South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

June 7, 2024

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

June 7, 2024
1:00 – 3:00 PM CT
12:00 – 2:00 PM MT

Meeting Link:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_NzBhMzM4ODItNzQ1MS00NmQ5LTkyMzgtOTE3N2NhZDU5ZjQ2%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
425899727@t.plcm.vc
Video Conference ID: 116 195 962 48

Join by phone
+1 952-222-7450
Phone Conference ID: 320 271 058#

Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **Vijoice PA reviews**
- **Linzess PA reviews**
- **Opioid update**
- **MAT drug review**

New business
- **PA reviews on low volume requests**
- **Rezdiffra**
- **Auvelity**
- **Exxua**
- **Lybalvi**
- **Veozah**

Public input accepted after individual topic discussion
Next meeting date September 20, 2024 & adjournment

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

Friday, March 8, 2024
1:00 – 3:00 pm CT

Members and DSS Staff

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

Administrative Business

Van Gilder called the meeting to order at 1:02 pm. The minutes of the December meeting were presented. Baack made a motion to approve. Oehlke seconded the motion. The motion was unanimously approved.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from October 1, 2023, to December 31, 2023. A total of 2,845 PAs were reviewed of which 173 requests (6.1%) were received via telephone, 131 requests (4.6%) were received via fax, 940 (33%) were reviewed electronically, and 1,594 (56%) were received via ePA. After a full year since ePA implementation, it continues to dominate. There was a 17.8% increase in PAs received compared to the previous quarter. The therapeutic class ADHD/Anti-narcolepsy debut on the Top Classes for PAs reviewed.

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, 2023, to December 31, 2023. The top five therapeutic classes based on paid amount were atypical antipsychotics, disease-modifying anti-rheumatic agents, skin and mucous membrane agents, incretin mimetics, and cystic fibrosis correctors. These top 15 therapeutic classes comprise 22.67% of total claims. The committee also reviewed the top 50 drugs based on amount paid and number of claims. The top 50 drugs by amount paid make up 8.36% of total claims.

Old Business

Seglentis & tramadol review

The committee reviewed the Seglentis utilization. Stanley commented that there is not a clinical benefit or reason to support a combination drug. Baack motioned to adopt PA similar to State B for prescribers to provide a letter necessity. Stanley seconded the motion. Van Gilder inquired if there was any public comment. There was none. The motion was approved unanimously.

Hepatitis C review

The committee had inquired on the number of members that were not treated for hepatitis C since the PA criteria was changed. Based on the number of rejected claims and number treated, the state will investigate if the untreated members are still part of the current Medicaid population.

Opioid Update
The committee reviewed 4Q2023 opioid outcomes compared to the previous quarter from the opioid initiatives. There was an increase in opioid utilization and utilizers during 4Q2023 with corresponding increase in total eligibility and utilizers. The committee also reviewed the average MME/day/utilizer graph. Ladwig and Baack were satisfied with the downward trend. Jockheck reviewed the hospitalization rates due to opioids, which has also dropped. Jockheck mentioned they were not able to provide deaths due to opioids because the cause of death is not always provided. The use of opioids at high dosage in person without cancer tracking showed a response rate decrease from 9.55% to 4.47%. Stanley expressed interest in reviewing MAT trends at the next meeting to determine if more opioid use disorder is being treated and to help determine the success of the opioid initiatives. Stanley stated guidelines from ACOG are clearer with education and better studies coming out to support interventions and the best ways to address it.

New Business

PMPM comparison
The committee reviewed the PMPM trend compared to other Medicaid states and managed Medicaid from the past year. Ladwig commented on the comparison of managed Medicaid PMPM which was higher than FFS Medicaid plans. Jockheck clarified the PMPM figures are not net of rebates.

Brand Inhalers review
The strategy and potential savings of preferring brand inhalers over generics was presented to the committee. Ladwig mentioned all product availability changed as of January 1st which Jockheck concurred had been discussed internally. Preferring brand over generics could be an alternative strategy that the state may be utilizing to drive to the lowest net drug.

Van Gilder inquired if there was any public comment on agenda items covered thus far. There was none.

Glucose Test Strip Review
The committee reviewed the glucose test strip utilization and discussed reducing the quantity limit for all members and for members using a CGM. After discussion, it was agreed to reduce the quantity to 150 per 30 days for members aged 6 years and older. For members newly diagnosed with diabetes to allow a quantity of 306 per 30 days for one year. For children under 5 years old and under, to allow a quantity of 306 per 30 days. Baack made the motion and Ladwig seconded it. Van Gilder inquired if there was any public comment. There was none. The motion was approved unanimously.

Zorvye
Zorvye cream and form clinical information was presented for review. After discussion, Van Gilder made the motion to apply the same criteria as Vtama with appropriate age and diagnosis for cream and foam with initial criteria for 6 months and reauthorization for 12 months. Ladwig seconded the motion. Van Gilder inquired if there was any public comment. There was none. The motion was approved unanimously.

Zurzuvae
Zurzuvae clinical information was presented for review. Baack expressed concern on the drug's embryo-fetal toxicity and causing somnolence on breastfed infants. The appropriateness of a trial and failure of a SSRI was discussed. Stanley stated it would be wise to be cautious until there is more clinical experience with this drug. Van Gilder agreed drug should be used with caution when breastfeeding. Daphne Ni, Medical Liaison from Biogen, provided public comment. After discussion, the committee agreed with the

PA criteria for Zurzuvae. Baack motioned as discussed. Stanley seconded the motion. The motion was approved unanimously.

Adjournment

The next meeting is scheduled on June 7, 2024. The September meeting is scheduled for September 20, 2024. Van Gilder motioned to adjourn the meeting and Baack seconded the motion. The motion to adjourn the meeting was unanimous and the meeting adjourned at 2:58 pm CT.

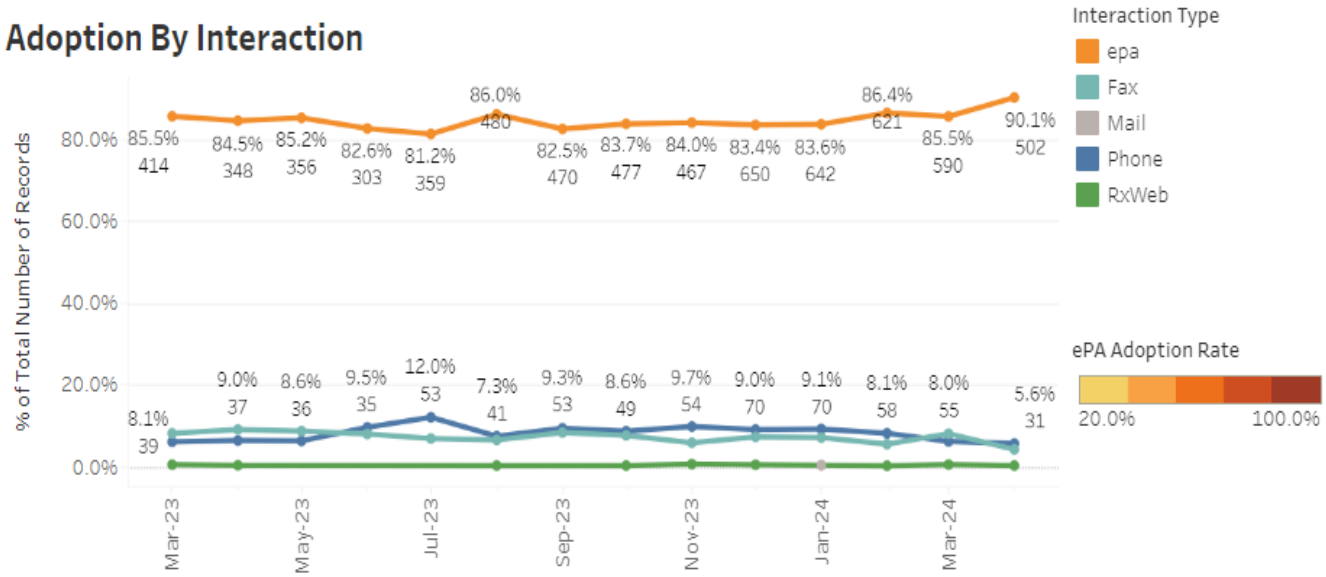
PA Report
1/1/2024 – 3/31/2024

Compliance Summary

Priority	Total PAs	PAs Compliant	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	3,056	3,056	0	100.00%	0.00%
Urgent	442	442	0	100.00%	0.00%
Grand Total	**3,498**	**3,498**	**0**		

Priority	Standard	Urgent
ePA	1,449	404
Fax	134	14
Phone	154	21
Real-Time	1,316	0
RxWeb	1	3
Mail	2	0

Request Summary	Total # of Requests	Phone Requests		Fax Requests		Real-Time PA		ePA PA	
		#	%	#	%	#	%	#	%
Total	**3,498**	**175**	**5%**	**148**	**4.2%**	**1,316**	**37.6%**	**1,853**	**53%**



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-24	1,069	195	1,264
Feb-24	891	207	1,098
Mar-24	905	230	1,135
1Q24	**2,865**	**632**	**3,497**
Percent of Total	**81.93%**	**18.07%**	

Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
ANTIDIABETICS	489	54	543	90.06%	15.53%	, OZEMPIC
MEDICAL DEVICES & SUPPLIES	412	88	500	82.40%	14.30%	, DEXCOM G7 SENSOR
ANTIPSYCHOTICS/ANTIMANIC	452	21	473	95.56%	13.53%	, VRAYLAR
DERMATOLOGICALS	207	54	261	79.31%	7.46%	DUPIXENT, EUCRISA
ANALGESICS - OPIOID	205	45	250	82.00%	7.15%	HYDROCODONE/APAP
OTHERS -	1,100	370	1,470	74.83%	42.04%	
1Q24	**2,865**	**632**	**3,497**	**81.93%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Jan-24	30	76.92%	9	23.08%	39
Feb-24	25	75.76%	8	24.24%	33
Mar-24	31	73.81%	11	26.19%	42
1Q24	**86**	**75.44%**	**28**	**24.56%**	**114**

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
27 - ANTIDIABETICS*	489	54	543	90.06%
97 - MEDICAL DEVICES AND SUPPLIES*	412	88	500	82.40%
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	452	21	473	95.56%
90 - DERMATOLOGICALS*	207	54	261	79.31%
65 - ANALGESICS - OPIOID*	205	45	250	82.00%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	193	34	227	85.02%
58 - ANTIDEPRESSANTS*	185	28	213	86.85%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	119	55	174	68.39%
67 - MIGRAINE PRODUCTS*	121	37	158	76.58%
52 - GASTROINTESTINAL AGENTS - MISC.*	104	29	133	78.20%
66 - ANALGESICS - ANTI-INFLAMMATORY*	75	20	95	78.95%
12 - ANTIVIRALS*	38	18	56	67.86%
16 - ANTI-INFECTIVE AGENTS - MISC.*	39	3	42	92.86%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	15	23	38	39.47%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	25	7	32	78.13%
41 - ANTIHISTAMINES*	19	12	31	61.29%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	18	12	30	60.00%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	25	4	29	86.21%
54 - URINARY ANTISPASMODICS*	17	12	29	58.62%
28 - THYROID AGENTS*	18	4	22	81.82%
72 - ANTICONVULSANTS*	15	7	22	68.18%
39 - ANTIHYPERLIPIDEMICS*	9	10	19	47.37%
75 - MUSCULOSKELETAL THERAPY AGENTS*	3	13	16	18.75%
34 - CALCIUM CHANNEL BLOCKERS*	7	7	14	50.00%
36 - ANTIHYPERTENSIVES*	6	6	12	50.00%
50 - ANTIEMETICS*	7	4	11	63.64%
33 - BETA BLOCKERS*	4	6	10	40.00%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	10	0	10	100.00%
83 - ANTICOAGULANTS*	7	3	10	70.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	6	0	6	100.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	2	3	5	40.00%
45 - RESPIRATORY AGENTS - MISC.*	2	3	5	40.00%
74 - NEUROMUSCULAR AGENTS*	1	3	4	25.00%
03 - MACROLIDES*	2	1	3	66.67%
86 - OPHTHALMIC AGENTS*	2	1	3	66.67%
01 - PENICILLINS*	1	1	2	50.00%
11 - ANTIFUNGALS*	1	1	2	50.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	2	0	2	100.00%
82 - HEMATOPOIETIC AGENTS*	0	2	2	0.00%
51 - DIGESTIVE AIDS*	1	0	1	100.00%
64 - ANALGESICS - NONNARCOTIC*	0	1	1	0.00%
79 - MINERALS & ELECTROLYTES*	1	0	1	100.00%
1Q24	**2,865**	**632**	**3,497**	
Percent of Total	**81.93%**	**18.07%**		

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
LINZESS	14	4	18	77.78%
MAVYRET	6	2	8	75.00%
DEXLANSOPRAZOLE	5	0	5	100.00%
AIMOVIG	4	0	4	100.00%
DEXCOM G7 SENSOR	4	0	4	100.00%
EVRYSDI	2	1	3	66.67%
SKYTROFA	2	1	3	66.67%
SOFOSBUVIR/VELPATASVIR	2	1	3	66.67%
AJOVY	2	0	2	100.00%
DAYVIGO	2	0	2	100.00%
DEXCOM G7 RECEIVER	1	1	2	50.00%
DUPIXENT	2	0	2	100.00%
EMGALITY	2	0	2	100.00%
HUMIRA PEN	1	1	2	50.00%
JAKAFI	1	1	2	50.00%
LUBIPROSTONE	2	0	2	100.00%
OZEMPIC	1	1	2	50.00%
QELBREE	2	0	2	100.00%
REPATHA SURECLICK	2	0	2	100.00%
RINVOQ	0	2	2	0.00%
SKYRIZI PEN	0	2	2	0.00%
TEZSPIRE	2	0	2	100.00%
VRAYLAR	2	0	2	100.00%
ADAPALENE/BENZOYL PEROXIDE	1	0	1	100.00%
ADDERALL	0	1	1	0.00%
BELSOMRA	1	0	1	100.00%
COSENTYX SENSOREADY PEN	1	0	1	100.00%
CYCLOBENZAPRINE HCL	0	1	1	0.00%
DEXCOM G6 SENSOR	1	0	1	100.00%
DEXCOM G6 TRANSMITTER	1	0	1	100.00%
DILANTIN INFATABS	1	0	1	100.00%
ENOXAPARIN SODIUM	0	1	1	0.00%
FREESTYLE LIBRE 3/SENSOR	1	0	1	100.00%
GEMTESA	1	0	1	100.00%
HYDROCODONE/APAP	1	0	1	100.00%
IVERMECTIN	0	1	1	0.00%
LANSOPRAZOLE	1	0	1	100.00%
LOSARTAN POTASSIUM	1	0	1	100.00%
METHADONE HCL	1	0	1	100.00%
MIGLUSTAT	1	0	1	100.00%
MODAFINIL	1	0	1	100.00%
MOTEGRITY	1	0	1	100.00%
MOUNJARO	0	1	1	0.00%
MYRBETRIQ	0	1	1	0.00%
NORDITROPIN FLEXPRO	1	0	1	100.00%
NUCYNTA	0	1	1	0.00%
PRALUENT	1	0	1	100.00%
PREGABALIN	0	1	1	0.00%
PULMOZYME	1	0	1	100.00%
QUVIVIQ	0	1	1	0.00%
REPATHA	1	0	1	100.00%

