	0.90%
28↑	Influenza Agents	OSELTAMIVIR	2,854	$65,893.76	$23.09	0.88%
29	Atypical Antipsychotics	ARIPIPRAZOLE	2,761	$38,681.24	$14.01	0.85%
30	Antianxiety Agents	**BUSPIRONE**	**2,712**	**$34,175.13**	**$12.60**	**0.84%**
31	Angiotensin II Receptor Antagonists & Combo	LOSARTAN	2,648	$30,473.94	$11.51	0.82%
32	Calcium Channel Blockers	AMLODIPINE	2,525	$25,711.22	$10.18	0.78%
33	Inhaled Bronchodilator	ALBUTEROL SULFATE	2,489	$49,693.87	$19.97	0.77%
34	Atypical Antipsychotics	QUETIAPINE	2,460	$32,199.55	$13.09	0.76%
35	Anticonvulsants - 2nd Generation	LAMOTRIGINE	2,426	$32,186.21	$13.27	0.75%
36	Muscle Relaxants & Combos	CYCLOBENZAPRINE	2,312	$24,163.00	$10.45	0.71%
37	Proton Pump Inhibitors	PANTOPRAZOLE	2,233	$27,650.25	$12.38	0.69%
38	Statins & Combos	ROSUVASTATIN	2,191	$26,697.30	$12.18	0.68%
39	Beta Blockers & Combos	METOPROLOL SUCCINATE ER	2,180	$27,443.44	$12.59	0.67%
40	Antihistamines	**ALLERGY RELIEF**	2,071	$20,086.06	$9.70	0.64%
41	Anticonvulsants - 2nd Generation	TOPIRAMATE	2,055	$25,224.37	$12.27	0.63%
42	Cephalosporins	CEFDINIR	2,005	$38,317.91	$19.11	0.62%
43	Cephalosporins	CEPHALEXIN	1,988	$28,978.20	$14.58	0.61%
44	Atypical Antipsychotics	RISPERIDONE	1,978	$25,697.90	$12.99	0.61%
45	Anticonvulsants - 2nd Generation	CLONAZEPAM	1,973	$22,546.10	$11.43	0.61%
46	Antidepressants	**VENLAFAXINE**	**1,943**	**$29,191.95**	**$15.02**	**0.60%**
47	Nonsteroidal Anti-Inflammatory Agents	MELOXICAM	1,902	$18,907.62	$9.94	0.59%
48	Nasal Steroids	FLUTICASONE PROPIONATE	1,877	$32,359.85	$17.24	0.58%
49	Antidepressants	MIRTAZAPINE	1,850	$24,507.64	$13.25	0.57%
50	Corticosteroids - Topical	TRIAMCINOLONE	1,722	$24,431.03	$14.19	0.53%
	Total Top 50 Drugs		**169,280**	**$3,132,609.85**	**$18.51**	**52.30%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 1/1/2025 – 3/31/2025						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Chronic Inflammatory Disease	DUPIXENT	533	$2,134,387.17	$4,004.48	0.16%
2	Chronic Inflammatory Disease	**HUMIRA, PEN**	**198**	**$1,690,396.47**	**$8,537.36**	**0.06%**
3	GLP-1 Receptor Agonists	MOUNJARO	1,580	$1,605,086.73	$1,015.88	0.49%
4	Cystic Fibrosis	TRIKAFTA	68	$1,604,028.73	$23,588.66	0.02%
5	Atypical Antipsychotics	**INVEGA SUSTENNA, TRINZA, HAFYERA**	**467**	**$1,501,139.85**	**$3,214.43**	**0.14%**
6	GLP-1 Receptor Agonists	OZEMPIC	1,546	$1,484,736.37	$960.37	0.48%
7	Chronic Inflammatory Disease	STELARA	48	$1,207,356.53	$25,153.26	0.01%
8	Atypical Antipsychotics	VRAYLAR	802	$1,081,480.85	$1,348.48	0.25%
9	Chronic Inflammatory Disease	**SKYRIZI, PEN**	**47**	**$1,018,245.32**	**$21,664.79**	**0.01%**
10	Rett Syndrome Agent	DAYBUE	15	$1,004,534.09	$66,968.94	0.00%
11	HIV-Multiclass Combo	BIKTARVY	241	$977,088.42	$4,054.31	0.07%
12	Chronic Inflammatory Disease	**COSENTYX, SENSOREADY, UNOREADY**	**92**	**$891,241.33**	**$9,687.41**	**0.03%**
13	SGLT-2 Inhibitors & Combos	JARDIANCE	1,259	$742,423.07	$589.69	0.39%
14	Chronic Inflammatory Disease	**ENBREL, SURECLICK, MINI**	**76**	**$577,668.87**	**$7,600.91**	**0.02%**
15	Atypical Antipsychotics	ARISTADA	199	$564,612.78	$2,837.25	0.06%
16	Chronic Inflammatory Disease	TALTZ	65	$560,359.31	$8,620.91	0.02%
17	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE DIMESYLA	3,506	$531,632.96	$151.64	1.08%
18	Diabetes Monitoring and Testing	**DEXCOM**	**1,450**	**$516,362.64**	**$356.11**	**0.45%**
19	Atypical Antipsychotics	**ABILIFY MAINTENA, ASIMTUFI**	**150**	**$473,167.60**	**$3,154.45**	**0.05%**
20	Oral Anticoagulants	**ELIQUIS**	**830**	**$461,437.52**	**$555.95**	**0.26%**
21	Anticonvulsants - 2nd Generation	EPIDIOLEX	180	$452,175.38	$2,512.09	0.06%
22	Atypical Antipsychotics	REXULTI	297	$405,084.17	$1,363.92	0.09%
23	Oncology	KISQALI	25	$358,630.89	$14,345.24	0.01%
24	Atypical Antipsychotics	CAPLYTA	217	$344,693.54	$1,588.45	0.07%
25	Growth Hormones	NORDITROPIN FLEXPRO	82	$343,911.00	$4,194.04	0.03%
26	Movement Disorder Drug Therapy	INGREZZA	47	$342,037.45	$7,277.39	0.01%
27	Antihemophilic Products	NOVOSEVEN RT	4	$333,342.20	$83,335.55	0.00%
28	Inhaled Asthma/COPD Combo	TRELEGY ELLIPTA	504	$325,616.18	$646.06	0.16%
29↓	Antihemophilic Products	HEMLIBRA	11	$319,303.63	$29,027.60	0.00%
30	Chronic Inflammatory Disease	RINVOQ	45	$316,472.56	$7,032.72	0.01%
31↓	ADHD & Narcolepsy Medications	VYVANSE	898	$315,213.30	$351.02	0.28%
32↑	Ophthalmic Nerve Growth Factors	OXERVATE	9	$288,564.35	$32,062.71	0.00%
33	Irritable Bowel Syndrome (IBS) Agt	LINZESS	534	$284,607.64	$532.97	0.16%
34	Oncology	REVLIMID	16	$281,007.29	$17,562.96	0.00%
35↑	Bile Acid Synthesis Disorder Agents	CHOLBAM	11	$279,383.36	$25,398.49	0.00%
36↑	Metabolic Modifiers	PALYNZIQ	5	$276,832.75	$55,366.55	0.00%
37	ADHD & Narcolepsy Medications	METHYLPHENIDATE	5,540	$273,022.70	$49.28	1.71%
38↑	Hepatitis C	MAVYRET	21	$270,090.92	$12,861.47	0.01%
39	Migraine Products	NURTEC	234	$266,766.19	$1,140.03	0.07%
40	Anti-Infective Agents - Misc.	XIFAXAN	90	$256,659.92	$2,851.78	0.03%
41↑	Platelet Receptor Agonists	PROMACTA	15	$234,981.89	$15,665.46	0.00%
42↓	Hepatitis C	SOFOSBUVIR/VELPATASVIR	28	$224,295.40	$8,010.55	0.01%
43	Movement Disorder Drug Therapy	AUSTEDO XR	24	$218,499.44	$9,104.14	0.01%
44	ADHD & Narcolepsy Medications	AZSTARYS	525	$209,408.17	$398.87	0.16%
45	Cystic Fibrosis	PULMOZYME	46	$207,477.14	$4,510.37	0.01%
46	HIV-Multiclass Combo	GENVOYA	50	$203,449.34	$4,068.99	0.02%
47	Chronic Inflammatory Disease	OTEZLA	44	$202,069.95	$4,592.50	0.01%
48	ADHD & Narcolepsy Medications	JORNAY PM	462	$200,740.45	$434.50	0.14%
49	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	5,992	$197,460.36	$32.95	1.85%
50↓	PIK3CA-Related Overgrowth Agent	VIJOICE	6	$195,063.30	$32,510.55	0.00%
	Total Top 50 Drugs		**29,128**	**$28,859,184.17**	**$990.77**	**9.00%**

New Business

Baclofen

Indications:

- **solution** (Ozobax), **tablet, granules** (Lyvispah), **suspension** (Fleqsuvy) – for treatment of spasticity, muscle spasm (not due to rheumatic conditions), myoclonus, and muscle rigidity in multiple sclerosis and spinal cord injury or other spinal cord diseases.

Fleqsuvy

Time frame: Years 2022 – 2024

Year	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
2022	51	$57,903.05	$1,135.35	205 per 28 days	10	2 – 26
2023	111	$142,181.81	$1,280.92	210 per 27 days	13	2 – 27
2024	32	$67,497.22	$2,109.29	360 per 27 days	5	5 – 16

Muscle Relaxants

Time frame: 1/1/2025 to 3/31/2025

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
baclofen TAB 5mg	125	$1,952.80	$15.62	86 per 26 days	62	3 – 92
baclofen TAB 10mg	870	$11,030.48	$12.68	88 per 27 days	396	3 – 92
baclofen TAB 15mg	5	$720.92	$144.18	81 per 27 days	2	24 – 38
baclofen TAB 20mg	224	$3,356.26	$14.98	99 per 28 days	81	7 – 64
baclofen SOL 5mg/5ml	2	$140.08	$70.04	45ml per 30 days	2	0 – 3
baclofen SOL 10mg/5ml	7	$3,945.11	$563.59	275ml per 30 days	3	1 – 8
baclofen SUSP 25mg/5ml	**74**	**$41,494.16**	**$560.73**	**140ml per 27 days**	**29**	**0 – 29**
FLEQSUVY SUSP 25mg/5ml	**3**	**$10,367.38**	**$3,455.79**	**600ml per 30 days**	**1**	**16**
LYVISPAH (oral granules)	0					
OZOBAX SOL 5mg/5ml**	0					
carisoprodol 250mg tab	2	$119.03	$59.52	90 per 30 days	1	60
carisoprodol 350mg tab	82	$1,193.60	$14.56	67 per 25 days	37	29 – 64
chlorzoxazone tab	12	$456.88	$38.07	78 per 24 days	6	41 – 62
cyclobenzaprine tab	2,310	$24,051.09	$10.41	41 per 19 days	1,424	9 – 73
cyclobenzaprine ER (Amrix)	2	$111.91	$55.96	30 per 30 days	1	46
dantrolene cap	9	$351.25	$39.03	63 per 26 days	4	24 – 47
metaxalone tab	85	$4,359.95	$51.29	59 per 22 days	42	27 – 64
methocarbamol tab	472	$5,893.83	$12.49	62 per 20 days	299	14 – 67
orphenadrine tab 100mg ER	41	$1,201.36	$29.30	44 per 24 days	27	34 – 64
tizanidine cap/tab	730	$9,686.93	$13.27	64 per 24 days	342	11 – 64

*Red font denotes drug is on PA

**not rebateable manufacturer

South Dakota Medicaid PA criteria

- Amrix (cyclobenzaprine cap ER) & Fexmid PA criteria:
  - 60-day trial of cyclobenzaprine 5 mg tab OR cyclobenzaprine 10 mg tab in the past 120 days

- Soma 250mg (carisoproldol 250mg) PA criteria:
  - Patient has had a 6-month trial of carisoprodol 350mg within the last 120 days

State A: Fleqsuvy, baclofen suspension, Lyvispah, Ozobax/DS, baclofen solution

1. Trial and failure, or intolerance to baclofen tablets OR
2. Patient is unable to swallow oral tablets

State B: Fleqsuvy, Lyvispah, baclofen suspension, baclofen solution

1. Diagnosis of spasticity with flexor spasms and concomitant pain, clonus, and/or muscular rigidity, (e.g., resulting from multiple sclerosis, spinal cord injury or disease) AND
2. Patient is unable to swallow baclofen tablets

State C: PA criteria for Fleqsuvy

1. Member is 12 to 17 years of age or unable to swallow tablets OR
2. Step Therapy: Try baclofen tab, chlorzoxazone, cyclobenzaprine IR, methocarbamol, orphenadrine, tizanidine tabs first

State D: PA criteria for baclofen oral solution, Fleqsuvy and Lyvispah

1. Age
2. Diagnosis of dysphagia

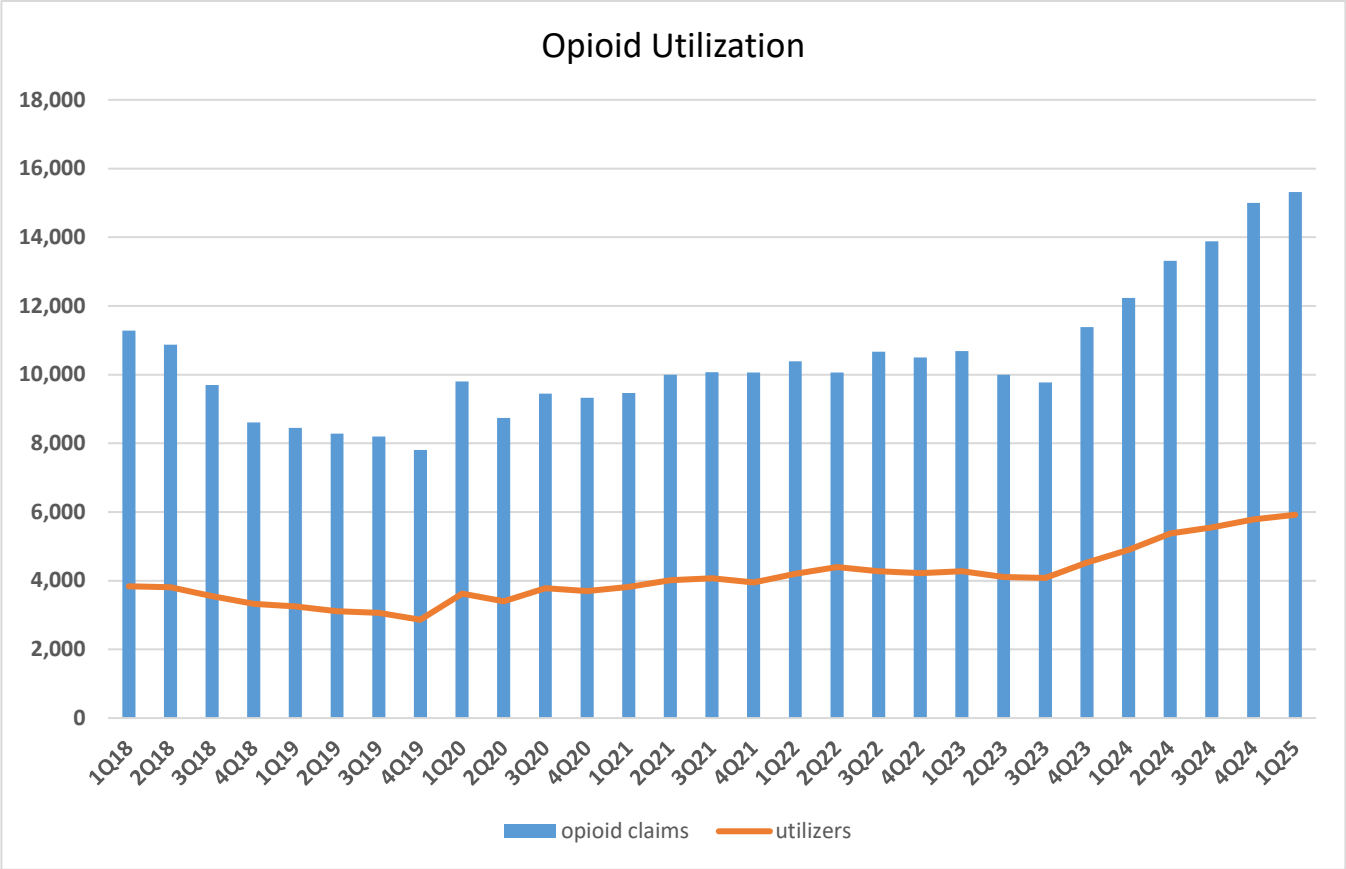
State E – Part 1: PA criteria for baclofen solution

1. Member is 12 to 17 years of age or unable to swallow tablets OR
2. Try baclofen tab, chlorzoxazone, cyclobenzaprine IR, methocarbamol, orphenadrine, tizanidine tabs first
3. Age 18 and over: provide rationale for not being able to swallow

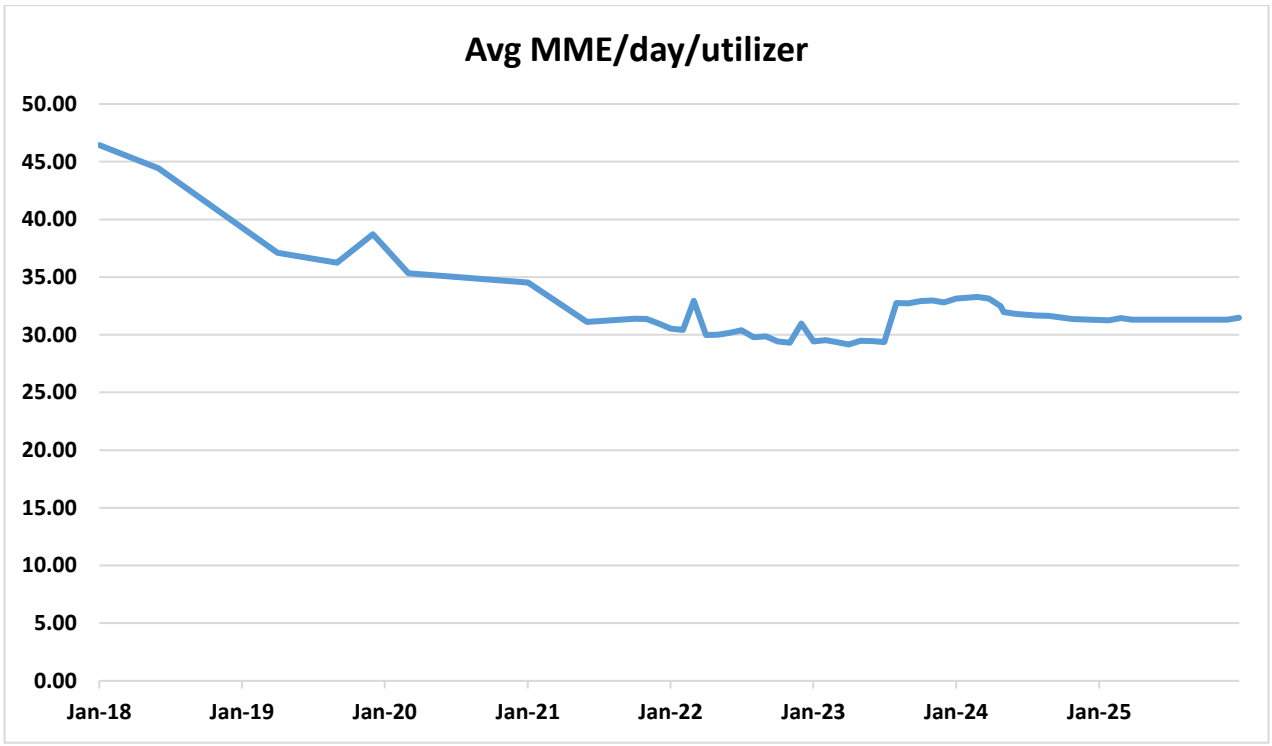
State E – Part 2: PA criteria for baclofen suspension, Fleqsuvy and Lyvispah

1. Member is 12 to 17 years of age or unable to swallow tablets OR
2. Try baclofen tab, chlorzoxazone, cyclobenzaprine IR, methocarbamol, orphenadrine, tizanidine tabs first
3. Try baclofen solution first
4. Age 18 and over: provide rationale for not being able to swallow

Opioid Summary



- 1Q18 to 4Q19 excludes IHS
- 1Q20 to current includes IHS
- March 13, 2020 – Pandemic Closure



Opioid Initiatives:

1. June 1, 2018 – early refill threshold for controlled substance changed from 75% to 85%
2. July 1, 2028 – PA for more than one LAO and one SAO
3. August 1, 2018 – opioid Naïve PA (initial 7-day supply and 60 MED limit)
4. October 1, 2018 to October 1, 2019 – decrease from 300 MED to 90 MED (cancer diagnosis excluded)

Other Initiatives:

- Buprenorphine PA (Bunavail/Suboxone/Zubsolv/Subutex) and ST (Belbuca/Butrans) removed 10/14/2019
- Lidoderm PA removed 8/1/2020

Total Eligibles and Utilizers

Quarter	Avg eligible members	Avg utilizing members of all drugs	% utilizing members of all drugs
1Q2020	123,573	27,090	21.9%
2Q2020	126,777	20,746	16.4%
3Q2020	132,373	23,417	17.7%
4Q2020	136,262	23,489	17.2%
1Q2021	139,748	24,407	17.5%
2Q2021	142,872	26,206	18.3%
3Q2021	146,023	27,933	19.1%
4Q2021	149,034	29,317	19.7%
1Q2022	151,735	29,092	19.2%
2Q2022	154,608	28,370	18.3%
3Q2022	157,627	29,167	18.5%
4Q2022	160,060	32,124	20.1%
1Q2023	162,684	31,612	19.4%
2Q2023	142,001	27,296	19.2%
3Q2023	131,292	26,218	19.9%
4Q2023	134,270	29,320	21.8%
1Q2024	141,162	32,891	23.3%
2Q2024	149,613	32,686	21.8%
3Q2024	159,160	35,263	22.2%
4Q2024	162,163	36,468	22.5%
1Q2025	164,446	38,367	23.3%

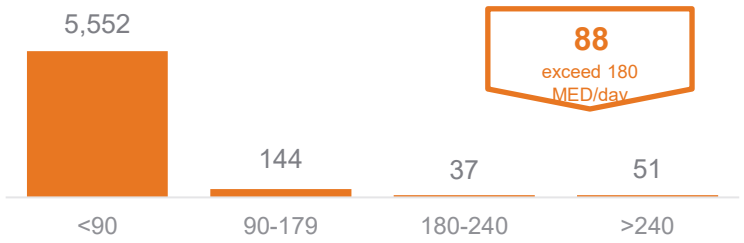
Opioid Utilization Snapshot

SDM 4Q2024
Sep 24 to Dec 24

Opioid Claims **14,999**
3.1% prescription claims filled for an opioid
1.3% higher than Medicaid FFS benchmark

Utilizers **5,784**
31.8% are high utilizers [1]
4.5% higher 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
77 opioid utilizing members with 3+ pharmacies

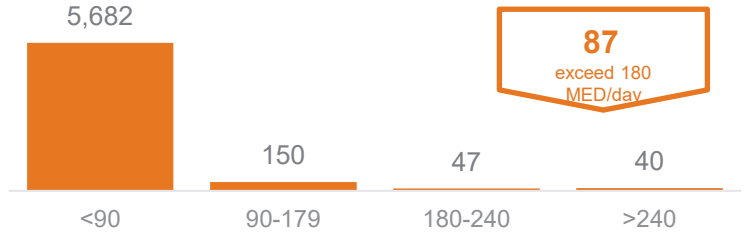
559 Shoppers: Poly Prescriber
opioid utilizing members with 3+ prescribers

1Q2025
Dec 24 to Mar 25

Opioid Claims **15,321**
3.1% prescription claims filled for an opioid
1.3% higher than Medicaid FFS benchmark

Utilizers **5,919**
32.1% are high utilizers [1]
4.9% higher 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
80 opioid utilizing members with 3+ pharmacies

533 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 1Q2025
Opportunities date range: Dec 2024 - Mar 2025
Benchmark: MEDICAID FEE FOR SERVICE

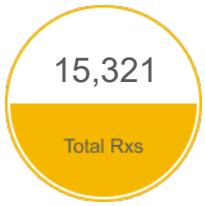
Utilizers: 5,919

3.1% 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.

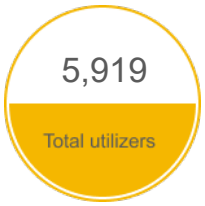
- Opioid prescriptions account for 3.1% of all prescriptions this period, which is 1.3% higher than the benchmark
- 1,898 high opioid utilizers were identified this period, which is 4.9% higher than the benchmark

Opioid claims



PERCENT NON-COMPLIANT
12.0%

Opioid utilizers

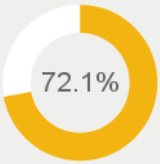


HIGH UTILIZERS
32.1%
1,898 high utilizers

4.9% over benchmark

High utilizers – view definition

Claim breakdown



short acting opioids

72.1% of all opioid Rxs were filled for short acting opioids. **3,299** Rxs were for medication assisted therapy (MAT) and **155** 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

87 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	5,682	150	47	40

MED – view definition

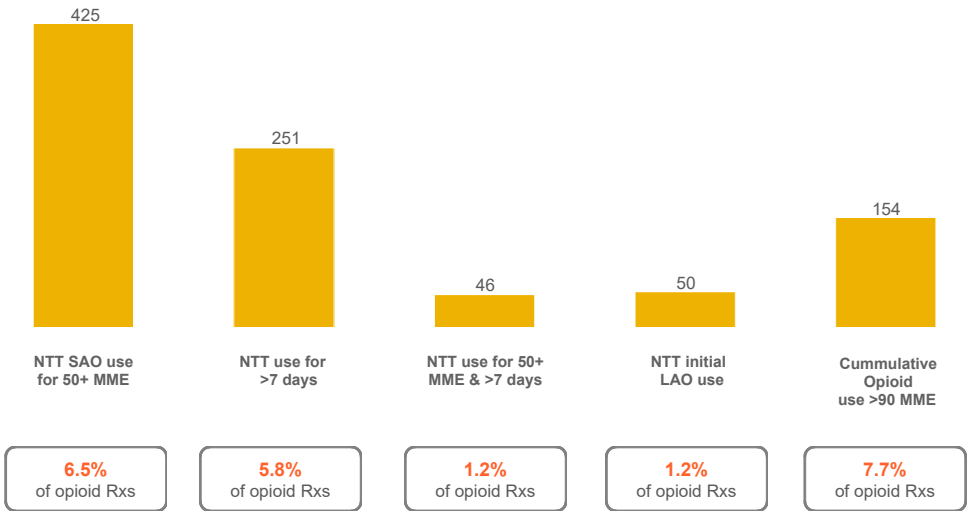
Opioid Opportunity Assessment

SDM 1Q2025
Opportunities date range: Dec 2024 - Mar 2025
Benchmark: MEDICAID FEE FOR SERVICE

Percent non-compliant: 12.0%

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?

80 opioid utilizing members use 3 or more pharmacies and 533 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
1,256	806	1,132	634	153

Anticonvulsants –view definition

New Business

Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonist Review

Time frame: 1/1/2025 to 3/31/2025

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
Aimovig 140mg/ml inj	78	$58,371.38	$748.35	2 per 29 days	34	17 – 63
Aimovig 70mg/ml inj	63	$45,466.74	$721.69	1 per 29.6 days	31	14 – 58
Ajovy 225mg/1.5ml inj	90	$65,598.50	$728.87	1.5 per 29.7 days	38	21 – 62
Emgality 120mg/ml inj	171	$127,666.06	$746.59	1.1 per 29 days	71	19 – 64

*Red font denotes drug is on PA/ST

South Dakota Medicaid PA criteria

CGRP PA criteria

Episodic Migraines Prophylaxis

1. Diagnosis of episodic migraines
2. Patient is 18 years of age or older
3. Patient has 4 to 14 migraines per month, but no more than 14-headache days per month
4. Prescribed by or in consultation with one of the following:
   - Neurologist, pain or headache specialist
5. Trial and failure, defined as at least 2 months of therapy with >80% adherence, or an intolerance/contraindication to at least one medication from TWO of the following prophylactic therapies
   - Beta-blockers (e.g., atenolol, propranolol, nadolol, timolol, or metoprolol)
   - Anti-epileptics (e.g., topiramate or divalproex sodium)
   - Antidepressants (e.g., venlafaxine or tricyclic antidepressants such as amitriptyline or nortriptyline)
6. Medication will not be used in combination with another CGRP inhibitor

Migraines Prophylaxis

1. Diagnosis of chronic migraines
2. Patient is 18 years of age or older
3. Patient has been evaluated for rebound headaches caused by medication overuse and if diagnosed, treatment will include a plan to taper off the offending medication or does not suffer from rebound headaches (more than 12 doses per month of narcotics, triptans, caffeine, or NSAIDs)
4. Patient has greater than or equal to 15-headache days per month, of which at least 8 must be migraine days for at least 3 months
5. Prescribed by or in consultation with one of the following specialists:
   - Neurologist, pain or headache specialist
6. Trial and failure, defined as at least 2 months of therapy with >80% adherence, or an intolerance/contraindication to at least one medication from each of the TWO prophylactic therapies [document drug]
   - Beta-blockers (e.g., atenolol, propranolol, nadolol, timolol, or metoprolol)
   - Anti-epileptics (e.g., topiramate or divalproex sodium)
   - Antidepressants (e.g., venlafaxine or tricyclic antidepressants such as amitriptyline or nortriptyline)
7. Medication will not be used in combination with another CGRP inhibitor

Other State CGRP PA criteria

State A

Aimovig, Ajovy
Initial criteria:

1. Diagnosis of migraine with or without aura requiring prophylaxis
2. Member is 18 years of age or older
3. One of the following:
    a. Member has prior adequate trial (90 days or greater) and failure of an agent from one of the following categories, as confirmed by claims history, chart documentation, or prescriber attestation including dates of trial:
        - Angiotensin receptor blockers (candesartan)
        - Antidepressants (venlafaxine)
        - Antiseizure agents (topiramate)
        - Beta-blockers (atenolol, metoprolol, propranolol, and/or timolol (can cumulate))
        - Tricyclic antidepressants (amitriptyline)
        - Valproic acid derivatives (divalproex and/or valproate (can cumulate))
    b. Prescriber has provided documented medical justification (intolerance, contraindication, etc.) as to why the member cannot utilize candesartan, venlafaxine, amitriptyline, divalproex, valproate, topiramate, atenolol, metoprolol, propranolol, AND timolol
4. Requested quantity does not exceed plan's quantity limit

Reauthorization criteria:

1. Evidence of therapy with the requested agent for at least 90 days within the past 120 days, confirmed by claims history or chart documentation (excluding claims with an emergency supply indicator)
2. Requested quantity does not exceed plan's quantity limit

Emgality 100mgl/ml
Initial criteria:

1. Diagnosis of episodic cluster headaches
2. Member is 18 years of age or older
3. Requested quantity does not exceed the plan's quantity limit

Reauthorization criteria:

1. Evidence of therapy with the requested agent for at least 90 days within the past 120 days, confirmed by claims history or chart documentation (excluding claims with an emergency supply indicator)
2. Diagnosis of episodic cluster headaches or previous approval at 300mg/month (100mg/ml strength)
3. Requested quantity does not exceed the plan's quantity limit

Emgality 120mg/ml
Initial criteria

1. Diagnosis of migraine with or without aura requiring prophylaxis^
2. Member is 18 years of age or older
3. One of the following:

3.1. Member has prior adequate trial (90 days or greater) and failure of an agent from one of the following categories, as confirmed by claims history, chart documentation, or prescriber attestation including dates of trial:
- Angiotensin receptor blockers (candesartan)
- Antidepressants (venlafaxine)
- Antiseizure agents (topiramate)
- Beta-blockers (atenolol, metoprolol, propranolol, and/or timolol (can cumulate))
- Tricyclic antidepressants (amitriptyline)
- Valproic acid derivatives (divalproex and/or valproate (can cumulate))

3.2. Prescriber has provided documented medical justification (intolerance, contraindication, etc.) as to why the member cannot utilize candesartan, venlafaxine, amitriptyline, divalproex, valproate, topiramate, atenolol, metoprolol, propranolol, AND timolol

4. Requested quantity does not exceed the plan's quantity limit

Reauthorization criteria:

1. Evidence of therapy with the requested agent for at least 90 days within the past 120 days, confirmed by claims history or chart documentation* (excluding claims with an emergency supply indicator)
2. Requested quantity does not exceed the plan's quantity limit

State B

Ajovy, Aimovig, Emgality

Initial criteria – Approval 3 months

1. Diagnosis of migraine with or without aura
2. Patient has greater than or equal to 4 migraine days per month
3. If request is for Ajovy, patient has tried and failed at least two preferred agents
4. Patient has tried and failed a 8 week trial of any 2 (different classes) of the following oral medication classes, unless contraindicated:
   - Antidepressants (i.e., amitriptyline, venlafaxine)
   - Beta blockers (i.e., propranolol, metoprolol, timolol, atenolol)
   - Anti-epileptics (i.e., valproate, topiramate)
5. Patient is utilizing prophylactic intervention modalities (e.g., behavioral therapy, physical therapy, or life-style modifications)

Reauthorization criteria – Approval 12 months

1. Patient has experienced positive response to therapy (e.g., decrease in the number, frequency, and/or intensity of headaches, improved function, decreased reliance on acute treatments for migraine headaches);
2. Patient does not have unacceptable toxicity (e.g., intolerable injection site pain)

Emgality 100mg/ml

Initial criteria – Approval 3 months

1. Diagnosis of cluster headache

Reauthorization criteria: Approval 12 months

1. Patient has experienced positive response to therapy (e.g., decrease in the number, frequency, and/or intensity of headaches, improved function, decreased reliance on acute treatment for headaches);
2. Patient has absence of unacceptable toxicity (e.g., intolerable injection site pain)

State C

Aimovig, Emgality 120mg/ml
Initial criteria:

1. One of the following:
   1.1. Both of the following:
      1.1.1. Diagnosis of episodic migraines
      1.1.2. Patient has 4 to 14 migraine days per month, but no more than 14 headache days per month
   1.2. All of the following:
      1.2.1. Diagnosis of chronic migraines
      1.2.2. Patient has greater than or equal to 15 headache days per month, of which at least 8 must be migraine days for at least 3 months
      1.2.3. Medication overuse headache has been considered and potentially offending medication(s) have been discontinued
2. Patient is 18 years of age or older
3. Two of the following:
   3.1. One of the following:
      - History of failure (after at least a two-month trial) or intolerance to Elavil (amitriptyline) or Effexor (venlafaxine)
      - Patient has a contraindication to both Elavil (amitriptyline) and Effexor (venlafaxine) OR

   1.2 One of the following:
      - History of failure (after at least a two-month trial) or intolerance to Depakote/Depakote ER (divalproex sodium) or Topamax (topiramate)
      - Patient has a contraindication to both Depakote/Depakote ER (divalproex sodium) and Topamax (topiramate)

   1.3 One of the following:
      - History of failure (after at least a two-month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol, or metoprolol
      - Patient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol, metoprolol
4. Prescribed by or in consultation with one of the following specialists:
      - Neurologist
      - Pain specialist
      - Headache specialist*
5. Medication will not be used in combination with another CGRP inhibitor for the preventive treatment of migraines

Reauthorization criteria:

1. Patient has experienced a positive response to therapy, demonstrated by a reduction in headache frequency and/or intensity
2. Use of acute migraine medications [e.g., nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen, naproxen), triptans (e.g., eletriptan, rizatriptan, sumatriptan)] has decreased since the start of CGRP therapy
3. Prescribed by or in consultation with one of the following specialists:
      - Neurologist, Pain specialist, Headache specialist*
4. For Chronic Migraine only: Patient continues to be monitored for medication overuse headache (MOH)
5. Medication will not be used in combination with another CGRP inhibitor for the preventive treatment of migraines

Emgality 100mg/ml
Initial criteria:
1. Diagnosis of episodic cluster headache
2. Patient has experienced at least 2 cluster periods lasting from 7 days to 365 days, separated by pain-free periods lasting at least three months
3. Patient is 18 years of age or older
4. Prescribed by or in consultation with one of the following specialists:
    - Neurologist
    - Pain specialist
    - Headache specialist*
5. Medication will not be used in combination with another injectable CGRP inhibitor

Reauthorization criteria:
1. Patient has experienced a positive response to therapy, demonstrated by a reduction in headache frequency and/or intensity
2. Prescribed by or in consultation with one of the following specialists:
    - Neurologist
    - Pain specialist
    - Headache specialist*
3. Medication will not be used in combination with another injectable CGRP inhibitor

Ajovy, Vyepti
Initial criteria
1. One of the following:
    1.1. Both of the following:
        1.1.1. Diagnosis of episodic migraines
        1.1.2. Patient has 4 to 14 migraine days per month, but no more than 14 headache days per month
    1.2. All of the following:
        1.2.1. Diagnosis of chronic migraines
        1.2.2. Patient has greater than or equal to 15 headache days per month, of which at least 8 must be migraine days for at least 3 months
        1.2.3. Medication overuse headache has been considered and potentially offending medication(s) have been discontinued
2. Patient is 18 years of age or older
3. Two of the following:
    3.1. One of the following:
        - History of failure (after at least a two-month trial) or intolerance to Elavil (amitriptyline) or Effexor (venlafaxine)
        - Patient has a contraindication to both Elavil (amitriptyline) and Effexor (venlafaxine)
    3.2. One of the following:
        - History of failure (after at least a two-month trial) or intolerance to Depakote/Depakote ER (divalproex sodium) or Topamax (topiramate)
        - Patient has a contraindication to both Depakote/Depakote ER (divalproex sodium) and Topamax (topiramate)

        or
    3.3. One of the following:
        - History of failure (after at least a two-month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol, or metoprolol
        - Patient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol, metoprolol

4. Trial and failure, contraindication, or intolerance to ALL of the following:
    - Aimovig
    - Emgality
5. Prescribed by or in consultation with one of the following specialists:
    - Neurologist
    - Pain specialist
    - Headache specialist*
6. Medication will not be used in combination with another CGRP inhibitor for the preventive treatment of migraines

Reauthorization criteria:

1. Patient has experienced a positive response to therapy, demonstrated by a reduction in headache frequency and/or intensity
2. Use of acute migraine medications [e.g., nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen, naproxen), triptans (e.g., eletriptan, rizatriptan, sumatriptan)] has decreased since the start of CGRP therapy
3. Trial and failure, contraindication, or intolerance to ALL of the following:
    - Aimovig
    - Emgality
4. Prescribed by or in consultation with one of the following specialists:
    - Neurologist
    - Pain specialist
    - Headache specialist*
5. For Chronic Migraine only: Patient continues to be monitored for medication overuse headache (MOH)
6. Medication will not be used in combination with another CGRP inhibitor for the preventive treatment of migraines

Antipsychotic Utilization (includes IHS) by Year and Age Group
Time frame: 2019 to 2024

Age Group	Year	Utilizer	Total Rx	Total Paid Amount
0 – 5	2019	46	209	$11,356.89
	2020	31	161	$4,001.14
	2021	35	152	$2,745.74
	2022	59	256	$4,493.72
	2023	65	320	$6,239.31
	2024	57	298	$7,558.40

Age Group	Year	Utilizer	Total Rx	Total Paid Amount
6 – 10	2019	367	2,585	$147,565.30
	2020	372	2,914	$176,348.59
	2021	373	2,915	$171,812.16
	2022	397	2,941	$182,974.81
	2023	396	2,882	$101,470.33
	2024	392	2,974	$110,175.60

Age Group	Year	Utilizer	Total Rx	Total Paid Amount
11 – 15	2019	738	6,144	$648,621.36
	2020	821	6,456	$815,933.50
	2021	851	6,557	$656,869.43
	2022	851	6,510	$699,483.78
	2023	783	5,828	$461,684.87
	2024	745	5,550	$346,011.02

Age Group	Year	Utilizer	Total Rx	Total Paid Amount
16 – 20	2019	603	4,491	$646,657.91
	2020	664	5,180	$1,003,937.12
	2021	774	5,872	$1,339,229.38
	2022	927	6,437	$1,624,433.52
	2023	930	6,257	$1,185,289.48
	2024	826	6,083	$1,276,069.72

Age Group	Year	Utilizer	Total Rx	Total Paid Amount
21 – 65	2019	2,143	21,114	$6,472,288.94
	2020	2,210	23,038	$7,850,287.38
	2021	2,461	24,176	$8,874,746.45
	2022	2,725	26,140	$10,298,722.09
	2023	3,364	26,857	$10,710,624.27
	2024	4,685	37,984	$16,175,306.22

Age Group	Year	Utilizer	Total Rx	Total Paid Amount
66+	2019	10	25	$787.95
	2020	7	29	$285.61
	2021	10	32	$364.97
	2022	15	98	$1,059.30
	2023	16	124	$1,520.82
	2024	21	166	$18,301.01

Utilization by Drug

Time frame: Year 2024

Antipsychotics	Total Rxs	Utilizers	Total Plan Cost
aripiprazole (Abilify)	11,085	1,997	$1,751,294.97
arpiprazole lauroxil **injectable**	904	133	$2,417,041.21
asenapine (Saphris)	45	5	$8,471.53
brexpiprazole (Rexulti)	937	148	$1,231,170.11
cariprazine (Vraylar)	2,782	490	$3,618,215.39
clozapine	2,730	157	$203,907.96
iloperidone (Fanapt)	13	3	$19,334.53
lumateperone (Caplyta)	784	134	$1,181,562.97
lurasidone (Latuda)	1,919	343	$73,394.82
olanzapine (Zyprexa)	5,792	1,059	$257,276.29
olanzapine pamoate (Zyprexa Relprevv) **injectable**	5	1	$4,264.75
Lybalvi (olanzapine-samidorphan)	455	70	$630,059.84
paliperidone (Invega)	699	95	$46,365.99
paliperidone palmitate **injectable**	1,961	286	$6,075,416.93
pimavanserin (Nuplazid)	0		
quetiapine (Seroquel)	11,003	1,647	$340,954.65
risperidone (Risperdal)	8,249	1,067	$384,775.96
risperidone microspheres **injectable**	126	8	$128,397.56
Uzedy **injectable** (risdperidone)	73	17	$181,215.03
xanomelin/tropsium (Cobenfy)	0		
ziprasidone (Geodon)	603	87	$35,116.02

*Red font denotes drug is on PA/ST

Utilization by Drug and Age Group

Time frame: Year 2024

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
aripiprazole	0 – 5	10	3	$167.44
	6 – 10	1,030	153	$35,844.22
	11 – 15	1,820	282	$81,449.68
	16 – 20	1,763	305	$208,864.62
	21 – 65	6,460	1,244	$1,424,940.09
	66+	2	2	$28.92

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
aripiprazole lauroxil **injectable**	16 – 20	72	10	$179,451.27
	21 – 65	832	123	$2,237,589.94

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
asenapine (Saphris)	11 – 15	6	1	$460.63
	16 – 20	39	4	$8,010.90

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
brexipiprazole (Rexulti)	6 – 10	15	3	$20,201.77
	11 – 15	40	8	$53,115.89
	16 – 20	81	15	$126,683.70
	21 – 65	788	121	$1,016,872.50
	66+	13	1	$14,296.25

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
cariprazine (Vraylar)	6 – 10	6	1	$6,637.88
	11 – 15	55	8	$62,438.18
	16 – 20	213	40	$281,484.03
	21 – 65	2,508	441	$3,267,655.30

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
clozapine	11 – 15	34	3	$906.75
	16 – 20	121	10	$2,786.25
	21 – 65	2,575	144	$200,214.96

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
Iloperidone (Fanapt)	21 – 65	13	3	$19,334.53

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
lumateperone (Caplyta)	11 – 15	12	2	$19,248.33
	16 – 20	48	10	$86,704.60
	21 – 65	724	122	$1,075,610.04

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
lurasidone (Latuda)	6 – 10	13	2	$259.87
	11 – 15	125	27	$2,434.39
	16 – 20	285	51	$7,012.50
	21 – 65	1,496	264	$63,688.06

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
olanzapine	0 – 5	5	3	$64.48
	6 – 10	86	15	$7,508.76
	11 – 15	235	49	$8,996.05
	16 – 20	542	107	$24,066.78
	21 – 65	4,918	884	$216,565.34
	66+	6	1	$74.88

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
olanzapine pamoate **injectable**	21 – 65	5	1	$4,264.75

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
Lybalvi (olanzapine-samidorphan)	11 – 15	55	8	$83,972.22
	16 – 20	90	14	$128,390.94
	21 – 65	310	47	$417,696.68

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
paliperidone (Invega)	11 – 15	66	4	$3,251.37
	16 – 20	25	9	$3,280.32
	21 – 65	608	82	$39,834.30

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
paliperidone palmitate **injectable**	16 – 20	51	8	$142,482.35
	21 – 65	1,910	278	$5,932,934.58

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
quetiapine	0 – 5	2	1	$1,438.00
	6 – 10	53	9	$659.94
	11 – 15	1,061	132	$18,012.38
	16 – 20	1,625	220	$36,180.37
	21 – 65	8,158	1,271	$281,187.58
	66+	104	13	$3,476.38

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
risperidone solution & tabs	0 – 5	195	29	$4,717.86
	6 – 10	1,454	178	$28,326.28
	11 – 15	1,714	202	$28,266.61
	16 – 20	1,178	132	$41,174.42
	21 – 65	3,669	525	$281,896.70
	66+	39	5	$394.09

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
risperidone microspheres **injectable**	21 – 65	126	8	$128,397.56

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
Uzedy (risperidone **injectable**)	16 – 20	8	1	$11,542.43
	21 – 65	65	16	$169,672.60

Drug Name	Age Group	Total Rx	Utilizer	Total Paid Amount
ziprasidone (Geodon)	11 – 15	7	3	$153.28
	16 – 20	89	12	$1,819.42
	21 – 65	507	73	$33,143.32

Atypical Antipsychotic PA Criteria:

1. For continuation of atypical antipsychotic agent **OR**
2. If request is for a long-acting injectable and is patient discharged from an in-patient psychiatric facility **OR**
3. Indicated diagnosis
OR
2.1 Both of the following:
2.1.1 Patient has a diagnosis of depression **AND**
2.1.2 Patient has tried and failed 2 different antidepressants
AND
4. Children younger than 6 years of age must have a psychiatrist, developmental pediatrician, child/adolescent psychiatrist, or pediatric neurologist involved in care
AND
5. For alternative dosage forms (e.g., rapid dissolve tablets, injectables, extended-release), one of the following criteria must be met:
5.1 The patient is unable to swallow **OR**
5.2 The patient failed a standard dosage form from this drug class in the last 30 days

Journavx (suzetrigine)
Time frame: 1/1/2025 to 3/31/2025

Indication: for the treatment of acute moderate pain and severe pain

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
Journavx 50mg tab	3	$977.15	$325.72	20 per 10 days	3	44 – 52

State A PA criteria

Approval: 14 day suppy, every 90 days

1. Member is 18 years of age or older
2. Must use within the plan limitation maximum of 7-day supply with (a) subsequent claim(s) not to exceed 7-day supply (for a total of 14 days of therapy, maximum of 29 tablets) every 90 days

State B PA criteria

Approval: 14 days

1. Patient is 18 years of age or older
2. Diagnosis of moderate to severe acute pain
3. Medication will not be used for longer than 14 days for any one acute pain occurrence
4. Prescriber attests that pain cannot be controlled with conventional pharmacological therapies such as acetaminophen, NSAIDS, and local anesthetics
5. Medication will not be used in combination with opioid products (e.g. oxycodone, hydrocodone)
6. Medication will not be used in combination with strong CYP3A inhibitors
7. For female patients with reproductive potential (aged 14-44 years), prescriber attest to BOTH of the following:
    - Patient is not pregnant prior to initiation of therapy
    - Patients taking concomitant hormonal contraceptives containing progestins other than levonorgestrel and norethindrone have been advised to use alternative contraceptives during Journavx treatment and for 28 days after discontinuation of therapy

Commercial PA criteria:

Approval: 14 days

1. Patient is 18 years of age or older
2. Patient is experiencing a new episode of moderate to severe acute pain
3. Medication will not be used for longer than 14 days for any one acute pain occurrence
4. Dosing frequency will be limited to twice daily
5. Medication is not used in combination with opioid products (e.g., oxycodone, hydrocodone, codeine)
6. Quantity requested does not exceed 60 tablets within the past 90 days**

Ohtuvayre (ensifentrine inhalation)
Time frame: 1/1/2025 to 3/31/2025

Indications:

- Ohtuvayre – for the maintenance treatment of chronic obstructive pulmonary disease (COPD)

- roflumilast – for the prevention of severe chronic obstructive pulmonary disease (COPD) exacerbations in chronic bronchitis patients with severe COPD associated with a history of COPD exacerbations

Selective PDE4 Inhibitor	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
Ohtuvayre	0		*~$3,000.00*			
roflumilast 250mcg tab	6	$409.19	$68.20	24 per 24 days	4	53 – 61
roflumilast 400mcg tab	9	$169.69	$18.85	25 per 25 days	5	50 – 64

State A PA criteria

1. Member has a diagnosis of COPD
2. Member has an FEV-1/FVC ratio of < 0.7 measured by spirometry (supported by submitted chart documentation)
3. Member has a Modified Medical Research Council (mMRC) dyspnea score of ≥ 2 (supported by submitted chart documentation)
4. One of the following:
    - Member is utilizing combination long-acting beta-agonist (LABA)/long-acting muscarinic antagonist (LAMA)/inhaled corticosteroid (ICS) therapy for at least 90 days in the past 120 days, as confirmed by claims history, chart documentation, or provider attestation including dates of use
    - Prescriber has provided medical rationale for the use of Ohtuvayre (ensifentrine) over combination LAMA/LABA/ICS therapy and one of the of the following:
        i. Member is utilizing combination LABA/LAMA therapy for at least 90 days in the past 120 days, as confirmed by claims history, chart documentation, or provider attestation including dates of use
        ii. Prescriber has provided medical rationale for the use of Ohtuvayre (ensifentrine) over combination LABA/LAMA therapy
5. One of the following:
    - Prescriber attests that member will continue to utilize appropriate adjunct therapy while on Ohtuvayre (ensifentrine) [PAS note: please include field for attestation] OR
    - Prescriber has submitted medical rationale for discontinuing use of adjunct therapy

Reauthorization

1. Must meet both of the following:
    - History of the requested agent for at least 90 days within the past 120 days, as confirmed by claims history, chart documentation, or provider attestation including dates of trial
2. One of the following:
    - Member is continuing to utilize adjunct therapy, as applicable
    - Medical rationale has been provided for not continuing adjunct therapy

State B PA criteria:

1. Patient is 18 years of age or older
2. Diagnosis of Chronic Obstructive Pulmonary Disorder (COPD)
3. Submission of medical records (e.g. chart notes) demonstrating that patient meets ALL the following:
   - Bronchodilator FEV1/FVC ratio of <0.7
   - FEV1 % predicted of ≤ 79%
   - modified Medical Research Council (mMRC) dyspnea scale score of ≥ 2
4. One of the following:
   - Trial and failure (as defined by continued symptoms, including exacerbations) of adequate treatment concomitantly with a long-acting beta-agonist (LABA) + long-acting antimuscarinic (LAMA) + inhaled corticosteroid
   - Trial and failure (as defined by continued symptoms, including exacerbations) of adequate treatment concomitantly with a long-acting beta-agonist (LABA) and long-acting antimuscarinic (LAMA)
5. Must be used as maintenance therapy only

Commercial PA criteria:

1. Diagnosis of chronic obstructive pulmonary disease (COPD)
2. Post-bronchodilator forced expiratory volume [FEV1] / forced vital capacity [FVC] ratio less than 0.70
3. Patient is symptomatic despite being on at least two therapies indicated for the treatment of COPD and will continue to be treated with the therapies (e.g. long-acting muscarinic antagonists [e.g., tiotropium], long-acting beta agonist [e.g., formoterol]), unless there is a contraindication or intolerance
4. Patient experiences dyspnea during everyday activities (e.g., short of breath when walking up a slight hill)

Reauthorization

1. Patient demonstrates a positive clinical response to therapy
2. Patient continues to be treated with at least two therapies indicated for the treatment of COPD (e.g. long-acting muscarinic antagonists [e.g., tiotropium], long-acting beta agonist [e.g., formoterol]), unless there is a contraindication or intolerance

Optum Rx®

Therapeutic Class Overview

Calcitonin gene related peptide (CGRP) inhibitors

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 (*Ailani et al 2021[a], Katsarava et al 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 who appear to have 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 13.8 to 15% 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 (*Stovner et al 2022*, *Global Burden of Disease Study [GBD] 2018, 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. For the treatment of acute migraine, options include triptans, ergots, nonsteroidal anti-inflammatory drugs (NSAIDs), certain oral calcitonin gene-related peptide (CGRP) inhibitors (rimegepant and ubrogepant), 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).*
- The CGRP pathway is important in pain modulation and the Food and Drug Administration (FDA) has approved 8 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, ubrogepant, and atogepant are small molecule oral CGRP receptor antagonists known as the “gepants”(*Ailani et al 2021[a], Dodick et al 2018[b], Edvinsson 2017, Goadsby et al 2017, Sun et al 2016, Tepper et al 2017, Qulipta prescribing information 2025*). Zavegepant, is the first intranasally administered CGRP inhibitor (*Zavzpret prescribing information 2025*).
- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene−related peptide (CGRP) receptor antagonists.