SAXENDA	0	1	1	0.00%
SIMPONI	1	0	1	100.00%
TAZAROTENE	1	0	1	100.00%
TIROSINT	0	1	1	0.00%
TRAMADOL HCL	1	0	1	100.00%
TRULANCE	1	0	1	100.00%
VIBERZI	1	0	1	100.00%
WINLEVI	1	0	1	100.00%
1Q24	**86**	**28**	**114**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 1/1/2024 – 3/31/2024					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	16,054	$206,820.52	$12.88	6.00%
2	ANTICONVULSANTS, MISCELLANEOUS	14,769	$1,142,469.38	$77.36	5.52%
3	ATYPICAL ANTIPSYCHOTICS	10,703	$3,584,343.51	$334.89	4.00%
4	AMINOPENICILLIN ANTIBIOTICS	9,794	$148,403.27	$15.15	3.66%
5	SELECTIVE BETA-2-ADRENERGIC AGONISTS	9,105	$458,583.27	$50.37	3.41%
6	PROTON-PUMP INHIBITORS	8,257	$219,381.58	$26.57	3.09%
7	ADRENALS	7,926	$869,456.38	$109.70	2.96%
8	RESPIRATORY AND CNS STIMULANTS	7,867	$827,621.54	$105.20	2.94%
9	AMPHETAMINES	7,663	$1,023,588.98	$133.58	2.87%
10	SECOND GENERATION ANTIHISTAMINES	7,389	$83,005.32	$11.23	2.76%
11	OPIATE AGONISTS	6,996	$223,023.06	$31.88	2.62%
12	ANXIOLYTICS,SEDATIVES,AND HYPNOTICS,MISC	6,640	$86,634.79	$13.05	2.48%
13	HMG-COA REDUCTASE INHIBITORS	5,449	$63,199.46	$11.60	2.04%
14	BETA-ADRENERGIC BLOCKING AGENTS	4,937	$74,541.33	$15.10	1.85%
15	SEL.SEROTONIN,NOREPI REUPTAKE INHIBITOR	4,932	$97,709.3	$19.81	1.84%
Total		**128,481**	**$9,108,781.69**	**$70.90**	**48.06%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 1/1/2024 – 3/31/2024					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	ATYPICAL ANTIPSYCHOTICS	10,703	$3,584,343.51	$334.89	4.00%
2	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	876	$3,540,500.19	$4,041.67	0.33%
3	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	463	$3,353,560.58	$7,243.11	0.17%
4	INCRETIN MIMETICS	2,238	$2,122,008.51	$948.17	0.84%
5	ANTINEOPLASTIC AGENTS	439	$1,583,431.66	$3,606.91	0.16%
6	CYSTIC FIBROSIS (CFTR) CORRECTORS	66	$1,581,314.96	$23,959.32	0.02%
7	ANTICONVULSANTS, MISCELLANEOUS	14,769	$1,142,469.38	$77.36	5.52%
8	HEMOSTATICS	63	$1,115,218.26	$17,701.88	0.02%
9	AMPHETAMINES	7,663	$1,023,588.98	$133.58	2.87%
10	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	4,296	$980,200.29	$228.17	1.61%
11	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	259	$945,286.47	$3,649.75	0.10%
12	ADRENALS	7,926	$869,456.38	$109.70	2.96%
13	RESPIRATORY AND CNS STIMULANTS	7,867	$827,621.54	$105.20	2.94%
14	SODIUM-GLUC COTRANSPORT 2 (SGLT2) INHIB	1,394	$763,184.95	$547.48	0.52%
15	GI DRUGS, MISCELLANEOUS	541	$655,590.27	$1,211.81	0.20%
Total		**59,563**	**$24,087,775.93**	**$404.41**	**22.28%**

Total Rx Claims from 1/1/2024 – 3/31/2024	**267,359**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 1/1/2024 – 3/31/2024						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Penicillins	AMOXICILLIN	7,266	$100,073.48	$13.77	2.72%
2	Antidepressants	***FLUOXETINE***	**5,530**	**$67,984.53**	**$12.29**	2.07%
3	ADHD & Narcolepsy Medications	METHYLPHENIDATE	5,027	$280,050.10	$55.71	1.88%
4	Antidepressants	***SERTRALINE***	**5,017**	**$62,262.41**	**$24.27**	1.88%
5	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	4,993	$178,452.71	$35.74	1.87%
6	Proton Pump Inhibitors	***OMEPRAZOLE***	**4,864**	**$53,862.34**	**$23.10**	1.82%
7	Anticonvulsants - 2nd Generation	GABAPENTIN	4,667	$74,866.62	$16.04	1.75%
8	Antidepressants	TRAZODONE	4,267	$45,375.02	$10.63	1.60%
9	Thyroid Hormones	LEVOTHYROXINE	4,030	$43,546.74	$10.81	1.51%
10	Antihistamines	***CETIRIZINE***	**3,970**	**$42,401.86**	**$10.68**	1.48%
11	Antidepressants	ESCITALOPRAM	3,938	$48,991.48	$12.44	1.47%
12	ADHD & Narcolepsy Medications	AMPHETAMINE/DEXTROAMP	3,846	$117,049.61	$30.43	1.44%
13	Biguanides & Combos	***METFORMIN***	**3,358**	**$38,523.58**	**$22.96**	1.26%
14	ACE Inhibitors & Combos	LISINOPRIL	3,215	$28,420.69	$8.84	1.20%
15	Antidepressants	***BUPROPION***	**3,162**	**$58,216.77**	**$18.41**	1.18%
16	Statins & Combos	ATORVASTATIN	3,159	$36,175.31	$11.45	1.18%
17	Leukotriene Modulators	MONTELUKAST	2,834	$36,447.32	$12.86	1.06%
18	Opioid Agonists & Combos	HYDROCODONE/AC	2,655	$41,327.21	$15.57	0.99%
19	Antiadrenergic Antihypertensives	CLONIDINE	2,639	$23,676.25	$8.97	0.99%
20	Antidepressants	***DULOXETINE***	**2,627**	**$39,418.21**	**$15.01**	0.98%
21	Penicillins	AMOXICILLIN/CLAVULANATE	2,524	$48,270.55	$19.12	0.94%
22	Antiemetics	ONDANSETRON ODT	2,492	$34,414.04	$13.81	0.93%
23	Antianxiety Agents	***HYDROXYZINE HCL***	**2,456**	**$29,911.68**	**$12.18**	0.92%
24	Glucocorticosteroids	PREDNISONE	2,368	$22,774.95	$9.62	0.89%
25	Atypical Antipsychotics	ARIPIPRAZOLE	2,299	$34,535.52	$15.02	0.86%
26	Inhaled Bronchodilator	ALBUTEROL SULFATE	2,188	$43,223.85	$19.75	0.82%
27	Antianxiety Agents	***BUSPIRONE***	**2,106**	**$26,076.71**	**$12.38**	0.79%
28	Macrolides	AZITHROMYCIN	1,983	$30,298.80	$15.28	0.74%
29	Atypical Antipsychotics	QUETIAPINE	1,955	$25,195.30	$12.89	0.73%
30	Calcium Channel Blockers	AMLODIPINE	1,946	$17,839.51	$9.17	0.73%
31	Anticonvulsants - 2nd Generation	LAMOTRIGINE	1,936	$26,139.43	$13.50	0.72%
32↓	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE	1,934	$313,866.39	$162.29	0.72%
33↑	Influenza Agents	OSELTAMIVIR	1,925	$55,637.51	$28.90	0.72%
34	Angiotensin II Receptor Antagonists & Combo	LOSARTAN	1,900	$20,415.39	$10.74	0.71%
35	Cephalosporins	CEPHALEXIN	1,852	$29,704.24	$16.04	0.69%
36	Atypical Antipsychotics	RISPERIDONE	1,832	$22,505.85	$12.28	0.69%
37	ADHD & Narcolepsy Medications	GUANFACINE ER	1,822	$30,495.31	$16.74	0.68%
38	Muscle Relaxants & Combos	CYCLOBENZAPRINE	1,813	$18,008.78	$9.93	0.68%
39	Cephalosporins	CEFDINIR	1,786	$39,381.40	$22.05	0.67%
40	Proton Pump Inhibitors	PANTOPRAZOLE	1,751	$22,982.60	$13.13	0.65%
41	Anticonvulsants - 2nd Generation	CLONAZEPAM	1,710	$19,115.03	$11.18	0.64%
42↑	Antidepressants	***VENLAFAXINE***	**1,668**	**$24,994.66**	**$29.01**	0.62%
43	Beta Blockers & Combos	METOPROLOL SUCCINATE ER	1,652	$20,081.22	$12.16	0.62%
44↑	ADHD & Narcolepsy Medications	VYVANSE	1,651	$550,685.45	$333.55	0.62%
45	Anticonvulsants - 2nd Generation	TOPIRAMATE	1,633	$20,496.85	$12.55	0.61%
46	Statins & Combos	ROSUVASTATIN	1,603	$19,168.17	$11.96	0.60%
47	Antihistamines	*LORATADINE*	**1,546**	**$16,743.48**	**$26.93**	0.58%
48	Corticosteroids - Topical	TRIAMCINOLONE ACETONIDE	1,537	$23,160.00	$15.07	0.57%
49	Nasal Steroids	FLUTICASONE PROPIONATE	1,534	$24,766.29	$16.14	0.57%
50	Anticonvulsants - 2nd Generation	LEVETIRACETAM	1,499	$30,805.88	$20.55	0.56%
	Total Top 50 Drugs		**137,965**	**$3,058,817.08**	**$22.17**	**51.6%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 1/1/2024 – 3/31/2024						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Cystic Fibrosis	TRIKAFTA	66	$1,581,314.96	$23,959.32	0.02%
2	Chronic Inflammatory Disease	*HUMIRA/**PEN***	**156**	**$1,504,477.49**	**$9,644.09**	0.06%
3	Chronic Inflammatory Disease	DUPIXENT	370	$1,433,749.73	$3,875.00	0.14%
4	Chronic Inflammatory Disease	STELARA	58	$1,301,580.09	$22,441.04	0.02%
5	Atypical Antipsychotics	*INVEGA **SUSTENNA**/TRINIZA/HAFYERA*	374	$1,206,120.56	$3,224.92	0.14%
6	GLP-1 Receptor Agonists	OZEMPIC	1,104	$1,030,974.05	$933.85	0.41%
7	Atypical Antipsychotics	VRAYLAR	608	$784,026.74	$1,289.52	0.23%
8↑	Chronic Inflammatory Disease	*SKYRIZI/**PEN***	**37**	**$747,714.75**	**$20,208.51**	0.01%
9	Rett Syndrome Agent	DAYBUE	20	$738,081.72	$36,904.09	0.01%
10	GLP-1 Receptor Agonists	MOUNJARO	726	$732,677.32	$1,009.20	0.27%
11	HIV-Multiclass Combo	BIKTARVY	157	$606,340.54	$3,862.04	0.06%
12↑	ADHD & Narcolepsy Medications	VYVANSE	1,651	$550,685.45	$333.55	0.62%
13	SGLT-2 Inhibitors & Combos	JARDIANCE	887	$499,315.61	$562.93	0.33%
14	Chronic Inflammatory Disease	*ENBREL/MINI/**SURECLICK***	**69**	**$484,550.53**	**$7,022.47**	0.03%
15	Atypical Antipsychotics	ARISTADA/INITIO	**170**	**$468,783.59**	**$2,757.55**	0.06%
16	Chronic Inflammatory Disease	TALTZ	48	$446,177.18	$9,295.36	0.02%
17	Chronic Inflammatory Disease	**COSENTYX SENSOREADY PEN**	50	$423,039.96	$8,460.80	0.02%
18	Anticonvulsants - 2nd Generation	EPIDIOLEX	138	$411,439.52	$2,981.45	0.05%
19	Hepatitis C	MAVYRET	28	$359,066.92	$12,823.82	0.01%
20	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE DIMESYLA	1,934	$313,866.39	$162.29	0.72%
21	Oral Anticoagulants	*ELIQUIS/STARTER PACK*	**577**	**$309,631.22**	**$536.62**	0.22%
22	Hepatitis C	SOFOSBUVIR/VELPATASVIR	38	$304,311.80	$8,008.21	0.01%
23	ADHD & Narcolepsy Medications	METHYLPHENIDATE	**5,060**	**$290,331.62**	**$57.38**	1.89%
24	Antihemophilic Products	HEMLIBRA	12	$285,588.70	$23,799.06	0.00%
25	Glucagon-Like Peptide-2 (GLP-2) Analog	GATTEX	6	$273,217.98	$45,536.33	0.00%
26	Oncology	KOSELUGO	15	$260,015.46	$17,334.36	0.01%
27	Atypical Antipsychotics	CAPLYTA	173	$258,719.79	$1,495.49	0.06%
28	Atypical Antipsychotics	REXULTI	199	$253,030.70	$1,271.51	0.07%
29	Atypical Antipsychotics	*ABILIFY **MAINTENA**/ASIMTUFII*	**91**	**$248,992.58**	**$2,736.18**	0.03%
30	Movement Disorder Drug Therapy	INGREZZA	31	$243,335.65	$7,849.54	0.01%
31	Antihemophilic Products	NOVOSEVEN RT	3	$241,231.65	$80,410.55	0.00%
32	Anti-Infective Agents - Misc.	XIFAXAN	80	$238,804.75	$2,985.06	0.03%
33↑	Inhaled Asthma/COPD Combo	TRELEGY ELLIPTA	344	$214,388.66	$623.22	0.13%
34	Pulmonary Arterial Hypertension	OPSUMIT	18	$213,241.98	$11,846.78	0.01%
35↑	Growth Hormones	NORDITROPIN FLEXPRO	63	$213,164.69	$3,383.57	0.02%
36	Chronic Inflammatory Disease	**COSENTYX** UNOREADY	13	$207,551.73	$15,965.52	0.00%
37	Spinal Muscular Atrophy (SMA) Agent	EVRYSDI	8	$205,123.08	$25,640.39	0.00%
38	HIV-Multiclass Combo	GENVOYA	53	$204,861.02	$3,865.30	0.02%
39	GLP-1 Receptor Agonists	TRULICITY	209	$194,587.12	$931.04	0.08%
40↑	Oncology	SPRYCEL	13	$190,922.13	$14,686.32	0.00%
41	Chronic Inflammatory Disease	TREMFYA	14	$187,100.67	$13,364.33	0.01%
42	Chronic Inflammatory Disease	RINVOQ	29	$185,827.35	$6,407.84	0.01%
43	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	4,993	$178,452.71	$35.74	1.87%
44	Irritable Bowel Syndrome (IBS) Agents	LINZESS	339	$177,347.41	$523.15	0.13%
45↓	Cystic Fibrosis	PULMOZYME	38	$170,396.01	$4,484.11	0.01%
46	Migraine Products	NURTEC	142	$167,598.70	$1,180.27	0.05%
47↑	Metabolic Modifiers	PALYNZIQ	3	$166,081.65	$55,360.55	0.00%
48↑	Asthma	NUCALA	46	$165,719.85	$3,602.61	0.02%
49↑	Antihemophilic Products	XYNTHA SOLOFUSE	3	$152,147.25	$50,715.75	0.00%
50↑	Oncology	REVLIMID	66	$1,581,314.96	$23,959.32	0.02%
	Total Top 50 Drugs		**21,273**	**$22,177,432.66**	**$1,042.52**	**7.96%**