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)*
Aimovig (erenumab-aooe) subcutaneous injection	–
Ajovy (fremanezumab-vfrm) subcutaneous injection	–
Emgality (galcanezumab-gnlm) subcutaneous injection	–
Nurtec ODT (rimegepant sulfate) orally disintegrating tablet	–
Qulipta (atogepant) tablet	–
Ubrelvy (ubrogepant) tablet	–
Vyepti (eptinezumab-jjmr) intravenous injection	–
Zavzpret (zavegepant) nasal spray	–

*For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.

(*Drugs@FDA 2025, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2025, Purple Book: Database of Licensed Biological Products 2025*)

Indications

Table 2. Food and Drug Administration Approved Indications

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

*Limitation of use: Not indicated for the preventive treatment of migraine.
†Indication includes both episodic migraine and chronic migraine.

(*Prescribing information: Aimovig 2025, Ajovy 2025, Emgality 2025, Nurtec ODT 2025, Qulipta 2025, Ubrelvy 2025, Vyepti 2025, Zavzpret 2025*)

- 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

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)*.
  - The reduction in MMD was sustained through 1 year of follow-up for the eptinezumab-jjmr 300 mg group (-5.3 days), which was significant compared to placebo (-4.1 days) at weeks 37 to 48 (difference, -1.2; 95% confidence interval [CI], -1.95 to -0.46). The reduction in the 100 mg group was significantly greater compared to placebo at 25 to 36 weeks (-4.7 vs -4.0, respectively; difference, -0.72; 95% CI, -1.43 to -0.01), but not at 37 to 48 weeks (-4.5 vs -4.1; difference, -0.38; 95% CI, -1.13 to 0.37) *(Smith et al 2020)*.
- DELIVER was a DB, PC, MC, Phase 3b trial in which 891 patients with episodic or chronic migraine with ≥ 4 MMDs and documented evidence of 2 to 4 previous preventive treatment failures within the past 10 years were randomized to eptinezumab-jjmr 100 mg (n = 299), eptinezumab-jjmr 300 mg (n = 294), or placebo (n = 298). Treatment 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 (AEs) that made treatment intolerable, or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. The primary outcome was change from baseline in the mean MMD during weeks 1 to 12. The change in mean MMD from baseline to week 12 was -4.8 days with eptinezumab-jjmr 100 mg, -5.3 days with eptinezumab-jjmr 300 mg, and -2.1 days with placebo. The difference from placebo in change in MMD from baseline was significant with eptinezumab-jjmr 100 mg (-2.7; 95% CI, -3.4 to -2.0; p < 0.0001) and eptinezumab-jjmr 300 mg (-3.2; 95% CI, -3.9 to -2.5; p < 0.0001) (*Ashina et al 2022*). A post-hoc analysis of data from the DELIVER trial reported an increase in the proportion of patients achieving a response (a ≥ 50% reduction in migraine days) from weeks 13 to 24 (52.3% and 59.1% for 100 and 300 mg doses, respectively) compared to weeks 1 to 12 (42.1% and 49.5%, respectively) (*Ashina et al 2024*).
  - A 48-week, blinded, long-term extension of the DELIVER trial, where all patients (N = 865) received active drug, evaluated response rates with eptinezumab-jjmr up to 72 weeks. At 36 weeks, response rates (≥ 50% reduction in monthly migraine days) were 59.6%, 61%, 48.6%, and 63% for patients continuing eptinezumab-jjmr 100 mg and 300 mg, and for placebo-treated patients switched to eptinezumab-jjmr 100 mg and 300 mg, respectively. At 72 weeks, corresponding response rates were 68.3%, 65.9%, 63.5%, and 69.9%, respectively (*Ashina et al 2023[a]*)

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% 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*). Data after 1 year of treatment found sustained efficacy in episodic migraine (*Goadsby et al 2020[a]*).
- 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*). Data after 2 and 3 years of treatment found sustained efficacy in episodic migraine *(Ferrari et al 2022, Reuter et al 2024)*.

- The HER-MES trial was a 24-week, DB, double-dummy, Phase 4 trial in which 777 patients with migraines occurring ≥ 4 days per month were randomized to erenumab-aooe 70 or 140 mg once monthly (n = 389) or topiramate 50 to 100 mg per day (n = 388). The primary endpoint of the proportion of patients who discontinued the medication due to an AE was lower with erenumab-aooe (10.6%) compared to topiramate (38.9%; OR, 0.19; 95% CI, 0.13 to 0.27; p < 0.001). A secondary endpoint of the proportion of patients with ≥ 50% reduction in MMD from baseline over months 4 to 6 of the DB treatment phase was 55.4% with erenumab-aooe compared to 31.2% with topiramate (OR, 2.76; 95% CI, 2.06 to 3.71; p < 0.001) *(Reuter et al 2022).*
- The APPRAISE trial was a 12 week, global, MC, active controlled, Phase 4, randomized controlled trial (RCT) evaluating the effect of early initiation of erenumab compared to non-specific preventative therapies (eg, beta-blocker, topiramate, tricyclic antidepressants) in 621 patients who have failed 1 or 2 previous preventative treatment. The primary endpoint was the proportion of patients completing 1 year of the initially assigned treatment and achieving a reduction of 50% or greater from baseline in MMDs at 12 months. Compared to non-specific treatments, patients treated with erenumab demonstrated a significant reduction in cumulative average MMD (-4.32 vs -2.65; treatment difference: -1.67 [0.35] days; p < 0.001). Additionally, fewer patients taking erenumab switch medications compared to controls (2.2% vs 34.6%) (*Pozo-Rosich et al 2024*).

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]*). Data after 1 year of treatment found sustained efficacy in episodic migraine (*Goadsby et al 2020[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 AEs 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 mean monthly migraine headache days (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) 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 AEs 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*). Data after 6 months of treatment found sustained efficacy in patients with episodic and chronic migraine (*Ashina et al 2021*).
  - A subgroup analysis found that fremanezumab-vfrm reduced MMDs compared to placebo regardless of whether patients had previously not responded to 2, 3, or 4 classes of migraine preventive medications (*Pazdera et al 2021*).

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 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*).
- CONQUER was a DB, PC, Phase 3b trial that evaluated 462 patients with episodic (58%) or chronic migraine (42%) who had previously not responded to 2 to 4 classes of migraine preventive medications for 12 weeks. All galcanezumab-gnlm patients were administered a 240 mg loading dose, then 120 mg per month. Failure was defined as discontinuation owing to no response or inadequate response, or a safety or tolerability event. At baseline, the MMHD was approximately 13.2 days with 9.3 in the episodic migraine group and 18.7 in the chronic migraine group. For the overall population, the MMHD reduction over 12 weeks was 1.0 (SE, 0.3) days for placebo, 4.1 (SE, 0.3) days for the monthly galcanezumab-gnlm group (LSMD, -3.1; 95% CI, -3.9 to -2.3 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMHD reduction over 12 weeks was 2.6 days for the galcanezumab-gnlm monthly group (95% CI, -3.4 to -1.7 days; p < 0.0001). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 41.8% in the monthly galcanezumab-gnlm group vs 17.1% with placebo (p < 0.0001). Compared to placebo, the monthly galcanezumab-gnlm arm achieved a statistically significant improvement of ≥ 75% sustained responder (3.7 vs 18.4%; OR, 5.9; 95% CI, 2.4 to 14.6; p = 0.0001) and 100% sustained responder (0 vs 7.7%; p < 0.0001). Treatment-emergent AEs were similar for placebo and galcanezumab-gnlm (53 vs 51%). Serious AEs were reported in 2 patients (1%) of each of the groups (*Mulleners et al 2020*). Data after 6 months of treatment found sustained efficacy in patients with episodic and chronic migraine (*Reuter et al 2021*).
  - A post-hoc analysis evaluated the time to treatment onset and showed a reduction in headache days with galcanezumab-gnlm beginning during the first month, which was significant compared to placebo (-4.0 vs -0.7,

respectively; p ≤ 0.001). There was also a significantly greater reduction in weekly headache days with galcanezumab-gnlm beginning week 1 compared to placebo (-1.1 vs -0.2; p < 0.01) *(Schwedt et al 2021[a])*.
    - A subgroup analysis evaluated the efficacy of galcanezumab-gnlm in 186 patients with chronic or episodic migraine who had previously not responded to 3 to 4 classes of migraine preventive medications; as in the overall trial population, galcanezumab-gnlm significantly reduced MMHD and increased the proportion of patients with a ≥ 50% response compared to placebo (*Okonkwo et al 2021*).
- A 3-month, Phase 4, DB, parallel-group, RCT compared the efficacy of galcanezumab and for preventative the treatment of episodic migraine in 580 patients. The primary endpoint was the proportion of participants with a ≥ 50% reduction in migraine headache days per month from baseline to 3 months. Results showed similar efficacy between both groups; 62% of patients meeting the primary endpoint with galcanezumab vs 61% with Rimegepant (p = 0.70). Demonstrating that both agents are effective for preventative treatment (*Schwedt et al 2024*).

Rimegepant

- Rimegepant was studied in a MC, DB, PC, Phase 2/3 trial in adults with migraine for ≥ 1 year and with 4 to 18 moderate-to-severe migraine attacks per month. A total of 747 adults with ≥ 6 migraine days were randomized to rimegepant 75 mg (n = 370) orally every other day vs placebo (n = 371) for 12 weeks. Patients were allowed to continue 1 preventive medication excluding another CGRP inhibitor (ie, topiramate, gabapentin, beta-blockers, and tricyclic antidepressants), and rescue medication (ie, triptans, NSAIDs, paracetamol, aspirin, caffeine, baclofen, antiemetics, and muscle relaxants). At baseline, patients had a mean of 7.8 moderate-to-severe attacks per month, 40% with aura, and 23% had a history of chronic migraine. After 12 weeks of treatment, a reduction from the observation period in MMD during weeks 9 to 12 was 4.3 vs 3.5 days for rimegepant vs placebo, respectively (p = 0.0099). A ≥ 50% reduction in moderate-to-severe MMDs during weeks 9 to 12 were observed in 49 vs 41% for rimegepant vs placebo, respectively (p = 0.044). A reduction in mean number of total migraine days per month during weeks 1 to 12 was 3.6 vs 2.7 days, respectively (p = 0.0017). Treatment related AEs were reported in 11% in the rimegepant arm vs 9% in the placebo arm. All other incidences of AEs were similar between groups. The most common AEs included nausea, nasopharyngitis, urinary tract infection, and upper respiratory tract infection (*Croop et al 2021*).

Atogepant

- The ADVANCE trial was a MC, DB, PC, Phase 3 trial in 873 adults with migraine for ≥ 1 year and 4 to 14 migraine days per month. Patients were randomized to receive placebo (n = 214), atogepant 10 mg daily (n = 214), atogepant 30 mg daily (n = 223), or atogepant 60 mg daily (n = 222) for 12 weeks. The primary endpoint was the change from baseline in mean MMD. Treatment with atogepant at any dose resulted in a greater decrease in MMD across weeks 1 through 12 compared to placebo (placebo, -2.5; 10 mg, -3.7; 30 mg, -3.9; 60 mg, -4.2; p < 0.001 for all doses compared to placebo). A ≥ 50% reduction in the 3-month average of MMDs occurred in 55.6%, 58.7%, 60.8%, and 29% of patients receiving atogepant 10 mg, 30 mg, 60 mg, and placebo, respectively (p < 0.001 for all comparisons to placebo) (*Ailani et al 2021[b]*). Atogepant demonstrated treatment benefits as early as the first day after treatment initiation, with 10.8% to 14.1% of patients on atogepant reporting a migraine on post-dose day 1 compared to 25.2% of patients receiving placebo (p ≤ 0.0071) (*Schwedt et al 2021[b]*). Patient-reported outcomes from the ADVANCE trial were also assessed. Compared to placebo, scores for quality of life-related questionnaires (including role function-prevention, performance of daily activities, and activity impairment) were significantly improved with atogepant (*Lipton et al 2023[a]*).
- A MC, DB, PC, Phase 2b/3 trial enrolled 825 adults with migraine for ≥ 1 year and 4 to 14 migraine days per month. Patients were randomized to receive placebo (n = 178), atogepant 10 mg daily (n = 92), atogepant 30 mg daily (n = 182), atogepant 60 mg daily (n = 177), atogepant 30 mg twice daily (n = 79), or atogepant 60 mg twice daily (n = 87) for 12 weeks. The primary endpoint was the change in mean MMD across the 12-week treatment period. Treatment with atogepant at any dose resulted in a greater decrease in MMD across weeks 1 through 12 compared to placebo (placebo, -2.9; 10 mg, -4.0; 30 mg, -3.8; 60 mg, -3.6; 30 mg twice daily, -4.2; 60 mg twice daily, -4.1; p-values significant for all doses compared to placebo) (*Goadsby et al 2020[c]*).
- The ELEVATE trial was a DB, PC, Phase 3b trial in adults with documented episodic migraine (with or without aura) and failure of 2 to 4 classes of oral migraine preventive treatment. Patients were randomized to receive atogepant 60 mg (n = 158) or placebo (n = 157) once daily for 12 weeks. The primary endpoint was change from baseline in mean MMD. Treatment with atogepant resulted in a greater decrease in MMD at week 12 compared to placebo (change from baseline of -1.9 for placebo and -4.2 for atogepant; p < 0.00001) (*Tassorelli et al 2024*).

- A network meta-analysis of randomized controlled trials for 5 CGRP inhibitors (atogepant, eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm) identified 24 double-blind trials for inclusion (*Sun et al 2023*). The majority of studies (N = 16) were specific to episodic migraine; however, 5 included only chronic migraine and 3 included both chronic and episodic migraine patients. Overall, fremanezumab-vfrm 225 mg was considered the most effective treatment for reduction of migraine days from baseline (standard mean difference, -0.49 [95% CI, -0.62 to -0.37]) and 50% response rate (risk ratio, 2.98 [95% CI, 2.16 to 4.10]), and erenumab-aooe 140 mg was the most effective for reducing acute medication days (standard mean difference, -0.68; [95% CI, -0.79 to -0.58]). Galcanezumab-gnlm 240 mg and fremanezumab-vfrm 675 had higher AE rates than placebo. In the subgroup of patients with episodic migraine, fremanezumab-vfrm remained the most effective treatment; however, erenumab-aooe was the most effective treatment in those with chronic migraine.

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-jjmr 100 and 300 mg was associated with significant reductions in MMDs across weeks 1 to 12 compared to placebo (placebo, -5.6; 100 mg, -7.7, $p < 0.0001$; 300 mg, -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[a]*). Updated data from PROMISE-2 demonstrated similar responses at 24 weeks as were observed at 12 weeks (*Silberstein et al 2020[a]*).
- The PREVAIL trial was an OL, single-arm, Phase 3 trial evaluating long-term outcomes for eptinezumab-jjmr for 2 years. A total of 128 adults with chronic migraine received eptinezumab-jjmr 300 mg every 12 weeks for up to 8 doses. The percentage of patients with severe disability measured using the Migraine Disability Assessment (MIDAS) tool decreased from 84.4% to 26.8% at week 12 and 20.8% at week 104 (*Kudrow et al 2021[a]*).

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]*).
  - A post-hoc analysis evaluated the time to treatment onset with erenumab-aooe. This analysis showed that 41.7% of the patients receiving erenumab-aooe 70 mg who responded at any point during the study had responded by month 1, and 77.8% had responded by month 2. Among patients receiving erenumab-aooe 140 mg, 52.5% of the patients who responded at any point during the study had responded by month 1, and 84.2% had responded by month 2 *(Tepper et al 2021)*.
- A systematic review and network meta-analysis of 20 RCTs assessed the efficacy and safety of erenumab for chronic and episodic migraine compared to placebo. Treatment with erenumab demonstrated a statistically significant improvement in MMD reduction, response rates, and quality of life scales compared to placebo. A subgroup analysis demonstrated greater erenumab efficacy in patients with previous treatment failures compared to patients without previous treatment failure. Constipation occurred with a greater incidence in patients treated with erenumab compared to placebo (risk ratio, 2.53; 95% CI, 1.6 to 4.02) (*Haseeb et al 2025*).

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*). Data after 1 year of treatment found sustained efficacy in chronic migraine (*Goadsby et al 2020[b]*).
  - A subgroup analysis evaluated the proportion of patients reverting to episodic migraine, defined as < 15 headache days per month. A total of 44.5% of patients in the placebo group reverted to episodic migraine compared to 50.5% in the quarterly fremanezumab-vfrm group (p = 0.108) and 53.7% in the monthly dosing group (p = 0.012) *(Lipton et al 2020[b]).*
- 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*).
  - In a 9-month open-label extension (OLE) study conducted after the 3-month DB treatment period, the mean change in the number of MMHD decreased from a baseline of 19.4 days by -8.5 days with placebo, -9.0 days with galcanezumab-gnlm 120 mg, and -8.0 days with galcanezumab-gnlm 240 mg. The proportion of patients with ≥ 50% response was 57%, 57%, and 53%, respectively *(Pozo-Rosich et al 2022).*
- CONQUER was previously described as including 462 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 42% were diagnosed with chronic migraine and were randomized to galcanezumab-gnlm 240 mg loading dose followed by 120 mg administered monthly (n = 95/193), or placebo (n = 98/193). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMHD reduction over 12 weeks was 3.7 days for the galcanezumab-gnlm monthly group (95% CI, -5.2 to -2.2 days; p < 0.0001) (*Mulleners et al 2020*).

Atogepant

- A MC, DB, PC, Phase 3 trial, PROGRESS, randomized patients (N = 778) with chronic migraine to atogepant 30 mg twice daily (n = 257), 60 mg once daily (n = 262), or placebo (n = 259) (*Pozo-Rosich et al 2023*). Both the 30 mg twice daily dose and the 60 mg once daily dose reduced MMDs compared with placebo (LSMD, -2.4 [95% CI, -3.5 to -1.3] and LSMD, -1.8 [95% CI, -2.9 to -0.8], respectively). Constipation, nausea, and weight loss were notable AEs.
- A MC, OL, Phase 3 RCT evaluated the efficacy of atogepant 60 mg once daily for prevention of migraine. Adults with migraine (N = 744) were randomized to atogepant or standard care migraine prevention for 52 weeks. The primary goal was to evaluate the safety of atogepant. Change from baseline in MMDs was evaluated as an efficacy endpoint. MMDs decreased by 3.8 days during the first month and by 5.2 days by week 52. The most common treatment-related AEs among patients who received atogepant were constipation (4.8%), nausea (2.9%), and fatigue (2.2%) (*Ashina et al 2023*).

Systematic review/meta-analyses

- A systematic review and network meta-analysis evaluated the efficacy of monoclonal antibodies targeting CGRP or its receptors (erenumab, fremanezumab, galcanezumab, and eptinezumab) and small molecules targeting the CGRP receptor (atogepant and rimegepant) in the prevention of migraine (chronic or episodic). The outcomes assessed included MMD and a ≥ 50% reduction responder rate. Compared to placebo, all CGRP inhibitors (excluding eptinezumab-jjmr 30 mg) were significantly more effective in reducing MMD, whether administered subcutaneously, intravenously, or orally. For a ≥ 50% reduction response rate, both subcutaneous and intravenous CGRP inhibitors were significantly more effective than placebo, with ORs ranging from 1.83 to 3.04, in favor of the CGRP inhibitors. Atogepant and rimegepant were not significantly different from placebo for this outcome (*Haghdoost et al 2023*).
- A systematic review and network meta-analysis evaluated 24 RCTs (N = 8789) to assess the efficacy and safety of prophylactic agents for chronic migraine. Compared to placebo, Botulinum toxin A and topiramate a statistically significant reduction in MMD. For the outcome of response rate of 50% reduction in MMD, topiramate was the most effective followed by fremanezumab, galcanezumab, erenumab, and eptinezumab; there was no significant difference between CGRP agents. No significant difference was found between any preventive drugs and placebo in improving the migraine disability assessment (MIDAS) score. In terms of the incidence of AEs, eptinezumab demonstrated the best safety profile compared to placebo (RR, 1.09; 95% CI, 0.8 to 1.54).
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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] 2024, Emgality prescribing information 2025, Goadsby et al 2019*).
- A systematic review and meta-analysis of 6 studies evaluated the efficacy and safety of galcanezumab for treatment and prevention of cluster headache. The pooled analysis demonstrated an overally efficacy of 76% (defined as at least 50% reduction in the weekly frequency of cluster headache and patient global impression of improvement scale). The incidence of AEs was 48%. The most common AEs included nasopharyngitis and injection site pain (*Barbosa et al 2025*).

Treatment of acute migraine (with or without aura)

Rimegepant ODT

- Rimegepant ODT was evaluated in a Phase 3, DB, MC, PC, 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 prescribing information 2025*).
  - 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 AEs were nausea and urinary tract infection. No serious AEs 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 AEs 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 AE associated with rimegepant was back pain (n = 1) (*Lipton et al 2019[c]*).
  - 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 to 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 to placebo (36.6 vs 27.7%; $p = 0.002$). Nausea and dizziness were the most common AEs reported in the rimegepant and placebo treatment groups, respectively. Serious AEs were reported in 2 patients treated with rimegepant and 1 patient treated with placebo (*Lipton et al 2018 [poster]*).
- Data is emerging on the combination use of rimegepant with CGRP monoclonal antibodies. A sub-study nested within a MC, OL, long-term safety study evaluated outcomes of 13 patients on CGRP monoclonal antibodies (erenumab-aooe, n = 7; fremanezumab-vfrm, n = 4; and galcanezumab-gnlm, n = 2) who received rimegepant 75 mg as needed *(Berman et al 2020)*. An average of 7.8 rimegepant doses were administered over a 4-week period, 5 patients experienced mild or moderate AEs, and no patients experienced severe AEs *(Berman et al 2020; Mullin et al 2020)*. Of note, this data is only available in a very small number of patients.

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 2025*).
  - 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 AEs 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 AEs within 48 hours were nausea (≤ 2.5% for all arms) and dizziness (≤ 2.1% for all arms). No serious AEs or AEs leading to discontinuation were reported 48 hours after the initial dose. In ACHIEVE II, the serious AEs at 30 days included appendicitis, spontaneous abortion, pericardial effusion, and seizure.

Zavegepant

- Approval of zavegepant was based on a DB, PC, MC, Phase 3 RCT in 1405 patients with a history of multiple severe migraine attacks per month. After stratification for preventive treatment use, patients received zavegepant 10 mg intranasal spray or placebo for self-administration for a migraine attack of moderate to severe pain intensity. The coprimary outcomes, freedom from pain and freedom from MBS, were assessed 2 hours after the dose. Freedom from pain occurred in 24% of the zavegepant group and 15% of the placebo group (risk difference, 8.8%; 95% CI, 4.5% to 13.1%; p < 0.0001) and freedom from MBS occurred in 40% of the zavegepant group and 31% of the placebo group (risk difference, 8.7%; 95% CI, 3.4% to 13.9%; p = 0.0012). Adverse events that occurred more frequently with zavegeapnt than placebo included dysgeusia, nasal discomfort, and nausea (*Lipton et al 2023[b]*).
- Another Phase 2/3 DB, PC, MC, RCT compared the efficacy of zavegepant and placebo in 1673 adults with acute migraine. Three zavegepant doses were evaluated (5 mg, 10 mg, and 20 mg). At 2 hours post-dose, zavegepant 10 mg and 20 mg were more effective than placebo for freedom from pain (22.5%, 23.1%, and 15.5%, respectively) and freedom from MBS (41.9%, 42.5%, and 33.7%, respectively) (*Croop et al 2022*).

Systematic Reviews

- A systematic review from the Agency for Healthcare Research and Quality (AHRQ) evaluated the benefits and harms of several treatments for acute episodic migraine. For CGRP inhibitors, the review included 6 RCTs with 7620 patients; the overall risk of bias was low for 2 RCTs, moderate for 2 RCTs, and high for 2 RCTs. Compared to placebo, both rimegepant (3 RCTs) and ubrogepant (3 RCTs) were associated with increased pain freedom at 2 hours (relative risk [RR], 1.80; 95% CI, 1.52 to 2.13 and RR, 1.58; 95% CI, 1.31 to 1.90 for rimegepant and ubrogepant, respectively) and increased pain relief at 2 hours (RR, 1.36; 95% CI, 1.26 to 1.46 and RR, 1.21; 95% CI, 1.12 to 1.31 for rimegepant and ubrogepant respectively). Strength of evidence for both these outcomes was moderate for rimegepant and high for ubrogepant. Both medications were also associated with improvements in sustained pain freedom at 1 day (RR, 2.24; 95% CI, 1.65 to 3.05; moderate strength of evidence for rimegepant and RR, 1.63; 95% CI, 1.29 to 2.07; high strength of evidence for ubrogepant). Rimegepant was associated with significant improvements in sustained pain freedom at 1 week compared to placebo (RR, 2.23; 95% CI, 1.6 to 3.09; moderate strength of evidence). The RR for sustained pain freedom at 1 week for ubrogepant compared to placebo was 1.89 (95% CI, 0.88 to 4.02; low strength of evidence) (*Singh et al 2020, VanderPluym et al 2021).*
- A 2024 systematic review and network meta-analysis that included 137 randomized trials with more than 89,000 patients compared 17 interventions for the acute treatment of migraine episodes in adults. All treatments were superior to placebo for freedom from pain at 2 hours, with eletriptan being the most effective followed by rizatriptan, sumatriptan

and zolmitriptan; these agents were more effective than lasmiditan, rimegepant, and ubrogepant, which performed comparably to NSAIDS. (*Karlsson et al 2024*).

- A systematic review and network meta-analysis of 15 RCTs compared the efficacy and safety of nasal zavegepant to oral CGRP inhibitors for the acute treatment of migraine. The primary outcome of pain freedom at 2 hours and most bothersome symptom freedom at 2 hours was significantly improved with zavegepant and oral CGRP inhibitors compared to placebo. No difference in pain freedom at 2 hours was found between zavegepant and oral CGRP inhibitors. Eptinezumab, ubrogepant, and rimegepant were the top 3 in ranking for freedom from the most bothersome symptom at 2 hours. The most common AE with zavegepant was dysgeusia. AEs similar between treatments were nausea and vomiting (*Zhu et al 2025*)

Treatment of medication overuse headache

Eptinezumab-jjmr

- A subgroup, exploratory analysis of the PROMISE-2 trial, which was previously described, evaluated eptinezumab-jjmr 100 mg (n = 139), 300 mg (n = 147), or placebo (n = 145) in patients with chronic migraine and medication overuse headache at baseline screening. Patients receiving eptinezumab-jjmr had a significantly greater reduction in MMDs compared to placebo over weeks 1 to 12 (placebo: change from baseline, -5.4; 100 mg: change from baseline, -8.4, difference from placebo, -3.0, 95% CI, -4.56 to -1.52, $p < 0.0001$ vs placebo; 300 mg: change from baseline, -8.6, difference from placebo, -3.2, 95% CI, -4.66 to -1.78, $p < 0.0001$) *(Diener et al 2021)*.
- Another exploratory subgroup analysis of PROMISE-2 evaluated acute headache medication usage in patients with chronic migraine and medication overuse headache. Patients receiving eptinezumab-jjmr had numerically greater reductions in total monthly acute headache medication use days compared to placebo over 24 weeks of treatment (placebo: change from baseline, -5.8 days/month; eptinezumab-jjmr 100 mg: change from baseline, -10 days/month; eptinezumab-jjmr 300 mg: -10.2 days/month) (*Marmura et al 2021*).
- A post hoc analysis of the PREVAIL study, which was previously described, evaluated the effectiveness of up to 2 years of treatment with eptinezumab in a subgroup of patients (n = 49) who had a diagnosis of medication overuse headache. Eptinezumab was associated with reductions in headache frequency, severity, disability, and headache impact at week 104; improvements in health-related quality of life were also demonstrated *(Blumenfeld et al 2024).*
- A subgroup analysis of the PROGRESS trial, which was previously described, evaluated the effectiveness of atogepant as a preventive treatment for chronic migraine in patients with or without acute medication overuse. A total of 500 of 755 (66.2%) patients at baseline met the criteria for acute medication overuse. After 12 weeks, there was a reduction of 52.1 to 61.9% in the proportion of patients treated with atogepant who met the criteria for medication overuse *(Goadsby et al 2024).*

Erenumab-aooe

- A subgroup analysis was performed to evaluate patients with chronic migraine and medication overuse included in a DB, PC study of 667 patients, previously described by *Tepper et al*. A total of 274 patients had medication overuse at baseline screening and were randomized to erenumab-aooe 70 mg (n=79) or 140 mg (n = 78) or placebo (n = 117). At month 3, there was a significant reduction in MMD in both erenumab-aooe dosing groups (-6.6) compared to placebo (-3.5; difference, -3.1; 95% CI, -4.8 to -1.4; $p < 0.001$). The percentage of patients with ≥ 50% response rate was significantly higher in the 70 mg group (36%; OR, 2.67; 95% CI, 1.36 to 5.22) and the 140 mg group (35%; OR, 2.51; 95% CI, 1.28 to 4.94) compared to placebo (18%) *(Tepper et al 2019)*.
- A Phase 4 RCT randomized 584 patients with nonopioid medication overuse headache to erenumab 140 mg, 70 mg, or placebo once monthly for 24 weeks. Remission of headache at month 6 was achieved in 69.1%, 60.3%, and 52.6% in the erenumab 140 mg, erenumab 70 mg, and placebo groups, respectively. Constipation and COVID-19 illness were the most common AEs (*Tepper et al 2024*).

Fremanezumab-vfrm

- The impact of fremanezumab-vfrm on medication overuse headaches in patients with chronic migraine was evaluated through a subgroup analysis of the HALO CM study, which was previously described. Of the 1130 patients enrolled in HALO CM, 587 had medication overuse at baseline and were randomized to fremanezumab-vfrm quarterly (n = 201), monthly (n = 198), or placebo (n = 188). Compared with placebo, the reduction in MMD was greater for patients

receiving fremanezumab-vfrm quarterly (-2.5 vs -4.7; difference, -2.2; 95% CI, -3.1 to -1.2; p < 0.0001) and monthly (-2.5 vs -5.2; difference, -2.7; 95% CI, -3.7 to -1.8; p < 0.0001) *(Silberstein et al 2020[b])*.

Galcanezumab-gnlm

- A post-hoc analysis of 3 previously described Phase 3 studies in patients with episodic migraine (EVOLVE-1 and EVOLVE-2) or chronic migraine (REGAIN) evaluated the efficacy of galcanezumab-gnlm in the prevention of migraine in patients with and without medication overuse *(Dodick et al 2021)*.
  - In the subgroup analysis of patients with medication overuse headaches and episodic migraine, there was a significantly greater reduction in MMD with both galcanezumab-gnlm 120 mg (-6.3; difference from placebo, -3.6; 95% CI, -4.7 to -2.4; p < 0.001) and 240 mg (-5.8; difference from placebo, -3.1; 95% CI, -4.2 to -2.0; p < 0.001) compared to placebo (-2.7).
  - In the subgroup analysis of patients with medication overuse headaches and chronic migraine, there was a significantly greater reduction in MMD with both galcanezumab-gnlm 120 mg (-4.8; difference from placebo, -2.5; 95% CI, -3.6 to -1.5; p < 0.001) and 240 mg (-5.6; difference from placebo, -2.3; 95% CI, -3.3 to -1.2; p < 0.001) compared to placebo (-2.5).

- A systematic review and meta-analysis evaluated the efficacy of several treatments for chronic migraine and medication overuse headache. For monoclonal antibody agents targeting CGRP or its receptor, 4 trials with 1388 patients were included. For the outcome of ≥ 50% reduction in headache days from baseline, CGRP inhibitors were associated with significantly greater response compared to placebo (OR, 2.91; 95% CI, 2.23 to 3.78) (*Giri et al 2023*).

Clinical Guidelines

Acute treatment of migraine

- The IHS published practice recommendations in 2024 based on existing global treatment guidelines and expert consensus. Triptans are recommended for those not responding to appropriate doses of analgesics or NSAIDs. For patients who achieve a partial response with a triptan, increasing the dose, switching to a different route of administration or adding an NSAID is recommended. Non-response to a triptan can be managed by switching to a different agent within the class however, after 3 different agents are tried, use of agents from another class is suggested (ie, CGRP, or lasmiditan). The CGRPs and lasmiditan are also recommended for patients who cannot tolerate or have contraindications to triptan therapy. Ergot derivatives are recommended if treatment options with better safety profiles have been exhausted (*Puledda et al 2024[a]*).
- The 2021 American Headache Society (AHS) consensus statement guidelines for migraine recommends the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans, dihydroergotamine (DHE), certain oral CGRP receptor inhibitors (rimegepant and ubrogepant), and the selective serotonin (5-HT_{1F}) receptor antagonist (lasmiditan) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate between 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 (*Ailani et al 2021[a]*):
  - **Established efficacy**: Triptans, ergotamine derivatives, oral CGRP inhibitors (rimegepant and ubrogepant), Lasmiditan, NSAIDs (aspirin, celecoxib oral solution, diclofenac, ibuprofen, naproxen), and combination medications (APAP/aspirin/caffeine)
  - **Probably effective**: Ergotamine or other forms of DHE, other NSAIDs (ketoprofen, ketorolac intramuscular or IV, flurbiprofen), magnesium IV, isometheptene compounds, antiemetics (chlorpromazine, droperidol, metoclopramide, prochlorperazine, promethazine).
  - The AHS indicates that rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans.

- The 2025 American College of Physicians (ACP) clinical guideline provides recommendations for treatment of acute episodic migraine in outpatient settings (*Qaseem et al 2025[a]*).
  - Treatments recommended based on comparative efficacy and safety, patient preference, and cost considerations include combination treatment with triptans + NSAID or APAP.
  - If the above combination therapies fails, treatments that can be considered based on efficacy but without sufficient comparative evidence include: CGRPs (rimegapant, ubrogepan, zavegepant), lasmiditan, and dihydroergotamine.

- In 2019, the American Academy of Neurology (AAN) and the AHS published a guideline on the acute treatment of migraine in children and adolescents, which was reaffirmed in October 2022. 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.
- A 2022 guideline on the use of monoclonal antibodies targeting CGRP for migraine prevention from the European Headache Federation provided evidence-based recommendations for these agents. Based on high or moderate evidence, eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm were strongly recommended for prevention in individuals with episodic migraine or chronic migraine. Based on low quality data, erenumab-aooe is strongly recommended over topiramate for prevention in patients with episodic or chronic migraine (*Sacco et al 2022*).

Prevention of migraine

- In 2024, the AHS published an updated position statement regarding the CGRPs (erenumab, fremanezumab, galcanezumab, eptinezumab, rimegepant and atogepant) indicating that CGRP therapies should be considered as a first-line therapy (along with previous first-line treatments) for migraine prevention, without a requirement for prior failure of other classes of migraine preventative treatments (*Charles et al 2024*).
- In 2024, the IHS published global practice recommendations for use of pharmacological measures to prevent migraine. Preventive medications suggested for chronic migraine in adults include CGRPs (atogepant, erenumab, eptinezumab, fremanezumab, galcanezumab), onabotulinumtoxinA, and topiramate (*Puledda et al 2024[b]*).
- The 2025 ACP clinical guideline provides recommendations for prevention of episodic migraine in outpatient settings (*Qaseem et al 2025[b]*). Due to the quality of evidence, all recommendations are classified as conditional with low-certainty evidence.
  - Initial treatments for monotherapy recommended based on comparative efficacy and safety, patient preference, and cost considerations include: Metoprolol or propranolol, valproate, venlafaxine, amitriptyline.
  - If initial monotherapy fails due to lack of efficacy or intolerability, second-line agents include CGRPs (atogepant, Rimegepant, eptinezumab, erenumab, fremanezumab, galcanezumab).
  - Topiramate is suggested as a third-line agent when initial and second-line agents fail due to lack of efficacy or intolerability.
- The 2021 AHS consensus guideline on migraine designates the following drugs as having efficacy in the preventive treatment of migraine (*Ailani et al 2021[a]*):
  - Established efficacy:
    - Candesartan
    - Frovatriptan (for short-term prevention of menstrual-related migraine; evaluated and rejected by the FDA for this indication)
    - Antiepileptic drugs (divalproex sodium, topiramate, valproate sodium)
    - Beta blockers (metoprolol, propranolol, timolol)
    - Injectable CGRP inhibitors (eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm)
    - Onabotulinumtoxin A
  - Probably effective:
    - Antidepressants (amitriptyline, venlafaxine)
    - Beta blockers (atenolol, nadolol)
    - Lisinopril
    - Memantine
    - Combination parenterals (onabotulinumtoxin A plus an injectable CGRP inhibitor)
- 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 [guideline reaffirmed in 2022]*):
  - 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 2024 IHS guideline suggests beta-blockers or flunarizine for migraine prevention in children and adolescents with the recognition that evidence of efficacy is very limited (*Puledda et al 2024[b]*).
- In 2019, the AAN/AHS published a guideline on the preventive treatment of migraine in pediatric patients, which was reaffirmed in October 2022. 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], reaffirmed 2022*):
  - 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 onabotulinumtoxin A 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 CBT (inform of the potential AEs, 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

- The European Academy of Neurology provides a weak recommendation with a low level of evidence for the use of the CGRP inhibitor, galcanezumab-gnlm, in episodic cluster headache (*May et al 2023*). The recommended treatment for acute attacks is oxygen and sumatriptan, while verapamil is recommended for prophylaxis. Corticosteroids are considered to be efficacious. Lithium, topiramate, and galcanezumab-gnlm are recommended as alternative therapies.

Safety Summary

- Ubrogepant is contraindicated with concomitant use of strong cytochrome P450 (CYP) 3A4 inhibitors.
- The CGRPs 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 in the post-marketing setting for eptinezumab-jjmr. 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, hypertension, and Raynaud's phenomenon.
  - Hypersensitivity: In some cases, reactions were reported within hours to 1 month after administration. Anaphylaxis has been reported in the post-marketing setting for Erenumab-aooe.
  - Hypertension: Post-marketing reports have documented new-onset and worsening of hypertension with some cases requiring pharmacological treatment and hospitalization. In most cases, hypertension developed within 7 days of starting the CGRP inhibitor and required its discontinuation.
  - Raynaud's phenomenon: The development of Raynaud's phenomenon of debilitating pain leading to hospitalization and disability has been reported in the post-marketing setting following the use of CGRP inhibitors. In most cases, resolution of symptoms was observed with discontinuation of the CGRP inhibitor.
  - An additional warning and precaution for Erenumab-aooe is constipation with serious complications; Some cases have required hospitalization, including surgery. Constipation was a common AE reported in up to 3% of patients.
    - Concurrent use of medication associated with decreased gastrointestinal motility may increase the risk of severe constipation.
- AEs
  - The most common AEs with injectable CGRP inhibitors include injection site reactions (subcutaneous CGRP inhibitors), constipation (erenumab-aooe only), and nasopharyngitis and hypersensitivity (eptinezumab-jjmr only).
  - The most common AEs with oral CGRP inhibitors include somnolence (ubrogepant); nausea (atogepant, ubrogepant, rimegepant, zavegepant); constipation and fatigue (atogepant); taste disorders, nasal discomfort, and vomiting (zavegepant).
- The long-term safety of CGRP inhibitors has been evaluated.
  - A phase 2/3 one-year, open-label study evaluated the long-term safety of zavegepant 10 mg nasal spray administered up to 8 times per month in 608 participants. There were seven serious AEs reported, none of which were deemed related to the study drug. The most common events related to treatment and reported in at least 5% of participants were taste disturbances, nasal discomfort, nasal congestion and throat irritation and back pain. Elevated aminotransferases >3 times the upper limit of normal were reported in 2.6% of participants (*Mullin et al. 2024).*
  - A subgroup analysis of a long-term, open-label study of 1800 patients evaluated the safety of rimegepant 75 mg for up to 52 weeks. Serious AEs were reported in 4.5% of patients who were using preventive medication and 2.3% of those who were not; most (9 of 10) were deemed unlikely related to rimegepant whereas one event of ischemic colitis was deemed possibly related. The most common AEs reported in at least 5% of participants were upper respiratory infection, nasopharyngitis, sinusitis, urinary tract infection and back pain (*Berman et al 2024).*
  - The incidence of cardiovascular disease in Medicare beneficiaries with migraine receiving either CGRP inhibitors (n=5153) or onabotulinumtoxin A (n=4000) was compared in a retrospective cohort study. The median time to follow-up of the primary outcome was approximately 4.5 months. The time to first myocardial infarction or stroke (composite CVD outcome) was not significantly different between treatments (adjusted HR, 0.88; 95% CI, 0.44 to 1.77). Secondary outcomes of hypertensive crisis, peripheral vascularization, or Raynaud phenomenon also did not demonstrate a significant difference between treatments (*Yang et al 2025*)
- 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 or prefilled syringe (70 mg/mL or 140 mg/mL)	SC	*Prevention of migraine*: Once monthly (70 or 140 mg)	May be self-administered by patients in the abdomen, thigh, or back of upper arm. 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 at room temperature.
Ajovy (fremanezumab-vfrm)	Auto-injector or prefilled syringe (225 mg/1.5 mL)	SC	*Prevention of migraine*: 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. Must be refrigerated and protected from light until time of use. If necessary, fremanezumab-vfrm may be stored at room temperature for a maximum of 7 days. After removal from the refrigerator, fremanezumab-vfrm must be used within 7 days or discarded.
Emgality (galcanezumab-gnlm)	Prefilled pen (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 (120 mg) *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. Must be refrigerated and protected from light until time of use. If necessary, galcanezumab-gnlm may be stored at room temperature for a maximum of 7 days. Once removed from the refrigerator, galcanezumab-gnlm

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				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. *Prevention of episodic migraine*: Every other day. Maximum dose: 75 mg in 24 hours.	The safety of using > 18 doses in a 30-day period has not been established. Avoid concomitant administration with strong inhibitors of CYP3A4, moderate inhibitors of CYP3A4 within 48 hours, moderate or strong inducers of CYP3A, or P-gp inhibitors.
Qulipta (atogepant)	Oral tablets (10, 30, and 60 mg)	PO	*Prevention of episodic migraine*: Once daily (10, 30, or 60 mg) *Prevention of chronic migraine:* Once daily (60 mg)	Dose adjustments are warranted with certain concomitant drugs or in cases of severe renal impairment/end stage renal disease (CrCL < 30 mL/min). Avoid use in patients with severe hepatic impairment. Take with or without food.
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 initial dose. Maximum dose: 200 mg in 24 hours.	The safety of treating > 8 migraines in a 30-day period has not been established. Dose adjustments are warranted with certain concomitant drugs or in cases of severe renal or hepatic 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	*Prevention of migraine*:	Dilute with 0.9% sodium chloride injection.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			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.	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. After dilution, eptinezumab-jjmr may be stored at room temperature.
Zavzpret (zavegepant)	Nasal spray (10 mg)	Intra nasal	*Acute migraine treatment:* One spray (10 mg) in one nostril as needed	The maximum dose in 24 hours is 10 mg (one spray). The safety of treating more than 8 migraines in a 30-day period has not been established. Avoid concurrent administration with nasal decongestants or drugs that induce or inhibit organic anion transporting polypeptide 1B3 or sodium taurocholate co-transporting polypeptide. Avoid use in patients with severe hepatic impairment or CrCl < 30 mL/min.

Abbreviations: CrCL = creatinine clearance; CYP = cytochrome P450; IV = intravenous; ODT = orally disintegrating tablet; P-gp = P-glycoprotein; PO = oral; SC = subcutaneous
*The rimegepant every other day dosing may not be optimized for preventive therapy. The FDA has required that the manufacturer conduct a study evaluating the efficacy of rimegepant once daily dosing vs rimegepant once every other day dosing vs placebo for a duration of 3 months in order to characterize potential gaps (*FDA letter 2021*).
See the current prescribing information for full details

- 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 and zavegepant is a nasal CGRP inhibitor indicated for acute treatment of migraine with or without aura. Rimegepant is also indicated for the prevention of episodic migraine. Atogepant is the only oral CGRP inhibitor that is indicated for the prevention of both episodic and chronic migraine.
- The injectable CGRP inhibitors eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm are indicated for the prevention of migraine, including chronic types. 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:
  - For acute treatment of migraines in adults, guidelines generally recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans, DHE, oral CGRP receptor inhibitors or the selective serotonin (5-HT_{1F}) receptor antagonist (lasmiditan) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics.
  - For the prevention of 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. The AHS and IHS guidelines both recommend CGRPs as first-line agents for migraine prevention.
  - 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. Galcanezumab-gnlm has been studied for episodic cluster headache and received a weak recommendation for use according to the European Academy of Neurology.
- Head-to-head studies with the CGRP inhibitors are limited, and no agent is clearly superior to others. Evidence for the CGRP inhibitors has 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 like 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 injectable CGRP inhibitors when prescribed for prophylactic migraine therapy consistently demonstrated modest but statistically significant reductions in primary endpoint measures (eg, MMD, MMH, or MMHD) ranged from 0.7 to 3.5 days after 3 to 6 months of treatment. The numbers needed to treat (NNTs) ranged from 3 to 10 in order to achieve a ≥ 50% reduction in MM(H)D. Subgroup analyses from Phase 3 CGRP inhibitor trials showed consistent benefit for prevention of migraine in patients with medication overuse headaches.
    - Rimegepant had a significant reduction of 0.8 MMD after 3 months of treatment. The NNT was 13 to achieve a ≥ 50% reduction in moderate-to-severe MMDs.
    - Atogepant had a significant reduction of 1.2 to 1.7 MMDs compared to placebo after 3 months of treatment.
    - A meta-analysis of preventive migraine treatments demonstrated CGRPs to have a significant impact on response rate (defined as ≥50% reduction in MMD).
  - 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. Additionally, ubrogepant allows for 2 dosing options (50 or 100 mg), and rimegepant allows for one (75 mg).
  - Rimegepant ODT demonstrated efficacy compared to placebo for acute use. 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 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%). Additional trials evaluating the efficacy and safety of rimegepant were considered supportive for approval.
  - Ubrogepant demonstrated efficacy compared to placebo for 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.
  - A 30-day comparative Phase 4 study demonstrated similar efficacy between galcanezumab-gnlm and rimegepant for the primary endpoint of ≥ 50% reduction in migraine headache days per month from baseline to 3 months.

- Zavegepant is an intranasal CGRP inhibitor that is approved for acute treatment of migraine. Compared to placebo, zavegepant led to significantly greater freedom from pain (risk difference, -8.8%) and freedom from MBS (risk difference, -8.7%). One comparative meta-analysis did not demonstrate a significant difference in onset of action compared to oral CGRP inhibitors. Dysgeusia was more commonly observed with zavegepant.
- 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, ubrogepant, and atogepant 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.
- Warnings and precautions associated with the CGRP inhibitors include hypersensitivity reactions, hypertension, and Raynaud's phenomenon. Erenumab-aooe carries an additional warning for constipation.
- Common AEs For the oral CGRP inhibitors include nausea (atogepant, ubrogepant and rimegepant); somnolence (ubrogepant); constipation and fatigue (atogepant). Common AEs reported with the nasal CGRP inhibitor, zavegepant, was nausea, vomiting, taste disorders, and nasal discomfort.
- Overall, the CGRP inhibitors are recognized across various guidelines as established therapies for acute treatment or prevention of episodic or chronic migraine. These agents have demonstrated efficacy in reducing migraine frequency and severity, offering a generally mild safety profile. Injectable CGRP inhibitors are particularly effective for chronic migraine prevention and have demonstrated efficacy in harder-to-treat or refractory patients.
  - Galcanezumab-gnlm is the only CGRP inhibitor indicated for difficult-to-treat episodic cluster headaches.
  - Fremanezumab-vfrm and eptinezumab-jjmr are the only agents in the class which may be administered quarterly.
  - Zavegepant nasal administration may be useful for patients who experience nausea/vomiting during migraine attacks.

Appendices

Appendix A. AAN levels of evidence classification (*Silberstein et al 2012 [reaffirmed in 2022], 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

References

- Ailani J, Burch RC, Robbins MS; Board of Directors of the American Headache Society. The American Headache Society consensus statement: update on integrating new migraine treatments into clinical practice. *Headache.* 2021[a];61(7):1021-1039.
- Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the preventive treatment of migraine. *N Engl J Med*. 2021[b];385(8):695-706.
- Aimovig. Package insert. Amgen, Inc.; April 2025.
- Ajovy. Package insert. Teva Pharmaceuticals, Inc.; March 2025.
- American Migraine Foundation (AMF). Non−invasive neuromodulation devices. April 2, 2020. Web site. Accessed April 21, 2025. https://americanmigrainefoundation.org/resource-library/neuromodulation-for-migraine-treatment/.
- Ashina M, Cohen JM, Galic M, et al. Efficacy and safety of fremanezumab in patients with episodic and chronic migraine with documented inadequate response to 2 to 4 classes of migraine preventive medications over 6 months of treatment in the phase 3b FOCUS study. *J Headache Pain*. 2021;22(1):68.
- Ashina M, Lanteri-Minet M, Pozo-Rosich P, et al. Safety and efficacy of eptinezumab for migraine prevention in patients with two-to-four previous preventive treatment failures (DELIVER): a multi-arm, randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet Neurol*. 2022;21(7):597-607.
- Ashina M, Lipton R, Ailani J, et al. Responder rates with eptinezumab over 24 weeks in patients with prior preventive migraine treatment failures: post hoc analysis of the DELIVER randomized clinical trial. *Eur J Neurol.* 2024;31:e16131.
- Ashina M, Saper J, Cady R, et al. Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1). *Cephalalgia*. 2020;40(3):241-254.
- Ashina M, Tepper S, Gendolla A, et al. Long-term effectiveness of eptinezumab in patients with migraine and prior preventive treatment failures: extension of a randomized controlled trial. *J Headache Pain.* 2023[a[;24:155.
- Ashina M, Tepper SJ, Reuter U, et al. Once-daily oral atogepant for the long-term preventive treatment of migraine: Findings from a multicenter, randomized, open-label, phase 3 trial. *Headache.* 2023;63(1):79-88.
- Barbosa da Silva M, Baroni Coelho de Oliveira Ferreira D, Mendieta CD, Pereira da Silva H, Aguiar Nogueira-Rosa L, Moraes-Figueiredo N. Efficacy and safety of galcanezumab for cluster headache preventive treatment: a systematic review and meta-analysis. *Neurol Res*. 2025 Jan;47(1):63-76. doi: 10.1080/01616412.2024.2440022.
- Berman G, Croop R, Kudrow D, et al. Safety of Rimegepant, an oral CGRP receptor antagonist, plus CGRP monoclonal antibodies for migraine. *Headache.* 2020; 60(8):1734-1742.
- Berman G, Thiry A, Croop R. Safety of Rimegepant in Patients Using Preventive Migraine Medications: A Subgroup Analysis of a Long-Term, Open-Label Study Conducted in the United States. J Pain Res. 2024 May 21;17:1805-1814.
- Blumenfeld A, Kudrow D, McAllister P, Boserup LP, Hirman J, Cady R. Long-term effectiveness of eptinezumab in the treatment of patients with chronic migraine and medication-overuse headache. Headache. 2024 Jul-Aug;64(7):738-749. doi: 10.1111/head.14767. Epub 2024 Jun 24.
- Charles A, Digre K, Goadsby P, et al. Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: Am American Headache Society position statement update. *Headache.* 2024; Mar 11. doi: 10.1111/head.14692.
- Clinicaltrials.gov. A study of galcanezumab in participants with episodic cluster headache (NCT02397473). September 9, 2019. Accessed April 22, 2025. https://www.clinicaltrials.gov/ct2/show/NCT02397473?term=NCT02397473&rank=1
- Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. *Lancet*. 2019;394(10200):737-745.
- Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. *Lancet*. 2021;397(10268):51-60.

- Croop R, Madonia J, Stock DA, et al. Zavegepant nasal spray for the acute treatment of migraine: A Phase 2/3 double-blind, randomized, placebo-controlled, dose-ranging trial. *Headache*. 2022;62(9):1153-1163. doi:10.1111/head.14389
- Detke, H, Goadsby PJ, Wang S, et al. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018;91(24):e2211-e2221.
- Diener H, Marmura MJ, Tepper SJ, et al. Efficacy, tolerability, and safety of eptinezumab in patients with a dual diagnosis of chronic migraine and medication-overuse headache: subgroup analysis of PROMISE-2. *Headache.* 2021;61(1):125-136.
- Dodick DW, Ashina M, Brandes JL, et al. ARISE: A phase 3 randomized trial of erenumab−aooe for episodic migraine. *Cephalalgia*. 2018[a]:38(6):1026-37.
- Dodick DW, Doty EG, Aurora SK, et al. Medication overuse in a subgroup analysis of phase 3 placebo-controlled studies of galcanezumab in the prevention of episodic and chronic migraine. *Cephalalgia.* 2021;41(3):340-352.
- Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the treatment of migraine. *N Engl J Med*. 2019;381(23):2230-2241.
- Dodick DW, Silberstein SD, Bigal ME, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial (HALO EM). *JAMA*. 2018[b];319(19):1999-2008.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. Accessed April 21, 2025. https://www.accessdata.fda.gov/scripts/cder/daf/.
- Edvinsson L. The trigeminovascular pathway: role of CGRP and CGRP receptors in migraine. *Headache*. 2017;57 Suppl 2:47−55.
- Emgality. Package insert. Eli Lilly and Company; April 2025.
- FDA letter. Supplement approval: Nurtec ODT (rimegepant) [prevention]. NDA 212728/S-006. May 27, 2021. Accessed April 22, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/212728Orig1s006ltr.pdf
- Ferrari MD, Diener HC, Ning X, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet*. 2019;394(10203):1030-1040.
- Ferrari MD, Reuter U, Goadsby PJ, et al. Two-year efficacy and safety of erenumab in participants with episodic migraine and 2-4 prior preventive treatment failures: results from the LIBERTY study. *J Neurol Neurosurg Psychiatry*. 2022;93(3):254-262.
- Förderreuther S, Zhang Q, Stauffer VL, et al. Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies. *J Headache Pain*. 2018;19(1):121.
- GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2018;17(11):954-976.
- Giri S, Tronvik E, Linde M, et al. Randomized controlled studies evaluating topiramate, botulinum toxin type A, and mABs targeting CGRP in patients with chronic migraine and medication overuse headache: a systematic review and meta-analysis. *Cephalagia.* 2023;43(4):1-16.
- Goadsby PJ, Friedman DI, Holle-Lee D, et al. Efficacy of Atogepant in Chronic Migraine With and Without Acute Medication Overuse in the Randomized, Double-Blind, Phase 3 PROGRESS Trial. Neurology. 2024 Jul 23;103(2):e209584. doi: 10.1212/WNL.0000000000209584. Epub 2024 Jun 26.
- Goadsby P, Reuter U, Hallstrom Y, et al. One-year sustained efficacy of erenumab in episodic migraine: Results of the STRIVE study. *Neurology*. 2020[a] Aug 4;95(5):e469-e479.
- Goadsby P, Silberstein S, Yeung P, et al. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: A randomized study. *Neurology*. 2020[b] Nov 3;95(18):e2487-e2499.
- Goadsby PJ, Dodick DW, Ailani J, et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. *Lancet Neurol*. 2020[c];19(9):727-737.
- Goadsby PJ, Dodick DW, Leone M, et al. Trial of galcanezumab in prevention of episodic cluster headache. *N Engl J Med*. 2019;381(2):132-141.
- Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab−aooe for episodic migraine (STRIVE). *N Engl J Med*. 2017;377(22):2123−32.
- Haghdoost F, Puledda F, Garcia-Azorin D, et al. Evaluating the efficacy of CGRP mAbs and gepants for the preventive treatment of migraine: a systematic review and network meta-analysis of phase 3 randomised controlled trials. *Cephalalgia.* 2023;43(4):1-14.
- Haseeb ME, Mohammed HE, Yaser H, et al. Unveiling the efficacy and safety of Erenumab, a monoclonal antibody targeting calcitonin gene-related peptide (CGRP) receptor, in patients with chronic and episodic migraine: a GRADE-assessed systematic review and meta-analysis of randomized clinical trials with subgroup analysis. *Head Face Med*. 2025 Mar 26;21(1):19. doi: 10.1186/s13005-025-00494-w.
- Hoffman J and May A. Diagnosis, pathophysiology, and management of cluster headache. *Lancet Neurol*. 2018;17(1):75-83.
- International Headache Society (IHS). Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
- Karlsson WK, Ostinelli EG, Zhuang ZA, et al. Comparative effects of drug interventions for the acute management of migraine episodes in adults: systematic review and network meta-analysis. BMJ. 2024 Sep 18;386:e080107. doi: 10.1136/bmj-2024-080107.
- Katsarava Z, Buse DC, Manack AN, et al. Defining the differences between episodic migraine and chronic migraine. *Curr Pain Headache Rep*. 2012;16(1):86-92.
- Kudrow D, Cady RK, Allan B, et al. Long-term safety and tolerability of eptinezumab in patients with chronic migraine: a 2-year, open-label, phase 3 trial. *BMC Neurol*. 2021;21:126.
- Kudrow D, Dafer R, Dodick D, et al. Evaluation of vascular risk in patients with migraine with and without aura treated with erenumab: post hoc analysis of pooled long-term clinical trial data. *Headache.* 2023[b];63:418-428.
- Lipton R, Pozo-Rosich P, Blumenfeld A, et al. Effect of atogepant for preventive migraine treatment on patient-reported outcomes in the randomized, double-blind, phase 3 ADVANCE trial. *Neurology.* 2023[a];100(8):e764-e777.
- Lipton RB, Cohen JM, Bibeau K, et al. Reversion from chronic migraine to episodic migraine in patients treated with fremanezumab: post hoc analysis from HALO CM study. *Headache*. 2020[b];60(10):2444-2453.
- Lipton RB, Conway, CM, Stock, EG, et al. Efficacy, safety, and tolerability of rimegepant 75 mg, an oral CGRP receptor antagonist, for the treatment of migraine: Results from a phase 3, double-blind, randomized, placebo-controlled trial, Study 301. [poster]. Presented at the 60th Annual Scientific Meeting of the American Headache Society; San Francisco, CA; 2018.
- Lipton RB, Croop R, Stock DA, et al. Safety, tolerability, and efficacy of zavegepant 10 mg nasal spray for the acute treatment of migraine in the USA: a phase 3, double-blind, randomised, placebo-controlled multicentre trial. *Lancet Neurol*. 2023;22(3):209-217.

- Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med*. 2019[c];381(2):142-149.
- Lipton RB, Dodick DW, Ailani J, et al. Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: The ACHIEVE II randomized clinical trial. *JAMA*. 2019[a];322(19):1887-1898.
- Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology*. 2020[a];94(13):e1365-e1377.
- Lipton RB, Manack Adams A, Buse DC, et al. A comparison of the chronic migraine epidemiology and outcomes (CaMEO) study and American migraine prevalence and prevention (AMPP) study: demographics and headache−related disability. *Headache*. 2016;56:1280−9.
- Lipton RB, Tepper SJ, Reuter U, et al. Erenumab in chronic migraine: Patient-reported outcomes in a randomized double-blind study. *Neurology*. 2019[b];92(19):e2250-e2260.
- Ljubisavljevic S, Zidverc Trajkovic J. Cluster headache: pathophysiology, diagnosis and treatment. *J Neurol*. 2019;266(5):1059-1066.
- Manack AN, Buse DC, Lipton RB. Chronic migraine: epidemiology and disease burden. *Curr Pain Headache Rep*. 2011;15:70−8.
- Marcus R, Goadsby PJ, Dodick D, et al. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia*. 2014;34(2):114-25.
- Marmura MJ, Diener HC, Cowan RP, et al. Preventive migraine treatment with eptinezumab reduced acute headache medication and headache frequency to below diagnostic thresholds in patients with chronic migraine and medication-overuse headache. *Headache*. 2021;61(9):1421-1431.
- Marmura MJ, Silberstein SD, Schwedt TJ, et al. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55(1):3-20.
- May A, Evers S, Goadsby PJ, et al. European Academy of Neurology guidelines on the treatment of cluster headache. *Eur J Neurol*. 2023;30(10):2955-2979. doi:10.1111/ene.15956
- Mulleners W, Byung-Kun K, Lainex M, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet Neurol*. 2020;19(10):814-825.
- Mullin K, Croop R, Mosher L, et al. Long-term safety of zavegepant nasal spray for the acute treatment of migraine: A phase 2/3 open-label study. Cephalalgia. 2024 Aug;44(8):3331024241259456.
- Mullin K, Kudrow D, Croop R, et al. Potential for treatment benefit of small molecule CGRP receptor antagonist plus monoclonal antibody in migraine therapy. *Neurology*. 2020;94(20):e2121-e2125.
- Nurtec ODT. Package insert. Pfizer Labs; April 2025.
- Okonkwo R, Tockhorn-Heidenreich A, Stroud C, Paget MA, Matharu MS, Tassorelli C. Efficacy of galcanezumab in patients with migraine and history of failure to 3-4 preventive medication categories: subgroup analysis from CONQUER study. *J Headache Pain*. 2021;22(1):113.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. Accessed April 21, 2025. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.
- Oskoui M, Pringsheim T, Billinghurst L, et al. Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Headache*. 2019[b];59(8):1144-1157. Reaffirmed October 22, 2022.
- Oskoui M, Pringsheim T, Holler-Managan Y, et al. Practice guideline update summary: Acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2019[a];93(11):487-499. Reaffirmed October 22, 2022.
- Pazdera L, Cohen JM, Ning X, Campos VR, Yang R, Pozo-Rosich P. Fremanezumab for the preventive treatment of migraine: subgroup analysis by number of prior preventive treatments with inadequate response. *Cephalalgia*. 2021;41(10):1075-1088.
- Pozo-Rosich P, Ailani J, Goadsby P, et al. Atogepant for the preventive treatment of chronic migraine (PROGRESS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023 [b];402:775-785.
- Pozo-Rosich P, Detke HC, Wang S, et al. Long-term treatment with galcanezumab in patients with chronic migraine: results from the open-label extension of the REGAIN study. *Curr Med Res Opin*. 2022;38(5):731-742.
- Pozo-Rosich P, Dolezil D, Paemeleire K, et al. Early use of ernumab vs non-specific oral migraine preventatives: the APPRAISE randomized clinical trial. *JAMA Neurol*. 2024;81(5):461-470.
- Puledda F, Sacco S, Diener HC, et al. International Headache Society global practice recommendations for the acute pharmacological treatment of migraine. *Cephalalgia*. 2024[a] Aug;44(8):3331024241252666. doi: 10.1177/03331024241252666
- Puledda F, Sacco S, Diener et al. International Headache Society global practice recommendations for preventive pharmacological treatment of migraine. *Cephalalgia*. 2024[b] Sep;44(9):3331024241269735. doi: 10.1177/03331024241269735.
- Purple Book: Database of Licensed Biological Products. US Food and Drug Administration. Accessed April 21, 2025. https://purplebooksearch.fda.gov/.
- Qaseem A, Tice JA, Etxeandia-Ikobaltzeta I, et al. Pharmacologic treatments of acute episodic migraine headache in outpatient settings: a clinical guideline from the American College of Physicians. *Ann Intern Med*. 2025[a] Apr;178(4):571-578. doi: 10.7326/ANNALS-24-03095.
- Qaseem A, Cooney TG, Etxeandia-Ikobaltzeta I, et al. Prevention of episodic migraine headache using pharmacologic treatments in outpatient settings: a clinical guideline from the American College of Physicians. *Ann Intern Med*. 2025[b] Mar;178(3):426-433. doi: 10.7326/ANNALS-24-01052.
- Qulipta. Package insert. AbbVie, Inc.; March 2025.
- Reuter U, Ehrlich M, Gendolla A, et al. Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. *Cephalalgia*. 2022;42(2):108-118.
- Reuter U, Goadsby PJ, Ferrari MD, et al. Efficacy and safety of erenumab in participants with episodic migraine in whom 2-4 prior preventive treatments had failed: LIBERTY 3-year study. *Neurology*. 2024;102(10):e209349. doi:10.1212/WNL.0000000000209349
- Reuter U, Goadsby PJ, Lanteri-Minet M, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *Lancet*. 2018;392(10161):2280-7.
- Reuter U, Lucas C, Dolezil D, et al. Galcanezumab in patients with multiple previous migraine preventive medication category failures: results from the open-label period of the CONQUER trial. *Adv Ther*. 2021;38(11):5465-5483.

- Robbins MS, Starling AJ, Pringsheim TM, et al. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. *Headache*. 2016;56(7):1093-106.
- Sacco S, Amin FM, Ashina M, et al. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. *J Headache Pain*. 2022;23(1):67.
- Saely S, Croteau D, Jawidzik L, et al. Hypertension: A new safety risk for patients treated with erenumab. *Headache*. 2021;61(1):202-208.
- Schwedt TJ, Kuruppu DK, Dong Y, Standley K, Yunes-Medina L, Pearlman E. Early onset of effect following galcanezumab treatment in patients with previous preventative medication failures. *J Headache Pain.* 2021[a];22(1):15.
- Schwedt TJ, Lipton RB, Ailani J, et al. Time course of efficacy of atogepant for the preventive treatment of migraine: results from the randomized, double-blind ADVANCE trial. Published online 14, 2021[b]. *Cephalalgia*. 2021;3331024211042385.
- Schwedt TJ, Oakes TM, Martinex JM. Comparing the efficacy and safety of galcanezumab vs Rimegepant for prevention of episodic migraine: results from a randomized, controlled clinical trial. *Neurol Ther*. 2024;13(1):85-105.
- Silberstein SD, Cohen JM, Seminerio MJ, et al. The impact of fremanezumab on medication overuse in patients with chronic migraine: subgroup analysis of the HALO CM study. *J Headache Pain.* 2020[b];21(1):114.
- Silberstein SD, Diamond M, Hindiyeh N, et al. Eptinezumab for the prevention of chronic migraine: efficacy and safety through 24 weeks of treatment in the phase 3 PROMISE-2 (Prevention of migraine via intravenous ALD403 safety and efficacy-2) study. *J Headache Pain*. 2020[a];21(1):120.
- Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine (HALO CM). *N Engl J Med*. 2017;377(22):2113-22.
- Silberstein SD, Holland S, Freitag F, et al. Evidence−based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78(17):1337−45. Reaffirmed October 22, 2022.
- Singh RBH, VanderPluym JH, Morrow AS, et al. Acute treatments for episodic migraine: comparative effectiveness review, no. 239. Rockville (MD): Agency for Healthcare Research and Quality. December 2020. Accessed April 22, 2025. https://www.ncbi.nlm.nih.gov/books/NBK566246/.
- Skljarevski V, Matharu M, Millen BA, et al. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia*. 2018;38(8):1442-54.
- Smith TR, Janelidze M, Chakhava G, et al. Eptinezumab for the prevention of episodic migraine: sustained effect through 1 year of treatment in the PROMISE-1 study. *Clin Ther.* 2020;42(12):2254-2265.e3.
- Starling AJ and Dodick DW. Best practices for patients with chronic migraine: burden, diagnosis, and management in primary care. *Mayo Clin Proc*. 2015;90(3):408−14.
- Stauffer VL, Dodick DW, Zhang Q, et al. Evaluation of galcanezumab for the prevention of episodic migraine: The EVOLVE-1 randomized clinical trial. *JAMA Neurol*. 2018;75(9):1080-8.
- Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. *J Headache Pain*. 2022;23(1):34. doi: 10.1186/s10194-022-01402-2.
- Sun H, Dodick DW, Silberstein S, et al. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol.* 2016;15(4):382-90.
- Sun W, Cheng H, Xia B, et al. Comparative Efficacy and Safety of Five Anti-calcitonin Gene-related Peptide Agents for Migraine Prevention: A Network Meta-analysis. *Clin J Pain*. 2023;39(10):560-569. doi:10.1097/AJP.0000000000001136
- Tassorelli C, Nagy K, Pozo-Rosich P, et al. Safety and efficacy of atogepant for the preventive treatment of episodic migraine in adults for whom conventional oral preventive treatments have failed (ELEVATE): a randomised, placebo-controlled, phase 3b trial. *Lancet Neurol.* 2024; 23:382-392.
- Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab−aooe for preventive treatment of chronic migraine: a randomised, double−blind, placebo−controlled phase 2 trial. *Lancet Neurol*. 2017;16(6):425−34.
- Tepper SJ, Dodick DW, Lanteri-Minet M, et al. Efficacy and Safety of Erenumab for Nonopioid Medication Overuse Headache in Chronic Migraine: A Phase 4, Randomized, Placebo-Controlled Trial. *JAMA Neurol*. 2024 Sep 16;81(11):1140-9. doi: 10.1001/jamaneurol.2024.3043
- Tepper SJ, Diener H, Ashina M, et al. Erenumab in chronic migraine with medication overuse: subgroup analysis of a randomized trial. *Neurology*. 2019;92(20):e2309-e2320.
- Tepper SJ, Lucas S, Ashina M, et al. Timing and durability of response to erenumab in patients with chronic migraine. *Headache*. 2021;61(8):1255-1263.
- Ubrelvy. Package insert. Allergan; March 2025.
- VanderPluym JH, Halker Singh RB, Urtecho M, et al. Acute treatments for episodic migraine in adults: a systematic review and meta-analysis. *JAMA*. 2021;325(23):2357-2369.
- Vyepti. Package insert. Lundbeck Pharmaceuticals; March 2025.
- Walker CS and Hay DL. CGRP in the trigeminovascular system: a role for CGRP, adrenomedullin and amyline receptors? *Br J Pharmacol*. 2013; 170(7):1293-307.
- Yang S, Orlova Y, Park H, et al. Cardiovascular safety of Anti-CGRP monoclonal antibodies in older adults or adults with disability with migraine. *JAMA Neurol*. 2025 Feb 1;82(2):132-141. doi: 10.1001/jamaneurol.2024.4537.
- Zavzpret. Package insert. Pfizer Labs; April 2025.
- Zhao C, Li C, Yu X, Dai X, Zou W. Effectiveness and safety of pharmacological prophylaxis for chronic migraine: a systematic review and network meta-analysis. *J Neurol*. 2024 Sep;271(9):5762-5777. doi: 10.1007/s00415-024-12512-z
- Zhu Z, Tang Y, Li L, Ni H, Liu M, Chen Z, Wang Z. The efficacy and safety of zavegepant nasal inhalation versus oral calcitonin-gene related peptide receptor antagonists in the acute treatment of migraine: a systematic review and network meta-analysis of the literature *J Headache Pain*. 2025 Mar 10;26(1):48. doi: 10.1186/s10194-025-01984-7.

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Optum Rx®

Therapeutic Class Overview

Antipsychotics, atypical

Introduction

- Antipsychotic medications have been used for over 50 years to treat schizophrenia and a variety of other psychiatric disorders (*Miyamato et al 2005*).
- Antipsychotic medications generally exert their effect in part by blocking dopamine (D)-2 receptors (*Crismon et al 2020*).
  - They are divided into 2 distinct classes based on their affinity for D2 and other neuroreceptors: typical antipsychotics, also called first-generation antipsychotics (FGAs), and atypical antipsychotics, also called second-generation antipsychotics (SGAs) (*Miyamato et al 2005)*.
- Atypical antipsychotics do not have a uniform pharmacology or mechanism of action; these differences likely account for the different safety and tolerability profiles of these agents (*Crismon et al 2023, Jibson 2025*). The atypical antipsychotics differ from the early antipsychotics in that they have affinity for the serotonin 5-HT2A receptor in addition to D2.
  - Clozapine is an antagonist at all dopamine receptors (D1 to D5), with lower affinity for D1 and D2 receptors and high affinity for D4 receptors. Aripiprazole and brexpiprazole act as partial agonists at the D2 receptor, functioning as an agonist when synaptic dopamine levels are low and as an antagonist when they are high. Cariprazine is a partial agonist at D2 and D3. Pimavanserin does not have dopamine blocking activity and is primarily an inverse agonist at 5-HT2A receptors. The remaining atypical antipsychotics share the similarity of D2 and 5-HT2A antagonism but differ in activity at other central nervous system (CNS) receptor classes.
  - Cobenfy (xanomeline/trospium) is a novel dual muscarinic (M)1/M4 receptor agonist/antagonist with no direct D2 dopamine receptor blocking activity (*Kaul et al 2024a*).
- Food and Drug Administration (FDA)-approved indications for the atypical antipsychotics vary and may include irritability associated with autistic disorder, bipolar disorder, Tourette's disorder, major depressive disorder (MDD), schizophrenia, schizoaffective disorder, agitation associated with dementia due to Alzheimer's disease, and hallucinations and delusions associated with Parkinson's disease (PD) psychosis.
- Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairment in socialization, communication, and behavior (*Weissman et al 2023*). The pathogenesis of ASD is not completely understood but is believed to have a genetic component, which alters brain development (*Augustyn 2024*).
  - Data from the Autism and Developmental Disabilities Monitoring Network in the United States (U.S.) reported a prevalence of 1 in 31 children aged 8 years with ASD; ASD is 3 times more common in males than females (*Centers for Disease Control [CDC] 2025*).
  - Overall treatment goals include maximization of functioning, improvement in quality of life, and helping the patient achieve and maintain independence. Specific treatment goals include improving social, communication, and adaptation skills, improving academic functioning, and decreasing nonfunctional behaviors. Therapies may include educational and behavioral programs and pharmacologic interventions to treat targeted symptoms including aggression, impulsivity, hyperactivity, anxiety, sleep disturbances, and depression (*Weissman et al 2023*).
- Major depressive disorder (MDD) manifests with symptoms of depressed mood, loss of interest or pleasure in almost all activities, altered sleep, change in appetite or weight, poor energy and/or concentration, thoughts of worthlessness, and potentially thoughts of death or suicide (*Vandenberg 2023*).
  - For the diagnosis of MDD, patients must have ≥ 5 symptoms that have been present during the same 2-week period or represent a change from previous functioning; at least 1 of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. The goal of treatment is full remission (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, [DSM-5-TR] 2022*). Approximately 8.3% of individuals aged ≥ 18 years in the U.S. have experienced ≥ 1 episode of MDD; with a higher prevalence among adult females compared to males (10.3% vs 6.2%, respectively) (*National Institute of Mental Health [NIMH] 2023*).
- Schizophrenia and bipolar disorder are severe psychiatric disorders which result from complex interplay between genetic and environmental factors. It is well-established that they are highly heritable disorders. Their prevalence is approximately 0.7% and 1% of the population, respectively (*Robinson and Bergen 2021*).
  - Bipolar disorder is characterized by discrete mood instability with periods of mania and depression. Drugs commonly used to treat acute mania or hypomania include lithium, anticonvulsants, and antipsychotics. Benzodiazepines may be helpful when adjunctive treatment is needed for insomnia, agitation, or anxiety (*Stovall 2024*).

- Schizophrenia is a disorder involving chronic or recurrent psychosis and is associated with significant functional impairment. Schizophrenia is believed to be caused by abnormal activity of dopamine in the mesolimbic and/or mesocortical regions of the brain (*Keepers et al 2020).*
  - Symptoms of the disease can be classified as positive (eg, hallucinations, delusions, and disorganized speech, or grossly abnormal psychomotor behavior including catatonia), negative (eg, diminished expression of emotions, lack of motivation, flat affect, decreased expressiveness, apathy), and cognitive (eg, impaired attention, memory, and executive functioning) (*DSM-5-TR 2022, Keepers et al 2020*).
  - The diagnosis of schizophrenia includes ≥ 2 symptoms that have been present for a significant portion of time during a 1-month period and continuous signs of the disturbance that persist for at least 6 months. Symptoms must include at least 1 positive symptom, but may also include grossly disorganized or catatonic behavior, and negative symptoms. The DSM-5-TR criteria provide more clear separation between schizophrenia and schizoaffective disorder. A diagnosis of schizoaffective disorder requires that a major depressive or manic episode occur concurrently with the active-phase symptoms and that the mood symptoms be present for most of the total duration of the active periods (*DSM-5-TR 2022*).
- Tourette's disorder is characterized by persistent and repetitive motor and/or vocal tics, and onset is typically observed in childhood. For diagnosis, tics need to be present for at least 1 year. The pathophysiology of chronic tic disorders is not known but believed to be due to motor issues at both cortical and subcortical levels that are not properly modulated at the cortico-striatal-thalamo-cortical circuits. The prevalence of chronic tic disorders has been estimated as 0.5% to 3%, with approximately 7% of school-age children having had tics in the previous year. Tourette's disorder ranges greatly in terms of symptom severity and is often associated with comorbidities such as attention-deficit/hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD) (*Murphy et al 2013*).
- Parkinson's disease (PD) psychosis affects approximately 60% of patients with PD. Diagnosis includes primary diagnosis of PD presenting with at least delusions, hallucinations, illusions, or false sense of presence; symptoms recurrent or continuous for ≥ 1 month; and exclusion of dementia-related psychosis or psychotic disorders (*Bozymski et al 2017*).
- Agitation in patients with Alzheimer's disease occurs regardless of whether patients are living at home or in long-term care facilities. Its prevalence increases with disease severity. Symptoms may include emotional distress, excessive motor activity (eg, pacing, rocking) and verbal and physical aggression (*Grossberg et al 2020*).
- Medispan class: Antipsychotics/Antimanic agents; Antipsychotics – Misc., Quinolinone derivatives, Dibenzo-oxepino Pyrroles, Dibenzodiazepines; Muscarinic Agents.

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity*)
Single Entity Agents	
Abilify (aripiprazole tablets)	✔
Abilify MyCite (aripiprazole tablet with sensor)	-
aripiprazole ODT, oral solution	✔
Caplyta (lumateperone capsules)	-
clozapine ODT	✔
Clozaril (clozapine tablets)	✔
Fanapt (iloperidone tablets)	-
Geodon (ziprasidone HCl capsules)	✔
Geodon (ziprasidone mesylate injection)	✔
Invega (paliperidone ER tablets)	✔
Latuda (lurasidone tablets)	✔ ‡
Nuplazid (pimavanserin tablets, capsules)	-
Opipza (aripiprazole soluble film)	-
Rexulti (brexpiprazole tablets)	-
Risperdal (risperidone tablets, oral solution)	✔
Saphris (asenapine tablets)	✔

Drug	Alternative Available (same molecular entity*)
Secuado (asenapine transdermal system)	-
Seroquel (quetiapine tablets)	✔
Seroquel XR (quetiapine ER tablets)	✔
Versacloz (clozapine oral solution)	-
Vraylar (cariprazine capsules)	-
Zyprexa (olanzapine tablets)	✔
Zyprexa (olanzapine injection)	✔
Zyprexa Zydis (olanzapine ODT)	✔
Long-Acting Injectable (LAI) Agents	
Abilify Asimtufii (aripiprazole)	-
Abilify Maintena (aripiprazole ER)	-
Aristada (aripiprazole lauroxil ER)	-
Aristada Initio (aripiprazole lauroxil ER)	-
Erzofri (paliperidone palmitate ER)	-
Invega Hafyera (paliperidone palmitate)	-
Invega Sustenna (paliperidone palmitate)	-
Invega Trinza (paliperidone palmitate)	-
Perseris (risperidone ER)	-
Risperdal Consta (risperidone microspheres)	-
Rykindo (risperidone ER)	-
Uzedy (risperidone ER)	-
Zyprexa Relprevv (olanzapine pamoate)	-
Combination Agents	
Cobenfy (xanomeline/trospium chloride)	-
Lybalvi (olanzapine/samidorphan tablets)	-
Symbyax (olanzapine/fluoxetine capsules)	✔

Abbreviations: ODT = orally disintegrating tablets, HCl – hydrochloride, ER = extended release
*For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.
† Abilify MyCite is the only drug-device combination product, comprised of a tablet with an embedded sensor, a wearable sensor patch, a smartphone application, and a web-based portal. There are 2 MyCite systems: a 1-component patch (containing aripiprazole tablets with sensor and patches), and a 2-component patch (containing a 30 Day Starter kit and a Maintenance kit). The 30 Day Starter kit contains aripiprazole tablets with sensor, adhesive strips, and a pod (removable electronics module), and the Maintenance kit contains aripiprazole tablets with sensor and adhesive strips.
‡ Not all lurasidone generics have an indication for treatment of schizophrenia

(*Drugs@FDA 2025, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2025*)

Indications

Table 2. Food and Drug Administration Approved Indications

- The following summarizes all FDA-approved indications:
  - **Autism**: Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years and 5 to 17 years, respectively).
  - **Bipolar disorder**: Not all oral agents in this class are approved for bipolar disorder (see Table 2 for FDA indications); Aripiprazole ER (Abilify Maintena and Abilify Asimtulfii) and Risperidone ER (Risperdal Consta and Rykindo) are the only long-acting injectable agents (LAIs) indicated for the treatment of bipolar disorder.
    - Oral aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, asenapine, and lurasidone are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Oral olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder.

- **Depression**: Aripiprazole, brexpiprazole, cariprazine, and quetiapine ER are indicated as adjunctive treatment for MDD in patients already taking an antidepressant. Olanzapine/fluoxetine is indicated for treatment-resistant depression.
- **Schizophrenia**: All agents in this class review are indicated for use in schizophrenia with the exception of pimavanserin, certain generics of lurasidone, and the combination agent, Symbyax (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding Invega Trinza and Invega Hafyera, are indicated for the treatment of schizoaffective disorder. Clozapine is the only agent in this class that is FDA-approved for treatment-resistant schizophrenia.
  - Oral aripiprazole (with the exception of tablets with sensor), brexpiprazole, lurasidone, olanzapine, quetiapine, and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia.
- **Tourette's Disorder**: Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged 6 to 18 years.
- **Parkinson's disease psychosis**: Pimavanserin is the first atypical antipsychotic FDA-approved for use in patients with PD psychosis.
- **Agitation associated with dementia** due to Alzheimer's disease: Brexpiprazole is the first atypical antipsychotic FDA-approved for this indication.
- Prescribing considerations: The labeling for iloperidone and ziprasidone state that when deciding among the alternative treatments, the prescriber should consider that these drugs are associated with prolongation of the QTc interval. Refer to package inserts for specific titration requirements.

- Table 2 highlights FDA-approved indications at a high level.

Table 2. Food and Drug Administration approved indications.

Agent	Autism	Agitation associated with dementia due to Alzheimer's disease	Bipolar disorder: manic/mixed episodes	Bipolar disorder: Depressive episodes	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder	Parkinson's disease psychosis
Single Entity Agents											
aripiprazole	✔ *	-	✔ *	-	-	✔	-	✔ *	-	✔ *	-
aripiprazole with sensor	-	-	✔	-	-	✔	-	✔	-	-	-
asenapine	-	-	✔ *††	-	-	-	-	✔	-	-	-
asenapine TD	-	-	-	-	-	-	-	✔	-	-	-
brexpiprazole	-	✔ #	-	-	-	✔	-	✔ *	-	-	-
cariprazine	-	-	✔	✔	-	✔	-	✔	-	-	-
clozapine	-	-	-	-	-	-	✔	-	✔	-	-
iloperidone	-	-	✔	-	-	-	-	✔	-	-	-
lumateperone	-	-	-	✔	-	-	-	✔	-	-	-
lurasidone**	-	-	-	✔ * ††	-	-	-	✔ *	-	-	-
olanzapine‖	-	-	✔ *	✔ *	✔	-	-	✔ *	-	-	-
paliperidone	-	-	-	-	-	-	✔	✔ *	-	-	-
pimavanserin	-	-	-	-	-	-	-	-	-	-	✔
quetiapine	-	-	✔ *	✔	-	✔ †	-	✔ *	-	-	-
risperidone	✔ *	-	✔ *	-	-	-	-	✔ *	-	-	-
ziprasidone §	-	-	✔	-	-	-	-	✔	-	-	-
LAI Agents											

Agent	Autism	Agitation associated with dementia due to Alzheimer's disease	Bipolar disorder: manic/mixed episodes	Bipolar disorder: Depressive episodes	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder	Parkinson's disease psychosis
Abilify Asimtufii (aripiprazole ER)	-	-	✔	-	-	-	-	✔	-	-	-
Abilify Maintena (aripiprazole ER)	-	-	✔	-	-	-	-	✔	-	-	-
Aristada, Aristada Initio (aripiprazole lauroxil ER)	-	-	-	-	-	-	-	✔	-	-	-
Erzofri (paliperidone palmitate ER)	-	-	-	-	-	-	✔	✔	-	-	-
Invega Sustenna (paliperidone palmitate)	-	-	-	-	-	-	✔	✔	-	-	-
Invega Trinza (paliperidone palmitate)	-	-	-	-	-	-	-	✔	-	-	-
Invega Hafyera (paliperidone palmitate)	-	-	-	-	-	-	-	✔	-	-	-
Risperdal Consta (risperidone microspheres)	-	-	✔	-	-	-	-	✔	-	-	-
Rykindo (risperidone ER)	-	-	✔	-	-	-	-	✔	-	-	-
Perseris (risperidone ER)	-	-	-	-	-	-	-	✔	-	-	-
Uzedy (risperidone ER)	-	-	-	-	-	-	-	✔	-	-	-
Zyprexa Relprevv (olanzapine pamoate ER)	-	-	-	-	-	-	-	✔ ‡	-	-	-
Combination Agents											
Cobenfy (xanomeline/ trospium)	-	-	-	-	-	-	-	✔	-	-	-
Lybalvi (olanzapine/ samidorphan)	-	-	✔	-	-	-	-	✔	-	-	-
Symbyax (olanzapine/ fluoxetine)	-	-	-	✔ *	✔	-	-	-	-	-	-

Abbreviations: ER = extended release, IM = intramuscular, ODT = orally disintegrating tablet, TD= transdermal
* FDA-approved indications for pediatric and/or adolescent patients.
** Not all lurasidone generics have indication of schizophrenia
† Indicated for the ER formulation.
‡ Patients must be observed by a health care professional for 3 hours post-dose administration with Zyprexa Relprevv.

§ IM injection indicated for acute agitation associated with schizophrenia.
‖ IM injection indicated for acute agitation associated with schizophrenia and bipolar mania
¶ Indicated for the drug-device combination with tablet and sensor. The ability to improve patient compliance or modify aripiprazole dosage has not been established. The ability to track drug ingestion in "real-time" or during an emergency is not recommended because detection may be delayed or not occur.
# Limitation of use (brexpiprazole): is not indicated as an as needed ("prn") treatment for agitation associated with dementia due to Alzheimer's disease.
†† In adults, this agent is indicated as monotherapy or adjunctive with lithium or valproate. In pediatrics (10 to 17 yrs), this agent is indicated as monotherapy only.