Old Business

Vijoice PA Reviews

Total PAs reviewed during 3Q23			3Q2023	4Q2023	1Q2024
2 patients under 18 years old	Female with PIK3CA. Segmental overgrowth associated with mutation in PKI3CA gene.	Total Rx	2	6	3
	Male: Dx is appropriate for PIK3CA related overgrowth syndrome (severe)	Paid Amount	$65,021.10	$195,063.30	$97,531.65

Linzess PA Appeal Reviews

Linzess PA criteria

1. Patient is 18 years of age or older **AND**
2. One of the following:
   - **2.1.** Diagnosis of chronic idiopathic constipation **OR**
   - **2.2.** Diagnosis of irritable bowel syndrome with constipation (IBS-C)

Linzess Appeals Detail

Quarter	Approved	Denied	Total	Approval Rate
3Q2023	14	0	14	100%
4Q2023	15	1	16	93.75%
1Q2024	14	4	18	77.78%

Linzess Initial PA Reviews

Quarter	Approved	Denied	Total	Approval Rate
3Q2023	19	17	36	52.7%
4Q2023	9	21	30	30%
1Q2024	13	23	36	36.1%

Total Linzess Approval Rate

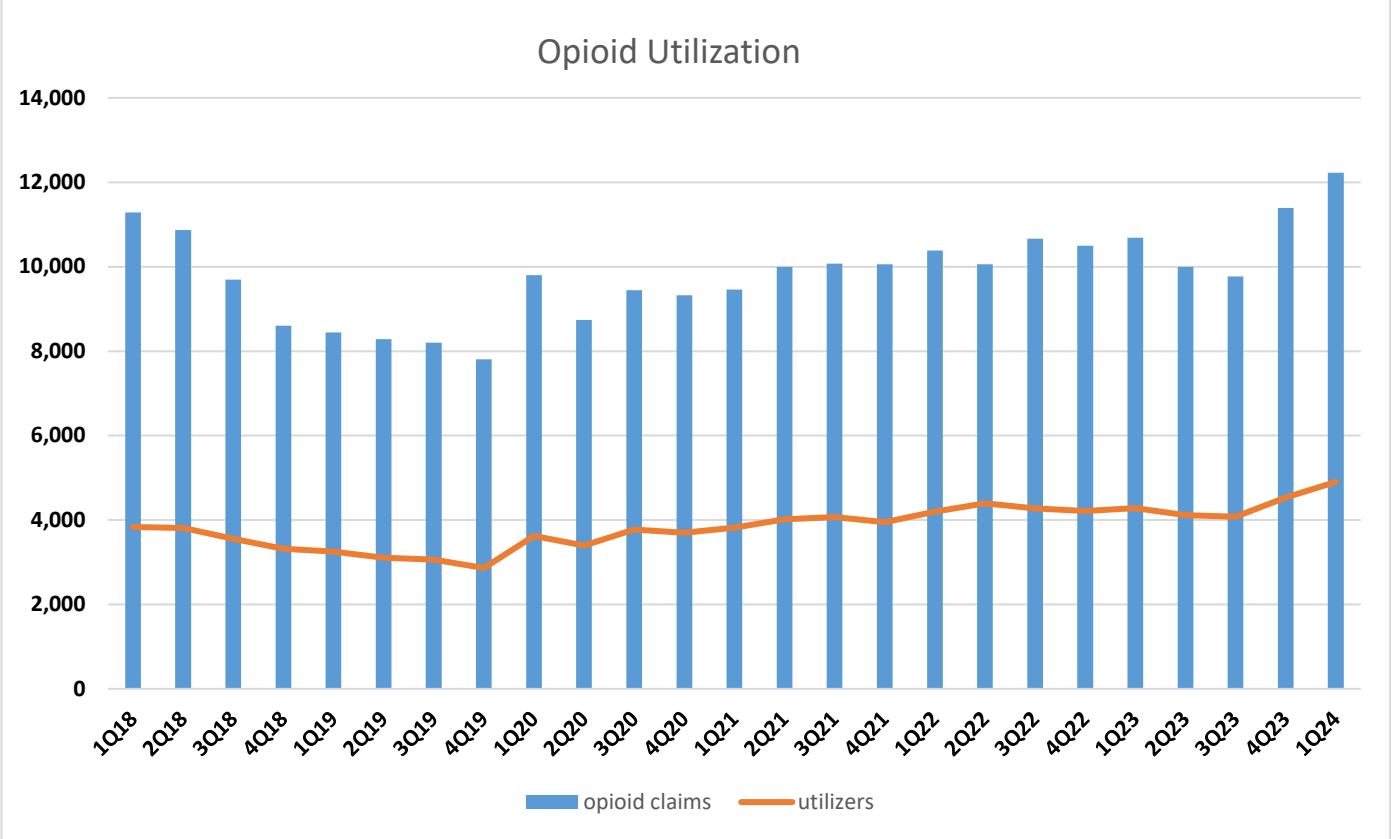
Quarter	Approved	Denied	Total	Approval Rate
3Q2023	33	17	50	66%
4Q2023	24	22	46	52.2%
1Q2024	27	27	54	50%

Time Period: 1Q2024

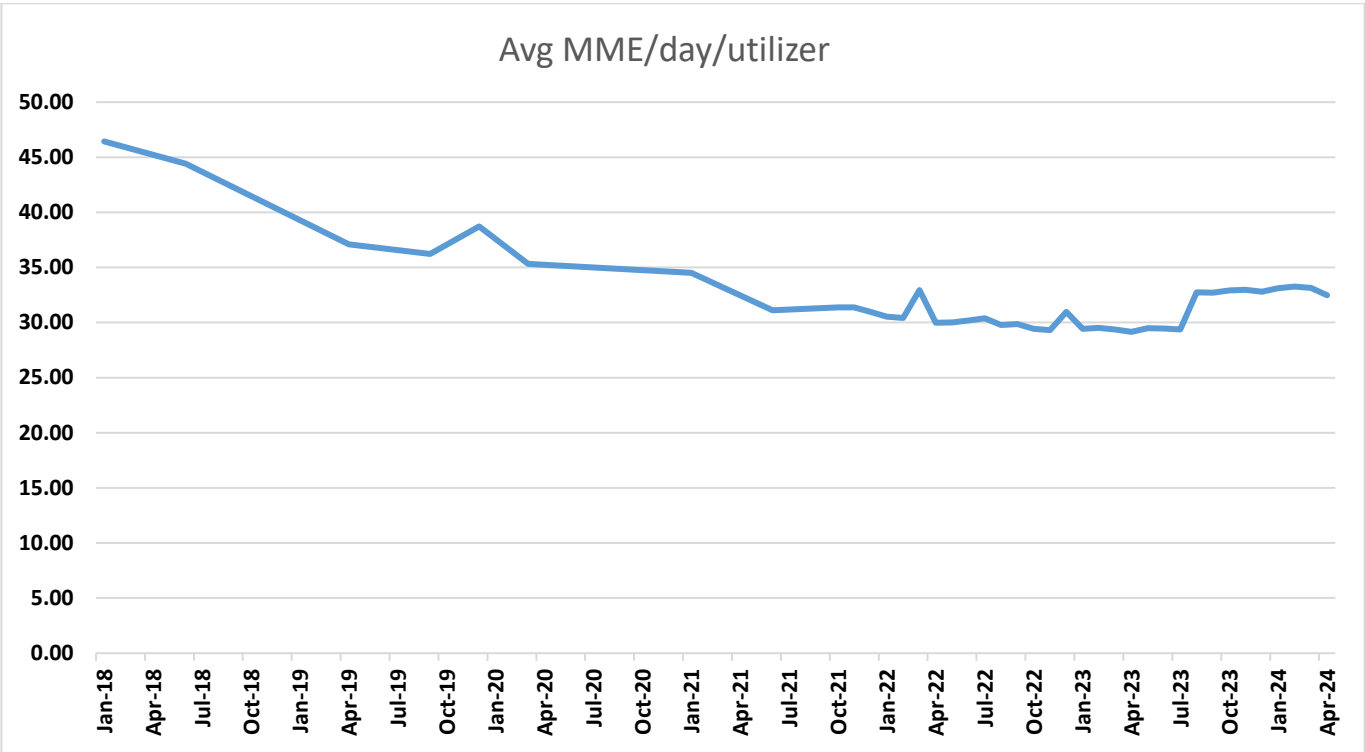
Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Age Range
Linzess 72 mcg	144	$75,809.97	$526.46	73	8 – 64 34 utilizers < 18 yrs
Linzess 145 mcg	126	$65,371.00	$518.82	62	10 – 64 4 utilizers < 18 yrs
Linzess 290 mcg	76	$39,761.44	$523.18	36	16 – 64 1 utilizer < 18 yrs

Linzess new indication on 6/13/2023 – Ironwood Pharmaceuticals announced the FDA approval of Linzess (linaclotide), for the treatment of functional constipation in pediatric patients 6 to 17 years of age – **applies to Linzess 72mcg only.**

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)

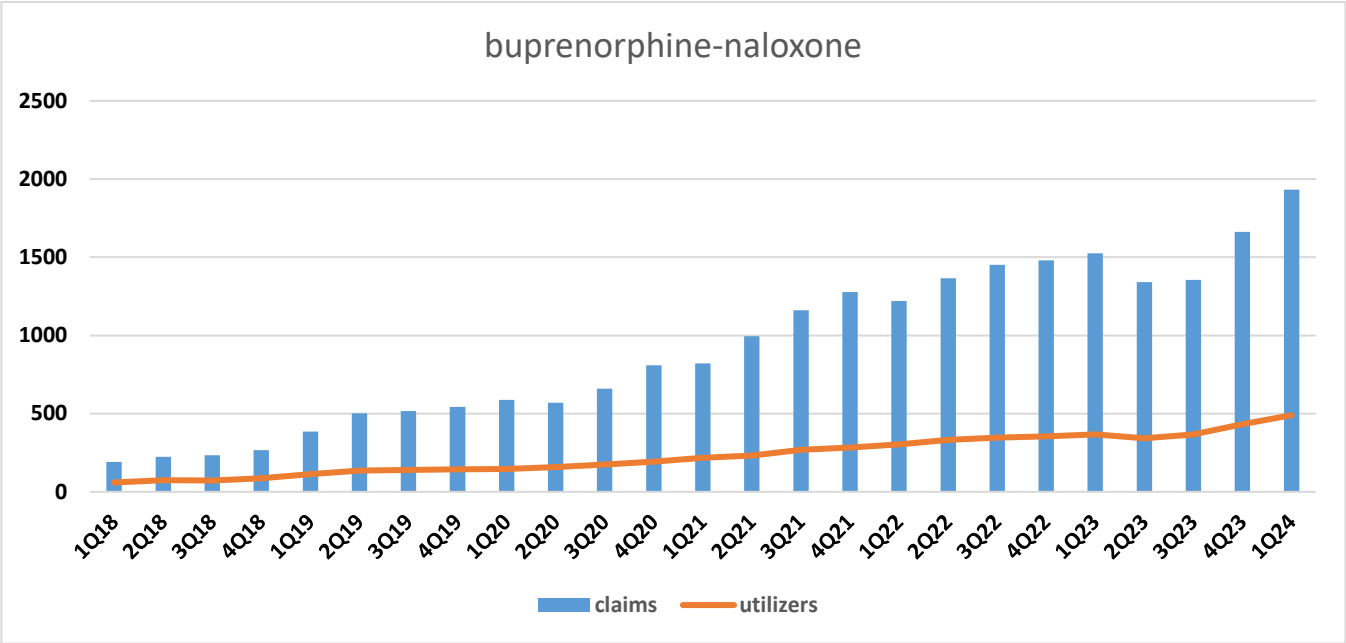
Other Initiatives:

- 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%

MAT Trend



Time Period: 1Q2024

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
BELBUCA MIS 150MCG	7	$2,890.67	$412.95	60/30 days	14	28 – 64
BELBUCA MIS 300MCG	8	$4,557.10	$569.64	52.5/26 days		
BELBUCA MIS 450MCG	2	$1,774.36	$887.18	60/30 days		
BELBUCA MIS 600MCG	7	$8,002.03	$1,143.15	72.8/30 days		
BELBUCA MIS 750MCG	3	$2,980.74	$993.58	60/30 days		
BELBUCA MIS 75MCG	4	$1,672.32	$418.08	60/30 days		
BELBUCA MIS 900MCG	3	$2,858.82	$952.94	56/28 days		
bupren/nalox MIS 12-3 mg	23	$9,317.94	$405.13	50.4/24.5 days	181	18 – 64
bupren/nalox MIS 2-0.5 mg	26	$1,774.44	$68.25	27.7/**17** days		
bupren/nalox MIS 4-1 mg	**108**	$30,161.28	$279.27	50.6/**20** days		
bupren/nalox MIS 8-2 mg	**537**	$144,985.51	$269.99	35.9/**15** days		
bupren/nalox SUB 2-0.5 mg	37	$3,524.02	$95.24	64.4/**18** days	171	17 – 63
bupren/nalox SUB 8-2 mg	**650**	$70,186.74	$107.98	28.6/**13** days		
buprenorphine DIS 10 mcg/HR	24	$4,001.55	$166.73	4/28 days	40	16 – 63
buprenorphine DIS 15 mcg/HR	10	$2,622.63	$262.26	4/28 days		
buprenorphine DIS 20 mcg/HR	21	$6,173.35	$293.97	3.8/21 days		
buprenorphine DIS 5 mcg/HR	25	$3,723.16	$148.93	4/28 days		
buprenorphine DIS 7.5/HR	9	$1,712.09	$190.23	4/28 days		
buprenorphine SUB 2mg	42	$2,797.06	$66.60	52.5/20 days	103	23 – 64
buprenorphine SUB 8mg	**295**	$19,710.47	$66.82	52.5/21 days		
BUTRANS DIS 10MCG/HR	1	$524.92	$524.92	4/4 days	1	37
SUBLOCADE INJ 100/0.5	5	$10,118.85	$2,023.77	0.5/30 days	6	27 – 42
SUBLOCADE INJ 300/1.5	6	$3,784.89	$540.70	1.5/30 days		
SUBOXONE MIS 2-0.5MG	7	$9,347.00	$584.19	73/24 days	10	23 – 59
SUBOXONE MIS 4-1MG	16	$2,808.59	$351.07	34.5/13 days		
SUBOXONE MIS 8-2MG	8	$13,243.77	$315.33	37.3/15.6 days		
ZUBSOLV SUB 5.7-1.4	42	$2,934.18	$419.17	31.5/14 days	13	23 – 50
ZUBSOLV SUB 8.6-2.1	7	$2,890.67	$412.95	28.3/14 days		

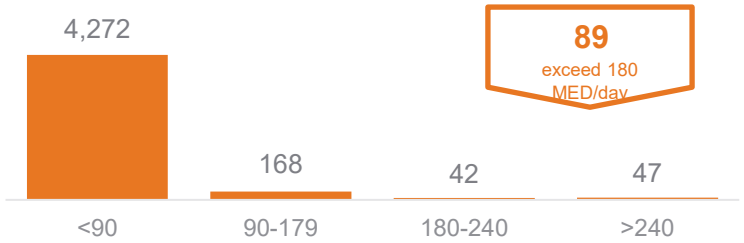
Opioid Utilization Snapshot

SDM 4Q2023
Sep 23 to Dec 23

Opioid Claims **11,389**
3.1% prescription claims filled for an opioid
1.3% higher than Medicaid FFS benchmark

Utilizers **4,529**
30.8% are high utilizers [1]
2.8% 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
62 opioid utilizing members with 3+ pharmacies

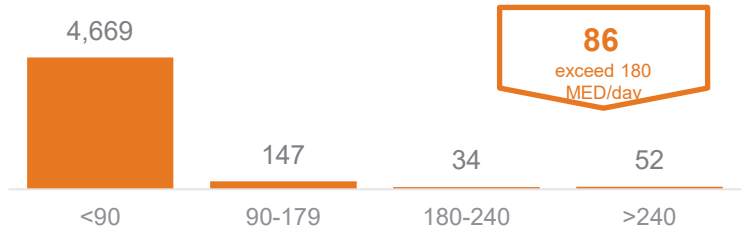
371 Shoppers: Poly Prescriber
opioid utilizing members with 3+ prescribers

1Q2024
Dec 23 to Jan 24

Opioid Claims **12,230**
3.2% prescription claims filled for an opioid
1.3% higher than Medicaid FFS benchmark

Utilizers **4,902**
31.4% are high utilizers [1]
3.5% 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
66 opioid utilizing members with 3+ pharmacies

403 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 1Q2024
Opportunities date range: Dec 2023 - Mar 2024
Benchmark: MEDICAID FEE FOR SERVICE

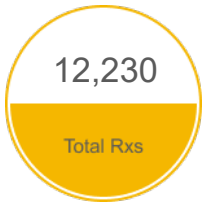
Utilizers: 4,902

3.2% 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 3.2% of all prescriptions this period, which is 1.3% higher than the benchmark
- 1,539 high opioid utilizers were identified this period, which is 3.5% higher than the benchmark

Opioid claims



PERCENT NON-COMPLIANT
14.1%

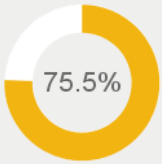
Opioid utilizers

HIGH UTILIZERS
31.4%
1,539 high utilizers

3.5% over benchmark

High utilizers – view definition

Claim breakdown



short acting opioids

75.5% of all opioid Rxs were filled for short acting opioids. **2,192** Rxs were for medication assisted therapy (MAT) and **98** 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

86 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	4,669	147	34	52

MED – view definition

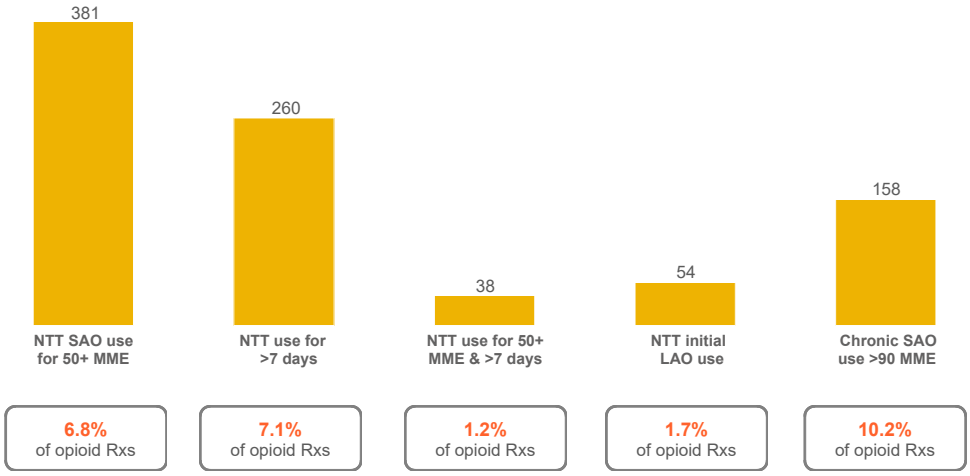
Opioid Opportunity Assessment

SDM 1Q2024
Opportunities date range: Dec 2023 - Mar 2024
Benchmark: MEDICAID FEE FOR SERVICE

Percent non-compliant: 14.1%

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?

66 opioid utilizing members use 3 or more pharmacies and 403 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
943	690	929	453	121

Anticonvulsants –view definition

New Business

PA review of low volume requests

Time frame: Year 2023

PA Type	Drug Class	Approved	Denied	Total	Mbr	Approval Rate
Qnty Limit	CEPHALOSPORINS cephalexin susp 250mg/5ml – **20ml per day**	**7** • 11 yrs (25ml/day) • 9 yrs • 12 yrs (28.5ml/day) • 6 yrs • 9 yrs (27ml/day) • 6 yrs (60ml/day) • 11 yrs(30ml/day)	**3** • 8 yrs (28ml/day) • 43 yrs (30ml/day) • 36 yrs (40ml/day)	10	10	70%
Qnty Limit	PENICILLINS amoxicillin susp 400/5ml – **30ml per day** amoxicillin susp 250/5ml – **30ml per day** amox/clav susp 250/5ml – **30ml per day**	**1** • 13 yrs (43ml/day) amoxicillin susp 400/5ml	**3** • 10 yrs (50ml/day) amoxicillin susp 400/5ml • 10 yrs (60ml/day) amoxicillin susp 250/5ml • 24 yrs (24ml/day) amox/clav susp 250/5ml	4	4	25%
PA	MACROLIDE Dificid – treatment of *C. difficile*	**5** • Dificid		5	5	100%
Qnty Limit PA	ANTIHYPERTENSIVES candesartan 4mg – **1½ per day** candesartan 8mg – **1½ per day** candesartan 16mg – **1½ per day** candesartan 32mg – **1 per day** losartan 25mg – **1½ per day** losartan 50mg – **1½ per day** losartan 100mg – **1 per day** losartan/hctz 50-12.5mg – **1 per day** losartan/hctz 100-25mg – **1 per day** valsartan 40mg – **1 per day** valsartan 80mg – **1 per day** valsartan 160mg – **1 per day** lisinopril/hctz 10-12.5mg – 1 per day Edarbi & Edarbyclor – trial of generic ACE or ARB first	**9** • losartan 25mg – 2/day **(2 PAs)** • losartan 50mg – 2/day **(4 PAs)** • losartan 100mg – 1.5/day • valsartan 40mg – 2/day • lisinopril/hctz 10-12.5mg	**9** • candesartan 32mg – 2/day • losartan 50mg – 2/day (2 PAs) • losartan 50mg – 3/day • losartan 100mg – 2/day • losartan/hctz 50-12.5mg – 2/day • valsartan 80mg – 2/day **(2 PAs)** • Edarbyclor	18	17	50%
PA Qnty Limit	BETA BLOCKERS Hemangeol 4.28mlg/ml (propranolol) metoprolol succ ER 25mg – **1½ per day** metoprolol succ ER 50mg – **1½ per day** metoprolol succ ER 100mg – **1½ per day**	**17** • Hemangeol **(2 PAs)** • metoprolol ER 25mg – 2/day **(4 PAs)** • metoprolol ER 50mg – 2/day **(5 PAs)** • metoprolol ER 50mg – 3/day **(2 PAs)** • metoprolol ER 100mg – 2/day **(2 PAs)** • metoprolol ER 100mg – 3/day **(2 PAs)**	**7** • Hemangeol • metoprolol ER 25mg – 2/day • metoprolol ER 50mg – 2/ day **(3 PAs)** • metoprolol ER 100mg – 2/day **(2 PAs)**	24	23	70.8%

*Red font denotes drug is on PA or ST

Rezdiffra (resmetirom) – in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis)

- NASH, also referred to as metabolic dysfunction associated steatohepatitis (MASH), is a result of the progression of nonalcoholic fatty liver disease (NAFLD) where liver inflammation, over time, can lead to liver scarring and liver dysfunction. NASH is often associated with other health problems such as high blood pressure and type 2 diabetes.
- Rezdiffra is a partial agonist of the thyroid hormone receptor-beta (THR-β). THR-β is the major form of THR in the liver, and stimulation of THR-β in the liver reduces liver fat accumulation.

Time frame April 2024

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
REZDIFFRA tab 60mg	1	$3,957.25	$3,957.25	30 per 30 days	1	61

State A

Initial Criteria

Must meet all of the following:

1. Patient is 18 years or older
2. Diagnosis of noncirrhotic nonalcoholic steatohepatitis (NASH) or metabolic dysfunction associated steatohepatitis (MASH)
3. Submission of medical records (e.g. chart notes) confirming disease is fibrosis stage F2 or F3 as confirmed by ONE of the following:
    a. FibroScan
    b. Fibrosis-4 index (FIB-4)
    c. Magnetic Resonance Elastography (MRE)
    d. Liver Biopsy
4. Prescriber attests patient is participating in a supervised comprehensive weight management program that encourages behavioral modification, reduced calorie diet, and increased physical activity
5. Patient does not have decompensated cirrhosis (Child-Pugh Class B or C)
6. Prescribed by or in consultation with a gastroenterologist or hepatologist

Renewal Criteria

Must meet all of the following:

1. Prescriber attest patient is participating in a supervised comprehensive weight management program that encourages behavioral modification, reduced calorie diet, and increased physical activity
2. Submission of medical records (e.g., chart notes) documenting a positive clinical response to therapy (e.g. NASH resolution, fibrosis stage improvements)

State B

Initial Authorization

Must meet all of the following:

1. Diagnosis of metabolic dysfunction-associated steatohepatitis (MASH) with moderate (F2) to advanced (F3) liver fibrosis, confirmed by both of the following (documentation required):
    a. One of the following tests indicating member has a diagnosis of steatohepatitis:
        - FibroScan-aspartate aminotransferase (FAST)
        - Liver biopsy
        - MRI – protein density fat fraction (MRI-P DFF)
        - MRI – aspartate aminotransferase (MAST)
    b. One of the following tests indicating member has moderate (F2) or advanced (F3) liver fibrosis:
        - Enhance Liver Fibrosis (ELF)
        - FibroScan
        - Fibrosis-4 index (FIB-4) – for those 35 years of age or older
        - Magnetic Resonance Elastography (MRE)
        - Vibration-Controlled Transity Elastography (VCTE)
2. Member is 18 years of age and older
3. Prescriber attests to the following: Member does not have decompensated MASH cirrhosis
4. Prescribed by, or in consultation with, an endocrinologist, gastroenterologist, or hepatologist
5. Dose requested does not exceed 100 mg/day AND the following:
    a. 60 mg strength – max of 1 tablet/day
    b. 80 mg strength – max of 1 tablet/day
    c. 100 mg strength – max of 1 tablet/day

Reauthorization

Must meet all of the following:

1. Prescriber must provide documentation of current clinical status, including both of the following:
    a. One of the following tests indicating improvement or stabilization of steatohepatitis:
        - FibroScan-aspartate aminotransferase (FAST)
        - Liver biopsy
        - MRI – protein density fat fraction (MRI-PDFF)
        - MRI – aspartate aminotransferase (MAST)
    b. One of the following tests indicating improvement or stabilization of fibrosis: • Enhance Liver Fibrosis (ELF)
        - FibroScan
        - Fibrosis-4 index (FIB-4) – for those 35 years of age or older
        - Magnetic Resonance Elastography (MRE)
        - Vibration-Controlled Transity Elastography (VCTE)
    c. Prescriber attests to all of the following:
        - Member does not have decompensated MASH cirrhosis
        - Member continues to have signs of MASH and/or contributing metabolic dysfunction factors (e.g., hyperlipidemia, hypertension, insulin resistance, obesity)
    d. Dose requested does not exceed 100 mg/day AND the following:
        - 60 mg strength – max of 1 tablet/day
        - 80 mg strength – max of 1 tablet/day
        - 100 mg strength – max of 1 tablet/day

Commercial
Initial Criteria
Must meet all of the following:

1. Diagnosis of metabolic dysfunction-associated steatohepatitis (MASH), formerly known as nonalcoholic steatohepatitis (NASH)
2. Patient does not have cirrhosis (e.g., decompensated cirrhosis)
3. Submission of medical records (e.g., chart notes) confirming diagnosis has been confirmed by one of the following: [1]
    - FibroScan-aspartate aminotransferase (FAST)
    - MRI-aspartate aminotransferase (MAST)
    - Liver biopsy
4. Submission of medical records (e.g., chart notes) confirming disease is fibrosis stage F2 or F3 as confirmed by one of the following:
    - FibroScan
    - Fibrosis-4 index (FIB-4)
    - Magnetic Resonance Elastography (MRE)
5. Presence of greater than or equal to 3 metabolic risk factors (e.g., Type 2 diabetes, hypertension, obesity) [3]
6. Submission of medical records (e.g., chart notes) confirming drug is used as an adjunct to lifestyle modification (e.g., dietary or caloric restriction, exercise, behavioral support, community based program)
7. Prescribed by or in consultation with one of the following:
    - Gastroenterologist
    - Hepatologist