(*Prescribing information: Abilify 2025, aripiprazole ODT 2024, aripiprazole oral solution 2025, Abilify Asimtufii 2025, Abilify Maintena 2025, Abilify MyCite 2025, Aristada 2025, Aristada Initio 2025, Caplyta 2023, Clozaril 2025, clozapine ODT 2025, Cobenfy 2024,* Erzofri 2025, *Fanapt 2025, Geodon 2025, Invega 2025, Invega Hafyera 2025, Invega Sustenna 2025, Invega Trinza 2025, Latuda 2025, lurasidone 2025, lurasidone 2025, Lybalvi 2025, Nuplazid 2025, Opipza 2025, Perseris 2025, Rexulti 2025, Risperdal 2025, Risperdal Consta 2025, Rykindo 2025, Saphris 2025, Secuado 2025, Seroquel 2025, Seroquel XR 2025, Symbyax 2025, Uzedy 2025, Versacloz 2025, Vraylar 2024, Zyprexa 2025, Zyprexa Relprevv 2025*)

- 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 goal of this summary is to evaluate key published literature regarding atypical antipsychotics for FDA-approved indications in children, adolescents, and adults. Numerous studies evaluating the efficacy of antipsychotic medications have been conducted. In clinical practice, the role of atypical antipsychotics has been clearly established for the treatment of bipolar disorder and schizophrenia. Clinical consensus guidelines do not differentiate one agent from another, supporting the concept that all patients will require an individualized approach to treatment selection; considering the agent's safety profile and patient's individual risk factors.
- Key clinical studies evaluating the roles of atypical antipsychotic agents in the treatment of FDA-approved indications are included in the review. However, in recognition of the vast number of published studies of older atypical antipsychotics in adults, only a selection of randomized controlled trials (RCTs), systematic reviews (SRs), and meta-analyses (MAs) are presented.

Children/Adolescents

- The Agency for Healthcare Research and Quality (AHRQ) conducted a SR evaluating the safety and efficacy of antipsychotics in children and adolescents. The review included 135 studies of atypical antipsychotics (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) conducted in patients 24 years of age or younger with various psychiatric conditions (eg, schizophrenia and related disorders, autism spectrum disorders, bipolar disorder, and tic disorder). Indications with moderate strength evidence for the use of atypical antipsychotics included schizophrenia and related psychoses, bipolar disorder, autism spectrum disorders, and ADHD. The risk of weight gain was highest for olanzapine, clozapine, and lurasidone. It was found that atypical antipsychotics probably increase short-term risk for high triglyceride levels, extrapyramidal symptoms, sedation, and somnolence vs placebo (*Pillay et al 2017*).

Autism Spectrum Disorder

- For the treatment of irritability associated with autistic disorder, risperidone has been approved in pediatric patients aged 5 to 17 years and aripiprazole has been approved in patients aged 6 to 17 years. Very few RCTs have been conducted evaluating the safety and efficacy for various behavior symptoms and most trials included less than 50 patients. The outcomes of these trials are more sensitive to variability due to the small effect size (*Aman et al 2002*, *Aman et al 2008, Capone et al 2008, Gagliano et al 2004, Gencer et al 2008, Luby et al 2006, Miral et al 2008, Nagaraj et al 2006*).
- The safety and efficacy of aripiprazole in children with autism was evaluated in 2 placebo-controlled (PC), 8-week trials. Over 75% of these subjects were under 13 years of age. In one of these trials, children and adolescents with autistic disorder (N = 98) received daily doses of placebo or aripiprazole 2 to 15 mg/day. The mean daily dose of aripiprazole at the end of the 8-week period was 8.6 mg/day. Aripiprazole significantly improved ABC-I subscale scores, including emotional and behavioral symptoms of irritability, aggression towards others, deliberate self-injuriousness, temper

tantrums, and quickly changing moods (*Owen et al 2009*). In the second of these trials in children and adolescents with autistic disorder (N = 218), 3 fixed doses of aripiprazole (5, 10, or 15 mg/day) were compared to placebo. ABC-I subscale scores were significantly decreased by 12.4 points with 5 mg/day, 13.2 with 10 mg/day, and 14.4 with 15 mg/day compared with 8.4 with placebo. The CGI-Improvement scores were significantly improved: 2.6 points with 5 mg/day, 2.5 with 10 mg/day, and 2.5 with 15 mg/day compared with 3.3 with placebo. At the higher doses, ABC stereotypy, hyperactivity, CGI-S (Severity of Illness) scores, and other secondary measures were also improved (*Marcus et al 2009*).

- The safety and efficacy of risperidone was evaluated in two 8-week and one 6-week, PC pivotal trials in children with serious behavioral problems associated with autism (*McCracken et al 2002, Shea et al 2004*). Approximately 90% of these subjects were under 12 years of age. In the two 8-week trials, patients aged 5 to 16 years (N = 101) received weight-based, twice-daily doses of 0.5 to 3.5 mg/day (the RUPP trial) and patients aged 5 to 12 years (N = 79) received 0.02 to 0.06 mg/kg/day given once or twice daily (*McCracken et al 2002, Shea et al 2004*). The 6-week trial measured efficacy and safety of lower than FDA-approved recommended dosing, and outcomes did not demonstrate efficacy (*Risperdal prescribing information 2022*). In the RUPP trial, risperidone-treated patients exhibited a 56.9% reduction in the mean ABC-I score from baseline, compared to a 14.1% reduction observed in the placebo group ($p < 0.001$) (*McCracken et al 2002*). Risperidone was generally well tolerated, and most adverse events were mild and transient. Due to the uncertainty of clear benefit with regard to the core symptoms of autism, the authors recommend that risperidone be reserved for the treatment of moderate-to-severe behavioral problems accompanying autism. In the second 8-week trial, risperidone patients demonstrated a 64% improvement in ABC-I subscale vs 31% improvement with placebo, which was a significant positive finding for hyperactivity (*Shea et al 2004*). Somnolence was the most frequently reported adverse event (72.5% vs 7.7%), and risperidone-treated subjects experienced statistically greater increases in weight (2.7 kg vs 1 kg), pulse rate, and systolic blood pressure.
  - In an extension of the RUPP trial, 63 responders received open-label (OL) risperidone for another 16 weeks. Risperidone dose adjustments were allowed up to a maximum total daily dose of 3.5 mg/day. At the end of the 4-month extension, an intention-to-treat analysis revealed a minor, but clinically insignificant increase in ABC-I scores. There was also a significant time effect on the ABC-I scale at the end of the 4-month extension phase ($p = 0.02$) (*McDougle et al 2005*).
- One head-to-head, prospective, 8-week trial was conducted comparing the effects of aripiprazole ≤ 10 mg/day (mean dose, 5.5 mg/day) to risperidone ≤ 3 mg/day (mean dose, 1.12 mg/day) in 59 patients aged 4 to 18 years of age. Approximately 65% of patients were diagnosed with autism, and additional diagnoses included Asperger syndrome, pervasive developmental disorder, and disruptive behavior disorder. Study authors stated double-blind (DB) techniques were not enforced for all patients. At the end of the trial, the mean change from baseline in ABC-I subscale score was not statistically different ($p = 0.06$), but numerically favored risperidone. No differences were detected between groups for each adverse event or in the rate of discontinuation due to adverse events. Study authors concluded that the safety and efficacy of both agents were comparable (*Ghanizadeh et al 2014*).
- An MA of 3 trials evaluating pediatric patients (N = 316) treated with aripiprazole demonstrated a greater increase in weight vs placebo (weight gain,1.13 kg; 95% confidence interval [CI], 0.71 to 1.54; $p < 0.00001$), and a higher relative risk (RR) for sedation (RR, 4.28; 95% CI, 1.58 to 11.6; $p = 0.004$) and tremor (RR, 10.26; 95% CI, 1.37 to 76.63; $p = 0.02$) (*Hirsch et al 2016*).
- A 2018 MA evaluated the efficacy of aripiprazole in patients with autism spectrum disorder (N = 408) and found aripiprazole significantly improved irritability, hyperactivity, and inappropriate speech but not social withdrawal in comparison with placebo. The RR for response rate was also improved with aripiprazole (RR, 2.08; 95% CI, 1.24 to 3.46) (*Maneeton et al 2018*).
- A network MA evaluated 8 clinical trials (N = 878) with risperidone, aripiprazole, lurasidone, and placebo in pediatric autism spectrum disorder. Both risperidone and aripiprazole significantly reduced irritability compared with placebo with similar safety profiles. Lurasidone was not significantly different from placebo (*Fallah et al 2019*).
- An MA of 64 RCTs measured the efficacy of various pharmacological agents (eg, antipsychotics, antidepressants, or others) for restricted and repetitive behaviors in ASD. Eight studies evaluated antipsychotics (risperidone, lurasidone [off label], aripiprazole) and found a small but significant score reduction of restricted and repetitive behaviors compared to placebo [standardized mean difference (SMD), 0.28; 95% CI, 0.08 to 0.49; $p = 0.01$] with modest heterogeneity (I^2 = 33.4%) (*Zhou et al 2021*).
- An MA of 21 RCTs evaluated outcomes of antipsychotics for people with autism of all ages. Analysis 10 PC, RCTs (5 aripiprazole, 4 risperidone, 1 lurasidone [off label]) showed significant improvement in ABC-I in the patients treated with

aripiprazole (effect size, -5.23; p < 0.00001) and risperidone (effect size, -8.25; p < 0.00001) but not lurasidone (effect size, 0.93; p = 0.35). Pooled CGI data of 11 PC, RCTs showed an overall effect size of 0.84 (95% CI 0.48 to 1.21; p < 0.00001; I^2 = 55.4%). There was a significantly higher risk of overall adverse effects (p = 0.003) including weight gain (p < 0.00001), sedation (p < 0.00001) and increased appetite (p = 0.001) with antipsychotics (*Deb et al 2023*).

Bipolar Disorder

Manic/Mixed Episodes

- Aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine, and asenapine have FDA-approved indications for the treatment of pediatric patients diagnosed with bipolar disorder. All agents are approved for ages ≥ 10 years, except olanzapine which is approved in patients aged ≥ 13 years. In pediatric patients with bipolar disorder, evidence is extremely limited.
  - In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 19 trials measured efficacy and safety in adolescents with bipolar disorder. Compared with placebo, atypical antipsychotics decreased mania and depression symptoms slightly, and improved symptom severity and global functioning to a small extent. In addition, these agents probably increased response and remission rates vs placebo for manic/mixed phases (*Pillay et al 2017*).
  - In a 21-day, DB, PC trial, 403 patients aged 10 to 17 years with bipolar I disorder were randomized to placebo or asenapine 2.5 mg, 5 mg, or 10 mg twice daily. The primary endpoint, change from baseline in Young Mania Rating Scale (YMRS) score, demonstrated a statistically significant and dose-dependent mean difference (MD) in YMRS scores at 21 days for all asenapine groups vs placebo (2.5 mg, -3.2; p = 0.0008 vs 5 mg, -5.3; p < 0.001 vs 10 mg, -6.2; p < 0.001). Weight gain was higher across the asenapine groups, with 8% to 12% of patients experiencing ≥ 7% weight gain vs 1.1% of patients in the placebo group (p < 0.05). Fasting glucose, insulin, and cholesterol changes were also numerically higher in the asenapine groups vs placebo (p = not reported). Overall, asenapine was well tolerated and showed efficacy in the treatment of this pediatric population, although the duration of the study period was brief (*Findling et al 2015*).
- A 6-week, DB, RCT evaluated the efficacy of lithium vs quetiapine for the treatment of acute mania in 109 adolescents with early course bipolar disorder. For the primary outcome of change in the YMRS, patients taking quetiapine showed a significantly greater score reduction compared to lithium (-11.0 vs. -13.2, respectively; p < 0.001; effect size 0.39). Response rate was 72% with quetiapine and 49% with lithium (p = 0.012). However, no differences in remission rates were found (*Patino et al 2021*).
- An SR and network MA of 18 studies evaluated the comparative efficacy of 6 SGAs (aripiprazole, asenapine, olanzapine, quetiapine, risperidone, and ziprasidone) and 4 mood stabilizers (lithium, oxcarbazepine, topiramate, and valproate) for mania symptoms and mania response (co-primary endpoints) in children and adolescents. For mania symptoms, all 6 SGAs demonstrated greater efficacy in reducing manic symptoms compared to placebo (descending order of effect size reported as SMD; risperidone (-1.18) > olanzapine (-0.77) > aripiprazole (-0.67) > quetiapine (-0.60) > asenapine (-0.54) > ziprasidone (-0.43); no mood stabilizers were superior to placebo. For mania response, 5 SGAs (risperidone, olanzapine, aripiprazole, quetiapine, asenapine) and lithium demonstrated greater efficacy compared to placebo (*Vita et al 2024*).

Depressive Episodes

- An SR and MA of 4 studies (2 quetiapine, 1 lurasidone, 1 olanzapine plus fluoxetine combination) evaluated SGAs for the management of pediatric bipolar depression. Lurasidone demonstrated the highest reduction in depressive symptoms (MD -5.70; 95% CI, -8.67 to -2.73), followed by olanzapine plus fluoxetine combination (MD, -5.00; 95% CI -8.64 to -1.36) then quetiapine (MD, -2.30; 95% CI -6.80 to 2.20). Compared to placebo, a significantly higher response was demonstrated with lurasidone (59.5% vs 36.5%; p<0.001) and olanzapine plus fluoxetine combination (78.2% vs. 59.2%; p = 0.003) but not olanzapine. The weighted mean Children's Depression Rating Scale-Revised CDRS-R total score difference was -4.58 (95% CI, -6.59 to -2.56) and overall effect was significant (p < 0.00001) (*Patel et al 2021*).
- An SR and network MA of 4 RCTs evaluated the efficacy and safety of atypical antipsychotics for bipolar depression in pediatric patients 10 to 18 years of age. Compared to placebo, a significant reduction in the CDRS-R baseline score was observed with lurasidone (-5.70, 95% CI -8.66 to -2.76) and olanzapine/fluoxetine (-5.01, 95% CI -8.63 to -1.38) but not with quetiapine. Compared to olanzapine/fluoxetine and quetiapine, lurasidone demonstrated smaller changes in

weight, cholesterol, and triglycerides. No difference in the extent of change in glucose levels between agents was observed. (*DelBello et al 2022*)

- Clinical trials measuring the safety and efficacy of atypical antipsychotics in depressive episodes in pediatric patients diagnosed with bipolar disorder are limited. Two trials examined efficacy of quetiapine in this population. In a small trial, a total of 32 patients aged 12 to 18 years were randomized to quetiapine 300 to 600 mg/day or placebo and followed over a period of 8 weeks. The primary endpoint was change in the CDRS-R score, in which both quetiapine and placebo groups exhibited statistically significant reductions in the CDRS-R scores from baseline ($p < 0.001$), with no difference between groups (19 vs 20; $p = 0.89$). All other efficacy measures were not statistically different from placebo (*DelBello et al 2009*).
- A similar 8-week trial enrolled 193 patients aged 10 to 17 years with acute bipolar depression. Patients were randomized to placebo or quetiapine XR 150 to 300 mg/day. The primary endpoint was change in CDRS-R score from baseline, with mean CDRS-R scores decreasing from baseline in both placebo (-29.6) and treatment (-27.3) groups. The difference between groups was not statistically significant (95% CI, -6.22 to 1.65; $p = 0.25$). Triglyceride levels were elevated in 9.3% of the quetiapine XR group vs 1.4% of the placebo group. Mean weight gain was 1.3 kg in the quetiapine XR group vs 0.6 kg in the placebo group (p = not reported) (*Findling et al 2014*).
- In a DB, PC trial, 291 patients aged 10 to 17 years with bipolar I disorder, and depressive episodes were randomized 2:1 to olanzapine/fluoxetine or placebo for 8 weeks. Doses of olanzapine/fluoxetine were titrated to 12/50 mg daily over 2 weeks. The olanzapine/fluoxetine group had a 5-point greater mean decrease in CDRS-R score from baseline vs placebo (-28.4 vs -23.4; $p = 0.003$). A total of 78.2% olanzapine/fluoxetine patients achieved response (defined as ≥ 50% reduction of CDRS-R score from baseline and a YMRS item 1 score ≤ 2) vs 59.2% of placebo group patients ($p = 0.003$). Weight gain was more common in the olanzapine/fluoxetine group vs placebo (4.4 vs 0.5 kg; $p < 0.001$), as well as increase in fasting total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (all $p < 0.001$). Mean prolactin increase was higher in the olanzapine/fluoxetine group vs placebo ($p < 0.001$) and increase in heart rate was also statistically significantly higher in the treatment group ($p = 0.013$). This trial demonstrated efficacy in pediatric patients, but also demonstrated serious adverse effects (*Detke et al 2015*).
- In a DB, PC trial, 347 patients aged 10 to 17 years were assigned to flexible doses of lurasidone 20 to 80 mg/day or placebo. The primary endpoint was the change from baseline to week 6 in the CDRS-R total score. At week 6 of therapy, treatment with lurasidone was associated with a significant improvement compared with placebo in CDRS-R total score (-21.0 vs -15.3; $p < 0.0001$). Lurasidone also was associated with statistically significant improvements in the CGI-Bipolar-Severity of Illness scale (CGI-BP-S) depression score (key secondary measure) and in measures of anxiety, quality of life, and global functioning (*DelBello et al* 2017).

Schizophrenia and/or schizoaffective disorder

- In pediatric patients diagnosed with schizophrenia, FDA-approved treatments include aripiprazole, brexpiprazole, lurasidone, olanzapine, quetiapine, and risperidone for use in patients ≥ 13 years of age and paliperidone oral products in patients aged ≥ 12 years. Many trials include a small sample size of patients or are not well-designed. However, efficacy has been demonstrated, and results are similar to adult trials.
  - The approval of brexpiprazole for the treatment of schizophrenia in pediatric patients aged ≥ 13 years was based on pharmacokinetic modeling data from 5 Phase 1 trials (3 trials in adults, 2 trials in children; N = 161; 61% adults) extrapolating similar drug exposures in adult and pediatric patients (*Zhang et al 2024*). A long-term, open label (OL), safety and tolerability study in 194 pediatric patients aged 13 to 17 years was also completed (*Atkinson et al 2024*). Interim analysis of the OL study demonstrated a similar safety profile as observed in adults. The most common adverse effects included somnolence, headache, weight gain, and nasopharyngitis.
  - A randomized, DB, parallel-arm, PC, Phase 3 study compared the short-term safety and efficacy of brexpiprazole (n = 110), aripiprazole (n = 102), and placebo (n = 104) for the treatment of schizophrenia in adolescents aged 13-17 years. At the end of 6 weeks, both aripiprazole and brexpiprazole had greater reductions in the Positive and Negative Syndrome Scale (PANSS) total score than placebo. The most frequently reported treatment-related adverse events were headache and nausea for brexpiprazole and somnolence, fatigue, and akathisia with aripiprazole (*Ward et al 2025*).
- An SR and network MA of 12 RCTs (N = 2158) evaluated 8 antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone) for the treatment of children and adolescents with schizophrenia-spectrum disorders. The network MA found that the change in PANSS total, positive, and negative symptoms did not differ significantly between agents except for ziprasidone, which was inferior on PANSS total

symptoms vs molindone, olanzapine, paliperidone, quetiapine, and risperidone, and inferior on PANSS negative symptoms vs molindone, olanzapine, and risperidone. All antipsychotics were superior to placebo on PANSS total symptom change except asenapine and ziprasidone. All antipsychotics, except ziprasidone, were superior to placebo on PANSS positive symptom change; additionally, all antipsychotics, except paliperidone, quetiapine, and ziprasidone, were superior to placebo on PANSS negative symptom change. Weight gain was primarily associated with olanzapine, while prolactin was increased with risperidone, paliperidone, and olanzapine (*Pagsberg et al 2017*).

- In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 39 studies evaluated efficacy and safety in adolescents with schizophrenia. Compared with placebo, atypical antipsychotics as a class probably increase response rates; decrease slightly (not clinically significant for many patients) negative and positive symptoms; and improve slightly global impressions of improvement, severity, and functioning. Six studies comparing risperidone vs olanzapine found little or no difference in their effects for negative and positive symptoms, response rates, and global impressions of severity (*Pillay et al 2017*).
- A Cochrane review compared atypical antipsychotic medications to placebo, typical antipsychotics, or another atypical antipsychotic in adolescents with psychosis. Compared to typical antipsychotics, there were no significant differences in Brief Psychiatric Rating Scale (BPRS) scores in an analysis of 5 trials with 236 patients. There was no evidence to suggest the superiority of atypical antipsychotics over typical antipsychotics; however, fewer adolescents dropped out due to adverse effects when administered an atypical antipsychotic (RR, 0.65; 95% CI, 0.36 to 1.15). Minimal evidence was available comparing one atypical antipsychotic to another. In terms of the number of patients who did not respond (defined as ≤ 30% reduction in BPRS score), results significantly favored clozapine, but increases in salivation, sweating, and glucose levels were observed vs olanzapine in 1 trial with 39 patients. Treatment with olanzapine, risperidone and clozapine was associated with weight gain. Aripiprazole was not associated with increased prolactin or dyslipidemia. Low-dose risperidone significantly decreased improvement in PANSS total score but also reduced the rate of extrapyramidal symptoms (EPS) vs standard-dose risperidone in 1 trial with 255 patients. Overall, efficacy between atypical and typical antipsychotics may be similar; however, safety benefits may favor treatment with atypical antipsychotics (*Kumar et al 2013*).
- A 6-week, randomized, PC trial evaluating the efficacy of lurasidone in acutely symptomatic adolescents with schizophrenia found that the least squares (LS) mean change in PANSS total score from baseline to week 6 was greater for the lurasidone 40 mg/day group (-18.6; $p < 0.001$; effect size = 0.51) and the lurasidone 80 mg/day group (-18.3; $p < 0.001$; effect size = 0.48) vs the placebo group (-10.5). The LS mean change from baseline to week 6 in CGI-S score was significantly greater for the lurasidone 40 mg/day group (-1.0; $p < 0.001$; effect size = 0.49) and the lurasidone 80 mg/day group (-0.9; $p = 0.0015$; effect size = 0.45) compared with the placebo group (-0.5). The most common adverse events in the lurasidone groups were nausea, anxiety, akathisia, somnolence, and vomiting (*Goldman et al 2017*).

Tourette's Disorder

- Aripiprazole is the only agent indicated for the treatment of Tourette's disorder. Efficacy and safety were based on low quality evidence in one fixed-dose and one flexible-dose trial. There is minimal evidence of safety and efficacy in this population.
- In one published, DB, PC, 10-week trial, aripiprazole significantly reduced total tic score (Yale Global Tic Severity Scale [YGTSS-TTS]; -15 vs -9.6) and phonic tic score (YGTSS-PTS; -7.4 vs -4.2), but not motor tic score, compared with placebo in patients aged 6 to 18 years with Tourette's disorder. The response rate (score of 1 or 2 on the Tourette's syndrome CGI-Improvement scale) was 66% vs 45%, respectively (*Yoo et al 2013*).
- In another similarly designed, unpublished, 8-week trial in patients aged 7 to 17 years who received weight-based aripiprazole, significant improvements compared with placebo were seen on YGTSS-TTS with a change of -13.4 and -16.9 points with low- and high-dose aripiprazole compared to -7.1 with placebo (*Abilify prescribing information 2025*).
- Aripiprazole was associated with increased body weight compared to placebo (range, 0.4 to 1.5 kg). Additional adverse reactions (incidence ≥ 5% and at least twice that for placebo) were sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, and increased appetite (*Abilify prescribing information 2025*). In one safety trial, aripiprazole had a safer cardiovascular profile vs pimozide, and was associated with a lower frequency of QT prolongation (*Gulisano et al 2011*).

Adults

Oral atypical antipsychotics

- The AHRQ conducted an SR of literature on the safety and efficacy of antipsychotics in adults comparing typical and atypical antipsychotics. The review included studies of atypical antipsychotics (aripiprazole, asenapine, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone), conducted in patients 18 to 64 years of age, and used for the following FDA-approved indications: bipolar disorder, schizophrenia, and schizophrenia-related psychoses. The most frequent comparisons involved haloperidol; 43 studies compared haloperidol with risperidone and 37 studies compared haloperidol with olanzapine. Nevertheless, the number of studies available for each comparison and outcome was often limited (*Abou-Setta et al 2012*).
  - Overall, indications associated with moderate to low strength evidence for the use of atypical antipsychotics included schizophrenia and schizophrenia-related psychoses. Bipolar disorder was associated with low strength of evidence. Few differences of clinical importance for outcomes of effectiveness were found.
  - In terms of efficacy, few differences were found between typical and atypical antipsychotic agents, specifically when compared to haloperidol, and clinical significance (defined as ≥ 20% difference between interventions) was rarely found.
  - Data were sparse for the 4 key adverse events deemed to be most clinically important to draw firm conclusions (ie, diabetes, tardive dyskinesia, metabolic syndrome, and mortality). No differences were found in mortality for chlorpromazine vs clozapine and haloperidol vs aripiprazole, or in metabolic syndrome for haloperidol vs olanzapine. The most frequently reported adverse events with significant differences were EPS; in most cases, the atypical antipsychotic had fewer EPS than haloperidol.

Bipolar Disorder

Manic/Mixed Episodes

- All oral atypical antipsychotic agents in this class review are indicated for use in bipolar disorder, except clozapine, paliperidone, brexpiprazole, and pimavanserin. The following summarizes direct comparative evidence and recent MAs and SRs.
  - A 2018 AHRQ SR of 156 trials concluded that symptoms of acute mania were modestly improved with asenapine, cariprazine, quetiapine, and olanzapine compared to placebo. Risperidone, ziprasidone, and paliperidone may also be effective for acute mania symptoms. Lithium was effective in the treatment of acute mania and prolonged the time to relapse compared to placebo, and this was the only agent that achieved a minimal clinically important difference in symptoms. All of these results were based on low-strength evidence because moderate and strong evidence was lacking (*Butler et al 2018*).
  - In a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 12 measured efficacy and safety in adults with bipolar disorder. Compared to haloperidol, there was no difference in YMRS score for manic episodes for aripiprazole, olanzapine, and risperidone, and no difference in Montgomery-Asberg Depression Rating Scale (MADRS) score for aripiprazole in a total of 9 trials. In 1 trial of 350 patients, haloperidol was favored in terms of YMRS score over ziprasidone. Haloperidol produced lower relapse rates than aripiprazole in 1 trial with 347 patients and provided better response rates than ziprasidone in one trial of 350 patients. The most frequently reported adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be an equally effective treatment compared with the atypical antipsychotics; however, it is associated with more incidences of EPS compared to other agents (*Abou-Setta et al 2012*).
  - An SR and MA of 15 RCTs and 1 observational study was conducted to evaluate the efficacy of maintenance treatment in bipolar disorder using atypical antipsychotics, either as monotherapy or as adjunctive therapy. As adjunctive therapy to lithium or valproate, MAs showed that treatment with aripiprazole (RR, 0.65; 95% CI, 0.50 to 0.85), quetiapine (RR, 0.38; 95% CI, 0.32 to 0.46), or ziprasidone (RR, 0.62; 95% CI, 0.40 to 0.96) reduced the overall risk of relapses in patients that had responded during the stabilization phase. Quetiapine was the only drug that reduced both manic and depressive episodes. Due to high risk of bias and low levels of evidence, no conclusions could be drawn for olanzapine or risperidone. For monotherapy, quetiapine was shown to be better than lithium/valproate for both manic and depressive relapses; no reliable conclusions could be made for olanzapine due to the low quality of evidence. Monotherapy with olanzapine, quetiapine, and risperidone were shown to be superior vs placebo in reducing the overall risk of relapse; no reliable conclusions could be made for aripiprazole due to the low quality of evidence (*Lindström et al 2017*).

- One SR of 9 RCTs (N = 1289) compared the effectiveness of atypical antipsychotics to placebo, either as monotherapy or as adjunctive treatment with a mood stabilizer. Atypical antipsychotics, either alone or in combination with mood stabilizers, had superior efficacy in treating manic symptoms of mixed episodes compared to placebo in short-term trials lasting 3 to 6 weeks ($p < 0.00001$). Atypical antipsychotics also had superior efficacy in treating depressive symptoms of mixed episodes ($p < 0.001$) (*Muralidharan et al 2013*).

- The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in 6 PC and active-controlled (olanzapine) studies in adult patients, with or without psychotic features (*McIntyre et al 2009[a], McIntyre et al 2010[a], McIntyre et al 2009[b], McIntyre et al 2010[b], Szegedi et al 2011, Szegedi et al 2018*). In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in YMRS scores at week 52 of therapy (*McIntyre et al 2010[b]*). A MA of various anti-manic therapy options found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (MD, -0.3; 95% CI, -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 95% CI, 0.08 to 0.37) (*Cipriani et al 2011*). The most commonly reported adverse events reported with asenapine included sedation, dizziness, somnolence and weight gain. Of note, it was calculated that for every 9 patients treated with olanzapine over asenapine, one would experience clinically significant weight gain with olanzapine (19% vs 31%) (*McIntyre et al 2009[b]*).
- The approval of cariprazine was based on the efficacy and safety from 3 flexible-dose, DB, PC, 3-week trials (*Calabrese et al 2015, Durgam et al 2015[a], Sachs et al 2015*). A total of 1047 adult patients with acute manic or mixed episodes were administered placebo or cariprazine 3 to 12 mg per day based on tolerability. Across trials, the mean daily dose was 8.8 mg per day and the mean final dose was 10.4 mg per day (*FDA/CDER summary review 2018*). All doses were superior to placebo in reducing YMRS and CGI-S scores and a significant reduction in YMRS was observed as early as 4 days in some studies and persisted until week 3. The proportion of YMRS remitters was significantly higher in the cariprazine group than placebo (difference range, 15 to 19%) (*Calabrese et al 2015, Durgam et al 2015[a], Sachs et al 2015*). A post-hoc analysis of 3 Phase 3 RCTs evaluating cariprazine demonstrated meaningful changes from baseline on reducing symptoms of hostility, irritability, and agitation on YMRS ($p \leq 0.0001$), PANSS hostility ($p \leq 0.001$), and PANSS-Excited Component ($p \leq 0.001$) scores, in patients with manic/mixed episodes of bipolar 1 disorder (*Citrome et al 2024*).
  - Of note, doses higher than 6 mg had similar efficacy, but adverse events were less tolerable. Due to the long half-life and pharmacokinetics of the active metabolite, DDCAR, drug steady state was not achieved in trials (*FDA/CDER summary review 2018*). It is anticipated that late-onset of adverse reactions would be observed if assessed for a longer period. In bipolar studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). According to a pooled analysis (n = 1940 cariprazine-treated patients) within the FDA summary review, the most frequently observed adverse events include akathisia (14.2%), EPS (20.8%), constipation (7.6%), and nausea/vomiting (6 to 8%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 1 to 3% across cariprazine doses.
- The efficacy of the combination agent, olanzapine plus samidorphan (an opioid receptor antagonist), in the treatment of patients with bipolar I disorder is based on well-controlled studies of orally administered olanzapine (*Lybalvi prescribing information 2025)*.
  - The efficacy of olanzapine/samidorphan as monotherapy was demonstrated in 2 short-term (one 3-week and one 4-week) PC studies. The primary outcome in these studies was the change from baseline in the YMRS total score. In the 3-week study (N = 67), olanzapine (in a dose range of 5 to 20 mg/day, once daily, starting at 10 mg/day) was superior to placebo in the reduction of YMRS total score. In the 4-week study (N = 115), olanzapine (in a dose range of 5 to 20 mg/day, once daily, starting at 15 mg/day) was also superior to placebo in the reduction of YMRS total score.
  - The efficacy of olanzapine/samidorphan as adjunct to lithium or valproate was demonstrated in two 6-week, PC, combination studies (N = 175; N = 169), in which patients were randomized to receive either olanzapine or placebo, in combination with their original therapy. In both studies, olanzapine (in a dose range of 5 to 20 mg/day, once daily, starting at 10 mg/day) combined with lithium (in a therapeutic range of 0.6 to 1.2 mEq/L) or valproate (in a therapeutic range of 50 to 125 µg/mL) was superior to lithium or valproate alone in the reduction of YMRS total score.
- The efficacy and safety of risperidone 1 to 6 mg/day compared to olanzapine 5 to 20 mg/day were evaluated in a 3-week, DB, RCT in patients hospitalized for bipolar I disorder, manic or mixed episode, without psychotic features. Olanzapine and risperidone mean doses were 14.7 mg/day and 3.9 mg/day, respectively. There were no differences between groups in many outcome measures in remission or response in YMRS, 21-item Hamilton Rating Scale for

Depression (HAM-D-21), or MADRS scales. More patients given olanzapine completed the trial compared with patients given risperidone (78.7% vs 67%, respectively). In total, 62.1% of patients in the olanzapine group and 59.5% of patients in the risperidone group were categorized as responders (defined as ≥ 50% reduction in the YMRS score at endpoint). Olanzapine-treated patients experienced significantly greater elevations in liver function enzymes and weight gain (2.5 kg vs 1.6 kg). Risperidone-treated patients experienced significantly more prolactin elevations and sexual dysfunction (*Perlis et al 2006[a]*).

- The approval of iloperidone for the treatment of manic or mixed episodes of bipolar I disorder in adults was based on the results of a 4-week, MC, DB, PC trial. The trial randomized 206 patients to iloperidone 12 mg twice daily and 208 patients to placebo. The primary endpoint, mean change from baseline to week 4 in YMRS total score, demonstrated significant improvement with iloperidone (-14) compared to placebo (-10) (difference, -4; 95% CI, -5.7 to -2.25; p=0.000008) (*Torres et al 2024*).

Depressive Episodes

- Placebo-controlled trials measuring effects for the treatment of bipolar depression have demonstrated efficacy with cariprazine, lurasidone, lumateperone, quetiapine (immediate- and extended-release [ER]), and olanzapine/fluoxetine as monotherapy and adjunctive treatment (*Calabrese et al 2005, Calabrese et al 2021, Caplyta prescribing information 2023, Corya et al 2006, Loebel et al 2014[a], Loebel et al 2014[b], McElvoy et al 2010, Shelton et al 2005, Suppes et al 2010, Thase et al 2007, Tocco et al 2024, Yatham et al 2020, Young et al 2010*).
  - The approval of lumateperone for the treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate was based on the results of two 6-week, randomized, DB, PC, MC studies (*Caplyta prescribing information 2023*).
    - The efficacy of lumateperone as monotherapy was established in a 6-week RCT (N = 381) in which patients were randomized to receive lumateperone 42 mg or placebo. The primary efficacy measure was the change from baseline in MADRS total score, and the secondary endpoint was the change from baseline in CGI-BP-S total score, at week 6. At day 43, the lumateperone group demonstrated significantly greater improvement compared to the placebo group from baseline in the MADRS score (LSMD, -4.6 points; effect size, -0.56) and CGI-BP-S total score (LSMD, -0.9; effect size, -0.46). Patients treated with lumateperone experienced somnolence and nausea at a clinically meaningful greater rate compared to the placebo group (*Calabrese et al 2021).*
    - The efficacy of lumateperone as adjunctive therapy with lithium or valproate was established in a 6-week RCT (N = 529) in which patients were randomized to receive lumateperone 28 mg, lumateperone 42 mg, or placebo. The primary and secondary endpoints was the change in the MADRS total score and CGI-BP-S total score between baseline and week 6, respectively. At day 43, patients randomized to the lumateperone 42 mg group showed a statistically significant improvement compared to the placebo group from baseline in the MADRS total score (LSMD, -2.4 points) and the CGI-BP-S depression score. The treatment effect in the lumateperone 28 mg group (vs placebo group) was not statistically significant (*Suppes et al 2023*).
- Treatment with olanzapine/fluoxetine was superior to monotherapy with olanzapine and lamotrigine in achieving greater improvements in MADRS and CGI-BP (*Tohen et al 2003, Brown et al 2009*). Patients treated with olanzapine/fluoxetine had significantly greater rates of treatment response and remission compared to those receiving olanzapine monotherapy (*Tohen et al 2003*). It is not clear if quetiapine outperforms lithium in terms of treatment of bipolar depression, as various studies have produced different results (*Chiesa et al 2012, Young et al 2010*).
- Several MAs have found that lurasidone or combination treatment with olanzapine/fluoxetine may be the optimal treatment for bipolar depression compared to other treatment options. However, the overall evidence quality was considered low, trials had limited durations, and a high placebo effect was observed. Olanzapine, quetiapine, lurasidone, valproate, selective-serotonin reuptake inhibitors (SSRIs), lithium, and tricyclic antidepressants (TCAs) also appeared to be effective, but with varied acceptability (*Aronica et al 2025*, *Bahji et al 2020*, *Fornaro et al 2016, Kadakia et al 2021, Ostacher 2017*, *Silva et al 2013, Taylor et al 2014, Vieta et al 2010, Yildiz et al 2023*). No notable efficacy differences were identified between atypical antipsychotics, suggesting that lurasidone, quetiapine, and olanzapine/fluoxetine may be reasonable choices.
- An SR and MA of 4 studies found that lumateperone was more effective than placebo in reducing depressive symptoms of bipolar depression as assessed by MADRS score (SMD, -0.36; 95% CI, -0.59 to -0.13); it also showed a higher response rate (RR, 1.27; 95% CI, 1.07 to 1.51). Lumateperone did not increase the risk for extrapyramidal symptoms compared to placebo (RR, 1.46; 95% CI, 0.84 to 2.53); adverse effects reported included somnolence, dry mouth, dizziness, nausea, and headache (*Peng et al 2024*).

Major Depressive Disorder (MDD)

Key MDD Meta-Analyses

- A number of MAs and SRs have been conducted evaluating the safety and efficacy of atypical antipsychotics to augment treatment for MDD. Aripiprazole, brexpiprazole, and quetiapine ER are indicated for the treatment of MDD as adjunctive treatment; and olanzapine, in combination with fluoxetine, is indicated for the treatment of treatment-resistant depression. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.
  - One MA, which followed Cochrane methodologies, evaluated 17 trials of short-term duration ranging from 4 to 12 weeks. The analysis compared adjunctive atypical antipsychotics in combination with an SSRI/serotonin-norepinephrine reuptake inhibitor (SNRI) to SSRI or SNRI monotherapy in patients with refractory or treatment-resistant MDD. Results demonstrated that the augmentation of antidepressants with atypical antipsychotics (olanzapine, quetiapine, aripiprazole, and risperidone [Note: risperidone is not FDA-approved for this indication]) was more effective than antidepressant monotherapy in improving response and remission rates. However, adjunctive atypical antipsychotic therapy was associated with a higher discontinuation rate due to adverse effects (9.1% vs 2.6%). The attributable risk for the discontinuation rate due to adverse effects was 0.07 (number needed to harm [NNH], 16; 95% CI, 12 to 20) (*Wen et al 2014*).
  - Another MA evaluated 14 trials in patients with current MDD and an inadequate response to at least 1 course of antidepressant medication treatment. Compared to placebo, the atypical antipsychotics significantly improved remission rates: aripiprazole (odds ratio [OR], 2.01; 95% CI, 1.48 to 2.73), olanzapine/fluoxetine (OR, 1.42; 95% CI, 1.01 to 2), quetiapine (OR, 1.79; 95% CI, 1.33 to 2.42) and risperidone (OR, 2.37; 95% CI, 1.31 to 4.3). In terms of remission, all atypical antipsychotics were efficacious; however, olanzapine/fluoxetine had a higher number needed to treat (NNT) compared to other agents (NNT for olanzapine/fluoxetine, 19 vs NNT for aripiprazole, quetiapine, risperidone, 9). Treatment was associated with several adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all 4 drugs, especially olanzapine/fluoxetine). However, little to no information was provided in detail regarding the adverse events (*Spielmans et al 2013*).
- An SR and MA evaluated 33 RCTs of patients with unipolar non-psychotic depression with an inadequate response to an antidepressant receiving augmentation with an atypical antipsychotic. Compared to placebo, response rates (defined as a 50% decrease in total scores on MADRS or HAM-D depression scales) compared to placebo were significantly higher with all atypical antipsychotics evaluated except ziprasidone: olanzapine (OR 1.34, 95% CrI 1.04-1.74), cariprazine (OR 1.34, 95% CrI 1.07-1.67), brexpiprazole (OR 1.43, 95% CrI 1.21-1.70), quetiapine OR 1.58, 95% CrI 1.24-2.01), aripiprazole (OR 1.83, 95% CrI 1.53-2.19), and risperidone (2.17, 95% CrI 1.38-2.42). Additionally, cariprazine was not effective for remission (*Yan et al 2022*).
- One MA found improved response rates and reduction in depression scores with adjunctive antipsychotic therapy (ie, aripiprazole brexpiprazole, olanzapine quetiapine) compared to placebo with no significant differences in efficacy between agents (*Wang et al 2023).*
- Another SR and MA of 5 RCTs evaluated the efficacy of adjunctive cariprazine for MDD and concluded that results of included studies were conflicting with only 1 study showing significant reductions in depression symptoms, while all studies showed a non-significant improvement in remission rates (*Gill et al 2024*).

Adjunctive treatment for MDD

- Aripiprazole, brexpiprazole, cariprazine, and quetiapine ER are indicated for the treatment of MDD as adjunctive treatment. The following information describes the pivotal trials used for FDA-approval.
  - The FDA-approval of aripiprazole for the adjunctive treatment of MDD was based on 2 PC, 6-week trials in adult patients (N = 381; N = 362) who had failed 1 to 3 courses of antidepressant therapy, including an inadequate response to 8 weeks of antidepressant treatment. Aripiprazole was superior to placebo in reducing the mean MADRS total scores and remission rates. The NNT to reduce remission rates (defined as MADRS total score ≤ 10 and ≥ 50% reductions in MADRS) was 10 (*Berman et al 2007, Marcus et al 2008*). Increased incidences of akathisia were seen across trials with one trial reporting an NNH of 4 (*Marcus et al 2008*). One pooled analysis of 3 similarly designed trials (N = 409) measured the effects of aripiprazole in older vs younger patients. Results demonstrated that adjunctive aripiprazole was effective in improving depressive symptoms in older patients (50 to 67 years), and akathisia was the most commonly reported adverse event in both the older (17.1%) and younger (26%) patient groups (*Steffens et al 2011*). Other trials have demonstrated similar results (*Kamijima et al 2013, Papakostas et al*

2005). In a 12-week, randomized, DB, PC trial evaluating the safety and efficacy of aripiprazole for adjunctive MDD treatment in patients over the age of 60 years (N = 181), a higher percentage of patients achieved remission (defined as a MADRS score of ≤ 10) in the aripiprazole group as compared to placebo (44% vs 29%; p = 0.03; NNT 6.6). Similar to other studies, akathisia was the most common side effect in the aripiprazole group (26% vs 12%), and Parkinsonism was also more often reported (17% vs 2%) (*Lenze et al 2015*).

- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, pivotal, 6-week trials in adult patients as an adjunct to antidepressant therapy for MDD. In the pivotal studies, brexpiprazole 2 mg daily doses significantly reduced the mean MADRS score, the primary endpoint, compared with placebo (Study 1 [N = 353], -8.4 points with brexpiprazole 2 mg vs -5.2 points with placebo) (*Thase et al 2015[a]*). In an FDA analysis, the brexpiprazole 1 mg and 3 mg dose did not reduce the mean MADRS score; however, an FDA analysis found evidence of efficacy based on Phase 2 data, and per protocol and intention-to-treat analyses of Study 2 (*Thase et al 2015[b], FDA briefing document 2015*). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); and in schizophrenia trials were increased weight (NNH, 48) and tremor (NNH, 51) (*Correll et al 2015, Kane et al 2015[a], Thase et al 2015[b]*). An SR and MA of 4 DB, randomized, PC trials evaluating the efficacy and safety of brexpiprazole for adjunctive treatment of MDD found that it was superior to placebo for MADRS (MD, -1.76; 95% CI, -2.45 to -1.07; p < 0.00001) and the HAM-D-17 (MD, -1.21; 95% CI, -1.71 to -0.72; p < 0.00001). The RRs for response and remission were 1.57 (95% CI, 1.29 to 1.91) and 1.55 (95% CI, 1.22 to 1.96), respectively (*Yoon et al 2017*).
- The FDA-approval of quetiapine fumarate ER as an adjunct to antidepressant therapy for the treatment of MDD was based on two 6-week, PC, fixed dose trials (N = 939) in doses of 150 mg or 300 mg/day. A pooled analysis of the 2 RCTs demonstrated that quetiapine fumarate 300 mg/day (58.3%; p < 0.01; NNT, 9) significantly improved the MADRS response (defined as ≥ 50% decrease in MADRS total score), but quetiapine fumarate 150 mg/day (53.7%; p = 0.06) did not, compared to placebo (46.2%). However, MADRS remission was significantly improved for both the quetiapine fumarate 300 mg/day (36.5%; p < 0.001; NNT, 8) and 150 mg/day doses (35.6%; p < 0.01; NNT, 9) vs placebo (24.1%). The most common adverse events leading to discontinuation were somnolence and sedation. For the quetiapine fumarate 300 mg/day, 150 mg/day, and placebo groups, the mean weight gain was 1.3, 0.9, and 0.2 kg, and the incidence of EPS was 6.4, 3.8, and 4.2%, respectively (*Bauer et al 2010*).
- Two PC trials evaluated the efficacy of cariprazine in patients with MDD with an inadequate response to 1 to 3 previous antidepressants.
  - In the 6-week study, patients (N=751) were randomized to placebo or cariprazine 1.5 mg or 3 mg; both groups continued to receive baseline antidepressant treatment. The change from baseline in the MADRS score (the primary endpoint) was significantly greater with cariprazine 1.5 mg compared to placebo (-2.5, 95% CI -4.2 to -0.9) No significant difference was observed between cariprazine 3 mg compared to placebo. (*Sachs et al 2023*)
  - In the 8-week study, patients (N=808) were randomized to placebo cariprazine 1 to 2 mg daily, or cariprazine 2 to 4.5 mg per day in addition to antidepressant treatment. The change from baseline in the MADRS score (the primary endpoint) was significantly greater with cariprazine 2 to 4.5 mg compared to placebo (-2.2, 95% CI -3.7 to -0.6) No significant difference was observed between cariprazine 1 to 2 mg compared to placebo. (*Durgam et al 2016*)
- Another 6-week RCT evaluated the efficacy of cariprazine in patients with MDD and an inadequate response to ongoing therapy with 1 to 3 antidepressants. A total of 751 patients were randomized 1:1:1 to cariprazine 1.5 mg/day, cariprazine 3 mg/day, or placebo, all along with ongoing antidepressant therapy. The change from baseline to week 6 in MADRS score (the primary endpoint) was -13.8 for cariprazine 1.5 mg/day, -14.8 for cariprazine 3 mg/day, and -13.4 for placebo; differences versus placebo did not reach statistical significance (*Riesenberg et al 2023*).