Reauthorization
Must meet all of the following:

1. Patient demonstrates positive response to therapy (e.g., NASH resolution, fibrosis stage improvement, etc.)
2. Submission of medical records (e.g., chart notes) confirming drug will continue to be used as an adjunct to lifestyle modification (e.g., dietary or caloric restriction, exercise, behavioral support, community-based program)

Auvelity (dextromethorphan-bupropion) for the treatment of major depressive disorder (MDD) in adults

Time frame 1Q2024

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
AUVELITY tab 45-105mg	42	$35,353.56	$841.7547	30 per 30 days or 60 per 30 days	19	20 – 64
bupropion/SR/XL	3,208	$59,586.07	$18.35	38 per 31 days	1,409	6 – 64
bupropion tab 450mg XL	40	$14,074.44	$351.86	29.9 per 29.9 days	18	18 – 61
citalopram tab/sol	1,042	$10,403.70	$9.98	31 per 31 days	478	5 – 81
escitalopram/LEXAPRO	3,944	$51,614.29	$13.09	33 per 30.5 days	1,779	6 – 84
desvenlafaxine ER	616	$15,611.70	$25.34	29 per 28.8 days	229	12 – 64
duloxetine/CYMBALTA	2,630	$40,418.86	$15.37	40 per 30.7 days	1,074	7 – 94
fluoxetine ca/tab/sol	5,526	$67,937.88	$12.29	39.7 per 30.5 days	2,316	3 – 65
fluvoxamine tab/cap ER	77	$3,386.13	$43.98	46.5 per 31.7 days	29	9 – 66
mirtazapine/ODT	1,470	$19,262.07	$13.10	28 per 28.8 days	629	5 – 92
paroxetine/ER/susp	435	$9,174.21	$21.09	37.5 per 30.5 days	188	33 – 65
sertraline cap/tab/sol	5,016	$62,254.42	$12.41	36.6 per 30.7 days	2,275	4 – 99
venlafaxine/EFFEXOR/ER	1,676	$33,483.99	$19.98	35.5 per 29.8 days	637	9 – 99
trazodone	4,265	$45,352.86	$10.63	35 per 30 days	1,934	3 – 64

South Dakota Antidepressant PA Criteria

1. Patient is already stabilized on therapy with the requested medication **OR**
2. Patient has had a trial with a first-tier agent in the past 12 months
   - tricyclic agents
   - trazodone
   - bupropion/ER/SR/XL
   - SSRI
   - SNRI

State A

1. Diagnosis of Major Depressive Disorder (MDD)
2. Patient is 18 years of age or older
3. Trial and failure, or contraindication, intolerance to 2 preferred antidepressants
4. Patient does not have ANY of the following:
   - Seizure disorder
   - Current or prior diagnosis of bulimia or anorexia nervosa
   - Undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs
5. Prescriber attests patient has not received MAOI therapy within 14 days and will not receive during therapy

State B

Approval Criteria

1. The patient is unresponsive to other treatment modalities, unless contraindicated (i.e. other medications or behavioral modification attempted)
2. The physician attests that the requested medication is medically necessary. (Document rationale for use)
3. Patient has a history of failure, contraindication or intolerance to at least 3 preferred alternatives*
    - bupropion/SR/XL
    - citalopram
    - duloxetine
    - escitalopram
    - esketamine (Spravato)
    - fluoxetine
    - fluvoxamine
    - mirtazapine
    - paroxetine
    - sertraline
    - trazodone
    - venlafaxine/ER

Commercial

Approval Criteria

A. Both of the following:
    1. Requested drug is being used for a Food and Drug Administration (FDA)-approved indication
    2. One of the following
        a. Trial and failure (of a minimum 30-day supply), contraindication, or intolerance to any three of the following generics:
            - bupropion
            - citalopram tablets or oral solution
            - desvenlafaxine ER
            - duloxetine
            - escitalopram
            - fluoxetine
            - mirtazapine
            - paroxetine/ER
            - sertraline tablets or oral solution
            - venlafaxine/ER
        b. Patient has treatment-resistant depression as defined by a failure to respond to a trial of at least 2 antidepressants after at least 4 to 6 weeks of treatment at the maximally tolerated dose [A]

OR

B. For continuation of prior therapy

Exxua (gepirone ER) for the treatment of major depressive disorder (MDD) in adults

Time frame 1Q2024

	Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Mbr	Age Range
Serotonin Modulators	EXXUA tab	0					
	nefazodone	0					
	trazodone	4,265	$45,352.86	$10.63	35 per 30 days	1,934	3 – 64
	TRINTELLIX (vortioxetine)	162	$71,885.69	$443.74	28 per 27days	66	16 – 64
	vilazodone/VIIBRYD	239	$11,804.26	$49.39	30 per 28 days	97	15 – 88

*Red font denotes drug is on PA or ST

South Dakota Antidepressant PA Criteria

1. Patient is already stabilized on therapy with the requested medication **OR**
2. Patient has had a trial with a first-tier agent in the past 12 months
   - tricyclic agents
   - trazodone
   - bupropion/ER/SR/XL
   - SSRI
   - SNRI

Commercial

Approval Criteria

1. Both of the following:
   1.1. Requested drug is being used for FDA-approved indication
   1.2. Trial and failure of a minimum 30-day supply, contraindication, or intolerance to any TWO of the following generics:
      - bupropion
      - citalopram tablets or oral solution
      - desvenlafaxine succinate extended-release (ER)
      - duloxetine
      - escitalopram
      - fluoxetine
      - mirtazapine
      - paroxetine, paroxetine ER
      - sertraline tablets or oral solution
      - venlafaxine, venlafaxine ER

OR

2. For continuation of prior therapy

Lybalvi (olanzapine-samidorphan) for the treatment of

— Schizophrenia in adults

— Bipolar I disorder in adults: (1) as acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate or (2) maintenance monotherapy treatment.

Time Period: 1Q2024

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
LYBALVI	103	$144,033.55	$1,398.38	28.6 per 27.5 days	39	13 – 59
LYBALVI TAB 10-10MG	37	$49,721.37	$1,343.82	26.8 per 29 days	14	13 – 59
LYBALVI TAB 15-10MG	13	$20,548.19	$1,580.63	31.7 per 25 days	7	15 – 59
LYBALVI TAB 20-10MG	21	$25,754.80	$1,226.42	24.5 per 29 days	7	20 – 50
LYBALVI TAB 5-10MG	32	$48,009.19	$1,500.29	32.3 per 27 days	16	13 – 48
olanzapine-fluoxetine	4	$1,611.60	$402.90	30 per 30 days	2	52, 58
olanzapine tab	1,190	$15,980.79	$13.43	31 per 26.7 days	445	7 – 76
olanzapine ODT	51	$1,385.00	$27.16	30.7 per 0.9 days	21	7 – 61

South Dakota Atypical Antipsychotic PA Criteria

A. For continuation of a second generation atypical antipsychotic agent **OR**

B. All of the following

1. One of the following:
    a. Diagnosis of one of the following:
        - Aphagia
        - Autistic disorder
        - Bipolar depression
        - Bipolar disorder
        - Bipolar II disorder
        - Conduct disorders
        - Cyclothymic disorder
        - Dementia in other diseases
        - Dementia, unspecified
        - Dysphagia, unspecified
        - Dysthymic disorder
        - Intermittent explosive disorder
        - Mania
        - Mood (affective) disorders, unspecified
        - Oppositional defiant disorder
        - Persistent mood (affective) disorders
        - Schizophrenia
        - Schizophreniform disorder
        - Tourette's syndrome
        - Unspecified psychosis
        - Vascular dementia

    OR

    a. Both of the following:
        - Patient has a diagnosis of depression
        - Patient has tried and failed 2 different antidepressants
2. Children younger than 6 years of age must have a psychiatrist, developmental pediatrician, child/adolescent psychiatrist or pediatric neurologist involved in care

State A

Approval Criteria

One of the following:

A. All of the following:
   1. Diagnosis of schizophrenia
   2. Both of the following:
      a. Patient has a history of failure, contraindication or intolerance to at least FOUR of the following:
         - aripiprazole oral (generic Abilify)
         - aripiprazole injectable formulations (Abilify Maintena, Aristada, Aristada Initio)
         - clozapine/clozapine ODT
         - lurasidone
         - paliperidone oral
         - paliperidone injectable formulations (e.g., Invega Trinza, Invega Sustenna, Invega Hafyera)
         - Quetiapine
         - Risperidone/risperidone ODT
         - Risperidone injectable formulations (Perseris, Risperdal Consta)
      b. Failure to respond to generic olanzapine given at maximum dosage

OR

B. All of the following:
   1. Diagnosis of bipolar I disorder
   2. History of failure, contraindication or intolerance to ALL of the following preferred alternatives:
      - lamotrigine
      - lithium
      - valproate
   3. History of failure, contraindication or intolerance to THREE of the following preferred alternatives:
      - aripiprazole
      - lurasidone
      - quetiapine
      - risperidone

OR

C. One of the following:
   1. The patient has been receiving treatment with the requested medication, and is new to the plan (enrollment effective date within the past 90 days)
   2. The patient is currently receiving treatment with the requested medication in the hospital and must continue upon discharge

State B

1. Patient is ≥18 years of age
2. One of the following:
    - Diagnosis of schizophrenia
    - Diagnosis of Bipolar I disorder and will be used for the acute treatment of manic or mixed episodes
    - Diagnosis of Bipolar I disorder and will be used as maintenance monotherapy treatment
3. Prescriber must attest that patient does not meet any of the following:
    - Patient is using opioids or has used a short-acting opioid in the last 7 days or a long-acting opioid in the last 14 days
    - Patient is undergoing acute opioid withdrawal
4. Clinically valid reason why preferred olanzapine formulations cannot be used

Commercial

Approval Criteria

1. Both of the following:
    a. Requested drug is being used for a Food and Drug Administration (FDA)-approved indication
    b. Trial and failure (of a minimum 30-day supply), contraindication, or intolerance to TWO of the following:
        - aripiprazole
        - olanzapine
        - quetiapine IR/ER
        - risperidone
        - clozapine
        - ziprasidone
        - paliperidone
        - asenapine

    OR
2. For continuation of prior therapy

Veozah (fezolinetant) for the treatment of moderate to severe vasomotor symptoms due to menopause

Time frame 1Q24

	Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Mbr	Age Range
Non-hormonal agents	VEOZAH tab 45mg	19	$10,030.54	$527.92	30 per 30 days	11	33 – 64
Estrogen single entity agents	estradiol valerate inj	10	$1,307.07	$130.71	5 per 29 days	7	19 – 34
	Depo-Estradiol cyp inj	5	$935.90	$187.18	4 per 31 days	3	21 – 43
	estradiol DIS transdermal	55	$3,698.53	$67.25	7 per 29 days	26	19 – 61
	Dotti (estradiol transdermal)	59	$4,061.91	$68.85	9 per 29 days	28	19 – 58
	estradiol tablet	199	$2,365.42	$11.89	41 per 30 days	93	14 – 64
	estradiol gel	5	$600.90	$120.18	30 per 30 days	3	29 – 59
	estradiol vaginal cream	46	$1,512.08	$32.87	42.5 per 29 days	37	1 – 64
	estradiol 10mcg vaginal tab	6	$547.01	$91.17	11 per 26 days	4	46 – 57
	Yuvafem 10mcg vaginal tab	2	$449.28	$224.64	31 per 31 days	4	46 – 57
	Premarin vaginal	18	$7,894.36	$438.58	30 per 31 days	16	3 – 63
	Premarin tab	42	$7,974.32	$189.86	28 per 28 days	17	20 – 62
Combo products	Climara Pro (estradiol/levonorgestrel transdermal system)	2	$496.84	$248.42	4 per 28 days	2	16, 54
	CombiPatch (estradiol/norethindrone transdermal system)	8	$1,957.88	$244.74	8 per 28 days	5	34 – 60
	Bijuva tab (estradiol/progesterone)	0					

State A

Must meet all of the following:

1. Diagnosis of moderate to severe vasomotor symptoms due to menopause
2. Trial and failure, contraindication, or intolerance to TWO of the following:
    - Gabapentin
    - Menopausal hormone therapy (e.g., estrogen monotherapy or estrogen + progesterone)
    - Oxybutynin
    - SSRI (e.g., paroxetine, escitalopram, citalopram)
    - SNRI (e.g., venlafaxine and desvenlafaxine)

State B

Initial Criteria

Must meet all of the following:

1. Diagnosis of moderate to severe vasomotor symptoms due to menopause
2. Member has tried and failed to achieve an adequate response with at least TWO preferred oral estrogen or estrogen/progestin products

Reauthorization

Documentation of positive clinical response to therapy (e.g., decrease in frequency and severity of vasomotor symptoms from baseline, etc.)

State C

Initial Authorization

Must meet all of the following:

1. Diagnosis of moderate to severe vasomotor symptoms due to menopause
2. Member is 18 years of age or older
3. One of the following:
    - Member has tried and failed at least 90 days of therapy with ONE hormonal agent (e.g., oral, injectable, topical, transdermal, or vaginal), confirmed by claims history or chart documentation
    - Member has contraindication to hormonal therapy (must submit supporting chart documentation) and has tried and failed at least 90 days of therapy with ONE non-hormonal agent (e.g., gabapentin, paroxetine, venlafaxine, oxybutynin), confirmed by claims history or chart documentation
    - Prescriber has submitted valid medical justification for the use of Veozah (fezolinetant) over hormonal therapy AND other non-hormonal therapy
4. Prescriber attests to the following:
    - Member does not have cirrhosis
    - Member does not have severe renal impairment or end-stage renal disease (ESRD)
    - Member is not currently utilizing a CYP1A2 inhibitor and will not be initiated on CYP1A2 inhibitor therapy while on concomitant Veozah (fezolinetant) therapy
5. Dose requested does not exceed 45 mg (1 tablet) per day

Reauthorization

Must meet all of the following:

1. History of the requested agent for at least 90 days of the past 120 days, confirmed by claims history or chart documentation
2. One of the following:
    - Member has previously tried and failed at least 90 days of therapy with ONE hormonal agent (e.g., oral, injectable, topical, transdermal, or vaginal), confirmed by claims history or chart documentation
    - Member has contraindication to hormonal therapy and has previously tried and failed at least 90 days of therapy with ONE non-hormonal agent (e.g., gabapentin, paroxetine, venlafaxine, oxybutynin), confirmed by claims history or chart documentation
    - Prescriber has submitted valid medical justification for the use of Veozah (fezolinetant) over hormonal therapy AND other non-hormonal therapy
3. Prescriber attests to the following:
    - Member does not have cirrhosis
    - Member does not have severe renal impairment or end-stage renal disease (ESRD)
    - Member is currently not on a CYP1A2 inhibitor and will not be initiated on a CYP1A2 inhibitor while on concomitant Veozah (fezolinetant) therapy
4. Dose requested does not exceed 45 mg (1 tablet) per day

Commercial

Must meet all of the following:

1. Diagnosis of moderate to severe vasomotor symptoms due to menopause
2. Submission of medical records (e.g., chart notes, paid claims history) documenting trial and failure, contraindication, or intolerance to both of the following (document drug, date, and duration of trial):
    - Menopausal hormone therapy (e.g., Premarin, Bijuva, Estrogel, etc.)
    - Non-hormonal therapy (e.g. paroxetine mesylate, venlafaxine, clonidine, etc.)

Reauthorization
Documentation of positive clinical response to therapy (e.g., decrease in frequency and severity of vasomotor symptoms from baseline, etc.)

Optum Rx®

New Drug Overview

Rezdiffra (resmetirom)

Introduction

- Nonalcoholic fatty liver disease (NAFLD) is a spectrum of liver disease characterized by ≥ 5% hepatic steatosis which may lead to various forms in the absence of heavy alcohol consumption (*Rinella et al 2023a*). Nonalcoholic fatty liver (NAFL) is a relatively benign form that may be reversible with lifestyle changes and treatment of metabolic comorbidities. However, NAFL can progress to nonalcoholic steatohepatitis (NASH), a severe, progressive, inflammatory form that can cause fibrosis and eventually cirrhosis. Unfortunately, it is hard to determine which NASH patients will progress to cirrhosis due to the complex interplay between genetics, lifestyle, and nutritional factors (*Heyens et al 2021*, *National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] 2021*).
- In June 2023, updated nomenclature was developed via consensus of 3 large liver associations. NASH was reclassified as metabolic dysfunction-associated steatohepatitis (MASH), and NAFLD was reclassified as metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD includes patients with hepatic steatosis and at least 1 of 5 cardiometabolic risk factors. A new category was also developed termed metabolic and alcohol related/associated liver disease (MetALD), to describe those with metabolic dysfunction-associated steatotic liver disease, who consume greater amounts of alcohol per week (*Rinella et al 2023b)*.
  - Cardiometabolic risk factors include central obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension.
  - To note, guidelines and recent clinical trials use historical nomenclature due to the timing of the changes. Terminology may be used interchangeably in this review.
- In the general population, the prevalence of NAFLD is estimated to be between 25% to 30%, while NASH is estimated to be between 1.5% and 6.5% (*Food and Drug Administration [FDA] integrated review 2023*, *Institute for Clinical and Economic Review [ICER] 2023, Rinella et al 2023a*).
- While the pathogenesis of NASH is not fully understood, insulin resistance is thought to play a key role in steatohepatitis (*Tendler et al 2022*).
- In most patients, NAFLD is asymptomatic or associated with vague symptoms. Definitive diagnosis and staging of NASH are determined through histology (*Rinella et al 2023a*). The stages of NASH associated fibrosis range from absent (F0) to cirrhosis (F4). Patients with stage ≥ F2 NASH are referred to as “at-risk”, and have a notably higher risk of liver-related morbidity and mortality (*Rinella et al 2023a*).
- Currently, the standard of care includes lifestyle management with reduced calorie diet and increased exercise (*FDA integrated review 2023*).
- Rezdiffra (resmetirom) is the first FDA-approved treatment for NASH, approved via the accelerated approval pathway in March 2024. It is a thyroid hormone receptor-beta (THR-β) agonist. THR-β is the major form of THR in the liver, and stimulation of THR-β reduces intrahepatic triglycerides (*Rezdiffra prescribing information 2023*).
- Medispan class: Gastrointestinal Agents – Misc; Hepatotropics

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Brand (generic)
The treatment of adults with noncirrhotic NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis), in conjunction with diet and exercise.*	-

- *This indication is approved under accelerated approval based on improvement of NASH and fibrosis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

- Limitation of use: Avoid use in patients with decompensated cirrhosis.

(Prescribing information: Rezdiffra 2023)

- 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 efficacy and safety of resmetirom is being evaluated in the MAESTRO clinical program, which consists of 4 studies (MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLE, MAESTRO-NASH, and MAESTRO-NASH-OUTCOMES) (*Harrison et al 2024a*)
- The pivotal Phase 3 MAESTRO-NASH study is an ongoing, 54-month, multicenter, randomized, placebo-controlled trial evaluating safety and efficacy of resmetirom 80 mg and 100 mg in adults with biopsy confirmed NASH and a fibrosis stage of F1B, F2, or F3. Liver biopsies were planned at screening, week 52, and month 54. The 2 co-primary endpoints evaluated at the week 52 analysis in 966 participants were NASH resolution (defined as hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAFLD activity score by ≥2 points) with no worsening of fibrosis and a reduction in fibrosis by at least 1 stage with no worsening of the NAFLD score. A key secondary endpoint was the percent change from baseline in the low-density lipoprotein (LDL) cholesterol level at week 24 (*Harrison et al 2024b*).
  - At 52 weeks, 24.2% and 25.9% of patients treated with resmetirom 80 mg and 100 mg, respectively, achieved a ≥ 1-stage improvement in fibrosis stage with no worsening of the NAFLD activity score when read by 2 central pathologists (and confirmed with a consensus read) vs 14.2% of those treated with placebo ($p = 0.002$ for resmetirom 80 mg and $p < 0.001$ for resmetirom 100 mg vs placebo).
  - At 52 weeks, 25.9% and 29.9% of patients treated with resmetirom 80 mg and 100 mg, respectively, achieved NASH resolution without worsening of fibrosis when read by 2 central pathologists (and confirmed with a consensus read) vs 9.7% of those treated with placebo ($p < 0.001$ for both vs placebo).
  - Statistically significant decreases were also seen in LDL-C in those treated with resmetirom compared to placebo.
  - These endpoints will be confirmed at the month 54 analysis of MAESTRO-NASH. Additionally, a time to composite outcome consisting of all-cause mortality, liver transplant, and significant hepatic events (hepatic decompensation events, histological progression to cirrhosis, and a confirmed increase Model for End-stage Liver Disease [MELD] score from < 12 to ≥ 15) will be evaluated (*Harrison 2024a*).
- MAESTRO-NAFLD-1 (N = 972) was a randomized, double-blind, placebo-controlled, Phase 3 study that evaluated the safety and tolerability of once daily oral resmetirom 80 mg and 100 mg vs placebo. At week 52, the rate of treatment-emergent adverse events (AEs), the primary endpoint, was 86.5% (open-label 100 mg resmetirom), 86.1% (100 mg resmetirom), 88.4% (80 mg resmetirom), and 81.8% (placebo). Most AEs were considered mild to moderate, and the most common AEs were diarrhea and nausea (*Harrison et al 2023).*
- MAESTRO-NAFLD-OLE was a 36-week, Phase 2 trial that focused on the safety and non-invasive assessment of both resmetirom 80 mg and 100 mg (*Harrison et al 2021*).
- In a 2023 review from ICER, the data of 2 trials for obeticholic acid (REGENERATE and FLINT) and 3 trials for resmetirom (MAESTRO-NASH, MAESTRO-NAFLD-1, and a Phase 2 trial) were reviewed for the treatment of NASH. Obeticholic acid was assigned the evidence rating I (insufficient) in NASH patients with F2 fibrosis and a rating of P/I (promising but inconclusive evidence) in patients with F3 fibrosis. Resmetirom was assigned the evidence rating of C++ (comparable or better) to the standard of care in NASH patients with F2 or F3 fibrosis. Overall, the report noted uncertainties about long-term benefits due to the short duration of clinical trials (*ICER 2023*).

Clinical guidelines

- Although liver biopsy has been the standard for diagnosing NASH, non-invasive testing has emerged as a key tool to facilitate the risk stratification and diagnosis of patients with NAFLD. Several United States (U.S.) guidelines have recommendations in place for the treatment of NAFLD and/or NASH, including the AASLD, American Diabetes Association (ADA), American Gastrointestinal Association (AGA), and American Association of Clinical Endocrinology (AACE). All guidelines underscore the importance of lifestyle modifications (eg, diet, exercise, limiting alcohol use, weight loss) and management of metabolic comorbidities to prevent progression of NAFLD (*AASLD 2023, ADA 2024*, *Cusi et al 2022, Kanwal et al 2021, Rinella et al 2023a, Wattacheril et al 2023*, *Younossi et al 2021).*
- The 2023 AASLD guideline on the clinical assessment and management of NAFLD indicates that diet, exercise, and weight loss are key lifestyle interventions to promote cardiovascular (CV) and liver heath and improve metabolic comorbidities (*Rinella et al 2023a*).
  - Weight loss improves hepatic steatosis, NASH, and hepatic fibrosis in a dose dependent manner. All patients should be encouraged to increase activity level as much as possible; individualized prescriptive exercise may increase sustainability. Bariatric surgery can be considered in patients who meet criteria, as it effectively resolves NAFLD/NASH in most patients without cirrhosis and reduces mortality from CVD and malignancy.

- In terms of pharmacotherapy, there were no FDA approved medications for the treatment of NAFLD at the time of guideline development. However, drugs approved to treat associated comorbidities may be considered in the appropriate clinical setting.
  - Semaglutide can be considered for its approved indications (T2DM/obesity) in patients with NASH; it confers CV benefit and improves NASH.
  - Pioglitazone improves NASH and can be considered for patients with NASH and T2DM.
  - Vitamin E can be considered as it improves NASH in some patients without diabetes.
  - Of note, data on semaglutide, pioglitazone, and vitamin E do not demonstrate an antifibrotic benefit and have not been carefully studied in patients with cirrhosis.
  - Metformin, ursodeoxycholic acid, dipeptidyl peptidase IV (DPP-4) inhibitors, statins, and silymarin are well studied, but have not demonstrated a benefit in NASH; they should not be used for the treatment of NASH.
- The 2024 ADA guideline for diabetes care recommends comprehensive CV risk factor management and lifestyle changes (eg, structured nutrition and exercise plans) to promote weight loss in patients with T2DM who are overweight or obese and have NAFLD. Pharmacotherapy recommendations with NASH benefit include the use of glucagon-like peptide-1 (GLP-1) agonists and pioglitazone, though other agents may be continued as clinically indicated. Insulin is the preferred agent in patients with T2DM and decompensated cirrhosis. Bariatric surgery should be considered in appropriate candidates to treat NASH and improve CV outcomes (*ADA 2024*).
- The 2022 AACE guideline recommends the management of extrahepatic complications (eg, T2DM, dyslipidemia, hypertension, CVD) based on current standard of care for patients with NAFLD (*Cusi et al 2022*).
  - Key lifestyle modifications include physical activity (through a structured program when possible), weight loss of ≥ 5% and preferably ≥ 10%, and dietary modifications to allow calorie deficit.
  - Pharmacotherapy recommendations include the following:
    - The use of pioglitazone, or a GLP-1 agonist for individuals with T2DM and biopsy-proven NASH.
    - Pioglitazone, GLP-1 agonists or sodium-glucose cotransporter-2 (SGLT2) inhibitors for cardiometabolic benefit in individuals with T2DM and NAFLD; however, SGLT2 inhibitors have not shown benefit for steatohepatitis.
    - Metformin, acarbose, DPP-4 inhibitors, and insulin are not recommended for the treatment of steatohepatitis due to lack of evidence; however, they should be continued as needed for hyperglycemia in patients with T2DM and NAFLD or NASH.
    - Vitamin E can be considered for the treatment of NASH in patients without T2DM. There is not enough evidence for use in people with T2DM and advanced fibrosis.
    - Obesity pharmacotherapies to aid in weight management, such as semaglutide 2.4 mg/week (preferred) or liraglutide 3 mg/day, particularly in patients with BMI ≥ 27 kg/m^2 with NAFLD or NASH and to promote cardiometabolic health.
  - Bariatric surgery may be considered as an option to treat NASH in patients with BMI ≥ 35 kg/m^2 (≥ 32.5 kg/m^2 in Asian populations).
- The 2021 AGA clinical care pathway for risk stratification and management of patients with NAFLD recommends a focus on lifestyle interventions to modify unfavorable cardiometabolic risk factors, particularly weight loss in overweight or obese patients through diet (eg, Mediterranean diet), exercise (eg, structured weight loss programs), and the use of anti-obesity medications. Bariatric surgery should be considered in appropriate individuals with clinically significant fibrosis and obesity from comorbidities (*Kanwal et al 2021, Younossi et al 2021*).
  - Pharmacotherapy recommendations include the use of vitamin E supplementation to improve steatosis. In patients who are intermediate and at high risk of advanced fibrosis, GLP-1s and pioglitazone are the preferred antidiabetic agents that confer a benefit for NASH. In patients with NAFLD and T2DM, GLP-1s and SGLT2 inhibitors are recommended.

Safety summary

- Contraindications: none
- Warnings and precautions: hepatotoxicity and gallbladder-related adverse reactions (eg, cholelithiasis and cholecystitis).
- Most common AEs: diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness.
- Key drug interactions: avoid concomitant use with strong cytochrome (CYP) 2C8 inhibitors (eg, gemfibrozil) and organic anion transporting polypeptides (OAT) P1B/PB3 inhibitors (eg, cyclosporine), reduce resmetirom dose with moderate CYP2C8 inhibitors (eg, clopidogrel), limit daily dose of certain statins (eg, atorvastatin, pravastatin, rosuvastatin, simvastatin), monitor patients more frequently for AEs when used with CYP2C8 substrates.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Rezdiffra (resmetirom)	Tablet	PO	< 100 kg, 80 mg once daily ≥ 100 kg, 100 mg once daily	Avoid use in patients with decompensated cirrhosis (Child-Pugh class B or C).

See the current prescribing information for full details.