Treatment-resistant depression

- Olanzapine, combined with fluoxetine, is the only agent in this class review that is indicated for treatment-resistant depression. Approval of olanzapine/fluoxetine for the acute treatment of treatment-resistant depression was based on 3 clinical trials of 8- (2 trials) and 12-week duration. Treatment with olanzapine/fluoxetine was generally more effective than monotherapy with either olanzapine or fluoxetine in improving MADRS scores; however, results in trials have been mixed (*Corya et al 2006, Shelton et al 2005, Thase et al 2007*). In one 12-week, DB trial, olanzapine/fluoxetine was compared to olanzapine, fluoxetine, or venlafaxine monotherapy. Olanzapine/fluoxetine demonstrated a statistical MADRS advantage over all monotherapy agents after week 1 which was maintained up to week 6; however, this effect was only sustainable over olanzapine monotherapy at week 12 (*Corya et al 2006*). Other trial data

demonstrated that olanzapine/fluoxetine was not significantly different compared to other antidepressants such as nortriptyline and fluoxetine monotherapy in improving MADRS scores (*Corya et al 2006, Shelton et al 2005*).

- Treatment with olanzapine/fluoxetine has consistently demonstrated increases in the incidence (≥ 10%) of weight gain, increased appetite, somnolence, and dry mouth. Additional adverse events have varied in trials. Compared to fluoxetine and olanzapine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included peripheral edema and hypersomnia, which were significantly higher than that of fluoxetine monotherapy ($p < 0.001$) (*Thase et al 2007*). Compared to olanzapine, fluoxetine, or venlafaxine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included dizziness, asthenia, peripheral edema, and headache. More patients in the combination therapy group discontinued due to weight gain (*Corya et al 2006*). Compared to fluoxetine, olanzapine, and nortriptyline monotherapy, the most common adverse events for olanzapine/fluoxetine combination therapy (incidence ≥ 10%) were asthenia, headache, anxiety, tremor, nervousness, insomnia, and nausea (*Shelton et al 2005*).

Schizophrenia and/or Schizoaffective Disorder

- All oral atypical antipsychotic agents in this class review are indicated for use in schizophrenia with the exception of pimavanserin and the combination agent, olanzapine/fluoxetine. Clozapine is the only agent indicated for treatment-resistant schizophrenia. Clozapine and paliperidone products, excluding Invega Trinza and Invega Hafyera, are indicated for the treatment of schizoaffective disorder. The following is a summary of MAs and SRs, landmark trials in schizophrenia, and study evidence related to newer atypical antipsychotic agents (ie, asenapine, brexpiprazole, cariprazine, iloperidone, lurasidone, and olanzapine/samidorphan).
- The FDA approval of Cobenfy (xanomeline/trospium) was based on the safety and efficacy established in 2 Phase 3 trials, EMERGENT-2 and EMERGENT-3. Both studies were identically designed, 5-week, DB, PC, MC, RCTs in adults with schizophrenia who had a recent worsening of psychosis requiring a hospital admission, PANSS score of ≥ 80, and a CGI-S of ≥ 4. Both studies met the primary endpoint of the change from baseline in PANSS total score at week 5 (*Kaul et al 2024[a]*,*Kaul et al 2024[b]).* In EMERGENT 2 (N = 252), the change from baseline in PANSS score was -21.2 with xanomeline/trospium vs -11.6 with placebo (least squares mean [LSM] difference, -9.6; 95% CI, -13.9 to -5.2; $p < 0.0001$; Cohen's d effect size = 0.61). In EMERGENT 3 (N = 256), the change from baseline in PANSS score was -20.6 with xanomeline/trospium vs -12.2 with placebo (LSM difference, -8.4; 95% CI, -12.4 to -4.3; $p < 0.001$; Cohen d effect size = 0.60).
  - In a pooled analysis of 3 studies (EMERGENT-1 [Phase 2], EMERGENT-2, and EMERGENT-3), xanomeline/trospium demonstrated a significantly greater reduction in PANSS score at 5 weeks compared to placebo (-19.4 vs 19.6; $p < 0.0001$; Cohen's d = 0.65). The most common AEs across these studies (at least twice the placebo rate) included nausea, constipation, dyspepsia, vomiting, and dry mouth (*Kaul et al 2024[c]).*
  - Two, 52-week, OL, extension studies (EMERGENT-4 and EMERGENT-5) are currently underway.
    - EMERGENT-4 (N =110) evaluated the long-term safety, tolerability, and efficacy xanomeline/trospium in adults with schizophrenia who previously completed the treatment period of EMERGENT-2 or EMERGENT-3, while EMERGENT-5 is evaluating patients with a new diagnosis of schizophrenia. Published data are not yet available (*clinicatrials.gov [NCT04659174, NCT04820309], Bristol Myers Squibb press release 2024*).
- A report by the Institute for Clinical and Economic Review (ICER) completed an indirect network MA (N = 33) evaluating the comparative efficacy of xanomeline/trospium vs 3 SGAs (aripiprazole, risperidone, olanzapine) for the treatment of schizophrenia (xanomeline/trospium, 3 trials; aripiprazole, 4 trials; olanzapine, 13 trials; risperidone, 8 trials; head-to-head, 5 trials). All trials were 3 to 8 weeks in duration and included patients with a diagnosis of schizophrenia who were hospitalized with an acute exacerbation of symptoms. Outcomes evaluated were PANSS total score, PANSS response, weight gain, and all-cause discontinuation (*Tice et al 2024*).
  - Indirect analysis found that all antipsychotics had significant reductions in PANSS total score compared to placebo, with no statistically significant differences between agents (xanomeline/trospium, -9.78; aripiprazole, -8.38; olanzapine, -10.67; risperidone, -8.05). Similarly, all 4 agents had a statistically significant PANSS response rate compared to placebo (xanomeline/trospium, 2.03; aripiprazole, 1.37; olanzapine, 1.66; risperidone, 1.96).
  - In terms of weight change from baseline, xanomeline/trospium and aripiprazole demonstrated lower rates of weight gain vs placebo compared to olanzapine and risperidone vs placebo (xanomeline/trospium, -0.37; aripiprazole, 0.26; olanzapine, 2.49; risperidone, 1.69).
  - In terms of discontinuation rates, xanomeline/trospium had higher all-cause discontinuation than all 3 SGAs and placebo; however, only comparisons with olanzapine and risperidone were statistically significant.

- An SR and network MA of 45 studies (N = 11,238) evaluated the long-term efficacy of antipsychotic drugs in acutely ill patients with schizophrenia. Included trials were at least 6 months in duration. In terms of overall symptom improvement (primary endpoint), olanzapine was on average more efficacious than ziprasidone (SMD = 0.37), asenapine (SMD = 0.33), iloperidone (SMD = 0.32), paliperidone (SMD = 0.28), haloperidol (SMD = 0.27), quetiapine (SMD = 0.25), aripiprazole (SMD = 0.16), and risperidone (SMD = 0.12). However, the impact of olanzapine on weight gain was higher than all other antipsychotics (*Leucht et al 2023*).
- Based on a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 113 measured efficacy and safety in adults with schizophrenia or schizophrenia-related psychoses. Compared to haloperidol, there was no difference in PANSS (and/or Scale for the Assessment of Positive Symptoms [SAPS]) score for positive symptoms for aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. Outcomes measuring negative symptoms demonstrated a significant difference in PANSS scores favoring aripiprazole for 1701 patients in 3 trials, risperidone for 4043 patients in 20 trials, and olanzapine-treatment for 3742 patients in 14 trials. When compared with haloperidol, risperidone yielded lower relapse rates for 1405 patients in 6 trials and olanzapine provided better response rates for 4099 patients in 14 trials and remission rates for 582 patients in 3 trials. The most common adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be equally effective to treatment with the atypical antipsychotics in terms of positive symptoms; however, for negative symptom scores aripiprazole, risperidone, and olanzapine may be better options for treatment. Olanzapine and risperidone may be better options when remission/relapse rates are considered (*Abou-Setta et al 2012*).
- One large Bayesian MA of 212 RCTs compared 15 antipsychotic medications for efficacy and safety outcomes in patients with schizophrenia or related disorders in short-term trials. The primary endpoint was efficacy measured by mean overall change in symptoms after 6 weeks and all antipsychotics were significantly more effective than placebo. Clozapine had the greatest MD in the change in symptom scores and was significantly superior to all other antipsychotics, including olanzapine and risperidone which have demonstrated some efficacy in treatment-resistant patients. After clozapine, olanzapine and risperidone were significantly more effective than the other antipsychotics apart from paliperidone. Overall, effect sizes were small and there were some inconsistencies between results, but the authors did not consider that this was substantial enough to change the results. Safety assessment for the FDA-approved agents indicated that EPS was lowest for clozapine and highest for haloperidol; sedation was lowest for risperidone and highest for clozapine; weight gain was lowest for haloperidol and highest for olanzapine; prolactin increase was lowest for aripiprazole and highest for paliperidone; and QT prolongation was lowest for lurasidone and highest for ziprasidone. The authors concluded that the properties of antipsychotic drugs differed greatly among agents and that treatment should be fit to individual patients' needs. As the MA had many limitations, including substantial differences between studies, and uncertainties surround indirect comparisons, generalizability of the findings and authors' conclusions are limited. This is similar to many large atypical antipsychotic MAs (*Leucht et al 2013*).
- One Cochrane SR evaluated aripiprazole vs other atypical antipsychotics for the treatment of schizophrenia. Differences in efficacy between aripiprazole and other atypical antipsychotics (olanzapine, risperidone, and ziprasidone) demonstrated no advantage in terms of overall global state (defined as MD in CGI-S score) or mental state (defined as MD total change in PANSS score). When compared with any one of several new generation antipsychotic drugs in one RCT (N = 523), the aripiprazole group showed improvement in energy, mood, negative symptoms, somnolence, and weight gain. More nausea was seen in patients given aripiprazole (N = 2881; RR, 3.13; 95% CI, 2.12 to 4.61). Weight gain with aripiprazole-treatment was less common (N = 330; RR, 0.35; 95% CI, 0.19 to 0.64). Attrition ranged from 30% to 40% (no differences between groups). Due to the high attrition rates, validity is limited, thereby making it difficult to make strong conclusions. There are limited data on the safety and efficacy of aripiprazole. Based on current available evidence, efficacy of aripiprazole appears to be similar and there may be benefits in terms of weight gain, but there appears to be an increased incidence of nausea compared to other agents (*Khanna et al 2016*).
- One Cochrane SR evaluated quetiapine compared to other atypical antipsychotics for the treatment of schizophrenia. Efficacy and safety were evaluated in 5971 patients across 35 RCTs. For the primary efficacy endpoint, PANSS total score, the comparator drugs may be more effective than quetiapine, but the clinical meaning of these data is unclear. There were no significant differences in efficacy between quetiapine and clozapine, but quetiapine was associated with fewer adverse events. Quetiapine demonstrated fewer movement disorders compared to risperidone (RR, 0.5;

95% CI, 0.36 to 0.69), olanzapine (RR, 0.51; 95% CI, 0.32 to 0.81), and paliperidone (RR, 0.64; 95% CI, 0.45 to 0.91). There are limited studies; however, data provide evidence that quetiapine-treated patients may need to be hospitalized more frequently than those taking risperidone or olanzapine. Quetiapine may be slightly less effective than risperidone and olanzapine in reducing symptoms, and it may cause less weight gain and fewer side effects and associated problems (such as heart problems and diabetes) than olanzapine and paliperidone, but more than risperidone and ziprasidone (*Asmal et al 2013*).

- Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, MC study initiated by the NIMH to examine the effectiveness of SGAs compared to FGAs in patients with chronic schizophrenia. It was intended to include patients treated in typical clinical settings and to reflect typical clinical practice in which individuals with schizophrenia may require multiple medication trials before finding one that is adequately both efficacious and tolerable. The study design allowed for patients who discontinued 1 study antipsychotic drug to enter subsequent phases of the study to receive additional antipsychotic medications (*Lieberman et al 2005, Stroupe et al 2006, Stroupe et al 2009*). An analysis was done in patients who discontinued treatment with olanzapine, quetiapine, risperidone or ziprasidone and randomly assigned to open-label treatment with clozapine, or DB treatment with another atypical antipsychotic not previously received (eg, olanzapine, quetiapine, risperidone). For the primary outcome of Calgary Depression Scale for Schizophrenia, clozapine was found to be more effective than quetiapine for depressive symptoms, but comparable efficacy to olanzapine and risperidone (*Nakajima et al 2015*).
- An SR and MA of 402 RCTs (N = 53,463) evaluated the comparative efficacy of 32 antipsychotics for the treatment of adults with multi-episode schizophrenia. For the majority of medications, treatment was associated with a statistically significant reduction in overall symptoms vs placebo, and there were few significant differences between drugs. Clozapine, olanzapine, and risperidone exhibited greater efficacy in reducing negative symptoms than many other antipsychotic medications for overall symptoms, with the greatest benefit noted with clozapine. Overall, the authors concluded that antipsychotics vary more in side effect profile than efficacy, thus choice of medication should be individualized for each patient (*Huhn et al 2019*).
- The efficacy of asenapine in the treatment of schizophrenia in adults was evaluated in 4 published, randomized, DB, PC, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from 6 weeks to 1 year (*Kane et al 2011, Kane et al 2010[a], Potkin et al 2007, Schoemaker et al 2010*). Asenapine was associated with statistically significant improvement in PANSS scores from baseline compared to placebo, starting from week 2 of therapy. CGI-I and CGI-S scores were also significantly improved with asenapine therapy compared to placebo. Moreover, an extension study demonstrated a reduced risk of relapse associated with continuation of asenapine therapy (*Kane et al 2011*). However, a direct-comparison study suggests that asenapine is less effective than olanzapine in terms of changes from baseline in PANSS and CGI-S scores. Furthermore, study discontinuation due to inadequate efficacy was noted in only 14% of patients receiving olanzapine compared to 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine (*Shoemaker et al 2010*). In another study, while 17% of patients receiving risperidone experienced a weight gain of at least 7% from baseline, 9% of patients in the asenapine group were noted to exhibit clinically significant weight gain (*Potkin et al 2007*).
- The approval of Secuado was based on the unpublished HP-3070-GL-04 clinical trial (N = 614), a 6-week, Phase 3, DB, PC, multinational, inpatient RCT. Patients with schizophrenia in an episode of acute exacerbation lasting ≤ 8 weeks and length of hospitalization ≤ 21 days were randomized to receive Secuado 3.8 mg (n = 204), Secuado 7.6 mg (n = 204), or placebo (n = 206) transdermal system once daily. Compared to placebo, both doses of Secuado demonstrated statistically significant improvements in PANSS total score ($p < 0.001$ for 3.8 mg; $p = 0.003$ for 7.6 mg) and CGI-S ($p < 0.001$ for both doses) (*FDA Secuado review 2018, Secuado prescribing information 2023*).
- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, 6-week trials in adults with schizophrenia. In the pivotal studies, brexpiprazole 2 mg and 4 mg daily doses significantly reduced the PANSS score (-20.73 and -19.65 vs -12.01 points with placebo), the primary endpoint, compared with placebo; however, in the BEACON trial, only the brexpiprazole 4 mg dose significantly reduced the PANSS score (-20 vs -13.53 points with placebo) (*Correll et al 2015; Kane et al 2015[a]*). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); in schizophrenia trials, the most common adverse effects were increased weight (NNH, 48) and tremor (NNH, 51) (*Correll et al 2015, Kane et al 2015[a], Thase et al 2015[b]*). The safety and efficacy of brexpiprazole for maintenance therapy of schizophrenia was evaluated in a randomized, DB, MC, PC trial. It enrolled 524 patients with an acute exacerbation of psychotic symptoms to be stabilized on brexpiprazole 1 to 4 mg daily. Patients who achieved stabilization (criteria including PANSS total score ≤ 70, CGI-S score ≤ 4 [moderately ill], no current suicidal behavior, or violent or aggressive behavior) for 12 weeks then entered a

52-week maintenance phase where they were randomized to their stabilization dose of brexpiprazole (N = 97) or placebo (N = 105). The co-primary endpoints were time to exacerbation of psychotic symptoms or impending relapse, defined as worsening of CGI-I and PANSS scores, hospitalization due to worsening of psychotic symptoms, suicidal behavior, or violent/aggressive behavior. In the maintenance phase, 13.5% of patients in the brexpiprazole group experienced impending relapse vs 38.5% of placebo patients ($p < 0.0001$) and time to impending relapse was statistically significantly lower (hazard ratio [HR], 0.34; $p = 0.0008$). However, based on results of an interim analysis, the trial was terminated early. Only a small number of patients were exposed to brexpiprazole for the prescribed 52 weeks and, therefore, conclusions cannot be drawn for long-term use (*Fleischhacker et al 2016*).

- The efficacy and safety of cariprazine in schizophrenia were demonstrated in 3 DB, randomized, PC, 6-week trials (*Durgam et al 2014, Durgam et al 2015[b], Kane et al 2015[b]*). A total of 1792 adult patients with acute exacerbation of schizophrenia were administered placebo or cariprazine 1.5 to 9 mg per day. Two trials were fixed-dose studies and included active comparators, risperidone 4 mg and aripiprazole 10 mg, to assess sensitivity; one study was a flexible-dose study with no active comparator. In the flexible-dose study, the mean daily dose ranged from 5 to 8 mg per day (*Kane et al 2015[b]*). All doses were superior to placebo in reducing PANSS and CGI-S scores and a significant PANSS reduction was observed as soon as 7 days for the higher doses and 2 to 3 weeks for the lower doses (*FDA/CDER summary review 2015*). Of note, higher doses do result in quicker control of symptoms; however, if high doses continue resulting in accumulation of the active metabolite DDCAR, it is not clear how this may influence safety results. Delayed incidences of akathisia occurred. According to pooled analysis (n = 1317 cariprazine-treated patients) within the FDA clinical summary, the most common adverse events reported in schizophrenia trials were EPS (28.5%) and akathisia (11.2%) (*FDA/CDER summary review 2015*). The akathisia observed at cariprazine doses ≤ 6 mg is comparable to those observed with aripiprazole, but accumulation of the DDCAR metabolite may result in later-onset effects. In schizophrenia studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 8 to 17% across cariprazine doses. In an OL 48-week extension (N = 97) of a 6-week trial, safety and tolerability were found to be maintained. The most common adverse events were akathisia (14%), insomnia (14%), and weight gain (11.8%) (*Durgam et al 2014, Durgam et al 2017*). Another study evaluated cariprazine for maintenance therapy for schizophrenia relapse in 765 patients. A flexible-dose, OL, 8-week, run in phase was followed by a 12-week, fixed-dose, stabilization phase. Patients completing the OL phase (N = 264) entered a DB phase and received cariprazine (3 to 9 mg/day), or placebo for up to 72 weeks. During the DB phase, 24.8% of the cariprazine group experienced relapse vs 47.5% of the placebo group (HR, 0.45; 95% CI, 0.28 to 0.73). Time to relapse was statistically significantly longer for the cariprazine group vs placebo (25^{th} percentile time to relapse, 224 vs 92 days, respectively; $p < 0.001$). The long-term safety profile of cariprazine was found to be consistent with findings from previous trials (*Durgam et al 2016).*
- Iloperidone has been studied as monotherapy for the treatment of adults with an acute or subacute exacerbation of schizophrenia. Three 6-week, randomized, DB, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo (*Potkin et al 2008*). Another 4-week, placebo- and active comparator- (ziprasidone) controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo (*Cutler et al 2008*). Two analyses of these 4 studies corroborated earlier data, finding iloperidone more effective than placebo in terms of improvement from baseline in various subscales of the PANSS scale and BPRS scores (*Citrome et al 2011, Citrome et al 2012*). The long-term efficacy and safety of iloperidone in the treatment of schizophrenia was evaluated in an MA that pooled the follow-up data (up to 52 weeks) from 3 prospective RCTs. The MA found the long-term efficacy of iloperidone, assessed via the time to relapse endpoint, to be comparable to haloperidol ($p = 0.85$), with a more favorable long-term safety profile (*Kane et al 2008*). Moreover, another MA designed to evaluate the short-term safety of iloperidone found the following dose-related adverse effects: dry mouth, dizziness, somnolence and dyspepsia. EPS was noted in association with iloperidone but was more common with haloperidol and risperidone therapies. Iloperidone was also associated with QTc prolongation and weight gain (1.5 to 2.1 kg) (*Weiden et al 2008*). The efficacy of iloperidone for relapse-prevention during maintenance phase of schizophrenia treatment was evaluated in a DB, PC, randomized withdrawal study. Patients were not blinded and were stabilized for 24 weeks. If clinically stable for 12 weeks, they were then randomized to iloperidone (8 to 24 mg/day) (N = 153) or placebo (N = 150) for 26 weeks. The primary endpoints were time to relapse and proportion of patients experiencing relapse (defined as hospitalization due to worsening schizophrenia, worsening of PANSS and CGI-I scores, suicidal or aggressive behavior, or treatment escalation [ie, dose increases or additional medications]). The trial was stopped early due to superior iloperidone relapse prevention. Time to relapse was statistically significantly longer with iloperidone vs placebo (140 vs 95 days, respectively; $p < 0.0001$). The relapse rate for placebo was 64% vs 17.9% for iloperidone ($p < 0.0001$). The safety was comparable to

other trial results, with dizziness, insomnia, headache, dry mouth, and somnolence being the most common adverse events. Weight gain ≥ 7% occurred in 25.2% of iloperidone-treated patients in the relapse-prevention phase. Mean change in QTcF from baseline was 4.9 ms in the iloperidone group (vs 1 ms in placebo) during the relapse-prevention phase. Rates of EPS (2.5% in stabilization phase/1.3% in relapse-prevention phase) and akathisia (3.7% and 1%, respectively) were consistently low in iloperidone-treated patients as well (*Weiden et al 2016*).

- An SR and MA of 3 studies evaluating the efficacy and safety of lumateperone for the treatment of patients with schizophrenia found no difference from the placebo group with regard to improvement in PANSS scores, but found higher response rates compared to placebo (RR, 1.44; 95% CI, 1.12 to 1.86). Lumateperone did not increase the risk for extrapyramidal symptoms compared to placebo (RR, 1.46; 95% CI, 0.84 to 2.53); adverse effects reported included somnolence, dry mouth, dizziness, nausea, and headache (*Peng et al 2024*). The efficacy of lumateperone was also evaluated in a Phase 2 and two Phase 3 PC trials. All 3 trials enrolled patients who had demonstrated prior response to antipsychotic drug therapy (ie, not treatment-naïve and not treatment-resistant) who were experiencing an acute exacerbation of psychosis starting within the previous 4 weeks.
  - The phase 2 trial (Study 005) was a 4-week RCT enrolling 335 patients (*Lieberman et al 2016*). Patients received lumateperone 42 mg daily (the marketed dose), lumateperone 84 mg daily, risperidone 4 mg daily, or placebo.
    - The primary endpoint was the change in total score on the PANSS. Results on the PANSS demonstrated LS mean changes of -7.4, -13.2, -8.3, and -13.4 in the placebo, lumateperone 42 mg, lumateperone 84 mg, and risperidone 4 mg groups, respectively. The difference between lumateperone 42 mg and placebo was -5.8 (95% CI, -10.5 to -1.1; multiplicity-adjusted p = 0.04), which was larger than that of the higher dose tested and comparable to that of risperidone.
  - The first phase 3 trial (Study 301) was a 4-week RCT enrolling 450 patients (*Correll et al 2020*). Patients received lumateperone 42 mg daily, lumateperone 28 mg daily, or placebo.
    - Results for the PANSS total score (the primary endpoint) demonstrated LS mean changes of -10.3, -14.5, and -12.9 in the placebo, lumateperone 42 mg, and lumateperone 28 mg groups, respectively. The difference between lumateperone 42 mg and placebo was -4.2 (95% CI, -7.8 to -0.6; multiplicity-adjusted p = 0.05).
    - The key secondary endpoint was the change in the CGI-S score. Results demonstrated LS mean changes of -0.5 for the placebo group and -0.8 for both lumateperone groups. The difference between lumateperone 42 mg and placebo was -0.3 (95% CI, -0.5 to -0.1; multiplicity-adjusted p = 0.05).
  - The other Phase 3 trial (Study 302) enrolled 696 patients (*FDA Caplyta multidisciplinary review 2019*). It had a similar design to the previous studies but had a duration of 6 weeks rather than 4 weeks. Patients received lumateperone 42 mg, lumateperone 14 mg, risperidone 4 mg, or placebo.
    - Results on the PANSS total score did not demonstrate a statistically significant efficacy benefit for either lumateperone dose vs placebo, with differences of 0.5 (95% CI, -2.9 to 3.8) and 0.1 (95% CI, -3.4 to 3.5) for the 42 mg and 14 mg doses, respectively. A significant difference for risperidone vs placebo was demonstrated (-5.4 [95% CI, -8.9 to -1.9]).
    - Results for secondary endpoints were not reported; the FDA reviewers deemed them irrelevant for discussion based on failure of the primary endpoint.
- Lurasidone was investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in 2 PC, 6-week studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily. In PC studies, lurasidone 40, 80, or 120 mg once daily was associated with significant improvements from baseline in PANSS and the BPRS scores, compared to placebo (*Meltzer et al 2011, Nakamura et al 2009*). The 2 direct-comparison studies demonstrated comparable improvements in the lurasidone and ziprasidone groups in terms of the reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-S scores, and several cognition scales. Likewise, the 2 groups were comparable in terms of rates of discontinuation for any reason and discontinuation due to adverse events (*Harvey et al 2011, Potkin et al 2011*). Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone (p = 0.046). Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant electrocardiogram abnormality. Extrapyramidal adverse events were noted in 3.3% of patients in the ziprasidone group and in 3.3% of patients receiving lurasidone (*Potkin et al 2011*). The efficacy of lurasidone in maintenance treatment was evaluated in a DB, PC, RCT. Patients (N = 676) with schizophrenia experiencing an acute exacerbation entered into an OL stabilization phase for 12 to 24 weeks. Patients achieving stabilization for 12 weeks (N = 285) were randomized into a 28-week, DB phase to receive lurasidone (40 to 80 mg/day) or placebo. The probability of relapse at the 28-week point was 42.2% vs 51.2% in the lurasidone and placebo groups, respectively (NNT = 12). Lurasidone statistically significantly delayed the time to relapse vs placebo

(p = 0.039). In patients receiving lurasidone in both the OL and DB phases, the most common adverse events were akathisia (16.7%), insomnia (12.5%), and headache (11.8%) (*Tandon et al 2016*).

- A 6-week, DB, MC, RCT (N =444) demonstrated the noninferiority of lurasidone and risperidone for the primary endpoint of change in PANSS total score (MD, -31.2 and -34.9, respectively) (*Feng et al 2020*).
- The efficacy of olanzapine/samidorphan in the treatment of schizophrenia was evaluated in a 4-week, randomized, DB, placebo- and active-controlled study (N = 401). Patients were randomized to receive olanzapine/samidorphan, olanzapine monotherapy, or placebo. The primary and key secondary efficacy endpoint assessed was the change in PANSS total score and CGI-S score between baseline and week 4, respectively. The study sought to compare olanzapine/samidorphan with placebo, not with olanzapine. Treatment with olanzapine/samidorphan, in comparison with placebo, resulted in significant improvements in the PANSS total score (LS mean ± standard error [SE], -6.4 ± 1.8; p < 0.001) and CGI-S score (LS mean ± SE, -0.38 ± 0.12; p = 0.002) from baseline to week 4. Olanzapine treatment resulted in similar improvements: PANSS (LS mean ± SE, -5.3 ± 1.84; p = 0.004) and CGI-S (LS mean ± SE, -0.44 ± 0.12; p < 0.001). Weight gain, dry mouth, somnolence, headache, and anxiety were the most common AEs (≥ 5%) with active treatment (*Potkin et al 2020*).
  - The safety and tolerability trends of olanzapine/samidorphan continued in a 52-week, long-term extension study which enrolled 265 patients, of which 167 patients completed the extension. Olanzapine/samidorphan was generally well tolerated; weight, waist circumference, fasting lipid and glycemic parameters, and schizophrenia symptoms remained stable over 52 weeks (*Kahn et al 2021*).
  - Additionally, a MA of 4 RCTs compared short-term weight and cardiometabolic changes between olanzapine/samidorphan and olanzapine. The primary outcomes were weight changes and all-cause dropout rates. The heterogeneous data demonstrated that the whole-sample, pooled standardized mean differences (SMD) of weight change was not significantly different between the olanzapine/samidorphan and olanzapine groups (SDM, -0.19; 95% CI, 0.45 to 0.07; $I^2 = 75\%$). The whole-sample, pooled RR of all-cause dropout rates (RR, 1.02; 95% CI, 0.84 to 1.23; $I^2 = 0\%$) was also not significant different between the olanzapine/samidorphan and olanzapine groups (*Srisurapanont et al 2021*).

Parkinson's Disorder Psychosis

- Pimavanserin is the only oral atypical antipsychotic FDA-approved for the treatment of hallucinations and delusions associated with PD psychosis. The FDA-approval of pimavanserin was based on a 6-week PC, DB, RCT of 199 patients evaluating the safety and efficacy of pimavanserin 40 mg once daily. Compared to placebo, the LSMD of total PD adapted SAPS (SAPS-PD) score change from baseline at day 43 favored pimavanserin 40 mg (-3.06; 95% CI, -4.91 to -1.20; p = 0.0014). The most common adverse events in the pimavanserin vs the placebo group included urinary tract infection (13 vs 12%), falls (11 vs 9%), peripheral edema (7 vs 3%), hallucinations (7 vs 4%), nausea (6 vs 6%), confusion (6 vs 3%), and headache (1 vs 5%) *(Cummings et al 2014).*
- One MA of pimavanserin included 4 RCTs measuring the efficacy and safety compared to placebo in patients with PD psychosis. Pimavanserin was associated with a significant decrease in SAPS-hallucination and delusions score compared to placebo (weighted MD,-2.26; 95% CI, -3.86 to -0.67; p = 0.005). Adverse effects were not significantly different from placebo, except pimavanserin was associated with a significantly lower incidence of orthostatic hypotension (RR, 0.33; 95% CI, 0.15 to 0.75; p = 0.008) *(Yasue et al 2016, Bozymski et al 2017)*.
- In a more recent MA, pimavanserin significantly improved CGI-S score vs placebo (-0.5; 95% CI, -0.9 to -0.2) in patients with PD psychosis; change in motor function based on the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) did not reach statistical significance (0.2; 95% CI, -1.4 to 1.9) *(Iketani et al 2020*). Other agents included in this MA are not FDA-approved for PD psychosis.

Agitation associated with Dementia due to Alzheimer's Disease

- Two randomized, DB, PC studies evaluated the efficacy of brexpiprazole in patients with agitation in Alzheimer's disease. Both studies evaluated change from baseline in scores from the Cohen-Mansfield Agitation Inventory (CMAI). In study 1 (N=433), patients received brexpiprazole 1 or 2 mg daily or placebo. At 12 weeks, a significant reduction from the baseline CMAI score was observed with brexpiprazole 2 mg compared to placebo (MD, -3.77, 95% CI -7.38 to -0.17). No difference was observed between placebo and brexpiprazole 1 mg. In Study 2 (N=270), patients received either a flexible dose of brexpiprazole (0.5 to 2 mg daily) or placebo. The average brexpiprazole dose was 1.54 mg daily. No significant difference in change in the CMAI score was observed between groups. Common adverse events in both studies included headache and somnolence (*Grossberg et al 2020*).

- Another Phase 2/3 MC, DB, PC, parallel-group study comparing brexpiprazole 1 mg, 2 mg, or placebo for 10 weeks in patients with agitation due to Alzheimer's disease. Both the 1 mg and 2 mg treatment groups had greater improvements in the CMAI compared to placebo (LSMD, -3.7; 95% CI, -6.8 to -0.7; p=0.0175 for the 1 mg group and LSMD, -7.2; 95% CI, -10 to -4.3; p<0.0001 for the 2 mg group). Common adverse events reported in the brexpiprazole groups included somnolence, bradykinesia, insomnia, salivary hypersecretion, muscle rigidity, gait disturbance, fall, pyrexia, sedation complications, contusion, and decreased appetite (*Nakamura et al 2024*).

LAI Atypical Antipsychotics:

Bipolar Disorder

- Risperdal Consta (risperidone microspheres), Rykindo (risperidone once-every-2-weeks injection), Abilify Maintena (aripiprazole ER), and Abilify Asimtufii (aripiprazole once-every-2-months) are the only LAIs FDA-approved for bipolar I disorder in adults.
  - Abilify Maintena (aripiprazole ER) LAI is indicated as maintenance monotherapy treatment (*Calabrese et al 2017*). The efficacy of Abilify Asimtufii (aripiprazole LAI) for the treatment of bipolar 1 disorder in adults is based on adequate and well-controlled studies of Abilify Maintena (aripiprazole ER) (*Abilify Asimtufii prescribing information 2025*).
  - Risperdal Consta (risperidone microspheres) LAI is indicated as monotherapy or in combination with lithium or valproate for maintenance therapy. Compared to placebo, risperidone LAI has demonstrated superior efficacy in acute and non-acute patients with similar safety effects to that of oral risperidone (*Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*). The efficacy of Rykindo (risperidone once-every-2-weeks injection) for the treatment of bipolar 1 disorder in adults as mono therapy and adjunctive therapy is based on adequate and well-controlled studies of intramuscular risperidone LAI (*Rykindo prescribing information 2025).*
- In a DB, PC, 52-week randomized withdrawal study (N = 266), aripiprazole ER injection significantly delayed recurrence of any mood episode compared with placebo, with a 55% reduction in risk of experiencing a mood episode over 1 year (HR, 0.45; 95% CI, 0.3 to 0.68). The proportion of patients experiencing recurrence of a manic episode was significantly less with aripiprazole ER injection (9.1% vs 30.1%); however, the recurrence rate for either depressive or mixed episodes was not different between treatment groups. After acute treatment of a manic episode with oral aripiprazole and transition to monotherapy with aripiprazole ER 400 mg intramuscularly (IM) once every 4 weeks (reduction to 300 mg was allowed for adverse reactions) for a 12-week stabilization period, patients were randomized to continue aripiprazole IM or withdrawal to placebo for 52 weeks. Of note, a large proportion of patients did not complete the study. Of the 266 randomized patients, 48.1% (N = 64) of the aripiprazole group and 28.6% (N = 38) of the placebo group completed the study. Treatment-emergent adverse effects that lead to discontinuation more commonly occurred with placebo (25.6 vs 17.4%); those that occurred more often with aripiprazole included weight gain of 7% or greater (18 vs 12.9%), akathisia (21.2 vs 12.8%), and anxiety (6.8 vs 4.5%) (*Calabrese et al 2017*).
- For maintenance therapy, risperidone LAI monotherapy has demonstrated inconsistent results regarding the endpoint of delayed time to recurrence of any mood episode compared to placebo (*Quiroz et al 2010, Vieta et al 2012*). When risperidone LAI was used in combination with mood stabilizers (eg, lithium and valproate), antidepressants, or anxiolytics, the time to relapse was significantly longer with fewer proportions of patients relapsing compared to placebo (*Macfadden et al 2009*). An exploratory post hoc analysis showed that the time to recurrence of any mood episode was also significantly longer with oral olanzapine compared with risperidone LAI (p = 0.001) (*Vieta et al 2012*). The adverse effect profile of LAI therapy is not fully understood; however, EPS, weight gain, hyperprolactinemia, and cardiovascular events were observed in risperidone LAI therapy trials (*Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*).

Schizophrenia

All 13 LAI atypical antipsychotics are FDA-approved for the treatment of schizophrenia in adults. These agents include Abilify Maintena (aripiprazole ER), Aristada and Aristada Initio (aripiprazole lauroxil), Abilify Asimtufii (aripiprazole once-every-2-months), Zyprexa Relprevv (olanzapine pamoate ER), Erzofri (paliperidone palmitate once-a-month injection), Invega Sustenna (paliperidone palmitate once-a-month injection), Invega Trinza (paliperidone palmitate once-every-3-months injection), Invega Hafyera (paliperidone palmitate once-every-6-months injection), Risperdal Consta (risperidone microspheres), Perseris (risperidone once-a-month injection), Uzedy (risperidone once-monthly-or-every-2-months), and Rykindo (risperidone once-every-2-weeks injection).

- Invega Sustenna and Erzofri are FDA-approved for the treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants.
- A number of MAs and SRs have been conducted evaluating LAI atypical antipsychotics compared to oral antipsychotics for the treatment of schizophrenia. Comparative effectiveness data between LAI atypical antipsychotics are lacking, and there is insufficient evidence to draw firm conclusions. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.
- One MA of atypical antipsychotics included 13 RCTs measuring the efficacy and safety of LAI atypical antipsychotics vs oral antipsychotics or placebo in patients with schizophrenia. LAI atypical antipsychotics were not associated with a significant decrease in the PANSS total score from baseline from oral antipsychotics ($p = 0.33$); therefore, both formulations had similar efficacy. No additional significant differences were noted. The LAI atypical antipsychotics were associated with a higher incidence of EPS compared to placebo ($p < 0.001$) and oral antipsychotics ($p = 0.048$) (*Fusar-Poli et al 2013*).
- One recent SR and MA compared LAIs and oral antipsychotics for schizophrenia in 32 RCTs, 65 cohort studies, and 40 pre-post studies. The primary outcome was assessed in studies that reported on hospitalization or relapse. The risk of hospitalization or relapse, with preferential use of hospitalization over relapse, was significantly lower with LAIs than oral antipsychotics in each of the 3 study designs (RCTs: 29 studies, n = 7833, RR, 0.88 [95% CI, 0.79 to 0.99], $p = 0.033$; cohort studies: 44 studies, n = 106136, RR, 0.92 [95% CI, 0.88 to 0.98], $p = 0.0044$; pre-post studies: 28 studies, n = 17876, RR, 0.44 [95% CI, 0.39 to 0.51], $p < 0.0001$). For all secondary outcomes related to effectiveness, efficacy, safety, cognitive function, quality of life, and other outcomes (including hospitalization rate, hospitalization days, and, and adherence), LAIs were more beneficial than oral antipsychotics in 60 of 328 comparisons (18.3%), not different in 252 comparisons (76.8%), and less beneficial in 16 comparisons (4.9%) when analyzed by study design (*Kishimoto et al 2021*).
- One MA compared outcomes for once-monthly LAIs of paliperidone palmitate and risperidone across 7 RCTs. Paliperidone palmitate was less likely to show no improvement in global state (defined as reduction in PANSS scores) vs placebo (RR, 0.79; 95% CI, 0.74 to 0.85). When comparing both active treatments, one trial favored paliperidone palmitate and one trial favored risperidone LAI; therefore, conclusions could not be made. In terms of safety, paliperidone palmitate and risperidone LAI were similar. Compared to placebo, paliperidone palmitate led to significant elevations in serum prolactin, regardless of patient gender (*Nussbaum et al 2012*).
- One SR of 41 trials measuring safety concluded that LAI atypical antipsychotics are associated with similar adverse effects to that of oral formulations, and no clinically significant trends can be conclusively drawn. Data suggested that olanzapine pamoate was associated with dose-dependent weight gain, lipid and glucose metabolism issues, and may increase prolactin levels even at low doses. Post-injection syndrome, due to accidental intravascular injection of olanzapine pamoate, was characterized by delirium and/or excessive sedation (incidence, 1.2%). The risperidone LAI may increase the risk of QT prolongation, although the clinical significance is unknown. Hyperprolactinemia, EPS, cardiovascular events (ie, tachycardia and orthostatic hypotension), and weight gain are known side effects of risperidone LAI and paliperidone palmitate. The most common adverse event associated with paliperidone palmitate was worsening of psychotic symptoms (incidence, 3.5 to 16%) (*Gentile et al 2013*).
- Newer LAIs include Aristada and Aristada Initio (aripiprazole lauroxil), Abilify Asimtufii (aripiprazole once-every-2-months injection), Invega Trinza (paliperidone palmitate once-every-3-months injection), Invega Hafyera (paliperidone palmitate once-every-6-months injection), Perseris (risperidone once-a-month injection), Uzedy (risperidone once-monthly-or-every-2-months injection), and Rykindo (risperidone once-every-2-weeks injection).
  - The efficacy of Abilify Asimtufii (aripiprazole once-every-2-months injection) for the treatment of schizophrenia in adults is based on adequate and well-controlled studies of Abilify Maintena (aripiprazole ER) (*Abilify Asimtufii prescribing information 2025*).
    - The efficacy of Rykindo (risperidone once-every-2-weeks injection) for the treatment of schizophrenia in adults is based on adequate and well-controlled studies of intramuscular risperidone LAI (*Rykindo prescribing information 2025*).
    - The efficacy of Uzedy is established based on efficacy of oral risperidone and a randomized withdrawal study in which 543 patients with schizophrenia were stabilized on oral risperidone 2 to 5 mg and then randomized to Uzedy once monthly or every 2 months or placebo until relapse or study completion. Both Uzedy dosing regimens led to a significantly longer time to relapse compared to placebo. (*Uzedy prescribing information 2025*)
    - The safety and efficacy of aripiprazole lauroxil in adult patients with schizophrenia was established in one PC, DB, RCT of 622 patients over a period of 12 weeks. Oral aripiprazole was administered concomitantly for the first 3

weeks of treatment. The PANSS total score was significantly decreased at day 85 by 10.9 with monthly IM injections of aripiprazole lauroxil 441 mg and by 11.9 with 882 mg IM monthly compared with placebo ($p < 0.001$ for both). PANSS was significantly improved as early as day 8 and maintained throughout the study. In terms of safety, more than double the proportion of patients taking aripiprazole lauroxil experienced akathisia (441 mg, 11.6%; 882 mg, 11.5%) compared to placebo (4.3%). The majority of the akathisia (75%) was experienced before the second injection within the first 3 weeks. Additional treatment-emergent adverse effects (incidence ≥ 2%) included insomnia, headache, and anxiety (*Meltzer et al 2015*). In an indirect comparison of aripiprazole lauroxil (441 or 882 mg) and aripiprazole ER injection (400 mg), all treatment groups had similar reductions in symptoms of schizophrenia as measured by PANSS total score (*Cameron et al 2018*). The incidence of akathisia and changes in weight were also similar between treatments; although, the occurrence of treatment emergent adverse events was potentially lower with aripiprazole lauroxil 882 mg vs aripiprazole ER injection (OR, 0.46; 95% CI, 0.22 to 0.97).
    - Aristada Initio is indicated only to be used as a single dose in conjunction with oral aripiprazole for the initiation of Aristada, when used for the treatment of schizophrenia in adults. Effectiveness of Aristada Initio was established by adequate and well-controlled studies of oral aripiprazole and Aristada in adult patients with schizophrenia and a single pharmacokinetics bridging study (*Aristada Initio prescribing information 2025*).
  - The FDA-approval of Invega Trinza, the 3-month IM paliperidone palmitate injection, was based on one PC, OL, DB trial of 305 patients with schizophrenia experiencing acute symptoms. Prior to administration of paliperidone palmitate once every 3 months injection, patients were administered flexible oral doses for 17 weeks, and then administered the paliperidone palmitate once monthly injection for 12 weeks. If stable, patients were then administered the once-every-3-months injection. Paliperidone palmitate once-every-3-months injection significantly lengthened the median time to first relapse vs placebo. The mean change in PANSS total scores showed greater improvement in the paliperidone group compared to placebo ($p < 0.001$). Due to the low percentage of relapse in treated patients (7.4%), the median time was not estimated; however, in the placebo group, 23% experienced relapse, with a median time of 274 days. The trial was stopped early due to demonstration of efficacy. Those adverse events noted more frequently in the group receiving paliperidone palmitate vs the placebo group included headache (9 vs 4%), increased weight (9 vs 3%), nasopharyngitis (6 vs 1%), and akathisia (4 vs 1%) (*Berwaerts et al 2015*).
  - The FDA-approval of Invega Hafyera, the 6-month IM paliperidone palmitate injection, was based on the results of a randomized, DB, active-controlled, interventional, parallel-group, MC, non-inferiority study. A total of 702 stabilized patients were randomized 2:1 to receive Invega Hafyera (n = 478) or Invega Trinza (n = 224) over a 12-month DB phase. The primary efficacy variable was time to first relapse in the DB phase. The study demonstrated non-inferiority of Invega Hafyera to Hafyera Trinza; a relapse event was experienced by 7.5% (n = 36) of patients in the Invega Hafyera group and 4.9% (n = 11) of patients in the Invega Trinza group, with the Kaplan-Meier estimated difference (Invega Hafyera - Invega Trinza) of 2.9% (95% CI, -1.1 to 6.8) (*Najarian et al 2021*).
  - The efficacy of risperidone ER monthly injection (Perseris) was evaluated in an 8-week, DB, randomized, PC trial in 354 patients who were experiencing an acute schizophrenia exacerbation. Patients received risperidone 90 mg, 120 mg, or placebo subcutaneously on days 1 and 29. LS mean change from baseline in PANSS total score (the primary outcome) was significantly greater with risperidone 90 mg (-6.148, $p = 0.004$) and 120 mg (-7.237, $p < 0.001$) compared to placebo. Compared to placebo, CGI-S scores were also significantly decreased in both risperidone dose groups ($p = 0.0002$ and $p < 0.0001$, respectively). Adverse effects were similar between groups, with the exception of weight gain (13% in the risperidone 90 mg group, 12.8% in the risperidone 120 mg group, and 3.4% in the placebo group) (*Nasser et al 2016*).
- The AHRQ conducted an SR of 71 studies on the pharmacological and psychosocial treatment for schizophrenia. Most evidence was for older SGAs, with clozapine, olanzapine, and risperidone superior on more outcomes than other SGAs. Older SGAs were similar to haloperidol on benefit outcomes but had fewer adverse event outcomes. Additionally, results from a subgroup analysis found that that patients experiencing a first episode of schizophrenia did not show significant differences in response or remission when treated with olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, or paliperidone (*McDonagh et al 2017).*
- An SR and MA of 501 RCTs (N = 16,812) comparing the efficacy of 32 LAI antipsychotics for the maintenance treatment of patients with schizophrenia or schizoaffective disorder with stable symptoms. While all agents demonstrated a risk ratio < 1.00 (range, 0.20 to 0.65) for relapse prevention compared to placebo, there was no clear evidence to support the superiority of one antipsychotic over another. The authors concluded that choice of treatment should be guided by their tolerability (*Schneider-Thoma et al 2022*).
- An SR and MA of 66 RCTs (N = 16,457) found that all 4 SGA-LAIs (olanzapine, aripiprazole, risperidone, paliperidone) reduced overall acute symptoms more than placebo (SMD, -0.66, -0.64, -0.62, -0.42, respectively) (*Wang et al 2024a*).