Conclusion

- NAFLD is a spectrum of liver disease characterized by ≥ 5% hepatic steatosis in the absence of heavy alcohol consumptom. NAFL is a relatively mild form that may be reversible with lifestyle changes and treatment of metabolic comorbidities. However, NAFL can progress to NASH a severe inflammatory form that can cause fibrosis and cirrhosis The prevalence of NAFLD in the general population is estimated to be 25% to 30%, with a prevalence of NASH of 1.5% to 6.5%.
- There is a consensus among guidelines regarding the importance of lifestyle modifications and management of metabolic comorbidities to prevent progression of NAFLD to more advanced disease. This includes guideline-directed therapy for managing T2DM, dyslipidemia, and hypertension and the utilization of diet and exercise programs with or without anti-obesity medications or consideration of bariatric surgery. Key recommended pharmacotherapies for NASH (off-label) include GLP-1s or pioglitazone (in patients with T2DM) and vitamin E (in patients without T2DM).
- In March 2024, Rezdiffra (resmetirom) is the first agent to be approved for any form of NAFLD. Resmetirom received accelerated approval for the treatment of adults with noncirrhotic NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis), in conjunction with diet and exercise.
  - In the MAESTRO-NASH trial, resmetirom demonstrated superiority over placebo in the co-primary endpoints of NASH resolution or an improvement in fibrosis stage, at the 12 month interim analysis. In this ongoing trial, liver biopsy and a time to composite outcome will be performed at 54 months to determine long-term clinical outcomes.
  - Resmetirom has no contraindications but carries warnings for hepatotoxicity, gallbladder-related AEs (eg, cholelithiasis and cholecystitis), and drug interactions with statins.
  - The most common AEs reported with resmetirom (incidence ≥ 5% and higher than placebo) include diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness.
- With limited data and lack of long-term outcomes to date, resmetirom's ultimate role in the treatment of NASH is remains unknown. Full FDA approval for its indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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Optum Rx®

Therapeutic Class Overview

Antidepressants, other

Introduction

- Major depressive disorder (MDD) is a highly prevalent and disabling disorder characterized by symptoms such as depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide (*Rush 2023*).
- MDD is associated with higher rates of chronic disease, impaired functioning, and increased healthcare utilization. (*Villarroel and Terlizzi 2020)*. In 2021, an estimated 21 million adults (8.3%) in the United States experienced an episode of depression with the highest prevalence among individuals aged 18 to 25 years old (*National Institute of Mental Health [NIMH] Web site 2023*).
- Current guidelines recommend first-line treatment with a second-generation antidepressant (SGA) and/or cognitive behavioral therapy (CBT). Efficacy is generally comparable between and within classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). The SSRIs, SNRIs, and certain other agents (eg, mirtazapine, bupropion) are considered optimal for the initial treatment of MDD in most patients (*Qaseem et al 2023, Veterans Affairs/Department of Defense [VA/DoD] 2022*).
  - An estimated 40% of patients do not respond to initial SGA therapy; approximately 70% do not achieve remission on initial SGA therapy. In patients who have demonstrated partial or no response to initial maximized monotherapy after a minimum of 4 to 6 weeks of treatment, switching to another monotherapy (pharmacotherapy or CBT) or augmenting with a second medication or psychotherapy is recommended (*VA/DoD 2022*).
- This review includes SGAs other than those classified as SSRIs. It does not include first-generation antidepressants such as MAOIs and TCAs. It also does not include Zulresso (brexanolone) injection or Spravato (esketamine) nasal spray, which are administered under physician supervision for the treatment of postpartum depression (PPD) and treatment-resistant depression, respectively.
- The focus of this review is the safety and efficacy of the SNRIs, serotonin modulators, and atypical antidepressants in the treatment of MDD and other psychiatric FDA-approved indications.
  - The SNRIs approved for MDD include Cymbalta (duloxetine), Effexor (venlafaxine), Effexor XR (venlafaxine extended-release [ER]), Fetzima (levomilnacipran), desvenlafaxine ER, and Pristiq (desvenlafaxine succinate ER). These agents work by blocking presynaptic serotonin and norepinephrine transporter proteins, thereby inhibiting neurotransmitter reuptake (*Nelson 2023*).
- Savella (milnacipran) is an SNRI approved only for fibromyalgia; therefore, it will not be included in this review. Although duloxetine is approved for other indications (ie, chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia), these indications will not be addressed in this review (*Nelson 2023*).
- The serotonin modulators include trazodone, nefazodone, Trintellix (vortioxetine), and Viibryd (vilazodone); They act as serotonin receptor antagonists and/or agonists and inhibit reuptake of postsynaptic serotonin to different affinities for various serotonin (5HT) receptors. In 2023, Exxua (gepirone ER) was the first novel selective 5HT-1A partial agonist to be approved by the FDA. Gepirone is an azapirone that is structurally similar to buspirone, which is approved for generalized anxiety disorder (*Exxua prescribing information 2023; Hirsch and Birnbaum 2023[a]*).
- The atypical antidepressants include bupropion and mirtazapine (*Hirsch and Birnbaum 2023[b]*).
  - Bupropion is a monocyclic aminoketone that inhibits the presynaptic reuptake of dopamine and norepinephrine. Bupropion is available in a variety of formulations, including Aplenzin (bupropion hydrobromide), Forfivo XL (bupropion hydrochloride ER), Wellbutrin (bupropion hydrochloride), Wellbutrin SR (bupropion hydrochloride sustained-release), and Wellbutrin XL (bupropion hydrochloride ER). In 2022, the FDA approved Auvelity (dextromethorphan-bupropion), a first rapid acting oral treatment for MDD.
  - Mirtazapine is a piperazinoazepine compound that acts as an antagonist of presynaptic α_2-adrenergic receptors and postsynaptic 5-hydroxytryptamine (5-HT)$_2$, 5-HT$_3$, and histamine receptors, and a moderate antagonist of peripheral α_1-adrenergic and muscarinic receptors.
- Some of the products included in this review have additional psychiatric indications other than MDD, including MDD with a seasonal pattern (formerly known as seasonal affective disorder), generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder, and PPD.
  - MDD with a seasonal pattern is characterized by a regular temporal relationship between particular periods of the year and the onset and remission of depressive symptoms (*Avery 2022*).

- GAD is characterized by excessive anxiety and worry. Symptoms of GAD include restlessness, being easily fatigued, irritability, difficulty concentrating, muscle tension, and sleep disturbances (*Bandelow et al 2012*).
- PD is characterized by recurrent unexpected panic attacks followed by concern about subsequent panic attacks or maladaptive change in behavior related to the attacks. Panic attacks are discrete periods of intense fear or discomfort accompanied by somatic and psychic symptoms (eg, palpitations, sweating, trembling, dyspnea, chest pain, nausea) (*Bandelow et al 2012*).
- Social anxiety disorder is characterized by persistent fear of being observed or evaluated negatively by others in social performance or interaction situations. Patients with social anxiety disorder often avoid social interactions or endure them with intense anxiety or distress (*Bandelow et al 2012*).
- PPD is a common perinatal condition that affects around 17% of women during pregnancy or up to 12 months postpartum. PPD is a leading cause of maternal mortality, and because of maternal function, can pose serious risks to infants (*American College of Obstetricians and Gynecologists [ACOG] 2023[a], Deligiannidis et al 2023[a], Kanes et al 2017*). In 2023, the FDA approved Zurzuvae (zuranolone), an oral gamma-aminobutyric acid (GABA)-A receptor positive modulator specifically for the treatment of PPD.

- Medispan Classes: Antidepressants; Antidepressants – Misc; Miscellaneous Combinations; Alpha-2 Receptor Antagonists (Tetracyclics); GABA receptor Modulator; SNRIs; Serotonin Modulators;

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)*
Atypical Agents	
Aplenzin (bupropion hydrobromide ER)	-
Auvelity (dextromethorphan-bupropion)	-
bupropion hydrochloride	✔
Forfivo XL (bupropion hydrochloride ER)	✔
Wellbutrin SR (bupropion hydrochloride ER)	✔
Wellbutrin XL (bupropion hydrochloride ER)	✔
Remeron, (mirtazapine)	✔
Remeron SolTab (mirtazapine)	✔
GABA- A Modulators	
Zurzuvae (zuranolone)	-
SNRIs	
Cymbalta (duloxetine DR)	✔
Effexor XR (venlafaxine ER)	✔
Fetzima (levomilnacipran)	-
desvenlafaxine ER	✔
Pristiq (desvenlafaxine succinate ER)	✔
venlafaxine	✔
Serotonin Modulators	
Exxua (gepirone ER)	-
nefazodone	✔
trazodone	✔
Trintellix (vortioxetine)	-
Viibryd (vilazodone)	✔

Abbreviations: ER = extended release, DR = delayed release
*For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.

(*Drugs@FDA 2024, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2024*)

Indications

Table 1. FDA Approved Indications for Atypical Agents

Indication	Aplenzin (bupropion hydrobromide)	Auvelity (dextromethorphan-bupropion)	Forfivo XL (bupropion hydrochloride ER)	Remeron, Remeron SolTab (mirtazapine)	bupropion hydrochloride	Wellbutrin SR (bupropion hydrochloride sustained release)	Wellbutrin XL (bupropion hydrochloride ER)
MDD	✔	✔	✔	✔	✔	✔	✔
Prevention of seasonal major depressive episodes in patients with a diagnosis of seasonal affective disorder	✔						✔

(*Prescribing information: Aplenzin 2022, Forfivo XL 2019, Remeron/Remeron SolTab 2023, bupropion 2023, Wellbutrin SR 2022, Wellbutrin XL 2022*)

Table 3. FDA Approved Indications for GABA Modulators

Indication	Zurzuvae (zuranolone)
PPD	✔

(*Prescribing information: Zurzuvae 2023*)

Table 4. FDA Approved Indications for SNRIs

Indication	Cymbalta (duloxetine)	Effexor XR (venlafaxine ER)	Fetzima (levomilnacipran)	desvenlafaxine ER	Pristiq (desvenlafaxine succinate ER)	venlafaxine
MDD	✔	✔	✔	✔	✔	✔
Chronic musculoskeletal pain	✔					
Diabetic peripheral neuropathy	✔					
Fibromyalgia	✔ *					
GAD	✔ †	✔				
PD		✔				
Social anxiety disorder		✔				

*Adults and pediatric patients ≥ 13 years of age
†Adults and pediatric patients ≥ 7 years of age

(*Prescribing information: Cymbalta 2023, desvenlafaxine 2023, Effexor XR 2023, Fetzima 2023, Pristiq 2023, venlafaxine 2023*)

Table 5. FDA Approved Indications for Serotonin Modulators

Indication	Exxua (gepirone ER)	nefazodone	trazodone	Trintellix (vortioxetine)	Viibryd (vilazodone)
MDD	✔	✔	✔	✔	✔

(*Prescribing information: Exxua 2023, nefazodone 2021, trazodone 2023, Trintellix 2023, Viibryd 2023*)

- 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

MDD

- Although there is conflicting evidence, most meta-analyses and systematic reviews conclude that antidepressants have comparable efficacy across and within classes in the treatment of MDD. No robust or replicated results have established clinically meaningful differences (*Rush 2023*).
- A 2011 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review [archived] evaluated bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine in the treatment of adults with depressive disorders (*Gartlehner et al 2011*).
  - Results from direct and indirect comparisons based on 61 head-to-head trials and 31 placebo-controlled (PC) trials did not detect any substantial differences in efficacy among the SGAs for MDD (moderate strength of evidence).
  - While the overall adverse event (AE) profiles and rates of discontinuation are similar among SGAs, the incidence of specific AEs varies among agents (high strength of evidence).
    - Venlafaxine was associated with higher rates of nausea and vomiting than SSRIs based on a meta-analysis of 15 studies (high strength of evidence).
    - Mirtazapine was associated with higher weight gain than citalopram, fluoxetine, paroxetine, and sertraline based on results from 7 trials (high strength of evidence).
    - Sertraline was associated with a higher incidence of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine based on results of 15 studies (moderate strength of evidence).
    - Trazodone was associated with a higher rate of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine based on results from 6 trials (moderate strength of evidence).
    - Bupropion was associated with lower rates of sexual dysfunction than escitalopram, fluoxetine, paroxetine, and sertraline based on results from 6 trials (high strength of evidence).
  - Results from 7 trials suggested that mirtazapine has a significantly faster onset of action compared to citalopram, fluoxetine, paroxetine, and sertraline (moderate strength of evidence).
  - Separate meta-analyses of the available head-to-head trials also suggested comparable efficacy between SGAs. The clinical significance of the marginal but statistically significant differences reflected in certain head-to-head comparisons remains to be determined.
    - A meta-analysis of 6 studies (N = 1197) directly comparing venlafaxine to fluoxetine demonstrated a significantly higher odds ratio [OR] of response (defined as ≥ 50% reduction of symptoms from baseline) with venlafaxine (OR, 1.47; 95% confidence interval [CI], 1.16 to 1.86).
    - A meta-analysis of 3 studies (N = 470) directly comparing sertraline to venlafaxine demonstrated similar rates of response (OR, 1.18; 95% CI, 0.81 to 1.72).
    - A meta-analysis of 3 studies (N = 849) directly comparing paroxetine to duloxetine also demonstrated similar rates of response (OR, 0.84; 95% CI, 0.63 to 1.12).
- The newer SGAs, levomilnacipran, vilazodone, and vortioxetine, were not included in the 2011 AHRQ review but were included in the 2015 AHRQ comparative effectiveness review [archived], which evaluated SGAs and nonpharmacological treatments for adult patients with MDD. The available evidence did not warrant the selection of one