Another network MA of 91 studies (N = 24,765) evaluating all 4 SGA in both oral and LAI formulations demonstrated similar results when compared to placebo for the primary endpoint of change in overall symptoms. The ranked sequence was olanzapine LAI > olanzapine oral > aripiprazole LAI > risperidone oral > paliperidone oral > paliperidone LAI > aripiprazole oral. When comparing between antipsychotics, olanzapine oral and risperidone LAI were more efficacious than aripiprazole oral. Additionally, risperidone LAI was more efficacious than paliperidone LAI (*Wang et al 2024b*).

Clinical Guidelines

- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy.
- Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

Adults

- Bipolar disorders
  - The updated 2023 Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guideline recommends (*Keramatian et al 2023*:
    - Acute mania (first line): Lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone (> 6mg), risperidone, and cariprazine monotherapy or a combination of lithium/divalproex with either quetiapine, aripiprazole, risperidone, or asenapine.
    - Bipolar depression (first line): Quetiapine, lurasidone plus lithium/divalproex, lithium, lamotrigine, cariprazine, or adjunctive lurasidone
    - Bipolar I disorder (maintenance therapy): Monotherapy with lithium, quetiapine, divalproex, lamotrigine, asenapine, or aripiprazole (daily or once monthly), or combination therapy with lithium/divalproex with quetiapine or aripiprazole.
    - Bipolar II depression: Quetiapine for acute treatment; quetiapine, lithium or lamotrigine for maintenance.
  - The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders (acute and long-term treatment of mixed states in bipolar disorder) suggest that the best evidence for manic symptoms in bipolar mixed states is with olanzapine. For depressive symptoms, the addition of ziprasidone may be beneficial; however, the evidence is much more limited than for the treatment of manic symptoms. For maintenance treatment, olanzapine, quetiapine, valproate and lithium can be considered (*Grunz et al 2018*).
- MDD
  - The Veteran Administration and Department of Defense (VA/DoD) clinical practice guideline for the management of MDD and the American Psychiatric Association (APA) guideline for the treatment of patients with MDD indicate for the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment (*APA 2010 [legacy], VA/DoD 2022*). The American College of Physicians (ACP) guideline for the treatment of adult patients with MDD recommends cognitive behavioral therapy and/or second-generation antidepressants (eg, SSRI or SNRI) as first line treatment for the acute phase of moderate to severe MDD (*Qaseem et al 2023)*. While all 3 guidelines suggest that atypical antipsychotics may be useful to augment antidepressant therapy, the VA/DoD and ACP consider use of atypical antipsychotics as one of many options in patients with severe, persistent, or recurrent MDD who have had inadequate response to initial treatment.
- Schizophrenia
  - Per the 2020 APA practice guideline for the treatment of patients with schizophrenia, an evidence-based ranking of atypical antipsychotics or an algorithmic approach to antipsychotic selection is not possible due to the significant heterogeneity in clinical trial designs, the limited number of head-to-head comparisons, and the limited clinical trial data for a number of antipsychotics. The guideline notes that there may be clinically meaningful distinctions in response or tolerability of the various atypical antipsychotic agents in an individual patient; however, there is no definitive evidence that one typical or atypical antipsychotic will have consistently superior efficacy compared with another, with the possible exception of clozapine. Specific factors that may influence choice of an atypical antipsychotic include available formulation, drug interactions, pharmacokinetic properties, and adverse effects. The choice of an atypical antipsychotic is based on patient-specific factors such as symptoms, prior treatment response, and benefits and risks of treatment (*Keepers et al 2020*).
  - The initial goal of acute treatment with an antipsychotic medication is to reduce acute symptoms, to return individuals to their baseline level of functioning. Maintenance treatment aims to prevent recurrence of symptoms and maximize functioning and quality of life.

- Agitation associated with dementia
  - Per the 2016 APA guideline on use of antipsychotics to treat agitation in patients with dementia, the use of antipsychotics is recommended only after nonpharmacological interventions fail, the risk of adverse reactions is fully evaluated, and benefit of use outweighs this risk, and assessment of symptoms are rated as severe, dangerous, and cause significant distress to the patient. The use of haloperidol or long-acting agents are not recommended. Recommendations for the use of specific agents are not provided. (*Reus et al 2016*)

Children and Adolescents

There are few formal guidelines to guide the use of atypical antipsychotics in children and adolescents; numerous American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters are referenced below. Per the AACAP, these practice parameters become outdated after 5 years and cannot be assumed to reflect current knowledge and practice.

- Use of atypical antipsychotics – According to a practice parameter from the AACAP, prior to the initiation of antipsychotic therapy patients should undergo a thorough diagnostic assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (*Findling et al 2011*).
- Autism Spectrum Disorders (ASD)
  - An AACAP practice parameter states that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-approved for irritability associated with autism; other drugs that have been studied include clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (*Volkmar et al 2014*).
  - The 2020 American Academy of Pediatrics (AAP) guideline for the identification, evaluation, and management of children with ASD suggests that pharmacotherapy is used to help manage coexisting behavioral health disorders (eg, ADHD, mood disorders, or anxiety disorders) and problem behaviors or symptoms causing significant impairment and distress including: aggression, self-injurious behavior, sleep disturbance, mood lability, anxiety, hyperactivity, impulsivity, inattention. The guideline recommends the use of SGAs (aripiprazole or risperidone) to manage irritability and/or aggression in ASD. There is less evidence for the use of SGAs in decreasing hyperactivity, thus stimulants are recommended first line (*Hyman et al 2020*).
- Bipolar disorder
  - An updated 2022 AACAP algorithm for the treatment of pediatric bipolar mixed/mania and depressed episodes recommends monotherapy with an FDA-approved SGA (aripiprazole, asenapine, olanzapine, quetiapine, or risperidone) as first line treatment for an acute manic/mixed episode with or without psychosis. If there is no response or initial SGA is not tolerated, switching to another FDA approved SGA monotherapy is recommended. In patients with psychosis is well tolerated and partial response is achieved, but better control of symptoms is desired, then augmentation with lithium is recommended. In patients with psychosis, augmentation can be with lithium and/or lamotrigine. First line therapy in patients with bipolar depression is lurasidone; augmentation with lamotrigine is recommended if there is a partial response. If there is no response to lurasidone monotherapy, olanzapine plus fluoxetine is second line. While lurasidone and olanzapine plus fluoxetine combination have demonstrated similar efficacy, lurasidone appears to have lower metabolic side effect burden(*Hobbs et al 2022*).
  - According to an 2007 AACAP practice parameter for the treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (*McClellan et al 2007*).
  - The CANMAT/ISBD guideline provides recommendations for treatment in children and adolescents. Recommendations have a low level of evidence due to limited clinical trial data (*Keramatian et al 2023*).
    - First-line agents for acute mania include lithium, risperidone, aripiprazole, asenapine, and quetiapine; olanzapine and ziprasidone monotherapy and quetiapine adjunctive therapy are second-line agents; divalproex is third line.
    - First line for acute mania is lurasidone; second-line agents are lithium and lamotrigine; olanzapine plus fluoxetine and quetiapine are third-line agents.
    - For maintenance treatment of bipolar depression, first line agents are aripiprazole, lithium, and divalproex; no second line agents are recommended in the guideline; asenapine, quetiapine, risperidone, and ziprasidone can be considered for third-line treatment

- Schizophrenia – According to an AACAP practice parameter , antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (*McClellan et al 2013*).
- Tourette's disorder
  - According to an AACAP practice parameter for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents, and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (*Murphy et al 2013*).
  - The 2019 AAN guideline (reaffirmed in 2022) for the treatment of tics in people with Tourette syndrome and chronic tic disorders (*Pringsheim et al 2019*) recommends:
    - Providing information to families about the natural history of a disorder can help inform treatment decisions (Level A). Tics usually begin in childhood and demonstrate a waxing and waning course. Tics generally peak between 10 to 12 years old, with many children experiencing an improvement in tics in adolescence. Additionally, it is important that clinicians assess for co-morbid conditions that are common in people with Tourette syndrome, including ADHD, OCD, and other psychiatric disorders (eg, anxiety, mood).
    - Treatment options for tics include watchful waiting, comprehensive behavioral intervention for tic (CBIT), and pharmacotherapy.
      - People with tics receiving CBIT are more likely than those receiving psychoeducation and supportive therapy to have reduced tic severity. CBIT is a manualized treatment program consisting of habit reversal training (HRT), relaxation training, and a functional intervention to address situations that sustain or worsen tics.
      - The use of antipsychotics is recommended when benefits outweigh the risks. No one drug is recommended over another due to insufficient evidence. Haloperidol, risperidone, aripiprazole, and tiapride (not available in the United States) are probably more likely than placebo to reduce tic severity.

Safety Summary

- As of February 2025, participation in the clozapine Risk Evaluation and Mitigation Strategy (REMS) program is no longer required. However, providers are still encouraged to monitor ANC according to the recommended monitoring frequencies outlined in the prescribing information for clozapine-containing products (*FDA 2025)*.

Boxed warnings

- All atypical antipsychotic agents carry a boxed warning for the increased mortality in elderly patients with dementia-related psychosis. The boxed warning for pimavanserin further states that the drug is not approved for the treatment of patients with dementia who experience psychosis unless their hallucinations and delusions are related to Parkinson disease.
- Aripiprazole, brexpiprazole, cariprazine, lumateperone, lurasidone, quetiapine ER, olanzapine/fluoxetine: Increased risk of suicidal thoughts and behaviors.
- Zyprexa Relprevv: Incidences of post-injection delirium and/or sedation syndrome; this agent should not be used in patients with dementia-related psychosis.
- Abilify MyCite: Safety and effectiveness has not been established in pediatric patients.
- Clozapine-containing agents (ie, Clozaril and Versacloz) have a boxed warning for severe neutropenia, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, pericarditis, cardiomyopathy, and mitral valve incompetence.

Contraindications

- Asenapine is contraindicated in patients with severe hepatic impairment.
- Ziprasidone is contraindicated in patients with recent acute myocardial infarction (MI), uncompensated heart failure (HF), and history of QT prolongation, or those taking drugs that have demonstrated QT prolongation. Ziprasidone is also contraindicated in patient taking, or within 14 days of stopping, monoamine oxidase inhibitors.
- Lurasidone is contraindicated for concomitant use with strong cytochrome (CYP) 3A4 inducers and/or inhibitors.

- Olanzapine/fluoxetine is contraindicated in patients taking concurrent pimozide or thioridazine due to the potential for QT prolongation, and in patients taking concurrent monoamine oxidase inhibitors due to the potential for serotonin syndrome.
- Olanzapine/samidorphan is contraindicated in patients who are using opioids or who are undergoing acute opioid withdrawal.
- Xanomeline/trospium chloride is contraindicated in patients with urinary retention, moderate to severe hepatic impairment, gastric retention, history or hypersensitivity, and untreated narrow-angle glaucoma.

Warnings and precautions

- The atypical antipsychotics have warnings relating to risks of neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes (includes hyperglycemia, hyperlipidemia, and weight gain), falls, orthostatic hypotension, leukopenia/neutropenia/agranulocytosis, seizures, potential for cognitive and motor impairment, body temperature dysregulation, and dysphagia. Additional warnings for various agents include:
  - Aripiprazole, brexpiprazole: Pathological gambling and other compulsive behaviors
  - Aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lumataperone, lurasidone, paliperidone, quetiapine, risperidone, and ziprasidone: Cerebrovascular adverse events in elderly patients with dementia-related psychosis
  - Asenapine: QT prolongation, hyperprolactinemia, and hypersensitivity reactions
  - Cariprazine: Delayed adverse reactions due to long half-life including extrapyramidal symptoms or akathisia
  - Clozapine-containing products: Eosinophilia, hepatotoxicity, QT prolongation, pulmonary embolism, fever, gastrointestinal hypomotility with severe complications including perforation, ulceration or necrosis, and anticholinergic toxicity
  - Fluoxetine: QT prolongation, serotonin syndrome, risk of bleeding, angle-closure glaucoma, activation of mania/hypomania, hyponatremia, sexual dysfunction
  - Iloperidone: QT prolongation, hyperprolactinemia, priapism, and intraoperative floppy iris syndrome
  - Lurasidone: Hyperprolactinemia, increased sensitivity in patients with PD or dementia with Lewy bodies and activation of mania/hypomania
  - Olanzapine: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), anticholinergic effects, and hyperprolactinemia
  - Paliperidone: QT prolongation, hyperprolactinemia, priapism, and potential for gastrointestinal obstruction (due to non-deformable tablet)
  - Pimavanserin: QT prolongation
  - Quetiapine: QT prolongation, cataracts, hypothyroidism, hyperprolactinemia, increased blood pressure in children and adolescents, leukopenia, neutropenia and agranulocytosis, acute withdrawal symptoms, and anticholinergic effects
  - Risperidone: Priapism, hyperprolactinemia, increased sensitivity in patients with PD or dementia with Lewy bodies, patients with phenylketonuria (ODT tablets contain phenylalanine)
  - Samidorphan: may be cross-reactive with urinary immunoassay methods used for detecting opioids, resulting in false positive results, precipitation of severe opioid withdrawal and vulnerability to life-threatening opioid overdose
  - Ziprasidone: QT prolongation, serotonin syndrome, neuroleptic malignant syndrome, severe cutaneous reactions (eg, DRESS and Stevens-Johnson syndrome), rash, hyperprolactinemia, and priapism
- Warnings and precautions associated with the use of xanomeline/trospium chloride include increased risk of urinary retention in the elderly and patients with bladder obstruction or incomplete emptying, increased risk of livery injury in patients with biliary disease, decreased gastric motility, angioedema, increased heart rate, anticholinergic reactions in patients with renal impairment, and CNS effects.

Adverse effects

- The most common adverse effects associated with the use of xanomeline/trospium chloride (incidence ≥ 5% and at least twice the rate of placebo) were nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastrointestinal reflux disease.
- Post-marketing reports of intense urges, particularly for gambling, have been reported in patients taking aripiprazole and brexpiprazole. Other compulsive urges include sexual urges, shopping, eating or binge eating, and other compulsive behaviors. Dose reductions or stopping aripiprazole and brexpiprazole should be considered.

- In 2018, the FDA completed an analysis of reported post marketing deaths and serious adverse events with the use of pimavanserin, including those reported to the FDA Adverse Event Reporting System (FAERS). The FDA did not identify any new or unexpected safety findings, or findings inconsistent with the established safety labeling. The FDA's conclusion was that the benefits of pimavanserin outweighed its risks for patients with hallucinations and delusions of Parkinson's disease psychosis (*FDA Drug Safety and Availability 2018*).
  - In assessing the reports of deaths, FDA considered that patients with Parkinson's disease have psychosis, a higher mortality rate due to their older age, advanced Parkinson's disease, and other medical conditions. In FAERS reports that included a cause of death, there was no evident pattern to suggest a drug effect (*FDA Drug Safety and Availability 2018*).
- Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at an increased risk of extrapyramidal and/or withdrawal symptoms. Neonates exposed to fluoxetine, a component of Symbyax, late in the third trimester have developed complications arising immediately upon delivery requiring prolonged hospitalization, respiratory support, and tube feeding. These drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In general, a decision should be made whether to discontinue nursing or to discontinue the antipsychotic drug, taking into account the importance of the drug to the mother. It is recommended that women do not breastfeed during treatment with clozapine, iloperidone, lumateperone, and olanzapine.
- Many factors are taken into consideration when prescribing an atypical antipsychotic, including co-morbid conditions and safety risks. Common adverse events observed within the class include EPS, sedation, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including the risk of ventricular arrhythmias (QT prolongation). Table 3 outlines the relative adverse event trends observed between the various atypical antipsychotic agents:

Table 3. Relative adverse event risk observed in trials for atypical antipsychotic agents

Adverse Event	Aripiprazole	Asenapine	Brexpiprazole	Cariprazine	Clozapine*	Iloperidone	Lumateperone	Lurasidone	Olanzapine	Paliperidone	Pimavanserin	Quetiapine	Risperidone	Ziprasidone
Sedation – sleepiness	Low	Moderate	Moderate	Moderate	High	Moderate	Low	Moderate	High	Low	Low	High	Moderate	Moderate
Diabetes	Low	Moderate	Low	Low	High	Moderate	Low	Moderate	High	Low	Low	Moderate	Moderate	Low
EPS – akathisia (motor restlessness), parkinsonism (tremor rigidity, and slow movements), dystonia (continuous muscle spasms or contractions), and tardive dyskinesia (jerky movements)	Low to moderate	Low to moderate	Low to moderate	Low to moderate	Low	Low	Low	Moderate	Low to moderate	Moderate	Low	Low	Moderate	Low to moderate
Anticholinergic – blurred vision, constipation, dry mouth, drowsiness, memory impairment, etc.	Low	Low	Low	Moderate	High	Low	Low	Low	Moderate	Low	Low	Moderate	Low	Low
Orthostasis – low blood pressure resulting in dizziness when standing up	Low	Moderate	Low	Low	High	High	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Weight Gain	Low	Moderate	Low	Moderate	High	Moderate	Low	Low	High	Moderate	Negligible	Moderate	Moderate	Low
Prolactin – high levels linked to gynecomastia, sexual dysfunction, menstrual disruption, acne,	Low	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate	High	Low	Low	High	Moderate

Adverse Event	Aripiprazole	Asenapine	Brexpiprazole	Cariprazine	Clozapine*	Iloperidone	Lumateperone	Lurasidone	Olanzapine	Paliperidone	Pimavanserin	Quetiapine	Risperidone	Ziprasidone
amenorrhea, hirsutism, osteoporosis, increased risk of hip fracture, etc.														
QT prolongation	Negligible to low	Low	Negligible to low	Negligible to low	Moderate	Low	Negligible to low	Negligible to low	Moderate	Low	Low	High	Moderate	High
Hypercholesterolemia	Low	Moderate	Moderate	Low	High	Low	Low	Moderate	High	Moderate	Low	High	Low	Low

Abbreviation: EPS = extrapyramidal side effects
Note: Information is based on indirect comparisons and expert assessments; however, more head-to-head trials are warranted to substantiate observations
*Granulocytopenia or agranulocytosis has been reported in 1% of patients. Clozapine is associated with an excess risk of myocarditis and venous thromboembolism (VTE), including fatal pulmonary embolism (PE).

(*Jibson 2025*)

Dosing and Administration

Table 4. Dosing and administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Abilify (aripiprazole)	Tablet	Oral	Daily Tablet with sensor has a patch which should be changed weekly or sooner, as needed.	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers. The MyCite system is composed of an ingestible event marker (IEM) sensor, MyCite patch (wearable sensor), MyCite app, and a web-based portal for healthcare professionals and caregivers. Tablets with sensor may be administered with or without food. Most ingestions will be detected in 30 minutes to 2 hours. Patients should be instructed not to repeat doses if not detected. The 30-day starter kits contain: aripiprazole tablets with sensor, strips, and 1 pod; the maintenance kits contain aripiprazole tablets with sensor and strips.
aripiprazole	orally disintegrating tablet, oral solution			
Opipza (aripiprazole)	Oral film			
Abilify Mycite (aripiprazole with sensor)	Tablet with sensor			
Abilify Asimtufii (aripiprazole ER)	Injection	IM	Every 2 months	Must be administered by a healthcare professional.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Abilify Maintena (aripiprazole ER)			Monthly	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers. Aripiprazole-naïve patients should establish tolerability with oral formulations prior to initiating LAIs. Potential for dosing and medication errors; do not substitute/confuse Aristada Initio for Aristada.
Aristada (aripiprazole lauroxil)			Monthly (441 mg, 662 mg, or 882 mg) or every 6 weeks (882 mg) or every 2 months (1064 mg)	
Aristada Initio (aripiprazole lauroxil)			One dose of Aristada Initio 675 mg and aripiprazole 30 mg orally with the first Aristada injection	
Saphris (asenapine)	Sublingual tablet	Oral	Twice daily	Sublingual tablets should be placed under the tongue and left to dissolve completely; they should not be swallowed. Eating and drinking should be avoided for 10 minutes after administration.
Secuado (asenapine)	transdermal Patch	Transdermal	Daily	Patch should be applied once daily and left in place for 24 hours.
Rexulti (brexpiprazole)	Tablet	Oral	Daily	Dose adjustments are recommended in known CYP2D6 poor metabolizers and in concomitant CYP3A4 or CYP2D6 inhibitors, and/or strong CYP3A4 inducers. Dosage adjustments are recommended for hepatic and renal impairment.
Vraylar (cariprazine)	Capsule, therapy pack	Oral	Daily	Dose adjustments are recommended with concomitant CYP3A4 inhibitors. Concomitant use is not recommended with CYP3A4 inducers. Use of the drug is not recommended in severe hepatic or renal impairment since it has not been studied in these populations.
clozapine	ODT	Oral	Once or twice daily	Prior to initiating, a baseline ANC must be ≥ 1500/mcL (≥ 1000/mcL for patients with

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Clozaril (clozapine)	Tablet			BEN). To continue treatment, ANC must be monitored regularly. Dose adjustments are recommended in patients with renal/hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6, CYP1A2, CYP3A4 inhibitors and/or CYP3A4, CYP1A2 inducers. When restarting clozapine ODT in patients who missed 1 or more doses, the dosage must be reduced.
Versacloz (clozapine)	oral suspension			
Fanapt (iloperidone)	Tablet	Oral	Twice daily	Dose adjustments are recommended in patients with hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6 and/or CYP3A4 inhibitors.
Caplyta (lumateperone)	Capsule	Oral	Once Daily	CYP3A4 inducers: Avoid concomitant use. Dose adjustment recommended with concomitant use with a moderate or strong CYP3A4 inhibitor and moderate or severe hepatic impairment.
Latuda (lurasidone)	Tablet	Oral	Daily	Dose adjustment recommended with concomitant use with a moderate CYP3A4 inhibitor and renal/hepatic impairment. Do not use with strong CYP3A4 inhibitors/inducers. Should be administered with food (≥ 350 calories).
Zyprexa, Zyprexa Zydis (olanzapine)	Tablet, ODT injection	Oral, IM	Oral: daily IM: as needed; max. 3 doses 2 to 4 hrs apart	
Zyprexa Relprevv (olanzapine ER)	Injection	IM	Every 2 weeks (initial: 210 mg or 300 mg; maintenance: 150 mg, 210 mg, or 300 mg) or every 4 weeks (initial: 405 mg; maintenance: 300 mg or 405 mg)	This product is available only through a restricted distribution program and must be administered by a healthcare professional; patient observation is required for at least 3 hours after injection due to the potential for Post-Injection Delirium/Sedation Syndrome. Tolerability with oral olanzapine must be established prior to initiating therapy with this LAI.
Symbyax (olanzapine/fluoxetine)	Capsule	Oral	Daily	The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				The safety of doses above 12 mg of olanzapine and 50 mg of fluoxetine has not been evaluated in pediatric clinical studies. Start olanzapine/fluoxetine at 3 mg/25 mg or 6 mg/25 mg in patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine/fluoxetine (female gender, geriatric age, nonsmoking status).
Lybalvi (olanzapine/ samidorphan)	Tablet	Oral	Daily	Dose adjustments are recommended with concomitant CYP1A2 inducers and strong CYPA12 inhibitors. Concomitant use is not recommended with CYP3A4 inducers. Start olanzapine/samidorphan at 5 mg/10 mg once daily in patients who have a predisposition to hypotensive reactions, have potential for slower metabolism of olanzapine, or may be more pharmacodynamically sensitive to olanzapine.
Invega (paliperidone ER)	Tablet	Oral	Daily	Tablets should be swallowed whole and should not be chewed, divided, or crushed.
Erzofri (paliperidone ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dosage adjustment for mild renal impairment; not recommended in moderate to severe renal impairment. For patients naïve to oral paliperidone or oral or injectable risperidone, tolerability with oral paliperidone or oral risperidone must be established prior to initiating therapy with this LAI.
Invega Sustenna (paliperidone ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dosage adjustment for renal impairment. For patients naïve to oral paliperidone or oral or injectable risperidone, tolerability with oral paliperidone or oral risperidone must be established prior to initiating therapy with this LAI.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Invega Trinza (paliperidone ER)	Injection	IM	Every 3 months	Must be administered by a healthcare professional. Prior to initiation, patients must have been adequately treated with Invega Sustenna for at least 4 months. Dosage adjustment for mild renal impairment; not recommended in moderate to severe renal impairment.
Invega Hafyera (paliperidone ER)	Injection	IM	Every 6 months	Must be administered by a healthcare professional. Prior to initiation, patients must have been adequately treated with Invega Sustenna for at least 4 months, or Invega Trinza for at least one 3-month injection cycle. Dosage adjustment for mild renal impairment; not recommended in patients with moderate to severe renal impairment.
Nuplazid (pimavanserin)	Tablet, capsule	Oral	One 34 mg capsule once daily; or one 10 mg tablet with strong CYP3A4 inhibitors	No initial dosage titration. Dosage adjustment is required with concomitant use with strong CYP3A4 inhibitors; avoid use with strong or moderate CYP3A4 inducers.
Seroquel (quetiapine)	Tablet	Oral	Daily to twice daily	Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers.
Seroquel XR (quetiapine ER)	Tablet	Oral	Daily	Tablets should be swallowed whole and not split, chewed, or crushed. Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers
Risperdal (risperidone)	Tablet, ODT, oral solution	Oral	Daily to twice daily	Dosage adjustment for renal/hepatic impairment. Dosage adjustment for use with strong CYP2D6 inhibitors or strong CYP3A4 inducers. ODT contain phenylalanine.
Risperdal Consta (risperidone microspheres)	Injection	IM	Every 2 weeks	Must be administered by a healthcare professional.
Perseris (risperidone ER)	Injection	SC	Monthly	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Rykindo (risperidone ER)	Injection	IM	Every 2 weeks	Tolerability to oral risperidone must be established prior to initiating therapy with this LAI. Dose adjustment is required in patients with renal or hepatic impairment. Dosage adjustment for use with strong CYP2D6 inhibitors or strong CYP3A4 inducers. Supplementation with oral risperidone is not recommended.
Uzedy (risperidone ER)	Injection	SC	Monthly or every 2 months	
Cobenfy (xanomeline/trospium chloride)	Capsule	Oral	Twice daily	Take at least 1 hour before or 2 hours after a meal. Slower titration to max dose is recommended for geriatric patients. Not recommended in patients with hepatic impairment. Do not use in patients with moderate to severe renal impairment.
Geodon (ziprasidone HCl)	Capsule	Oral	Twice daily	
Geodon (ziprasidone mesylate)	Injection	IM	As needed; 10 mg every 2 hrs or 20 mg every 4 hrs up to a maximum of 40 mg/day	IM ziprasidone should be administered with caution to patients with impaired renal function as the cyclodextrin excipient is cleared by renal filtration.

See the current prescribing information for full details.

Conclusion

- Antipsychotics are divided into 2 distinct classes: typical antipsychotics, also called FGAs, and atypical antipsychotics, also called SGAs. Both classes generally exert their effect in part by blocking D2 receptors.
- Cobenfy (xanomeline/trospium chloride) is a first-in-class dual muscarinic agonist/antagonist approved for the treatment of schizophrenia.
- FDA-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, agitation in Alzheimer's disease, bipolar disorder, Tourette's disorder, MDD, schizophrenia, schizoaffective disorder, and PD psychosis. The indications vary by diagnosis, age, or by use as mono- or adjunctive-therapy.
  - All agents in this class are indicated for use in schizophrenia with the exception of the combination agent Symbyax (olanzapine/fluoxetine), certain generics of lurasidone, and pimavanserin.
  - Clozapine and paliperidone product (excluding Invega Trinza and Invega Hafyera) are indicated for the treatment of schizoaffective disorder.
  - Clozapine is the only agent in this class FDA-approved for treatment-resistant schizophrenia.
  - Aripiprazole, brexpiprazole, lurasidone, olanzapine, quetiapine, and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia.
  - All oral agents in this class are indicated for use in bipolar disorder, except clozapine, paliperidone, pimavanserin, xanomeline/trospium chloride, and brexpiprazole.

- Aripiprazole ER (Abilify Maintena and Abilify Asimtulfii) and Risperidone ER (Risperdal Consta and Rykindo) are the only LAIs indicated for the treatment of bipolar disorder.
- Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, lurasidone, and asenapine are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder.
- Olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder.
- Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively).
- Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients (aged ≥ 6 years).
- Aripiprazole, brexpiprazole, cariprazine, and quetiapine ER are indicated as adjunctive treatment for MDD in patients already taking an antidepressant.
- Olanzapine, when prescribed in combination with fluoxetine, is indicated for treatment-resistant depression.
- Pimavanserin is the only agent in the class FDA approved for treatment of PD psychosis.
- Brexpiprazole is the only agent in the class FDA approved for treatment of agitation in Alzheimer's disease.

- Each atypical antipsychotic has a distinctive chemical structure, mechanism of action, and neuropharmacological and adverse event profile. It should be noted that paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug. Additionally, plasma levels of cariprazine and its metabolite accumulate over time; adverse reactions may not appear until after several weeks of drug administration.
- Safety profiles vary between agents and are often an important component of treatment selection. The LAI antipsychotics are often prescribed for patients who demonstrate adherence issues with oral formulations.
- Common adverse events observed within the class include EPS, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including risk of ventricular arrhythmias (QT prolongation). When compared to the typical antipsychotics, the atypical antipsychotics are associated with a lower risk of EPS and tardive dyskinesia, making them a generally better-tolerated treatment option. (*Abou-Setta et al 2012, Jibson 2025).* However, certain atypical antipsychotic agents appear to have varying levels of risk according to the side effect profile (*Jibson 2025*). Additionally, the following factors may be considered when selecting certain agents in patients:
  - Metabolic syndrome – Metabolic effects influencing weight gain, glycemic effects, and lipid profiles have been reported to fluctuate with all atypical antipsychotics. Clozapine and olanzapine have been associated with the highest risks; aripiprazole, lurasidone, and ziprasidone have been associated with lower risks. Despite the stratified risks, routine monitoring of metabolic measures is recommended for patients on all antipsychotics.
  - EPS or tardive dyskinesia – Atypical antipsychotics have a lower risk of these side effects compared to typical antipsychotic agents. Tardive dyskinesia risks have been reported to be similar to the prevalence of EPS. Risperidone has been associated with a higher risk of EPS (up to 25% in adults); clozapine and quetiapine carry the lowest risk.
  - Anticholinergic effects – Anticholinergic side effects include dry mouth, constipation, blurred vision, and urinary retention. Clozapine has the strongest affinity for muscarinic receptors among the agents in this class review; therefore, anticholinergic side effects are reported most often. This is followed by olanzapine and quetiapine.
  - QT prolongation – QT prolongation has been reported with a number of atypical antipsychotic agents, but to a lesser degree than other classes of medications. Iloperidone and ziprasidone have been reported to prolong the QT interval (average increase in QTc of 9 to 10 msec) most often and should be avoided in high-risk patients.
  - Myocarditis and cardiomyopathy – Clozapine has been associated with fatal cases, often within the first few months of treatment.
  - Orthostatic hypotension and tachycardia – Changes in heart rate and blood pressure are most frequently observed with clozapine (9% to 25%) and iloperidone (3% to 12%). In pediatric patients, quetiapine has been associated with increased systolic/diastolic pressure in 15% to 41% of patients, but in adults' orthostatic hypotension and tachycardia have been reported in up to 7% of patients. Tachycardia has been reported in up to 16% of paliperidone-treated adult patients. Hypotension has been reported less frequently with aripiprazole, asenapine, brexpiprazole, cariprazine, lurasidone, and pimavanserin. However, fewer studies have been conducted with the newer agents.
  - Seizure – All atypical antipsychotics carry a risk for seizures; however, this appears to be associated with lowering the seizure threshold vs new-onset seizures.
  - Prolactin levels and sexual side effects – Elevations of prolactin have been most associated with risperidone and paliperidone. This is particularly concerning in pediatric patients as it is associated with changes in estrogen and testosterone levels and may result in gynecomastia and menstrual disturbances. In pediatric patients administered risperidone, hyperprolactinemia has been reported in 49% to 87% of patient's vs adults in which incidences range

from 1% to 4% depending on formulation (IM or oral routes). Abnormal prolactin levels have also been associated with sexual dysfunction, infertility, and galactorrhea. Of the atypical antipsychotics that are well studied, prolactin abnormalities are less frequently reported with olanzapine and ziprasidone. For patients in which sexual dysfunction is a concern, a number of MAs have referred to aripiprazole as the drug of choice (*Serretti et al 2011*).
  - Sedation – Clozapine is most associated with sedation (46%), followed by olanzapine (20% to 52%) and quetiapine (18% to 57%). In this class, aripiprazole is unique as insomnia was reported in ≥ 10% of adult patients, but somnolence/fatigue and insomnia were reported in ≥ 10% of pediatric patients.
  - Agranulocytosis – Agranulocytosis, leukopenia, and neutropenia are associated with use of clozapine. Within the first few months of treatment, this is particularly evident in patients with pre-existing low blood counts or those who had prior drug-induced blood dyscrasias.
  - Hypersensitivity – Olanzapine and ziprasidone have a specific warning for a fatal drug reaction with eosinophilia and systemic symptoms or DRESS. Asenapine has a warning for hypersensitivity reactions.
- The safety profile of xanomeline/trospium chloride is different than that of other atypical antipsychotics due to the unique mechanism of action that influences the muscarinic acetylcholine receptors in the CNS and peripheral tissues. Use is not recommended in patients with any degree of hepatic impairment, or in patients with moderate to severe renal impairment. Geriatric patients may be more sensitive to cholinergic effects; thus, a lower maximum dosage is recommended in this population. The most common adverse effects include nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastrointestinal reflux disease.
- In general, antipsychotics differ more in their side effects than efficacy, thus choice of therapy should be individualized. Comparative effectiveness data are most available for the treatment of schizophrenia and schizophrenia-like psychosis in adults; however, outcomes are often inconsistent. Study evidence demonstrates that there are no consistent differences in the efficacy between the atypical antipsychotics in acute or short-term trials, although clozapine has often been touted as significantly more effective for patients with treatment-resistant schizophrenia compared to all other atypical antipsychotics. Clozapine is often followed by olanzapine and risperidone in terms of improved efficacy
  - Cariprazine has demonstrated safe and effective use in doses ≤ 6 mg/day for the treatment of bipolar disorder or schizophrenia in short-term adult trials. The clinical implications of the long half-life have not been well characterized and some experts have cited safety concerns associated with the accumulating active metabolite. One 72-week (N = 264) and one 48-week (N = 97) extension trial in patients with schizophrenia have demonstrated comparable results to short-term trials of 6 weeks. Patients who are able to continue on treatment-maintained efficacy and tolerability at cariprazine doses of 1.5 mg to 9 mg daily during maintenance therapy.
  - For the treatment of Tourette's disorder, aripiprazole has demonstrated safe and effective use compared to placebo in trials of 8 to 10 weeks in pediatric patients aged ≥ 6 years. Adverse events most frequently observed included sedation-like effects, nausea, headache, nasopharyngitis, and increased appetite.
  - For the treatment of irritability associated with autism, one small, low-quality study (N = 59) compared the effects of aripiprazole and risperidone in patients aged 4 to 18 years over a period of 8 weeks, although FDA-approval stipulates therapy should be initiated for ages 5 to 6 years. No differences were detected in terms of safety or efficacy; however, the ABC-I scores numerically favored risperidone (p = 0.06). Both agents have demonstrated safe and effective use in PC trials and MAs.
  - For the treatment of PD psychosis, pimavanserin has demonstrated safe and effective use compared to placebo. Pimavanserin was associated with a significantly lower incidence of orthostatic hypotension.
  - For treatment of agitation in Alzheimer's disease, only studies conducted demonstrated a benefit in reduction of agitation with use of brexpiprazole 2 mg daily compared to placebo.
  - For the treatment of MDD, aripiprazole, brexpiprazole, cariprazine, and quetiapine ER have demonstrated effectiveness when combined with adjunctive treatment, generally in trials with a 6-week duration and combined with an SSRI or SNRI. Olanzapine/fluoxetine (Symbyax) has also demonstrated effectiveness in treatment-resistant depression. Results from RCTs and an MA demonstrate brexpiprazole' s efficacy vs placebo, and the safety profile appears to be similar to aripiprazole. Another MA concluded that aripiprazole and quetiapine may have an advantage in reducing remission compared to olanzapine/fluoxetine. Other MAs have also demonstrated reductions in depression scores and/or improved response rates with adjunctive antipsychotics for MDD (eg, olanzapine, cariprazine, brexpiprazole, quetiapine, aripiprazole, or risperidone) compared to placebo. Two MAs also concluded that cariprazine has not been shown to be effective for remission.
  - For the treatment of bipolar disorder, several atypical antipsychotics have demonstrated effective use for managing symptoms associated with manic or mixed episodes. Only a few agents have demonstrated efficacy for depressive episodes including lurasidone, lumateperone, quetiapine (immediate- and extended-release), and

olanzapine/fluoxetine; MAs have concluded that olanzapine/fluoxetine may be the optimal treatment compared to other treatment options for depressive episodes. In adolescents and children, aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine, and asenapine are FDA-approved for manic or mixed episodes, although only quetiapine and olanzapine/fluoxetine have been studied for depressive episodes. A 2017 AHRQ SR found that atypical antipsychotics decrease mania, decrease depression symptoms slightly, and improve symptom severity and global functioning to a small extent vs placebo. In addition, they probably increase response and remission rates vs placebo for manic/mixed phases. For depressive episodes in youth, 2 MAs demonstrated a response with lurasidone and olanzapine/fluoxetine but not with quetiapine when compared to placebo. Support for use of atypical antipsychotics in adult patients with bipolar disorder has been demonstrated in several MAs; Risperdal Consta (risperidone microspheres) and Abilify Maintena are the only LAIs in this class that have demonstrated safe and effective use for bipolar disorder.
    - For the treatment of schizophrenia, MAs evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo. Most analyses and studies have demonstrated that (except for clozapine), the atypical antipsychotics do not separate out robustly from the typical antipsychotics with respect to overall efficacy and times to treatment discontinuation. However, trends for respective efficacy suggest that clozapine, olanzapine, and risperidone may be more effective agents based on relapse and remission rates compared to typical antipsychotics or placebo. In general, due to high attrition rates in trials, validity is limited, thereby making it difficult to make strong conclusions.
- The safety and efficacy of xanomeline/trospium was demonstrated in two Phase 3 trials (EMERGENT-2, EMERGENT-3); researchers found a significantly greater reduction in PANSS score at 5 weeks compared to placebo. Additionally, a network MA concluded no statistically significant difference in total PANSS score reduction with xanomeline/trospium and 3 SGAs (aripiprazole, olanzapine, and risperidone) compared to placebo and between agents. However, the analysis found that xanomeline/trospium had higher all-cause discontinuation than all 3 SGAs and placebo, but only comparisons with olanzapine and risperidone were statistically significant.
- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

Adults

- MDD: For most patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment. Atypical antipsychotics may be useful to augment antidepressant therapy. Atypical antipsychotics may also be considered in patients with severe, persistent, or recurrent MDD who have had inadequate response to initial treatment.
- Bipolar Disorders: Recent guidelines from CANMAT/ISBD and WFSBP have recommended clear first line pharmacological therapies for various stages of bipolar disease. These include second generation antipsychotics, lithium, valproate, divalproex, and lamotrigine as monotherapy or combination therapy.
- Schizophrenia: Guidelines from the APA state that an evidence-based ranking of atypical antipsychotics or an algorithmic approach to antipsychotic selection is not possible due to the significant heterogeneity in clinical trial designs, the limited number of head-to-head comparisons, and the limited clinical trial data for a number of antipsychotics. There may be clinically meaningful distinctions in response or tolerability of the various atypicals in an individual patient; however, there is no definitive evidence that one atypical antipsychotic will have consistently superior efficacy compared with another, with the possible exception of clozapine. Specific factors that may influence choice of an atypical antipsychotic include available formulation, drug interactions, pharmacokinetic properties, and adverse effects.

Children and Adolescents

- Autism Spectrum Disorders (ASD): The AACAP practice parameters and AAP guideline recommend the use of FDA-approved SGAs (risperidone or aripiprazole) for irritability (both guidelines) and/or aggression (AAP only) in ASD. There is less evidence for the use of SGAs in decreasing hyperactivity; stimulants are recommended first line.
- Bipolar disorder: According to AACAP practice parameter for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents (first line include risperidone aripiprazole, asenapine, and quetiapine), with other adjunctive medications used as clinically indicated. For maintenance treatment of bipolar depression, the CANMAT/ISBD guidelines recommend aripiprazole, lithium, and divalproex as first-line. A 2022 AACAP algorithm for the acute treatment of pediatric bipolar disorder, indicates that first line therapy for acute manic/manic episode (with or without psychosis) is monotherapy with an FDA-approved SGA (aripiprazole, asenapine, olanzapine, quetiapine, or risperidone). First line therapy for acute depressive episodes is lurasidone monotherapy.

  - Schizophrenia: The AACAP indicates that antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost.
  - Tourette's disorder: The AACAP recommends pharmacotherapy for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents, and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine.
- Overall, pharmacologic therapy treatment is highly individualized and dependent on patient characteristics, response to treatment, and side effect profiles. In certain patient groups, such as pediatric patients, liquid formulations are useful for better dose-control, so clinicians may titrate and taper doses in those that may have sensitive responses to treatment. Agents with different chemical structures have different clinical responses and adverse events; therefore, access to the atypical antipsychotic medication class is important to allow individualized therapy for patients.

References

- Abilify. Package insert. Otsuka America Pharmaceutical, Inc.; January 2025.
- Abilify Asimtufii. Package insert. Otsuka America Pharmaceutical, Inc.; April 2025.
- Abilify Maintena. Package insert. Otsuka America Pharmaceutical, Inc.; April 2025.
- Abilify MyCite. Package insert. Otsuka America Pharmaceutical, Inc.; January 2025.
- Abou-Setta AM, Mousavi SS, Spooner C, et al. First-generation and second-generation antipsychotics in adults: Comparative Effectiveness Review. [Monograph on the internet]. Agency for Healthcare Research and Quality (AHRQ). Rockville, MD. 2012 Aug. No. 63. Accessed April 24, 2025. https://www.ncbi.nlm.nih.gov/books/NBK107254/pdf/Bookshelf_NBK107254.pdf.
- Aman MG, de Smedt G, Derivan A, Lyons B, Findling RL; Risperidone Disruptive Behavior Study Group. Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. *Am J Psychiatry*. 2002;159(8):1337-1346.
- Aman MG, Hollway JA, McDougle CJ, et al. Cognitive effects of risperidone in children with autism and irritable behavior. *J Child Adolesc Psychopharmacol*. 2008;18(3):227-236.
- American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition. October 2010. Accessed April 24, 2025. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf.
- American Psychiatric Association. Diagnostic and Statistical manual of Mental Disorders, 5th edition, Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Association; 2022.
- Aripiprazole ODT. Package insert. Dr. Reddy's Laboratories; August 2024.
- Aripiprazole oral solution. Package insert. Camber Pharmaceuticals; February 2025.
- Aristada. Package insert. Alkermes, Inc.; January 2025.
- Aristada Initio. Package insert. Alkermes, Inc.; January 2025.
- Aronica R, Pagani C, Favalli V, et al. Efficacy of lurasidone in adults with bipolar depression: A systematic review and meta-analysis of its impact on depressive symptoms and disability. *J Affect Disord*. 2025 Apr 2;381:100-107. doi: 10.1016/j.jad.2025.03.197.
- Asenjo Lobos C, Komossa K, Rummel-Kluge C, et al. Clozapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010;(11):CD006633.
- Asmal A, Flegar SJ, Wang J, et al. Quetiapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2013:11:CD006625.
- Augustyn M. Autism spectrum disorder: terminology, epidemiology, and pathogenesis. UpToDate website. Updated August 19, 2024. Accessed April 24, 2025. http://www.uptodate.com/
- Bahji A, Ermacora D, Stephenson C, Hawkens ER, Vazquez G. Comparative efficacy and tolerability of pharmacological treatments for the treatment of acute bipolar depression: A systematic review and network meta-analysis. *J Affect Disord*. 2020:269:154-184.
- Bauer M, El-Khalili N, Datto C, et al. A pooled analysis of two randomized, placebo-controlled studies of extended-release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. *J Affect Disord*. 2010;127:19-30.
- Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68(6):843-853.
- Berwaerts J, Liu Y, Gopal S, et al. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia. *JAMA Psychiatry*. 2015;72(8):830-839.
- Biederman J, McDonnel MA, Wozniak J, et al. Aripiprazole in the treatment of pediatric bipolar disorder: a systematic chart review. *CNS Spectrums*. 2005;10(2):141-148.
- Bozymski KM, Lowe DK, Pasternak KM, et al. Pimavanserin: a novel antipsychotic for Parkinson's disease psychosis. *Ann Pharmacother.* 2017;51(6):479-487.
- Bristol Myers Squibb (BMS) press release: BMS presents new pooled interim long-term safety and metabolic outcomes data from the EMERGENT program evaluating KarXT in schizophrenia at the 2024 Annual Congress of the Schizophrenia International Research Society. BMS Web Site. April 6, 2024.. Accessed April 24, 2025. https://news.bms.com/news/details/2024/.
- Brown E, Dunner DL, McElroy SL, et al. Olanzapine/fluoxetine combination vs lamotrigine in the 6-month treatment of bipolar depression. *Int J Neuropsychopharmaco*l. 2009;12:773-782.
- Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, Thao V, Sunderlin B. Treatment for Bipolar Disorder in Adults: A Systematic Review. Comparative Effectiveness Review No. 208. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.) AHRQ Publication No. 18-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2018. Doi 10.23970/AHRQEPCCER208

- Calabrese JR and Hertel P. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. *J Clin Psychiatry*. 2017;78(3):324-331.
- Calabrese JR, Durgam S, Satlin A, et al. Efficacy and safety of lumateperone for major depressive episodes associated with bipolar I or bipolar II disorder: a phase 3 randomized placebo-controlled trial. *Am J Psychiatry*. 2021;178(12):1098-1106.
- Calabrese JR, Keck PE, Starace A, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2015; 76(3):284-292.
- Cameron C, Zummo Jacqueline, Desai D, et al. Efficacy and safety of aripiprazole lauroxil once monthly versus aripiprazole once-monthly long-acting injectable formulations in patients with acute symptoms of schizophrenia: an indirect comparison of two double-blind placebo-controlled studies. *Curr Med Res Opin*. Jan 2018:1-9. doi:10.1080/03007995.2017.1410471.
- Caplyta. Package insert. Intra-Cellular Therapies, Inc.; June 2023.
- Capone GT, Goyal P, Grados M, et al. Risperidone use in children with Down syndrome, severe intellectual disability, and comorbid autistic spectrum disorders: a naturalistic study. *J Dev Behav Pediatr*. 2008;29:106-116.
- Centers for Disease Control and Prevention (CDC).Data and Statistics on Autism Spectrum Disorder.CDC Web site.. April 15, 2025. Accessed April 24, 2025. https://www.cdc.gov/autism/data-research/?CDC_AAref_Val=https://www.cdc.gov/ncbddd/autism/data.html
- Chiesa A, Chierzi F, De Ronchi D, et al. Quetiapine for bipolar depression: a systematic review and meta-analysis. *Int Clin Psychopharmacol*. 2012;27(2):76-90.
- Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet*. 2011;378(9799):1306-1315.
- Citrome L, Meng X, Hochfeld M. Efficacy of iloperidone in schizophrenia: a PANSS five-factor analysis. *Schizophrenia Research*. 2011;131:75-81.
- Citrome L, Meng X, Hochfeld M. Efficacy of iloperidone in the short-term treatment of schizophrenia: a post hoc analysis of pooled patient data from four phase III, placebo- and active-controlled trials. *Hum Psychopharmacol Clin Exp*. 2012;27:24-32.
- Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *Int J Clin Pract*. 2009;63(12):1762-1784.
- Clinicaltrials.gov. An open-label study to assess the long-term safety, tolerability, and efficacy of KarXT in adult patients with schizophrenia (EMERGENT-5). Identifier: NCT04820309. Updated August 20, 2024. Accessed April 24, 2025. https://clinicaltrials.gov/study/NCT04820309.
- Clozapine orally disintegrating tablet. Package insert. Mylan Pharmaceuticals; February 2025.
- Clozaril. Package insert. HLS Therapeutics; March 2025.
- Cobenfy, Package insert. E.R. Squibb & Sons, L.L.C.; September 2024.
- Correll CU, Davis RE, Weingart M, et al. Efficacy and safety of lumateperone for treatment of schizophrenia: a randomized clinical trial. *JAMA Psychiatry*. 2020;77(4):349-358. doi: 10.1001/jamapsychiatry.2019.4379.
- Correll CU, Litman R, Filts Y, et al. Efficacy and safety of once-monthly Risperidone ISM in schizophrenic patients with an acute exacerbation. *NPJ Schizophr*. 2020;6(1):37. doi: 10.1038/s41537-020-00127-y.
- Correll CU, Skuban A, Ouyang J, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: A 6-week randomized, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2015;172(9):870-880.
- Corya SA, Williamson D, Sanger TM, et al . A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depress Anxiety*. 2006;23:364-372.
- Crismon M, Smith TL, Buckley PF. Schizophrenia. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition*. McGraw Hill; 2023. Accessed April 24, 2025. https://accesspharmacy-mhmedical-com.chapman.idm.oclc.org/content.aspx?bookid=3097&sectionid=267918845.
- Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomized, placebo-controlled phase 3 trial. *Lancet*. 2014;383(9916):533-540.
- Cutler AJ, Kalali AH, Weiden PJ, et al. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. *J Clin Psychopharmacol*. 2008;28:S20-28.
- Deb S, Roy M, Limbu B, et al. Randomised controlled trials of antipsychotics for people with autism spectrum disorder: a systematic review and a meta-analysis. *Psychol Med*. 2023;53(16):7964-7972. doi: 10.1017/S003329172300212X.
- DelBello MP, Chang K, Welge JA, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disorders*. 2009;11:483-93.
- DelBello MP, Goldman R, Phillips D. Efficacy and safety of lurasidone in children and adolescents with bipolar I depression: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry*. 2017;56(12):1015-1025. doi:10.1016/j.jaac.2017.10.006.
- DelBello MP, Kadakia A, Heller V, et al. Systematic Review and Network Meta-analysis: Efficacy and Safety of Second-Generation Antipsychotics in Youths With Bipolar Depression. *J Am Acad Child Adolesc Psychiatry*. 2022;61(2):243-254. doi: 10.1016/j.jaac.2021.03.021.
- Detke HC, DelBello, MP, Landry J, et al. Olanzapine/fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2015;54(3):217-224.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration website. 2024. Accessed April 24, 2025 http://www.accessdata.fda.gov/scripts/cder/daf/.
- Durgam S, Cutler AJ, Lu K, et al. Cariprazine in acute exacerbation of schizophrenia: A fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *J Clin Psychiatry*. 2015[a]; 76(12):e1574-1582.
- Durgam S, Earley W, Guo H, et al. Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. *J Clin Psychiatry*. 2016;77(3):371-8. doi: 10.4088/JCP.15m10070.
- Durgam S, Earley W, Li R, et al. Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. *Schizophr Res*. 2016;176(2-3):264-271.
- Durgam S, Greenberg WM, Li D, et al. Safety and tolerability of cariprazine in the long-term treatment of schizophrenia: results from a 48-week, single-arm, open-label extension study. *Psychopharmacology*. 2017;234(2):199-209.
- Durgam S, Starace A, Li D, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: A phase II, randomized clinical trial. *Schizophr Res*. 2014;152(2-3):450-457.

- Durgam S, Starace A, Migliore R, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: A phase II trial. *Bipolar Disord*. 2015[b];17(1):63-75.
- Earley WR, Burgess MV, Khan B, et al. Efficacy and safety of cariprazine in bipolar I depression: A double-blind, placebo-controlled phase 3 study. *Bipolar Disord*. 2020;22(4):372-384. doi: 10.1111/bdi.12852.
- Erzofri extended-release. Package insert. Shandong Luye Pharmaceutical Co., Ltd; March 2025.
- Fallah MS, Shaikh MR, Neupane B, Rusiecki D, Bennett TA, Beyene J. Atypical antipsychotics for irritability in pediatric autism: A systematic review and network meta-analysis. *J Child Adolesc Psychopharmacol*. 2019. doi:10.1089/cap.2018.0115.
- Fanapt. Package insert. Vanda Pharmaceuticals Inc.; February 2025.
- Feng Y, Shi J, Wang L, et al. Randomized, double-blind, 6-week non-inferiority study of lurasidone and risperidone for the treatment of schizophrenia. *Psychiatry Clin Neurosci*. 2020;74(6):336-343.
- Findling RL, Drury SS, Jensen PS, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the use of atypical antipsychotic medications in children and adolescents. Approved by the AACAP Council on August 2, 2011. Accessed April 24, 2025. https://www.aacap.org/App_Themes/AACAP/docs/practice_parameters/Atypical_Antipsychotic_Medications_Web.pdf.
- Findling RL, Landbloom RL, Szegedi A, et al. Asenapine for the acute treatment of pediatric manic or mixed episode of bipolar I disorder. *J Am Acad Child Adolesc Psychiatry*. 2015;54(12):1032-1041.
- Findling RL, Pathak S, Earley W, et al. Efficacy and safety of extended-release quetiapine fumarate in youth with bipolar depression: an 8 week, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2014;24(6):325-335.
- Fleischhacker WW, Hobart M, Ouyang J, et al. Efficacy and safety of brexpiprazole (OPC-34712) as maintenance treatment in adults with schizophrenia: a randomized, double-blind, placebo-controlled study. *Int J Neuropsycholpharmacol*. 2016.pii:pyw076.
- Food and Drug Administration (FDA)/Center for Drug Evaluation and Research (CDER). Summary Review: Vraylar (cariprazine). Food and Drug Administration website. September 18, 2018. Accessed April 24, 2025. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/204370Orig1Orig2s000SumR.pdf.
- Food and Drug Administration (FDA)/Center for Drug Evaluation and Research (CDER). Caplyta (lumateperone) multidisciplinary review. December 20, 2019. Accessed April 24, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209500Orig1s000MultidisciplineR.pdf.
- Food and Drug Administration (FDA)/Center for Drug Evaluation and Research (CDER). Rexulti (brexpiprazole) medical review. July 10, 2015. Accessed April 24, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205422Orig1Orig2s000MedR.pdf.
- Food and Drug Administration (FDA)/ Center for Drug Evaluation and Research (CDER). Secuado (asenapine transdermal delivery system). Multi-discipline review.October 12, 2018. Accessed April 24, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212268Orig1s000MultidisciplineR.pdf.
- Food and Drug Administration (FDA). FDA Drug Safety and Availability: FDA analysis finds no new or unexpected safety risks associated with Nuplazid (pimavanserin), a medication to treat the hallucinations and delusions of Parkinson's disease psychosis. Food and Drug Administration website. September 20, 2018. Accessed April 24, 2025. https://www.fda.gov/Drugs/DrugSafety/ucm621160.htm?utm_campaign=FDA%20analysis%20finds%20no%20new%20or%20unexpected%20safety%20risks%20associated%20with%20Nuplazid&utm_medium=email&utm_source=Eloqua.
- Food and Drug Administration (FDA). Information on clozapine. Updated February 25, 2025. Accessed April 24, 2025. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-clozapine.
- Fornaro M, Stubbs B, De Barardis D, et al. Atypical antipsychotics in the treatment of acute bipolar depression with mixed features: a systematic review and exploratory meta-analysis of placebo-controlled clinical trials. *Int J Mol Sci*. 2016;17(2):241.
- Fusar-Poli P, Kempton MJ, Rosenheck RA. Efficacy and safety of second-generation long-acting injections in schizophrenia: A meta-analysis of randomized-controlled trials. *Int Clin Psychopharmacol*. 2013;28(2):57–66.
- Gagliano A, Germano E, Pustorino G, et al. Risperidone treatment of children with autistic disorder: effectiveness, tolerability, and pharmacokinetic implications. *J Child Adolesc Psychopharmacol*. 2004 Spring;14(1):39-47.
- Gencer O, Emiroglu FNI, Miral S, et al. Comparison of long-term efficacy and safety of risperidone and haloperidol in children and adolescents with autistic disorder: an open-label maintenance study. *Eur Child Adolesc Psychiatry*. 2008;217-225.
- Gentile S. Adverse effects associated with second-generation antipsychotic long-acting injection treatment: a comprehensive systematic review. *Pharmacotherapy*. 2013;33(10):1087-1106.
- Geodon [package insert]. New York, NY: Pfizer Pharmaceuticals; January 2025.
- Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry Hum Dev*. 2014;45(2):185-192.
- Gill H, Chen-Li D, Haikazian S, et al. Adjunctive cariprazine for major depressive disorder: a systematic review and meta-analysis. *CNS Spectr*. 2024;29(4):233-242.
- Glick ID, Correll CU, Altamura AC, et al. Mid-term and long-term efficacy and effectiveness of antipsychotic medications for schizophrenia: a data driven, personalized clinical approach. *J Clin Psychiatry*. 2011;72(12):1616-1627.
- Goldman R, Loebel A, Cucchiaro J, Deng L, Findling RL. Efficacy and safety of lurasidone in adolescents with schizophrenia: A 6-Week, randomized
- Grossberg GT, Kohegyi E, Mergel V, et al. Efficacy and Safety of Brexpiprazole for the Treatment of Agitation in Alzheimer's Dementia: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled Trials. *Am J Geriatr Psychiatry*. 2020;28(4):383-400. doi: 10.1016/j.jagp.2019.09.009
- Grunz H, Vieta E, Goodwin GM et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Acute and long term treatment of mixed states in bipolar disorder. *World J Biol Psychiatry*. 2018;19(1):2-58.
- Gulisano M, Cali PV, Cavanna AE, et al. Cardiovascular safety of aripiprazole and pimozide in young patients with Tourette syndrome. *Neurolo Sci*. 2011;32(6):1213-1217.
- Harvey PD, Ogasa M, Cucchiaro, et al. Performance and interview-based assessments of cognitive change in a randomized, double-blind comparison of lurasidone vs ziprasidone. *Schizophrenia Research*. 2011;127:188-194.
- Hirsch LE, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2016;(6):CD009043.
- Hobbs E, Reed R, Lorberg B, Robb AS, Dorfman J. Psychopharmacological treatment algorithms od manic/mixed and depressed episodes in pediatric bipolar disorder. *J Child Adolesc Psychopharmacol*. 2022;32(10):507-521.

- Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2019;394(10202):939-951.
- Hyman SL, Levy SE, Myers SM. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. *Pediatrics*. 2020;145(1):e20193447. doi: https://doi.org/10.1542/peds.2019-3447.
- Iketani R, Furushima D, Imai S, Yamada H. Efficacy and safety of atypical antipsychotics for psychosis in Parkinson's disease: A systematic review and Bayesian network meta-analysis. *Parkinsonism Relat Disord*. 2020;78:82-90. doi:10.1016/j.parkreldis.2020.07.021
- Invega. Package insert. Janssen Pharmaceuticals; February 2025.
- Invega Hafyera. Package insert. Janssen Pharmaceuticals; February 2025.
- Invega Sustenna. Package insert. Janssen Pharmaceuticals; February 2025.
- Invega Trinza. Package insert. Janssen Pharmaceuticals; February 2025.
- Jibson MD. Second-generation antipsychotic medications: Pharmacology, administration, and side effects. UpToDate website. Updated April 9, 2025. Accessed April 24, 2025. https://www.uptodate.com.
- Jones MP, Nicholl D, Trakas K, et al. Efficacy and tolerability of paliperidone ER and other oral atypical antipsychotics in schizophrenia. *Int J Clin Pharmacol Ther*. 2010;48(6):383-399.
- Kadakia A, Dembek C, Heller V, et al. Efficacy and tolerability of atypical antipsychotics for acute bipolar depression: a network meta-analysis. *BMC Psychiatry*. 2021;21(1):249. Published 2021 May 11. doi:10.1186/s12888-021-03220-3
- Kahn RS, Silverman BL, DiPetrillo L, et al. A phase 3, multicenter study to assess the 1-year safety and tolerability of a combination of olanzapine and samidorphan in patients with schizophrenia: Results from the ENLIGHTEN-2 long-term extension. *Schizophr Res*. 2021;232:45-53.
- Kamijima K, Higuchi T, Ishigooka J, et al. Aripiprazole augmentation to antidepressant therapy in Japanese patients with major depressive disorder: a randomized, double-blind, placebo-controlled study (ADMIRE study). *J Affect Disord*. 2013;151(3):899-905.
- Kane JM, Cohen M, Zhao J, et al. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *J Clin Psychopharmacol*. 2010[a];30:106-115.
- Kane JM, Lauriello J, Laska E, et al. Long-term efficacy and safety of iloperidone: results from three clinical trials for the treatment of schizophrenia. *J Clin Psychopharmacol*. 2008;28:S29-S35.
- Kane JM, Mackle M, Snow-Adami L, et al. A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *J Clin Psychiatry*. 2011;72(3):349-355.
- Kane JM, Skuban A, Ouyang J, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr Res*. 2015[a];164(1-3):127-135.
- Kane JM, Zukin S, Wang Y, et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: Results from an international, phase III clinical trial. *J Clin Psychopharmacol*. 2015[b]; 35(4):367-373.
- Kaul I, Sawchak S, Claxton A, et al. Efficacy of xanomeline and trospium chloride in schizophrenia: pooled results from three 5-week, randomized, double-blind, placebo-controlled, EMERGENT trials. Schizophrenia (Heidelb). 2024[c];10(1):102. doi: 10.1038/s41537-024-00525-6. Erratum in: Schizophrenia (Heidelb). 2025 Mar 18;11(1):44. doi: 10.1038/s41537-025-00595-0.
- Kaul I, Sawchak S, Correll CU, et al. Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline-trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomized, double-blind, placebo-controlled, flexible-dose phase 3 trial. *Lancet*. 2024[a];403(10422):160-170.
- Kaul I, Sawchak S, Walling DP, et al. Efficacy and safety of xanomeline-trospium chloride in schizophrenia: A randomized clinical trial. *JAMA Psychiatry*.2024[b];81(8):749-756.
- Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. 3rd edition. *Am J Psychiatry*. 2020 Sep;177(9):868-872. Accessed April 24, 2025. https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841.
- Keramatian K, Chithra NK, Yatham LN. The CANMAT and ISBD Guidelines for the Treatment of Bipolar Disorder: Summary and a 2023 Update of Evidence. Focus (Am Psychiatr Publ). 2023 Oct;21(4):344-353. doi: 10.1176/appi.focus.20230009.
- Khanna P, Suo T, Komossa K, et al. Aripiprazole versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2016;1:CD006569.
- Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. *Lancet Psychiatry*. 2021;8(5):387-404.
- Klemp M, Tvete IF, Skomedal T, et al. A review and Bayesian meta-analysis of clinical efficacy and adverse effects of four atypical neuroleptic drugs compared to haloperidol and placebo. *J Clin Psychopharmacol*. 2011;31:698-704.
- Komossa K, Rummel-Kluge C, Hunger H, et al. Olanzapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010 [a];(3):CD006654.
- Komossa K, Rummel-Kluge C, Hunger H, et al. Ziprasidone versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2009; (4):CD006627.
- Komossa K, Rummel-Kluge C, Schmid F, et al. Risperidone versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2011;(1):CD006626.
- Komossa K, Rummel-Kluge, Schmid F, et al. Aripiprazole versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2016;4:CD006569.
- Kumar A, Datta S, Wright S, et al. Atypical antipsychotics for psychosis in adolescents. *Cochrane Database Syst Rev*. 2013 Oct 15;10:CD009582.
- Latuda. Package insert.Sunovion Pharmaceuticals, Inc.; January 2025.
- Lenze EJ, Mulsant BH, Blumberger DM, et al. Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomized, double-blind, placebo-controlled trial. *Lancet*. 2015;386:2404-2412.
- Leucht S, Cipraini A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013; 382: 951-962.
- Leucht S, Corves C, Arbter D, et al. Second-generation vs first-generation drugs for schizophrenia: a meta-analysis. *Lancet*. 2009[a];373:31-41.

- Leucht S, Komossa K, Rummel-Kluge C, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry*. 2009[b];166:152-163.
- Leucht S, Schneider-Thoma J, Burschinski A, et al. Long-term efficacy of antipsychotic drugs in initially acutely ill adults with schizophrenia: systematic review and network meta-analysis. *World Psychiatry*. 2023;22(2):315-324. doi: 10.1002/wps.21089.
- Lieberman JA, Davis RE, Correll CU, et al. ITI-007 for the treatment of schizophrenia: a 4-week randomized, double-blind, controlled trial. *Biol Psychiatry*. 2016;79(12):952-961.
- Lieberman JA, Stroup TS, McElvoy JP, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-1223.
- Lindström L, Lindström E, Nilsson M, Höistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. *J Affect Disord*. 2017 ;213:138-150.
- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2014[a];171(2):169-177.
- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2014[b];171(2):160-168.
- Luby J, Mrakotsky C, Stalets MM, et al. Risperidone in preschool children with autistic spectrum disorders: an investigation of safety and efficacy. *J Child Adolesc Psychopharmacol*. 2006;16(5):575-587.
- Lurasidone. Package insert. Alembic Pharmaceuticals; January 2023.
- Lurasidone. Package insert. Accord Healthcare; October 2024
- Lybalvi. Package insert. Alkermes, Inc.; February 2025.
- Macfadden W, Alphs L, Haskins JT, et al. A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. *Bipolar Disorders*. 2009;11(8):827-839.
- Maneeton N, Maneeton B, Putthisri S, Suttajit S, Likhitsathian S, Srisurapanont M. Aripiprazole in acute treatment of children and adolescents with autism spectrum disorder: a systematic review and meta-analysis. *Neuropsychiatr Dis Treat*. 2018;14:3063-3072. doi: 10.2147/NDT.S174622.
- Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2008;28(2):156-165.
- Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1110-1119.
- McClellan J, Kowatch R, Findling RL, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *J Am Acad Child Adolec Psychiatry*. 2007;46(1):107-125.
- McClellan J, Stock S; for the American Academy of Children and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. *J Am Acad Child Adolec Psychiatry*. 2013;52(9):976–990.
- McCracken JT, McGough J, Shah J, et al. Risperidone in children with autism and serious behavioral problems (RUPP). *N Engl J Med*. 2002;347:314-321.
- McDonagh MS, Dana T, Selph S, et al. Treatments for schizophrenia in adults: A systematic review. comparative effectiveness review no. 198. 2017. AHRQ Publication No. 17(18)-EHC031-EF. Rockville, MD: Agency for Healthcare Research and Quality.
- McDougle CJ, Scahill L, Aman MG, et al. Risperidone for the core symptom domains of autism: results from the study by the Autism Network of the Research Units on Pediatric Psychopharmacology. *Am J Psychiatry*. 2005;162:1142-1148.
- McIntyre RS, Cohen M, Zhao J, et al. A three-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar Disorders*. 2009[a];11:673-686.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. *Journal of Affective Disorders*. 2010[b];126:358-365.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Affective Disorders*. 2010[a];122:27-38.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine vs olanzapine in acute mania: a double-blind extension study. *Bipolar Disorders*. 2009[b];11:815-826.
- Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo-and olanzapine-controlled study. *Am J Psychiatry*. 2011;168:957-967.
- Meltzer L, Risinger R, Nasrallah M, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *J Clin Psychiatry*. 2015;76(8):1085-1090.
- Miral S, Gencer O, Inal-Emiroglu FN, et al. Risperidone vs haloperidol in children and adolescents with AD: a randomized, controlled, double-blind trial. *Eur Child Adolesc Psychiatry*. 2008;17:1-8.
- Miyamato S, Duncan GE, Marx CE, et al. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Molecular Psychiatry*. 2005;10:79-104.
- Muralidharan K, Ali M, Silveira LE, et al. Efficacy of second generation antipsychotics in treating acute mixed episodes in bipolar disorder: a meta-analysis of placebo-controlled trials. *J Affect Disord*. 2013;150(2):408-414.
- Murphy TK, Lewin AB, Storch EA, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *J Am Acad Child Adolesc Psychiatry*. 2013;52(12):1341-1359.
- Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *J Child Neurol*. 2006;21(6):450-455.
- Najarian D, Sanga P, Wang S, et al. A randomized, double-blind, multicenter, noninferiority study comparing paliperidone palmitate 6-month versus the 3-month long-acting injectable in patients with schizophrenia. *Int J Neuropsychopharmacol*. 2022;25(3):238-251. doi:10.1093/ijnp/pyab071
- Nakajima S, Takuchi H, Fervaha G, et al. Comparative efficacy between clozapine and other atypical antipsychotics on depressive symptoms in patients with schizophrenia: analysis of the CATIE phase 2E data. *Schizophr Res*. 2015 Feb;161(2-3):429-433.
- Nakamura Y, Adachi J, Hirota N, et al. Brexpiprazole treatment for agitation in Alzheimer's dementia: A randomized study. Alzheimers Dement. 2024 Nov;20(11):8002-8011. doi: 10.1002/alz.14282.

- Nakamura M, Ogasa MS, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009;70(6):829-836.
- Nasser AF, Henderson DC, Fava M, et al. Efficacy, safety, and tolerability of RBP-7000 once-monthly risperidone for the treatment of acute schizophrenia: an 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study. *J Clin Psychopharmacol*. 2016;36(2):130-140. doi: 10.1097/JCP.0000000000000479.
- National Institute of Mental Health. Major Depression. Updated July 2023. Accessed April 24, 2025. https://www.nimh.nih.gov/health/statistics/major-depression.
- Nuñez NA, Joseph B, Pahwa M, et al. Augmentation strategies for treatment resistant major depression: a systematic review and network meta-analysis. *J Affect Disord*. 2022;302:385-400.
- Nuplazid. Package insert. Acadia Pharmaceuticals, Inc.; January 2025.
- Nussbaum A, Stroup T. Paliperidone palmitate for schizophrenia. *Cochrane Database Syst Rev*. 2012;6:CD008296.
- Opipza. Package insert. Carwin Pharmaceutical Associates, LLC; January 2025.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration website. Accessed April 24, 2025. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.
- Ostacher M, Ng-Mak D, Patel P, Ntais D, Schlueter M, Loebel A. Lurasidone compared to other atypical antipsychotic monotherapies for bipolar depression: A systematic review and network meta-analysis. *World J Biol Psychiatry*. 2017:1-11.
- Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009;124:1533-1540.
- Pagsberg AK, Tarp S, Glintborg D, et al. Acute antipsychotic treatment of children and adolescents with schizophrenia-spectrum disorders: A systematic review and network meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2017;56(3):191-202.
- Papakostas GI, Petersen TJ, Kinrys G, et al. Aripiprazole augmentation of selective serotonin-reuptake inhibitors for treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2005;66(10):1326-1330.
- Patel RS, Veluri M, Patel J, Patel R, Machado T, Diler R. Second-generation antipsychotic in management of acute pediatric bipolar depression: A systematic review and meta-analysis. *J Child Adolesc Psychopharmacol*. 2021;31(8):521-530.
- Patino, LR, Klein CC, Strawn JR, et al. A randomized, double-blind, controlled trial of lithium versus quetiapine for the treatment of acute mania in youth with early course bipolar disorder. *J Child Adolesc Psychopharmacol*. 2021;31(7):485-493.
- Peng H, Yan K, Liu S, et al. Efficacy and safety of lumateperone for bipolar depression and schizophrenia: a systematic review and meta-analysis. Int J Neuropsychopharmacol. 2024 Nov 1;27(11):pyae052. doi: 10.1093/ijnp/pyae052.
- Perlis RH, Baker RW, Zarate CA, et al. Olanzapine vs risperidone in the treatment of manic or mixed states in bipolar I disorder: a randomized, double-blind trial. *J Clin Psychiatry*. 2006[a];67:1747-1753.
- Perlis RH, Welge JA, Vornik LA, et al. Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2006[b];76:509-516.
- Perseris. Package insert. Indivior, Inc.; January 2025.
- Pillay J, Boylan K, Carrey N, et al. First- and second-generation antipsychotics in children and young adults: Systematic review update. Comparative Effectiveness Review No. 184. AHRQ Publication No. 17-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2017.. Accessed April 24, 2025. https://www.ncbi.nlm.nih.gov/books/NBK442352/.
placebo-controlled study. *J Child Adolesc Psychopharmacol*. 2017;27(6):516-525. doi:10.1089/cap.2016.0189.
- Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry*. 2007;68:1492-1500.
- Potkin SG, Kunovac J, Silverman BL, et al. Efficacy and safety of a combination of olanzapine and samidorphan in adult patients with an acute exacerbation of schizophrenia: outcomes from the randomized, phase 3 ENLIGHTEN-1 Study. *J Clin Psychiatry*. 2020;81(2):19m12769.
- Potkin SG, Litman RE, Torres R, et al. Efficacy of iloperidone in the treatment of schizophrenia: initial phase three studies. *J Clin Psychopharm*. 2008;28:S4-S11.
- Potkin SG, Ogasa M, Cucchiaro J, et al. Double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. *Schizophrenia Research*. 2011;132:101-107.
- Pringsheim T, Okun MS, Muller-Vahl K et al. Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology*. 2019 [reaffirmed 2022];92(19) 896-906.
- Qaseem A, Owens DK, Etxeandia-Ikobaltzeta I, et al. Nonpharmacologic and pharmacologic treatments of adults in the acute phase of major depressive disorder: a living clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2023;176(2):239-252.
- Quiroz JA, Yatham LN, Palumbo JM, et al. Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. *Biol Psychiatry*. 2010;68(2):156-162.
- Reus VI, Fochtmann LJ, Eyler AE, et al. The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia. *Am J Psychiatry*. 2016;173(5):543-6. doi: 10.1176/appi.ajp.2015.173501.
- Rexulti. Package insert. Otsuka Pharmaceuticals Co., Ltd; January 2025.
- Riedel M, Schennach-Wolff R, Dehning MS, et al. Neurocognition and its influencing factors in the treatment of schizophrenia-effects of aripiprazole, olanzapine, quetiapine and risperidone. *Hum Psychopharmacol Clin Exp*. 2010; 25:116-125.
- Riesenberg R, Yeung PP, Rekeda L, Sachs GS, Kerolous M, Fava M. Cariprazine for the adjunctive treatment of major depressive disorder in patients with inadequate response to antidepressant therapy: results of a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2023;84(5):22m14643. doi:10.4088/JCP.22m14643
- Risperdal. Package insert. Janssen Pharmaceuticals; February 2025.
- Risperdal Consta. Package insert. Janssen Pharmaceuticals; April 2025.
- Robinson N, Bergen SE. Environmental risk factors for schizophrenia and bipolar disorder and their relationship to genetic risk. Current knowledge and future directions. *Front Genet*. 2021:12:686666. doi: 10.3389/fgene.2021.686666
- Rykindo. Package insert. Teva Neurosciences; January 2025.

- Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: A double-blind, placebo-controlled, Phase III trial. *J Affect Disord*. 2015;174:296-302.
- Sachs GS, Yeung PP, Rekeda L, Khan A, Adams JL, Fava M. Adjunctive Cariprazine for the Treatment of Patients With Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study. *Am J Psychiatry*. 2023;180(3):241-251. doi: 10.1176/appi.ajp.20220504.
- Saphris. Package insert. Allergan USA, Inc.; January 2025.
- Schneider-Thoma J, Chalkou K, Dörries C, Bighelli, et al. Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2022 Feb 26;399(10327):824-836.
- Schoemaker J, Naber D, Vrijland P, et al. Long-term assessment of asenapine vs olanzapine in patients with schizophrenia or schizoaffective disorder. *Pharmacopsychiatry*. 2010; 43:e1-e10.
- Secuado. Package insert. Hisamitsu Pharmaceutical Co., Inc.; January 2025.
- Seroquel. Package insert. AstraZeneca Pharmaceuticals LP; January 2025.
- Seroquel XR. Package insert. AstraZeneca Pharmaceuticals LP; January 2025.
- Serretti A, Chiesa A. A meta-analysis of sexual dysfunction in psychiatric patients taking antipsychotics. *Int Clin Phsychopharm*. 2011;26:130.
- Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004;114:e634-e641.
- Shelton RC, Williamson DJ, Corya SA, et al. Olanzapine/ fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. *J Clin Psychiatry*. 2005;66:1289-1297.
- Silva MT, Zimmermann IR, Galvao TF, et al. Olanzapine plus fluoxetine for bipolar disorder: a systematic review and meta-analysis. *J Affect Disord*. 2013:146(3):310-318.
- Spielmans GI, Berman MI, Linardatos E, et al. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. *PLoS Med.* 2013;10(3):e1001403. doi: 10.1371/journal.pmed.1001403.
- Srisurapanont M, Suttajit S, Likhitsathian S, Maneeton B, Maneeton N. A meta-analysis comparing short-term weight and cardiometabolic changes between olanzapine/samidorphan and olanzapine. *Sci Rep*. 2021;11(1):7583.
- Steffens DC, Nelson JC, Eudicone JM, et al: Efficacy and safety of adjunctive aripiprazole in major depressive disorder in older patients: a pooled subpopulation analysis. *Int J Geriatr Psychiatry*. 2011; 26(6):564-572.
- Stovall J. Bipolar mania and hypomania in adults: choosing pharmacotherapy. UpToDate website. Updated June 21, 2024. Accessed April 24, 2025. http://www.uptodate.com/
- Stroup TS, Lieberman JA, McEvoy JP, et al; for the CATIE Investigators. Results of phase three of the CATIE schizophrenia trial. Schizophr Res. 2009;107(1):1-12.
- Stroup TS, Lieberman JA, McEvoy JP, et al; for the CATIE Investigators. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry*. 2006;163(4):611-622.
- Suppes T, Durgam S, Kozauer SG, et al. Adjunctive lumateperone (ITI-007) in the treatment of bipolar depression: Results from a randomized placebo-controlled clinical trial. Bipolar Disord. 2023 Sep;25(6):478-488. doi: 10.1111/bdi.13310.
- Symbyax. Package insert. Eli Lilly and Company; January 2025.
- Szegedi A, Durgam S, Mackle M, et al. Randomized, double-blind, placebo-controlled trial of asenapine maintenance therapy in adults with acute manic or mixed episode associated with bipolar I disorder. *Am J Psychiatry*. 2018;175(1):71-79. doi: 10.1176/appi.ajp.2017.16040419.
- Szegedi A, Zhao J, van Willigenburg A, et al. Effects of asenapine on depressive symptoms in patients with bipolar I disorder experiencing acute manic or mixed episodes: a post hoc analysis of two 3-week clinical trials. *BMC Psychiatry*. 2011;11:101.
- Tandon R, Cucchiaro J, Phillips D, et al. A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia. *J Psychopharmacol*. 2016;30(1):69-77.
- Tarr GP, Glue P, Herbison P. Comparative efficacy and acceptability of mood stabilizer and second generation antipsychotic monotherapy for acute mania-a systematic review and meta-analysis. *Journal of Affective Disorders*. 2011;134:14-19.
- Taylor DM, Cornelius V, Smith L, Young AH. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. *Acta Psychiatr Scand*. 2014;130(6):452-469.
- Thase ME, Corya SA, Osuntokun O, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2007;68:224-236.
- Thase ME, Youakim JM, Skuban A, et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. *J Clin Psychiatry*. 2015[b];76(9):1232-1240.
- Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder. *J Clin Psychiatry*. 2015[a];76(9):1224-1231.
- Tice JA, Whittington MD, McKenna A, Wright A, Richardson M, Pearson SD, Rind DM. KarXT for Schizophrenia: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, March 11, 2024. Accessed May 5, 2025. https://icer.org/wp-content/uploads/2024/03/ICER_Schizophrenia_Final-Evidence-Report_12-Month-Update.pdf.
- Tocco M, Mao Y. Safety and efficacy of adding lurasidone to ongoing therapy with lithium or valproate for the treatment of acute bipolar depressive episode: A post hoc analysis of 2 placebo-controlled trials. *J Clin Psychopharmacol*. 2024;44(4):345-355.
- Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;60(11):1079-1088.
- Torres R, Czeisler EL, Chadwick SR, et al. Efficacy and safety of iloperidone in bipolar mania: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2024;85(1):23m14966. doi:10.4088/JCP.23m14966.
- Uzedy. Package insert. Teva Neuroscience, Inc.; January 2025.
- Vandenberg AM. Depressive Disorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. *Pharmacotherapy: A Pathophysiologic Approach, 12th ed*. McGraw-Hill. Accessed April 24, 2025. https://accesspharmacy-mhmedical-com.proxy.cc.uic.edu/content.aspx?bookid=3097&sectionid=268013768
- Versacloz. Package insert. TruPharma, LLC.; February 2025.

- Veterans Administration (VA) and Department of Defense (DoD) Clinical Practice Guideline. Management of Major Depressive Disorder. 2022. VA/DoD website. Accessed April 24, 2025. http://www.healthquality.va.gov/guidelines/MH/mdd.
- Vieta E, Locklear J, Gunther O, et al. Treatment options for bipolar depression: a systematic review of randomized, controlled trials. *J Clin Psychopharmacol*. 2010;30:579-590.
- Vieta E, Montgomery S, Sulaiman AH, et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. *Eur Neuropsychopharmacol*. 2012;22(11):825-835.
- Vita G, Nöhles VB, Ostuzzi G, et al. Systematic review and meta-analysis: efficacy and safety of antipsychotics vs antiepileptics or lithium for acute mania in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2025 Feb;64(2):143-157. doi: 10.1016/j.jaac.2024.07.920.
- Volkmar F, Siegel M, Woodbury-Smith M, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):237–257.
- Vraylar. Package insert. Allergan USA, Inc.; November 2024.
- Wang D, Schneider-Thoma J, Siafis S, et al. Efficacy, acceptability and side-effects of oral versus long-acting- injectables antipsychotics: Systematic review and network meta-analysis. E*ur Neuropsychopharmacol*. 2024b:83:11-18. doi: 10.1016/j.euroneuro.2024.03.003.
- Wang D, Schneider-Thoma J, Siafis S, et al. Long-acting injectable second-generation antipsychotics vs placebo and their oral formulations in acute schizophrenia: A systematic review and meta-analysis of randomized controlled trials. *Schizophr Bull*. 2024a;50(1):132-144.
- Wang J, Wenwei L, Li M, Wu H, Qiu Z. Comparative efficacy and safety of 4 atypical antipsychotics augmentation treatment for major depressive disorder in adults: A systematic review and network meta-analysis. Medicine (Baltimore). 2023;102(38):e34670.
- Ward C, Pejović Milovančević M, et al. Efficacy and safety of brexpiprazole in adolescents with schizophrenia: a multicountry, randomised, double-blind, placebo-controlled, phase 3 trial with an active reference. Lancet Psychiatry. 2025 May;12(5):345-354. doi: 10.1016/S2215-0366(25)00043-4.
- Weiden PJ, Cutler AJ, Polymeropoulos MH, Wolfgang CD. A pooled analysis of six-week acute-phase pivotal trials. *J Clin Psychopharmacol*. 2008;28:S12-S19.
- Weiden PJ, Manning R, Wolfgang CD, et al. A randomized trial of iloperidone for prevention of relapse in schizophrenia: the REPRIEVE study. *CNS Drugs*. 2016;30(8):735-747.
- Weissman L. Autism spectrum disorders in children and adolescents: overview of management. UpToDate website Updated September 8, 2023. Accessed April 24, 2025. https://www.uptodate.com/.
- Wen XJ, Wang LM, Liu ZL, et al. Meta-analysis on the efficacy and tolerability of the augmentation of antidepressants with atypical antipsychotics in patients with major depressive disorder. *Braz J Med Res*. 2014;47(7):605-616.
- Yan Y, Yang X, Wang M, Chen B, Yin L, Ma X. Efficacy and acceptability of second-generation antipsychotics with antidepressants in unipolar depression augmentation: a systematic review and network meta-analysis. *Psychol Med*. 2022;52(12):2224-2231. doi: 10.1017/S0033291722001246.
- Yasue I, Matsunaga S, Kishi T, et al. Serotonin 2A receptor inverse agonist as a treatment for Parkinson's disease psychosis: a systematic review and meta-analysis of serotonin 2A receptor negative modulators. *J Alzheimers Dis*. 2016;50(3):733-740.
- Yatham LN, Fallu A, Binder CE. A six-month randomized open-label comparison of continuation of oral atypical antipsychotic therapy or switch to long acting injectable risperidone in patients with bipolar disorder. *Acta Psychiatr Scand Suppl*. 2007;(434):50-56.
- Yatham LN, Vieta E, McIntyre RS, et al. Broad efficacy of cariprazine on depressive symptoms in bipolar disorder and the clinical implications. Prim Care Companion CNS Disord. 2020 Sep 17;22(5):20m02611. doi: 10.4088/PCC.20m02611.Yildiz A, Siafis A, Mavridis D, Vieta E, Leucht S. Comparative efficacy and tolerability of pharmacological interventions for acute bipolar depression in adults: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2023;10(9):693-705.
- Yildiz A, Vieta E, Leucht S, et al. Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. *Neuropsychopharmacology*. 2011;36:375-389.
- Yoo HK. A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescents with Tourette's disorder. *J Clin Psychiatry*. 2013;74(8):e772-e780.
- Yoon S, Jeon SW, Ko YH, et al. Adjunctive brexpiprazole as a novel effective strategy for treating major depressive disorder: A systematic review and meta-analysis. *J Clin Psychopharmacol*. 2017;37(1):46-53.
- Young AH, McElroy SL, Bauer M, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry*. 2010;71(2):150-162.
- Zhou MS, Nasir M, Farhat LC, Kook M, Artukoglu BB, Bloch MH. Meta-analysis: Pharmacologic treatment of restricted and repetitive behaviors in autism spectrum disorders. *J Am Acad Child Adolesc Psychiatry*. 2021;60(1):35-45. doi: 10.1016/j.jaac.2020.03.007
- Zyprexa. Package insert. Eli Lilly and Company; January 2025.
- Zyprexa Relprevv. Package insert. Eli Lilly and Company; January 2025.

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Optum Rx®

New Drug Overview

Journavx (suzetrigine)

Introduction

- Pain is one of the most common reasons adults seek medical care in the United States (U.S.); it is defined as an unpleasant sensory and emotional response to a noxious stimuli (eg, injury, trauma, surgery) that is sudden in onset and lasts for a short duration of < 1 month (*Dowell et al 2022, International Association for the Study of Pain [IASP] 2024, U.S. Department of Health and Human Services 2019).*
- Moderate to severe acute pain can be a serious clinical condition that significantly impacts quality of life and physical functioning; inadequate pain management can negatively impact a patients' health and can increase the risk of developing chronic pain (*Journavx integrated review 2025*).
- The goals of acute pain management include pain relief, improved functioning, enhanced recovery, and patient satisfaction (*Mariano 2025*).
- Current pain management guidelines emphasize a multimodal approach, integrating pharmacologic and non-pharmacologic strategies to address acute, chronic, and post-operative pain. In general, nonopioid options are preferred due to their efficacy and lower risk of harms compared to opioids.
- Journavx (suzetrigine) is a first-in-class, nonopioid, oral analgesic that is Food and Drug Administration (FDA)-approved to treat moderate to severe acute pain. Suzetrigine functions as a selective inhibitor of the sodium voltage-gated sodium channel NaV1.8, which is predominantly expressed on nociceptors (pain-sensing neurons) in the peripheral nervous system. By inhibiting NaV1.8, suzetrigine inhibits the transmission of pain signals. It is the first nonopioid to be approved in over 20 years (*FDA website 2025*).
  - Suzetrigine does not carry the risk of drug abuse or dependence since there is no expression of NaV1.8 in the human brain; thus, abuse or addictive potential of suzetrigine is low.
- Medispan class: Analgesics- Sodium Channel Pain Signal Inhibitors, Selective NaV1.8 Sodium Channel Inhibitor

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Journavx (suzetrigine)
The treatment of moderate to severe acute pain in adults	✔

(Journavx prescribing information 2025)

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

Dosing and administration

- The recommended dosing regimen of suzetrigine is a one-time starting dose of 100 mg orally, followed by 50 mg orally every 12 hours administered 12 hours after the starting dose.
  - The starting dose should be taken on an empty stomach ≤ 1 hour before or ≥ 2 hours after food to avoid delay in onset of action. Clear liquids may be consumed during this time (eg, water, apple juice, vegetable broth, tea, black coffee)
  - After the initial 100 mg dose, suzetrigine may be administered with or without food.
  - Food or drink containing grapefruit should be avoided during treatment.
- Suzetrigine should be used for the shortest duration consistent with individual patient treatment goals. Suzetrigine has not been studied beyond 14 days for the treatment of moderate to severe acute pain.
- Full details for dosage adjustments due to hepatic impairment and/or concomitant use with CYP3A inhibitors can be found in the prescribing information.

Clinical Efficacy Summary

- The safety and efficacy of suzetrigine for the treatment of moderate or severe pain was established in 2 randomized, multicenter, double-blind, placebo and active-controlled trials. Adult patients aged 18 to 80 years old with postoperative pain rated as moderate or severe on the visual rating scale (VRS) with a pain score ≥ 4 on the numeric pain rating scale

(NPRS) after abdominoplasty (NAVIGATE 2; N = 1118; 12 sites in U.S.) or bunionectomy (NAVIGATE 1; N = 1073; 21 sites in U.S.) were included. In each trial, pain intensity was measured using a patient-reported 11-point NPRS, ranging from 0 to 10 (0 = no pain; 10 = the worst pain imaginable) (*ClinicalTrials.gov [NCT05553366, NCT05558410], FDA integrated review 2025*, *Journavx prescribing information 2025*).
  - For the primary endpoint of sum of pain intensity difference (SPID) measured over 48 hours (SPID48), suzetrigine demonstrated a significant reduction in pain compared to placebo:
    - NAVIGATE 1 (bunionectomy): least squares mean (LSM) difference, 29.3 (95% confidence interval [CI], 14.0 to 44.6; p = 0.0002)
    - NAVIGATE 2 (abdominoplasty): LSM difference, 48.4 (95% CI, 33.6 to 63.4; p < 0.0001)
  - For the first key secondary endpoint, suzetrigine monotherapy was not superior to low-dose hydrocodone/APAP (5 mg/325 mg every 6 hours) for SPID48.
  - For the second key secondary endpoint of time to ≥ 2-point reduction in NPRS from baseline, suzetrigine demonstrated a more rapid time to meaningful pain relief vs placebo in both trials, with a median time of:
    - NAVIGATE 1: 240 minutes vs 480 minutes, respectively (p < 0.0001)
    - NAVIGATE 2: 119 minutes vs 480 minutes, respectively (p < 0.0001)
    - Of note, results of the second key secondary endpoint were considered exploratory as testing was hierarchical and significance was not reached for the first key secondary endpoint.
- A Phase 3, open-label, single-arm study evaluated the safety and efficacy of suzetrigine in 256 adult patients with surgical (86.7%) and nonsurgical (13.3%) moderate to severe pain, for up to 14 days (mean, 9.6 days; median, 11 days) (*FDA integrated review 2025*, *McCoun et al 2024*).
  - For the primary endpoint of safety based on adverse events (AEs), suzetrigine was found to be well-tolerated, with the majority of AEs reported as mild or moderate; no serious AEs were attributed to treatment.
  - For the secondary endpoint evaluating the patient's perception of pain relief with suzetrigine, 83.2% of patients reported the effectiveness of suzetrigine in managing pain as good, very good, or excellent on a patient global assessment (PGA).
- An analysis by the Institute for Clinical and Economic Review (ICER) rated the evidence for suzetrigine for the treatment of acute pain (in comparison with no systemic treatment, opioid analgesics, or NSAIDs) as "promising but inconclusive (P/I)", defined as moderate certainty of a small or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit (*Rind et al 2025*).

Clinical guidelines

- Current pain management guidelines emphasize a multimodal approach that includes the use of pharmacologic and nonpharmacologic strategies to address acute, chronic, and postoperative pain. In general, nonopioid options are preferred due to their efficacy and lower risk of addiction compared to opioids. Of note, Suzetrigine has not yet been incorporated into guidelines.
  - The Centers for Disease Control and Prevention (CDC) recommends a multimodal approach to acute pain; maximizing the use of non-pharmacologic (ie, ice, heat, elevation, rest, immobilization, or exercise) and nonopioid therapies (eg, topical or oral nonsteroidal anti-inflammatory drugs [NSAIDS], acetaminophen [APAP]) for most acute pain conditions including low back pain, neck pain, musculoskeletal injuries (eg, sprains, strains, tendonitis, and bursitis), pain related to minor surgeries (with minimal tissue injury and mild postoperative pain), dental pain, kidney stones, and headaches (*Dowell et al 2022*).
    - Immediate release opioid therapy can have an important role in acute pain related to severe traumatic injuries (eg, crash injuries, burns), invasive surgeries that are associated with moderate to severe postoperative pain, or other acute pain conditions where NSAIDs or other therapies are contraindicated or likely to be ineffective. However, the use of opioids can be limited by their side effects (eg, nausea, vomiting, constipation) and carry significant risks including respiratory depression, addiction, overdose, and death (*Dowell et al 2022*).
  - The American Pain Society (APS), American Society of Regional Anesthesia and Pain Medicine (ASRA), and the American Society of Anesthesia (ASA) guidelines on the management of postoperative pain recommends a multimodal approach of pharmacological and nonpharmacological treatments for the treatment of postoperative pain in children and adults (*Chou et al 2016*).
    - Preoperatively, opioids are not recommended as an intervention to decrease postoperative pain; instead, a preoperative dose of celecoxib may be considered in adults with no contraindications.

- Postoperatively, short-acting oral opioids are preferred over intravenous opioids in patients who can use the oral route; long-acting opioids are not recommended postoperatively due to lack of evidence showing superiority over short-acting agents.
- The American Dental Association (ADA) guidelines for the pharmacologic management of acute dental pain in adolescents, adults, and older adults recommends that nonopioid medications represent first-line therapy when managing acute dental pain consecutive to tooth extraction(s) (simple, surgical) and the temporary management of toothache. NSAIDs alone (eg, ibuprofen 400 mg or naproxen 440 mg) or in combination with APAP (eg, 500 mg) are suggested for postoperative pain management (*Carrasco-Labra et al 2024*).
- The 2017 American College of Physicians (ACP) guidelines for the treatment of low-back pain recommend the use of nonpharmacologic therapies (eg, superficial heat, massage, acupuncture, spinal manipulation) as initial therapy. If medication is necessary, NSAIDS and skeletal muscle relaxants are preferred (*Qaseem et al 2017).*
- The 2020 ACP and American Academy of Family Physicians (AAFP) guidelines for nonpharmacologic and pharmacologic management of acute pain from nonlow back, musculoskeletal injuries in adults recommends a multimodal approach that utilizes topical NSAIDs and other nondrug therapies (eg, physical therapy, exercise) in addition to oral NSAIDs or APAP if needed for pain relief or improving physical function. Opioids are not recommended due to the risk of long-term use and associated harms (*Qaseem et al 2020).*
- The 2017 American College of Emergency Physicians (ACEP) policy statement on optimizing the treatment of acute pain in the emergency department emphasizes the importance of prompt, safe, and effective pain management tailored to individual patient needs. Key recommendations include a combination of pharmacologic and non-pharmacologic interventions to manage acute pain (*ACEP 2017*).
  - NSAIDs are recommended as first-line agents for many acutely painful conditions, prescribed at the lowest effective dose for the shortest duration to avoid complications.
  - APAP (oral or rectal) is suggested for mild to moderate pain. Intravenous acetaminophen is reserved for patients who cannot take medications orally or rectally.
  - Opioids may be considered for severe pain or when nonopioid treatments are ineffective; emphasizing the importance of using opioids judiciously and only after a thorough assessment of the patient's pain and overall status.
  - Other options such as regional anesthesia (ie, nerve blocks) or sub-dissociative dose ketamine may be used for certain acute pain conditions.

Safety summary

- Contraindication
  - Concomitant use of suzetrigine with strong cytochrome P450 (CYP)3A inhibitors
- Warnings and precautions
  - Moderate and severe hepatic impairment:
    - Suzetrigine should be avoided in patients with severe hepatic impairment (Child-Pugh Class C).
    - The dose of suzetrigine should be lowered in patients with moderate hepatic impairment (Child-Pugh Class B).
- Adverse effects
  - The most common AEs (occurring in ≥ 1% of patients treated with suzetrigine, and occurring at a greater rate than placebo) include pruritis, muscle spasms, increased creatine phosphokinase, and rash.
- Drug-drug interactions:
  - Suzetrigine is contraindicated with strong CYP3A inhibitors, and dose should be reduced with moderate CYP3A inhibitors. Patients should avoid food or drink with grapefruit.
  - In patients taking concomitant hormonal contraceptives containing progestins other than levonorgestrel and norethindrone, additional nonhormonal contraceptives (eg, condoms) or alternative contraceptives (eg, a combined oral contraceptive containing ethinyl estradiol as the estrogen and levonorgestrel or norethindrone as the progestin, an intrauterine system) should be administered during suzetrigine treatment and for 28 days after discontinuation of suzetrigine.
  - Suzetrigine is an inducer of CYP3A; dosage adjustments of concomitant CYP3A substrates may be required when initiating or discontinuing suzetrigine.

Conclusion

- Pain is one of the most common reasons adults seek medical care in the U.S. It is described as a response to a noxious stimulus that is sudden in onset and of limited duration (< 1 month).
- Suzetrigine is a first-in-class nonopioid analgesic approved for the treatment of moderate to severe acute pain, and the first pain medication with a novel mechanism of action approved in over 2 decades.
- Due to its mechanism of action as a selective inhibitor of the NaV1.8 sodium channels in the peripheral sensory nerves, there is no expression in the human brain; thus, abuse or addictive potential of suzetrigine is low.
- The role of treatment with suzetrigine is not yet clear due to the lack of long-term data. Clinical studies of up to 14 days have demonstrated superiority of suzetrigine vs placebo, but not low-dose hydrocodone/ APAP for postsurgical pain. Comparative efficacy vs NSAIDS or opioids have not been established.
- Current guidelines emphasize a multimodal approach that includes the use of pharmacologic and nonpharmacologic strategies to address acute, chronic, and postoperative pain. In general, nonopioid options are preferred due to their efficacy and lower risk of addiction compared to opioids. However, opioids may be considered when nonopioid treatments are ineffective, or their risks and benefits have been weighed after a thorough assessment of the patient's pain and overall status.
  - Suzetrigine has not yet been incorporated into pain management guidelines.

References

- American College of Emergency Physicians (ACEP): A joint policy statement of the ACEP, the American Academy of Emergency Nurse Practitioners, the Emergency Nurses Association, and the Society of Emergency Medicine Physician Assistants. Optimizing the treatment of acute pain in the emergency department. Updated April 2017. Accessed April 18, 2025. https://www.acep.org/patient-care/policy-statements/optimizing-the-treatment-of-acute-pain-in-the-emergency-department
- Bertoch T, D'Aunno D, McCoun J, et al. Randomized, placebo-controlled, phase 3 trials of suzetrigine, a non-opioid, pain signal inhibitor for treatment of acute pain after abdominoplasty of bunionectomy (NAVIGATE 1/NAVIGATE 2). Oral presentation at: The anesthesiology annual meeting; October 18 to 22, 2024; Philadelphia, PA.
- Carrasco-Labra A, Polk DE, Urquhart O, et al. Evidence-based clinical practice guideline for the pharmacologic management of acute dental pain in adolescents, adults, and older adults: A report from the American Dental Association Science and Research Institute, the University of Pittsburgh, and the University of Pennsylvania. *JADA*. 2024;155(2):102-117. doi.org/10.1016/j.adaj.2023.10.009
- Chou R, Gordon DB, de Leon-Casasola OA, et al. Guidelines on the management of postoperative pain: A clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain*. 2016;17(2):131-157. doi: 10.1016/j.jpain.2016.02.002
- Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain- United States, 2022. *MMWR Recomm Rep*. 2022;71(3). doi: 10.15585/mmwr.rr7103a1
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. Accessed April 18, 2025. https://www.accessdata.fda.gov/scripts/cder/daf/
- Evaluation of efficacy and safety of VX-548 for acute pain after an abdominoplasty. ClinicalTrials.gov identifier: NCT05558410. Updated August 27, 2024. Accessed April 16, 2026. https://clinicaltrials.gov/study/NCT05558410
- Evaluation of efficacy and safety of VX-548 for acute pain after bunionectomy. ClinicalTrials.gov identifier: NCT05553366. Updated March 20, 2024. Accessed April 16, 2025. https://clinicaltrials.gov/study/NCT05553366
- Food and Drug Administration (FDA). FDA News Release: FDA approves novel non-opioid treatment for moderate to severe acute pain. FDA. January 30, 2025. Accessed April 16, 2025. https://www.fda.gov/news-events/press-announcements/fda-approves-novel-non-opioid-treatment-moderate-severe-acute-pain
- International Association for the Study of Pain (IASP). Acute pain. IASP. Accessed April 18, 2025. https://www.iasp-pain.org/resources/topics/acute-pain/
- Journavx. Package insert. Vertex Pharmaceuticals Inc.; January 2025.
- Mariano ER. Approach to the management of acute pain in adults. UpToDate. Updated January 2025. Accessed April 18, 2025. https://www.uptodate.com
- McCoun J, Winkle P, Solanki D, et al. Suzetrigine, a non-opioid $Na_v1.8$ inhibitor with broad applicability for moderate-to-severe acute pain: a Phase 3 single-arm study for surgical or non-surgical acute pain. *J Pain Res*. 2025;18:1569-1576.
- Qaseem A, McLean RM, O'Gurek D, et al. Nonpharmacologic and pharmacologic management of acute pain from non-low back, musculoskeletal injuries in adults: a clinical guideline from the American College of Physicians and American Academy of Family Physicians. *Ann intern Med*. 2020;173:739-748. doi.10.7326/M19-3602
- Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments from acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2017;166:514-530. doi:10.7326/M16-2367.
- Rind DM, McQueen B, Nikitin D, et al. Suzetrigine for Acute Pain; Evidence Report. Institute for Clinical and Economic Review. March 31, 2025. Accessed April 18, 2025. https://icer.org/assessment/acute-pain-2025
- U.S. Department of Health and Human Services. Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. May 9, 2019. Accessed April 18, 2025. https://www.hhs.gov/sites/default/files/pmtf-final-report-2019-05-23.pdf

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Optum Rx®

Therapeutic Class Overview

Respiratory Phosphodiesterase (PDE) Inhibitors

Introduction

- The focus of this overview will include the selective phosphodiesterase (PDE) 4 and PDE3 and PDE4 inhibitors, Daliresp (roflumilast) and Ohtuvayre (ensifentrine).
  - Daliresp (roflumilast) is an orally administered, selective PDE4 inhibitor that is Food and Drug Administration (FDA)-approved to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Roflumilast is not a bronchodilator and is not indicated for the relief of acute bronchospasm (*FDA Website 2025*).
  - Ohtuvayre (ensifentrine) is an inhaled PDE3 and PDE4 inhibitor with both anti-inflammatory and bronchodilator effects, FDA approved for the maintenance treatment of COPD in adults (*FDA Website 2025*).
  - PDE3 inhibition causes smooth muscle relaxation through modulation of cyclic guanosine monophosphate (cGMP); PDE4 inhibition reduce inflammation by inhibiting the breakdown of intracellular cyclic adenosine monophosphate (cAMP), resulting in increased levels in lung cells (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2025*).
- COPD is a heterogeneous condition characterized by chronic respiratory symptoms resulting from persistent (often progressive) airflow limitation due to airway and/or alveolar abnormalities. These abnormalities are usually caused by genetic risk factors and/or environmental exposures (such as tobacco smoking and inhalation of toxic particles or gases) that occur over the lifetime of a person with COPD. Symptoms typically include dyspnea, chest tightness, fatigue, activity limitation, and cough with or without sputum production. Patients with COPD may also experience exacerbations, which are periods of acute worsening of respiratory symptoms (*GOLD 2025*). In 2021, 14.2 million adults in the United States (U.S.) (6.5% of the adult population) were estimated to have COPD (*Liu et al 2023*).
- The main treatment goals in COPD are to reduce symptoms and the risk of future exacerbations. Choice of therapy depends on a patient's severity of dyspnea and risk of exacerbations, and often includes the use of inhaled long-acting bronchodilators (ie, long-acting muscarinic antagonists [LAMAs] or long-acting β-agonists [LABAs]) and inhaled corticosteroids (ICSs) (*GOLD 2025*).
- The GOLD guidelines state that both roflumilast and ensifentrine are alternative additions to the treatment regimen of selected patients with severe COPD who are not adequately controlled by standard therapies (*GOLD 2025*).
- Medispan class: Anti-asthmatic and Bronchodilator Agents, Selective PDE4 Inhibitors; PDE3 & PDE4 Inhibitors

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)*
Daliresp (roflumilast)	✔
Ohtuvayre (ensifentrine)	-

*For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.

(*Drugs@FDA 2025, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2025*)

Indications

Table 2. Food and Drug Administration Approved Indications

Indication	Daliresp (roflumilast)	Ohtuvayre (ensifentrine)
To reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations	✔	
Maintenance treatment of COPD in adult patients		✔

- Limitations of use (roflumilast):
  - Roflumilast is not a bronchodilator and is not indicated for the relief of acute bronchospasm.
  - Roflumilast 250 mcg is a starting dose used only for the first 4 weeks of treatment and is not the effective (therapeutic) dose.

(*Prescribing information: Daliresp 2020, Ohtuvayre 2024*)

- 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

Roflumilast

- A Phase 3, double-blind (DB), placebo-controlled (PC), multicenter (MC), randomized controlled trial (RCTs) evaluated 1411 patients with moderate to severe COPD who were randomized to treatment with roflumilast 250 or 500 mcg/day or placebo for 6 months. Concurrent COPD medications were allowed, including short-acting β-agonists (SABAs) as rescue therapy and short-acting anticholinergics as daily use. After 6 months, patients treated with roflumilast achieved significant improvements in post-bronchodilator forced expiratory volume in 1 second (FEV_1) compared to baseline ($p < 0.05$ for both doses) and compared to patients treated with placebo ($p < 0.03$ for both doses). Improvements from baseline Saint George's Respiratory Questionnaire (SGRQ) scores were also significant for both doses of roflumilast ($p < 0.001$ and $p < 0.0001$, respectively), but not when compared to placebo ($p = 0.053$ and $p = 0.077$, respectively). For secondary end points, roflumilast was associated with significant reductions in acute COPD exacerbations vs placebo ($p = 0.0029$); the greatest effect was a 34% reduction with the 500 mcg dose compared to placebo (*Rabe et al 2005*).
- A 1-year DB, PC, parallel-group (PG) RCT evaluated the efficacy of roflumilast in 1513 patients ≥ 40 years of age with moderate to severe COPD. Patients were randomized to roflumilast 500 mcg daily (n = 760) or placebo (n = 753). Concurrent COPD medications allowed included SABA as rescue therapy, short-acting anticholinergics, and ICS (≤ 2000 mcg beclomethasone or equivalent). Patients treated with roflumilast achieved significant improvements in post-bronchodilator FEV_1 compared to placebo-treated patients ($p < 0.001$). However, the rate of moderate or severe COPD exacerbations (co-primary end point), was not significantly different between roflumilast- and placebo-treated patients (0.86 vs 0.92 per patient per year, respectively; p-value not reported). A post-hoc analysis of the data revealed that COPD exacerbations were more frequent in patients with GOLD Stage IV COPD. Within this group, exacerbations were significantly less frequent among those treated with roflumilast compared to those treated with placebo ($p = 0.024$). Changes in SGRQ scores were not found to differ between treatment groups ($p = 0.086$) (*Calverley et al 2007*).
- A pooled analysis evaluated the results from *Calverley et al 2007* with an identical, 1-year, PC, DB, RCT, both of which were inconclusive regarding the effect of roflumilast on exacerbations. Improvements in pre- and post-bronchodilator FEV_1, the primary and secondary end points, were significantly greater among roflumilast-treated patients compared to placebo-treated patients. In the pooled analysis, treatment with roflumilast was associated with a 14.3% lower rate of moderate to severe exacerbations (co-primary end point) vs placebo (0.52 vs 0.61 per year, respectively; $p = 0.026$) (*Rennard et al 2011*).
- Two identical, 1-year, PC, RCTS evaluated the effects of roflumilast on pre-bronchodilator FEV_1 values and rate of moderate or severe acute exacerbations (co-primary end points). Concurrent use of LABAs, in addition to SABAs as rescue therapy and short-acting anticholinergics were allowed in the trials. At the end of 1 year, pooled analysis revealed that patients treated with roflumilast achieved significant improvements in pre-bronchodilator FEV_1 ($p < 0.0001$) and had a significantly lower rate of moderate or severe acute exacerbations (relative risk [RR], 0.83; 95% confidence interval [CI], 0.75 to 0.95; $p = 0.0003$) compared to patients treated with placebo. Of the secondary outcomes, only the pooled Transition Dyspnea Index (TDI) focal scores were significantly improved in roflumilast-treated patients compared to placebo-treated patients ($p = 0.0009$). Mortality rates (p-values not reported) and time to mortality did not differ between treatment groups (206.1 vs 211.7 days; hazard ratio, 1.1; 95% CI, 0.7 to 1.8; $p = 0.5452$) (*Calverley et al 2009*).
- Pooled data from 2 DB, MC, RCTs compared roflumilast to placebo in 3091 patients with severe-to-very severe COPD. Concomitant respiratory medications permitted during the trials included SABAs as rescue medication, LABAs, and short-acting anticholinergics at stable doses. Results demonstrated that roflumilast led to improvements in pre-bronchodilator and post-bronchodilator FEV_1, as well as the rate of exacerbations per year. The reduction in exacerbations was similar in patients with and without concomitant LABA use (*Bateman et al 2011*).
- A 12-week DB, PC, PG RCT evaluated the effects of roflumilast on airway physiology during rest and exercise in 250 patients with COPD. Patients were allowed concomitant salbutamol as rescue medication, ipratropium at a constant daily dosage, and ICS at a constant daily dosage. Results demonstrated no significant treatment difference in the primary end point of exercise endurance time. For secondary end points, small changes in airway function were observed, including those for pre- and post-bronchodilator FEV_1 and FEV_1/forced vital capacity (FVC). Additionally,

small improvements in selected physiologic end points were noted during exercise, including ventilation at peak exercise and arterial oxygen saturation (*O'Donnell et al 2012*).

- Two DB, MC, PC trials in patients ≥ 40 years of age with moderate-to-severe COPD evaluated roflumilast 500 mcg daily vs placebo , in addition to tiotropium (Trial 1; n = 935) or salmeterol (Trial 2; n = 744). Both trials demonstrated improvements in pre-bronchodilator and post-bronchodilator FEV_1, and post-bronchodilator FVC with roflumilast. However, the rate of mild, moderate, or severe COPD exacerbations was not significantly reduced with roflumilast in either trial (*Fabbri et al 2009*).
- The 52-week DB, MC, PC, randomized REACT trial evaluated the efficacy of roflumilast 500 mcg tablets once daily vs placebo on exacerbation rate and pulmonary function in 1945 patients with COPD with severe airflow limitation (FEV_1/FVC < 0.7 and post-bronchodilator FEV_1 ≤ 50% predicted) and a history of ≥ 2 exacerbations in the previous year. Patients must have been receiving a combination ICS/LABA for ≥ 12 months with a stable dose for ≥ 3 months. Concomitant tiotropium was allowed but not required. The primary end point, the rate of moderate-to-severe COPD exacerbations per patient per year, was 0.805 with roflumilast and 0.927 with placebo (RR, 0.868; 95% CI, 0.753 to 1.002; p = 0.0529) according to the Poisson regression analysis. Results were similar using a different type of statistical analysis (ie, negative binomial regression), which demonstrated that results were statistically significant (p = 0.0424). Roflumilast reduced the incidence of severe exacerbations (RR, 0.757; p = 0.0175) and exacerbations necessitating hospital admission (RR, 0.761; p = 0.0209) vs placebo. Roflumilast treatment also improved FEV_1 and FVC, with differences from placebo of 56 mL and 92 mL, respectively (p < 0.0001 for both comparisons). Although results on the primary end point were of borderline statistical significance, this study demonstrates some benefit with roflumilast in this high-risk group of patients who were concomitantly treated with ICS/LABA (*Martinez et al 2015*).
- In the 52-week, DB, MC, PC, RCT (RE^2SPOND), patients with severe to very severe COPD, chronic bronchitis, ≥ 2 exacerbations in the previous year, and on standard ICS/LABA with or without LAMA therapy, were randomized to receive roflumilast (n = 1178) or placebo (n = 1176). The primary end point, reduction in moderate and/or severe exacerbations, was not found to be statistically significant (95% CI, 0.81 to 1.04; p = 0.163). Roflumilast was, however, shown to improve FEV_1 from baseline (p < 0.0001) as similarly demonstrated by previous studies. Post hoc analysis demonstrated a statistically significant reduction of moderate to severe exacerbations in the subset of patients with a history of higher exacerbation burden (> 3 exacerbations per year) and hospitalization, suggesting roflumilast may have a place in therapy for this demographic (*Martinez et al 2016*).
  - A pooled analysis of the REACT and RE^2SPOND trials found that compared to placebo, roflumilast reduced the rate of moderate or severe COPD exacerbations/patient/year (1.01 vs 1.16; p = 0.0086) and the rate of severe COPD exacerbations/patient/year (0.25 vs 0.30; p = 0.041). Roflumilast was associated with a reduced risk of moderate or severe exacerbations in certain subgroups, including those hospitalized for COPD exacerbations in the previous year (p = 0.0005), baseline eosinophils ≥ 150 cells/mcL (p = 0.002), and baseline eosinophils ≥ 300 cells/mcL (p = 0.026). A total of 5.7% more patients treated with roflumilast withdrew due to adverse events vs placebo (*Martinez et al 2018*).
- A meta-analysis reported pooled data from 4 PC RCTs (N = 5595) to evaluate the effects of roflumilast on dyspnea in patients with moderate to very severe COPD. The meta-analysis demonstrated that at week 52, roflumilast significantly improved the mean TDI focal score, with a difference of 0.327 units (95% CI, 0.166 to 0.488; p < 0.0001). This mean change was less than the minimum clinically important difference (MCID) of 1 unit. However, the authors reported that the percentage of TDI responders (≥ 1 unit) was greater in patients treated with roflumilast (39%) than in patients treated with placebo (33.9%) (p < 0.01) (*Rennard et al 2014*).
- A meta-analysis of 26 RCTs (N = 36,312) evaluated the efficacy roles of LABA, LAMA, ICS, and roflumilast therapy, both alone and in combination, on the rate of COPD exacerbations in patients with moderate to severe COPD. The primary end point was reported in terms of an absolute treatment effect, expressed as mean exacerbations experienced per patient per year. A regimen composed of roflumilast, LABA, LAMAs, and an ICS was associated with the greatest reduction in the number of exacerbations (absolute treatment effect, 0.53; 95% CI, 0.43 to 0.64), while the absolute treatment effect of roflumilast monotherapy was 1.01 (95% CI, 0.89 to 1.14). A combination of LAMA + LABA + ICS was associated with a treatment effect of 0.63 (95% CI, 0.54 to 0.73) (*Mills et al 2011*). A smaller meta-analysis of 8 clinical trials found that roflumilast reduced the overall rate of exacerbations compared to placebo (-0.41 events/patient-year; 95% CI, -0.72 to -0.11) (*Oba and Lone 2013*).
- A meta-analysis of 11 RCTs evaluated the effect of roflumilast (with or without bronchodilators) on pre-bronchodilator FEV_1, post-bronchodilator FEV_1, and exacerbation rates in patients with COPD. Roflumilast significantly improved both pre-bronchodilator FEV_1 (standardized mean difference [SMD] ± standard deviation [SD], 0.621 ± 0.161; 95% CI, 0.306

to 0.936, p < 0.001) and post-bronchodilator FEV_1 (SMD ± SD, 0.563 ± 0.149; 95% CI, 0.270 to 0.855; p < 0.001) compared with placebo. Roflumilast also significantly reduced exacerbation of COPD (SMD ± SD, 0.099 ± 0.020; 95% CI, 0.061 to 0.138; p < 0.001) and suppressed airway inflammation (SMD ± SD, 1.354 ± 0.260; 95% CI, 0.845 to 1.862; p < 0.001) compared with placebo. However, roflumilast significantly increased adverse effects such as diarrhea (rate ratio, 2.945; 95% CI, 2.453 to 3.536; p < 0.001) and weight loss (rate ratio, 3.814; 95% CI, 3.091 to 4.707; p < 0.001) compared with placebo (*Shen et al 2018*).

- A Cochrane systematic review evaluated the safety and efficacy of oral PDE4 inhibitors for the management of stable COPD in patients with moderate to very severe COPD with mean age of 64 years.A total of 42 RCTs were included in the review (roflumilast, 28 trials [n = 18,046 patients]; cilomilast [not available in U.S.], 14 trials [n = 6457]; tetomilast [not available in U.S.], 1 trial [n = 84]), which demonstrated treatment with PDE4 inhibitors was associated with a small, clinically insignificant improvement in FEV_1 over a mean of 40 weeks compared with placebo (mean difference [MD], 49.33 mL; 95% CI, 44.17 to 54.49; 29 trials [N = 20,815]; moderate-certainty evidence). FVC and peak expiratory flow (PEF) were also improved over 40 weeks (FVC: MD, 86.98 mL; 95% CI, 74.65 to 99.31; 17 trials [N = 22,108]; high-certainty evidence; PEF: MD, 6.54 L/min; 95% CI, 3.95 to 9.13; 6 trials [N = 4245]; low-certainty evidence). Improvements in quality of life were reported over a mean of 33 weeks. Treatment with a PDE4 inhibitor was associated with a reduced likelihood of COPD exacerbation over a mean of 40 weeks (odds ratio [OR], 0.78; 95% CI, 0.73 to 0.84; 27 trials [N = 20,382]; high-certainty evidence), ie, for every 100 patients treated with PDE4 inhibitors, 5 more remained exacerbation-free during the study period compared with those who were treated with placebo (number needed to treat for an additional beneficial outcome, 20; 95% CI, 16 to 27). No change in COPD-related symptoms nor in exercise tolerance was found. Roflumilast was associated with gastrointestinal adverse effects (diarrhea, nausea, abdominal pain, and weight loss), and psychiatric adverse effects (anxiety, depression, insomnia) (*Janjua et al 2020*).
- In a meta-analysis of 6 RCTs (N = 9715) evaluating the use of roflumilast in combination with ICS/LABA in patients with severe COPD compared with placebo, roflumilast was superior in patients treated with ICS/LABA combinations for the end point of FEV_1 before bronchodilator administration (MD, 46.62; 95% CI, 30.69 to 62.55; p < 0.00001), FEV_1 after bronchodilator administration (MD, 45.62; 95% CI, 34.95 to 56.28; p < 0.00001), and COPD exacerbation rate (RR, 0.90; 95% CI, 0.87 to 0.94; p = 0.001). Incidences of diarrhea, headache, nausea, weight loss, back pain, loss of appetite, and insomnia with roflumilast were markedly higher than that in the placebo group, and differences were statistically significant (*Zeng et al 2022*).
- The GOLD guidelines summarize the efficacy of roflumilast. Roflumilast reduces moderate and severe exacerbations treated with systemic corticosteroids in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations; effects on lung function are also seen when roflumilast is added to long-acting bronchodilators and in patients who are not controlled on fixed-dose LABA/ICS combinations. The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation, and there are no studies directly comparing roflumilast with an ICS (*GOLD 2025, Rabe et al 2017*).

Ensifentrine

- The efficacy of ensifentrine was evaluated in two 24-week, DB, PC, PG, RCTs (ENHANCE-1 and ENHANCE-2) in adult patients 40 to 80 years of age with COPD and a post-bronchodilator FEV_1 of 30% to 70% of predicted normal, and a modified Medical Research Council (mMRC) dyspnea scale score ≥ 2 (range, 0 to 4, with higher numbers indicating more severe breathlessness). Enrolled patients could not be taking long-acting maintenance therapy including dual bronchodilator therapy (LABA + LAMA) or triple therapy (LABA + LAMA + ICS); but they could be receiving 1 inhaled bronchodilator (LAMA or LABA) with or without ICS. Patients with a COPD exacerbation within 3 months prior to screening were also excluded. Patients were randomized 5:3 to receive ensifentrine 3 mg nebulized twice daily or placebo (*Anzueto et al 2023*).
  - The change from baseline in FEV_1 area under the curve $(AUC)_{0\text{-}12h}$ post dose at Week 12 (primary end point), was significantly improved for ensifentrine vs placebo in both studies:
    - ENHANCE-1: 61 mL vs -26 mL (difference, 87 mL; 95% CI, 55 to 119; p < 0.001)
    - ENHANCE-2: 48 mL vs -46 mL (difference, 94 mL; 95% CI, 65 to 124; p < 0.001)
  - Key secondary end points:
    - FEV_1 peak and FEV_1 trough at week 12 significantly favored ensifentrine.
    - Treatment with ensifentrine significantly improved symptoms (Evaluating Respiratory Symptoms [E-RS] scale) and quality of life (SGRQ) vs placebo at Week 24 ENHANCE-1 but not in ENHANCE-2.

- The trials also demonstrated that treatment with ensifentrine reduced the rate of moderate or severe exacerbations (ENHANCE-1, p = 0.050; ENHANCE-2; p = 0.009) and increased time to first exacerbation (ENHANCE-1, p = 0.038; ENHANCE -2; p = 0.009) vs placebo over 24 weeks.

- An Institute for Clinical and Economic Review (ICER) report based on pooled data from ENHANCE-1 and ENHANCE-2 found statistically significant improvements with use of ensifentrine vs placebo on lung function, E-RS (with a difference that did not exceed the MCID), TDI (with a difference that just met the MCID), use of rescue medication, and exacerbations. No significant effect was observed on SGRQ (*Lin et al 2024*).
  - Compared to maintenance therapy alone, ensifentrine was given evidence rating of "B+" (incremental or better; moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit).
  - The authors noted that they have somewhat greater certainty in the benefits when ensifentrine is added to the regimens studied (ie, no background therapy, or LAMA or LABA with or without ICS) vs to regimens with combined LAMA + LAMA. There remains some uncertainty about the magnitude of overall benefit in patients receiving the most optimized modern inhaler therapies for COPD; however, there was no effect modification by background therapy type in the trials.
- The GOLD guidelines state that ensifentrine improves lung function, dyspnea, and health status, but an effect on exacerbations has not been evaluated in patients at increased exacerbation risk (*GOLD 2025*).

Clinical Guidelines

- The 2025 GOLD guidelines state that the initial management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and risk of exacerbations; the risk of exacerbations is based on a patient's exacerbation history and severity. The algorithm for initial pharmacologic treatment addresses the clinical relevance of exacerbations independent of symptom level. Key recommendations from the GOLD guidelines are as follows (*GOLD 2025*):
  - Inhaled bronchodilators are central to symptom management in COPD and are commonly administered on a regular basis to prevent or reduce symptoms.
  - LAMAs and LABAs significantly improve lung function, dyspnea, and health status, and reduce exacerbation rates.
    - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea, and for immediate relief of symptoms in patients already receiving long-acting bronchodilators for maintenance therapy.
    - LAMAs have a greater effect on exacerbation reduction compared to LABAs and decrease hospitalizations.
  - For initial treatment with long-acting bronchodilators, a LAMA + LABA combination is the preferred choice. In patients with persistent dyspnea on 1 long-acting bronchodilator, treatment should be escalated to 2 long-acting bronchodilators (LAMA + LABA; administered as single or multiple inhaler treatment).
  - Long-term monotherapy with ICS is not recommended. Long-term treatment with ICS may cause pneumonia in patients with severe disease.
  - Initial treatment recommendations for patients with COPD are based on their GOLD patient group (Group A, B, or E; see Table 2).
    - Group A: Patients should be offered bronchodilator treatment (either short- or long-acting), based on its effect on breathlessness. If available and affordable, long-acting bronchodilator treatment is preferred except in patients with very occasional dyspnea. The treatment should be continued if symptomatic benefit is documented.
    - Group B: Initial therapy should consist of a LAMA + LABA combination, given there are no issues regarding availability, affordability, and adverse effects. In patients for whom this combination is not appropriate, treatment with either a LAMA or LABA is recommended; no evidence is available to support the use of one long-acting bronchodilator over another, hence the choice depends on the patient's perception of relief of symptoms. Patients in Group B are more likely to have comorbid conditions that may impact prognosis and symptomatic relief; these conditions should be treated in accordance with their respective clinical guidelines.
    - Group E: The preferred initial choice is a LAMA + LABA combination, given there are no issues regarding availability, affordability, and adverse effects. The use of ICS + LABA is not encouraged; if use of an ICS is indicated, ICS + LABA + LAMA is preferred since this combination has been shown to be superior to ICS + LABA. The use of ICS + LABA + LAMA may be considered in patients with a blood eosinophil count ≥ 300 cells/µL. Patients with concomitant asthma should be treated like patients with asthma, requiring use of an ICS.

Table 2. Assessment of symptoms and risk of exacerbations to determine GOLD patient group

Exacerbation history	Symptoms	
	mMRC 0 to 1 CAT < 10	mMRC ≥ 2 CAT ≥ 10
≥ 2 moderate exacerbations or ≥ 1 leading to hospital admission	E	
0 or 1 moderate exacerbations (not leading to hospital admission)	A	B

Abbreviations: CAT = COPD assessment test; mMRC = modified British Medical Research Council dyspnea questionnaire

- Follow-up pharmacological treatment: Subsequent adjustments to maintenance therapy may be to manage dyspnea or exacerbations irrespective of the patient GOLD group, as follows:
  - Dyspnea pathway: For persistent dyspnea, the use of 2 long-acting bronchodilators (LAMA + LABA) is recommended in patients receiving bronchodilator monotherapy and experiencing persistent breathlessness or exercise limitation. If the addition of a second long-acting bronchodilator does not improve patient symptoms, the following options may be considered:
    - Switching inhaler devices or molecules
    - Implementing or escalating non-pharmacologic treatment(s)
    - Adding ensifentrine
    - Investigating and treating other causes of dyspnea
  - Exacerbation pathway: In patients with persistent exacerbations on bronchodilator monotherapy, escalation to LAMA + LABA (or LAMA + LABA + ICS if blood eosinophil count ≥ 300 cells/µL) is recommended. For patients who develop further exacerbations, additional therapy options include escalation to a LAMA + LABA + ICS if eosinophil counts are ≥ 100 cells/µL, addition of roflumilast and/or azithromycin to LAMA + LABA if eosinophil counts are < 100 cells/µL, and addition of dupilumab to LAMA + LABA + ICS if eosinophil counts are ≥ 300 cells/µL.

- The American Thoracic Society (ATS) clinical practice guidelines recommend the following pharmacologic treatment for patients with COPD (Strong to conditional strength of recommendation/Moderate level of evidence) (*Nici et al 2020*):
  - Those who complain of dyspnea or exercise intolerance: LAMA/LABA combination therapy is recommended over LABA or LAMA monotherapy.
  - Those who complain of dyspnea or exercise intolerance despite dual therapy with LAMA/LABA: use of triple therapy with LAMA/LABA/ICS is recommended over dual therapy with LAMA/LABA in those patients with a history of ≥ 1 exacerbation(s) in the past year requiring antibiotics or oral steroids or hospitalization.
  - Those receiving triple therapy (LAMA/LABA/ICS): It is suggested that the ICS can be withdrawn if the patient has had no exacerbations in the past year.
  - No recommendation is made for or against ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia, except for those patients with a history of ≥ 1 exacerbation(s) in the past year requiring antibiotics or oral steroids or hospitalization, for whom ICS as an additive therapy is suggested.
  - The guidelines do not include information or recommendations about roflumilast or ensifentrine.
- The American College of Chest Physicians (ACCP) and Canadian Thoracic Society (CTS) guidelines for the prevention of acute exacerbations of COPD suggest the use of roflumilast to prevent acute exacerbations in patients with moderate to severe COPD with chronic bronchitis and a history of ≥ 1 exacerbation in the previous year (*Criner et al 2015*).
  - The guidelines do not include information or recommendations regarding ensifentrine.
- Key recommendations from the American College of Physicians (ACP)/ACCP/ATS/European Respiratory Society (ERS) include (*Qaseem et al 2011*):
  - For symptomatic patients with COPD and FEV_1 < 60% predicted, it is recommended that clinicians prescribe monotherapy using either LAMAs or LABAs (strong recommendation, moderate-quality evidence); in these patients, clinicians may administer combination inhaled therapies (LAMAs, LABAs, or ICS) (weak recommendation, moderate-quality evidence).
  - The guidelines do not include information or recommendations about roflumilast or ensifentrine.

Safety Summary

Ensifentrine

- Warnings and precautions include the following:

- Acute episodes of bronchospasm: Ensifentrine should not be used to treat acute symptoms of bronchospasm.
- Paradoxical bronchospasm: If paradoxical bronchospasm occurs, ensifentrine should be discontinued and alternative therapy should be initiated.
- Psychiatric reactions including suicidality: Prescribers should carefully weigh risks and benefits of treatment with ensifentrine before using in patients with a history of depression and/or suicidal thoughts or behavior.
  - One suicide attempt was reported in an ensifentrine-treated patient in the pooled 24-week safety population, and 1 completed suicide was reported in another controlled study.
  - Additional psychiatric adverse events (< 1% incidence) included insomnia, depression-related reactions, and anxiety.

- The most common (≥ 1%) adverse events included back pain, hypertension, urinary tract infection, and diarrhea.

Roflumilast

- Roflumilast is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).
- Warnings and precautions include the following:
  - Treatment of acute bronchospasm: Roflumilast is not a bronchodilator and should not be used for the relief of acute bronchospasm.
  - Psychiatric events including suicidality: Treatment is associated with an increase in psychiatric adverse effects, including insomnia, anxiety, and depression. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials with roflumilast in patients with and without a history of depression.
    - Prescribers should carefully weigh risks and benefits of treatment with roflumilast before using in patients with a history of depression and/or suicidal thoughts or behavior. Patients, caregivers, and families should be advised of the need to be alert for psychiatric adverse events.
    - An analysis of FDA Adverse Event Reporting System (FAERS) reports conducted by the Institute for Safe Medication Practices (ISMP) and published in April 2017 identified a confirming signal for suicidal and self-injurious behaviors (*ISMP 2017*).
  - Weight decrease: Weight loss may occur with roflumilast use.
- Drug Interactions include the following:
  - Strong cytochrome P450 (CYP) enzyme inducers (eg, carbamazepine, phenobarbital, phenytoin, rifampicin) decrease systemic exposure to roflumilast and may reduce its therapeutic effectiveness; concurrent use is not recommended.
  - Concurrent administration of roflumilast with CYP3A4 inhibitors or dual inhibitors that inhibit CYP3A4 and 1A2 simultaneously (eg, cimetidine, enoxacin [not available in the U.S.], erythromycin, fluvoxamine, ketoconazole) may increase roflumilast systemic exposure and may result in increased adverse effects. The risk of concurrent use should be weighed carefully against benefit.
  - The concurrent administration of roflumilast and oral contraceptives containing gestodene (not available in U.S.) and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased adverse effects. The risk of such concurrent use should be weighed carefully against benefit.
- Roflumilast has more adverse effects than inhaled medications for COPD (*GOLD 2025*). The most common adverse events (incidence ≥ 2%) include diarrhea, weight loss, headache, nausea, back pain, insomnia, influenza, dizziness, and decreased appetite.

Dosing and Administration

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Daliresp (roflumilast)	Tablets	Oral	Once daily	• May be taken with or without food • Starting with the lowest recommended dose for the first 4 weeks and then increasing to the recommended (therapeutic) dose thereafter may reduce the rate of treatment discontinuation in some patients.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ohtuvayre (ensifentrine)	Inhalation suspension	Inhalation (with nebulizer)	Twice daily	• Should be administered with a standard jet nebulizer with a mouthpiece • Should be used with caution in patients with hepatic impairment due to increased exposure of ensifentrine

See the current prescribing information for full details.

Conclusion

- The main treatment goals in COPD are to reduce symptoms and the risk of future exacerbations. Patients with COPD are managed predominantly with inhaled bronchodilators (LAMAs and/or LABAs), with the addition of ICS in certain patients. The 2025 GOLD guidelines have positioned the 2 PDE inhibitors, roflumilast and ensifentrine, as an additional therapeutic agent for patients.
  - Roflumilast is a once-daily, orally administered PDE4 inhibitor indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.
  - Ensifentrine is PDE3 and PDE4 inhibitor is administered twice daily via nebulization. It is indicated for the maintenance treatment of COPD in adults.
- Roflumilast improves lung function and reduces moderate and severe exacerbations treated with systemic corticosteroids in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations. The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators and in patients who are not controlled on fixed-dose LABA/ICS combinations. The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for acute exacerbation.
  - Roflumilast is associated with more adverse effects than the inhaled medications for COPD. The most frequent adverse events include diarrhea, nausea, weight loss, and headache. Adverse events occur early in treatment and are reversible. Potential drug interactions with CYP enzyme inducers, CYP3A4 inhibitors, and oral contraceptives should also be considered due to their effects on the systemic exposure of roflumilast.
- Ensifentrine improves lung function, dyspnea, and health status, but an effect on exacerbations has not been evaluated in patients at increased exacerbation risk. In 2 pivotal Phase 3 trials, ensifentrine demonstrated greater efficacy vs placebo on end points of lung function (FEV_1) and exacerbation rates. Improvements in patient symptom and quality of life scores were also demonstrated with ensifentrine vs placebo, but results were not consistent in both studies.
  - The most common adverse events with ensifentrine included back pain, hypertension, urinary tract infection, and diarrhea.
- Roflumilast and ensifentrine have warnings for psychiatric events including suicidality. Both agents should be used with caution in patients with depression.
- The GOLD guidelines place roflumilast as an additional therapeutic agent for patients with an $FEV_1 < 50\%$ predicted and chronic bronchitis who continue to experience COPD exacerbations despite therapy with LAMA + LABA (or LAMA + LABA + ICS with blood eosinophils ≥ 100 cells/µL). ACCP/CTS guidelines suggest the use of roflumilast to prevent acute exacerbations in patients with moderate to severe COPD with chronic bronchitis and a history of ≥ 1 exacerbation in the previous year.
- The GOLD guidelines place ensifentrine as additional therapeutic agent in patients who continue to experience dyspnea despite treatment with LAMA + LABA.
- Although not first-line agents, roflumilast and ensifentrine are unique because they are a different class of medications indicated for management of COPD and may play a role as add-on therapies in selected patients with COPD.

References

- Anzueto A, Barjaktarevic IZ, Siler TM, et al. Ensifentrine, a novel phosphodiesterase 3 and 4 inhibitor for the treatment of chronic obstructive pulmonary disease: Randomized, double-blind, placebo-controlled, multicenter Phase III trials (the ENHANCE Trials). *Am J Respir Crit Care Med*. 2023;208(4):406-416. doi: 10.1164/rccm.202306-0944OC.
- Bateman ED, Rabe KF, Calverley PM, et al. Roflumilast with long-acting β2-agonists for COPD: Influence of exacerbation history. *Eur Resp J*. 2011;38(3):553-560.
- Calverley PMA, Rabe KF, Goehring UM, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: Two randomized clinical trials. *Lancet*. 2009;374:685-694.

- Calverley PMA, Sanchez-Toril F, McIvor A, et al. Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;176:154-161.
- Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest*. 2015;147(4):894-942.
- Daliresp. Package insert. AstraZeneca Pharmaceuticals; March 2020.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. Accessed January 24, 2025. https://www.accessdata.fda.gov/scripts/cder/daf/.
- Fabbri LM, Calverly PMA, Izquierdo-Alonso JL, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long acting bronchodilators: Two randomized clinical trials. *Lancet*. 2009;374:695-703.
- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2025. Accessed January 24, 2025. https://goldcopd.org/2025-gold-report/.
- ISMP QuarterWatch. April 19, 2017 – New data from 2016 Q3. Depression and suicidal behaviors. Accessed January 24, 2025. https://www.ismp.org/quarterwatch/depression-and-suicidal-behaviors.
- Janjua S, Fortescue R, Poole P. Phosphodiesterase-4 inhibitors for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2020;5(5):CD002309. doi: 10.1002/14651858.CD002309.pub6.
- Lin G, Whittington MD, Wright A, McKenna A, Richardson M, Rind DM. Ensifentrine for the treatment of chronic obstructive pulmonary disease: Effectiveness and value. Institute for Clinical and Economic Review, July 16, 2024. https://icer.org/assessment/copd-2024/.
- Liu Y, Carlson SA, Watson KB, Xu F, Greenlund KJ. Trends in the prevalence of chronic obstructive pulmonary disease among adults aged ≥ 18 years - United States, 2011–2021. *MMWR Morb Mortal Wkly Rep*. 2023;72:1250-256. doi: http://dx.doi.org/10.15585/mmwr.mm7246a1.
- Martinez FJ, Calverley PMA, Goehring UM, et al. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): A multicentre randomised controlled trial. *Lancet*. 2015;385:857-866.
- Martinez FJ, Rabe KF, Calverley PM, et al. Determinants of response to roflumilast in severe chronic obstructive pulmonary disease. Pooled analysis of two randomized trials. *Am J Respir Crit Care Med*. 2018;198(10):1268-1278.
- Martinez FJ, Rabe KF, Sethi S, et al. Effect of roflumilast and inhaled corticosteroid/long-acting β_2-agonist on chronic obstructive pulmonary disease exacerbations (RE^{2}SPOND): A randomized clinical trial. *Am J Respir Crit Care Med*. 2016;194:559-567.
- Mills EJ, Druyts E, Ghemet I, et al. Pharmacotherapies for chronic obstructive pulmonary disease: A multiple treatment comparison meta-analysis. *Clinical Epidemiology*. 2011;3:107-129.
- Nici L, Mammen MJ, Charbek E, et al. American Thoracic Society Assembly on Clinical Problems. Pharmacologic management of chronic obstructive pulmonary disease: An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2020;201(9):e56-e69. doi: 10.1164/rccm.202003-0625ST.
- O'Donnell DE, Bredenbroker D, Brose M, et al. Physiological effects of roflumilast at rest and during exercise in COPD. *Eur Respir J*. 2012;39(5):1104-1112.
- Oba Y, Lone NA. Efficacy and safety of roflumilast in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Ther Adv Respir Dis*. 2013;7(1):13-24. doi: 10.1177/1753465812466167.
- Ohtuvayre. Package Insert. Verona Pharma, Inc; June 2024.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Rockville, MD: U.S. Food and Drug Administration. Accessed January 24, 2025. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.
- Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: A clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med*. 2011;155:179-191.
- Rabe KF, Bateman ED, O'Donnell D et al. Roflumilast-an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: A randomized controlled trial. *Lancet*. 2005;366:563-571.
- Rabe KF, Calverley PMA, Martinez FJ, et al. Effect of roflumilast in patients with severe COPD and a history of hospitalisation. *Eur Respir J*. 2017;50:1700158.
- Rennard SI, Calverley PMA, Goehring UM, et al. Reduction of exacerbations by the PDE4 inhibitor roflumilast-the importance of defining different subsets of patients with COPD. *Respir Res*. 2011;12(18):2-10.
- Rennard SI, Sun SX, Tourkodimitris S, et al. Roflumilast and dyspnea in patients with moderate to very severe chronic obstructive pulmonary disease: A pooled analysis of four clinical trials. *Int J Chron Obstruct Pulmon Dis*. 2014;9:657-673.
- Shen L, Lv X, Chen W, Yang Q, Fang Z, Lu W. Effect of roflumilast on chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Ir J Med Sci*. 2018;187:731-738.
- Zeng S, Bai H, Zou M. Effects of roflumilast on patients with chronic obstructive pulmonary disease treated with inhaled corticosteroid/long-acting *β* 2 agonist: A meta-analysis. *Comput Math Methods Med*, 2022; 2022:8101099. doi: 10.1155/2022/8101099.

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