SGA over another based on efficacy in initial therapy, switching SGAs, or augmenting SGAs for MDD (*Gartlehner et al 2015*).
  - Two direct comparisons (N = 1123) with patients who did not achieve remission following an initial adequate SGA trial and were switched to another SGA did not demonstrate a substantial difference in response rates between SGAs (moderate strength of evidence). Additionally, results from one of those studies (n = 727) did not demonstrate a substantial difference between the SGAs in remission rates, decrease in severity of depression, overall risk of AEs, or suicidal ideas or behaviors (low strength of evidence).
  - One direct comparison (n = 565) with patients who did not achieve remission following an initial adequate SGA trial and were treated with add-on therapy with another SGA did not demonstrate substantial differences in the rates of response or remission between SGAs (low strength of evidence).
- In a Cochrane review of 15 studies (N = 7746) with vortioxetine for MDD, patients on vortioxetine were more likely to respond to therapy than those on placebo (Mantel-Haenszel risk ratio [RR], 1.35; 95% CI, 1.22 to 1.49; 14 studies, 6220 participants) with a low quality of evidence. The response rate for vortioxetine was comparable to that of SNRIs as a class (RR, 0.91; 95% CI, 0.82 to 1.00; 3159 participants) but lower compared with duloxetine alone (RR, 0.86; 95% CI, 0.79 to 0.94; 6 studies, 2392 participants), with a very low quality of evidence. The clinical implications of these results are unclear (*Koesters et al 2017*).
- A network meta-analysis of 522 randomized controlled trials (RCTs) (N = 116,477) found clinically important differences when comparing 21 antidepressants for the acute treatment of adults with MDD. Agomelatine (not available in the US), amitriptyline, mirtazapine, escitalopram, paroxetine, venlafaxine, and vortioxetine were among the more efficacious antidepressants (ORs ranged from 1.19 to 1.96). The least efficacious antidepressants were fluoxetine, fluvoxamine, reboxetine (not available in the US), and trazodone (ORs ranged from 0.51 to 0.84). Agomelatine, fluoxetine, escitalopram, sertraline, citalopram, and vortioxetine were better tolerated than the other antidepressants. Antidepressants with the highest dropout rates were amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine (ORs ranged from 1.30 to 2.32) (*Cipriani et al 2018*).
- A meta-analysis of 17 RCTs (N = 14,779) identified mirtazapine or a TCA as antidepressants that achieve early improvement in symptoms among adults with MDD (*Wagner et al 2017*).
- A meta-analysis of 3 RCTs (N = 1120) demonstrated no significant differences between duloxetine and escitalopram on several endpoints, including mean changes on the Hamilton Depression Rating Scale (HAMD) and Clinical Global Impression (CGI)-Severity (CGI-S) scale, overall response rate by the HAMD, and remission rate by the HAMD and Montgomery-Asberg Depression Rating Scale (MADRS). However, some endpoints favored escitalopram, including the mean changes in the MADRS, mean end scores on the CGI-Improvement (CGI-I) scale, and overall response by MADRS. Although the overall discontinuation rate was not significantly different, patients treated with escitalopram had a higher rate of discontinuation due to AEs (RR, 0.47; 95% CI, 0.25 to 0.90). The authors suggested that larger studies could be more accurate for comparing the 2 antidepressants (*Maneeton et al 2019*).
- A network meta-analysis of 24 studies in patients with MDD demonstrated similar efficacy among levomilnacipran, vilazodone, or vortioxetine and other SGAs (*Wagner et al 2018*).
- A Bayesian meta-analysis of FDA reviews for 16 antidepressants (levomilnacipran, desvenlafaxine, duloxetine, venlafaxine, paroxetine, escitalopram, vortioxetine, mirtazapine, venlafaxine XR, sertraline, fluoxetine, citalopram, paroxetine CR, nefazodone, bupropion, and vilazodone) demonstrated that all medications except bupropion and vilazodone showed strong evidence for efficacy in the treatment of depression (*Monden et al 2018*).
- A systematic review of 26 clinical trials suggested that vortioxetine and bupropion possess procognitive effects compared with SSRIs and SNRIs in adults with cognitive impairment and MDD (*Blumberg et al 2020*).
- A network meta-analysis of 65 RCTs (N = 12,415) of augmentation therapies in adults with MDD resistant to treatment with 1 or more antidepressant therapies, including trials of bupropion and mirtazapine, indicated that relative to placebo, several antipsychotic, first-generation antidepressant, and non-antidepressant medications were effective for inducing response and/or remission; augmentation with other agents, including bupropion and mirtazapine, was not found to have effectiveness over placebo. Relative to placebo, all-cause discontinuation rates were significantly higher for mirtazapine cariprazine, and ziprasidone (*Nuñez et al 2022*).
- The randomized, open-label, multicenter OPTIMUM trial compared augmentation of current antidepressant therapy with aripiprazole, augmentation with bupropion, and switching current antidepressant therapy to bupropion in older adults with treatment-resistant depression. Following initial randomization, patients who did not benefit from assigned treatment were randomized to augmentation with lithium or switching to nortriptyline. Augmentation with aripiprazole produced significantly greater improvement in psychological well-being relative to switching to bupropion; no difference in this

outcome was found between augmentation with aripiprazole vs augmentation with bupropion or augmentation with bupropion vs switching to bupropion. The rate of falls was highest in patients assigned to augmentation with bupropion. Augmentation with lithium and switching to nortriptyline produced similar changes in psychological well-being in patients who underwent second randomization (*Lenze et al 2023*).

- The efficacy of Exxua (ER gepirone) for MDD was evaluated in 2 randomized, double-blind (DB), PC studies with flexible dosing in adults 18 to 69 years of age. The primary outcome was the change from baseline in the HAMD-17 total score at Week 8. In study 1 (gepirone, n = 101; placebo, n = 103), significantly greater reductions in HAMD-17 total scores occurred in gepirone-treated patients compared with placebo-treated patients at Weeks 3 (p = 0.013) and 8 (p = 0.018) (*Feiger et al 2003*). In study 2 (gepirone, n = 116; placebo, n = 122), significantly greater reductions in HAMD-17 total scores occurred in gepirone-treated patients compared with placebo-treated patients at Weeks 4 (p > 0.004), 6 (p = 0.006), and 8 (p = 0.032) (*Bielski et al 2008*). Per the prescribing information, the difference vs placebo in HAMD-17 total score reduction was -2.47 (95% CI, -4.41 to -0.53) in Study 1 and -2.45 (95% CI, -4.47 to -0.43) in Study 2 (*Exxua prescribing information 2023*). The final doses of gepirone varied, with approximately 65% of patients receiving 72.6 mg/day in both studies.
- A randomized, DB, PC study compared the effects of low-dose (10 to 50 mg) and high-dose (20 to 100 mg) ranges of ER gepirone with placebo in 145 patients with MDD. The results demonstrated statistically significant improvements in HAMD-17 total scores with high-dose gepirone compared to placebo at Weeks 1, 2, 4, and 6 (p < 0.05 for all). However, differences between low dose gepirone and placebo did not reach statistical significance at any of the measured time points (*Wilcox et al 1996*).
- A meta-analysis of 7 trials (2 pivotal trials, 5 supportive trials) found a small but significant difference in the change in HAMD-17 score (difference -1.22; 95% CI, -1.99 to -0.45; p = 0.002).
- The safety and efficacy of Auvelity (dextromethorphan-bupropion) was evaluated in two 6-week DB, multi-center RCTs in adult patients with MDD who experienced a major depressive episode ≥ 4 weeks (GEMINI and ASCEND).
  - GEMINI was a Phase 3, PC trial with 327 patients who were randomized to dextromethorphan-bupropion (n = 163) or placebo (n = 164). The primary endpoint was change from baseline to Week 6 in MADRS total score. Results on the MADRS demonstrated least squares mean (LSM) changes of -15.9 and -12.1 in the dextromethorphan-bupropion and placebo groups, respectively (difference, -3.9; 95% CI, -1.4 to -6.4 ; p = 0.002) (*Iosifescu et al 2022*).
    - The study also met key secondary endpoints including change from baseline to Week 1 in the MADRS total score (p = 0.007), change from baseline to Week 2 in the MADRS total score (p < 0.001), remission (defined as MADRS total score ≤ 10; p = 0.013 by week 2; p < 0.001 by week 6), and clinical response (defined as ≥ 50% reduction in MADRS total score (p < 0.001 by week 6).
  - ASCEND was a Phase 2, active-controlled trial in 97 patients who were randomized to dextromethorphan-bupropion (n = 48) or bupropion alone (n = 49). The primary endpoint was overall treatment effect on the MADRS total score (average of the change from baseline for weeks 1 through 6). Results demonstrated LSM changes of -13.7 and -8.8 in the dextromethorphan-bupropion and bupropion alone, respectively. The difference between dextromethorphan-bupropion and bupropion alone was -4.9 (95% CI, -3.1 to -6.8 ; p < 0.0001) (*Tabuteau et al 2022*).
    - The key secondary endpoint was the percentage of patients achieving clinical remission, defined as a MADRS total score ≤ 10. At 6 weeks, results demonstrated a 46.5% and 16.2% remission rate in the Auvelity and bupropion groups, respectively (95% CI, 11.2 to 49.4; p = 0.004).

MDD with a Seasonal Pattern: ER bupropion

- A Cochrane review of 3 RCTs (N = 1100) evaluated SGAs for the prevention of seasonal affective disorder in adults. Bupropion ER was shown to be an effective intervention compared to placebo (RR, 0.56; 95% CI, 0.44 to 0.72) for the prevention of depressive episodes in patients with MDD with a seasonal pattern, with a moderate quality of evidence. Bupropion therapy was also associated with a greater incidence of headaches, insomnia, and nausea compared with placebo. There was insufficient evidence to compare bupropion to other SGAs or other interventions such as light therapy, psychotherapy, or melatonin (*Gartlehner et al 2019*).

GAD: duloxetine and venlafaxine

- A non-inferiority RCT (N = 984) randomized adults with GAD to receive duloxetine, venlafaxine ER, or placebo. The primary outcome of response to therapy was defined as ≥ 50% reduction from baseline in Hamilton Anxiety Rating Scale (HAMA) total score. Response rates for duloxetine, venlafaxine ER, and placebo were 56%, 58%, and 40%, respectively. Duloxetine and venlafaxine ER both demonstrated superiority over placebo (p ≤ 0.001 for both). The

authors concluded that duloxetine met all statistical and clinical criteria for non-inferiority and exhibited a similar tolerability profile compared to venlafaxine ER for the treatment of adults with GAD (*Allgulander et al 2008*).

- A network meta-analysis of 89 RCTs (N = 25,441) evaluating treatment of GAD demonstrated improved efficacy vs placebo on the HAMA score with duloxetine (mean difference, -3.13, 95% credible interval [CrI], -4.13 to -2.13), pregabalin (-2.79; 95% CrI, -3.69 to -1.91), venlafaxine (-2.69; 95% CrI, -3.50 to -1.89), and escitalopram (-2.45; 95% CrI, -3.27 to -1.63). Mirtazapine was also efficacious but was studied in a small sample size (*Slee et al 2019*).
- A systematic review of 12 publications evaluated the use of antidepressants for anxiety (mainly GAD) in late life (age ≥ 60 years). The study demonstrated a significant reduction in anxiety with antidepressants, including duloxetine and venlafaxine, across all trials (*Balasubramanian et al 2019*).

PD: ER venlafaxine

- A Cochrane review of 35 DB RCTs (N = 6785) evaluated antidepressants and benzodiazepines as monotherapy for adults with PD. An analysis of 2 studies (N = 1316) directly comparing paroxetine with venlafaxine demonstrated similar response rates for PD (RR, 0.96; 95% CI, 0.75 to 1.23; 2 studies; 991 participants; high quality of evidence). Additionally, no difference in response rate was detected between antidepressants and benzodiazepines for PD (RR, 0.99; 95% CI, 0.67 to 1.47; 2 studies; 215 participants; low quality of evidence) (*Bighelli et al 2016*).
  - An update to this review utilized a network meta-analysis to compare pharmacotherapies for PD and used data from 70 studies. Consistent with the previous pairwise analysis, the comparison between venlafaxine and paroxetine showed no statistically significant difference in treatment response (RR, 1.01; 95% CrI, 0.84 to 1.26). Diazepam, alprazolam, clonazepam, paroxetine, venlafaxine, clomipramine, and fluoxetine showed the strongest effect, with diazepam, alprazolam and clonazepam ranking as the most effective (*Guaiana et al 2023*).
- In a meta-analysis of 50 studies (N = 5236) of antidepressants for PD, the following antidepressants (listed in increasing order of effectiveness) demonstrated superiority over placebo for the reduction from baseline in panic symptoms: citalopram, sertraline, paroxetine, fluoxetine, and venlafaxine. For overall anxiety symptoms, superiority vs placebo was demonstrated for paroxetine, fluoxetine, fluvoxamine, citalopram, venlafaxine, and mirtazapine (*Andrisano et al 2013*).

Social Anxiety Disorder: venlafaxine ER

- A systematic review and meta-analysis of 51 RCTs (N = 9914) evaluated pharmacotherapies for social anxiety disorder. Venlafaxine demonstrated a superior response rate, assessed by the CGI-I scale, vs placebo (RR, 1.59; 95% CI, 1.38 to 1.83; 4 studies; 1173 participants) (*Ipser et al 2008*).
- Another systematic review and meta-analysis of 3 head-to-head trials and 15 PC trials did not reveal significant differences in the efficacy of SGAs for social anxiety disorder. Pooled evidence from PC trials supported the superiority over placebo in the CGI-I response of escitalopram (relative benefit [RB], 1.3; 95% CI, 1.2 to 1.5), paroxetine (RB, 1.9; 95% CI, 1.5 to 2.3), sertraline (RB, 1.8; 95% CI, 1.5 to 2.2), and venlafaxine (RB, 1.7; 95% CI, 1.5 to 1.9). While the network meta-analysis did not find significant differences in efficacy among the SGAs, there were differences in the AE profiles; however, methods used to assess AEs and the quality of reporting of specific events differed among studies, limiting any conclusions (*Hansen et al 2008*).
- A Cochrane review of 66 RCTs (N = 11,597) assessed the effects of pharmacotherapy on social anxiety disorder in adults. Duration of treatment varied; most trials were short term (14 weeks or less). Key results are as follows (*Williams et al 2017*):
  - For venlafaxine vs placebo:
    - There was no evidence of a significant treatment effect for response (defined as much or very much improved) based on 4 trials with 1173 participants (RR, 1.30; 95% CI, 0.85 to 1.99; p = 0.22); evidence for this comparison was of low quality. However, based on moderate-quality evidence, there was evidence of benefit in reduction of total symptom severity with venlafaxine, with a mean difference of -11.91 points (95% CI, -16.06 to -7.76) on the Liebowitz Social Anxiety Scale (LSAS; range, 0 to 144).
    - The proportion of patients who discontinued the study due to AEs was higher with venlafaxine (16%) vs placebo (5%).
  - For SSRIs vs placebo:
    - There was evidence of a significant treatment effect for response for paroxetine, fluvoxamine, sertraline, fluoxetine, and citalopram (RR, 1.65; 95% CI, 1.48 to 1.85; p < 0.00001); evidence was of low quality. Also based on low-quality evidence, a benefit for reducing total LSAS symptom score was demonstrated, with a mean difference of -10.14 points (95% CI, -14.05 to -6.22).

- The proportion of patients who discontinued treatment due to AEs was higher with SSRIs (12%) than placebo (4%).

- A recent systematic review and network meta-analysis of 67 RCTs (N = 12,122) evaluated the efficacy and acceptability of pharmacologic interventions for the acute treatment of social anxiety disorder in adults, with outcomes evaluated at approximately 8 weeks of treatment (*Williams et al 2020*).
  - This analysis did not demonstrate a benefit on LSAS symptom severity with venlafaxine vs placebo; in contrast, the difference favored placebo (mean difference, 30.47; 95% CI, 7.76 to 53.18); evidence for this comparison was of low quality. No other drug therapies demonstrated a statistically significant improvement in symptom severity vs placebo, with the exception of paroxetine (mean difference, -15.89; 95% CI, -29.94 to -1.94; low to very low quality of evidence).
  - The likelihood of treatment response was significantly greater for several medications vs placebo, including the SSRIs paroxetine (OR, 2.64; 95% CI, 1.97 to 3.54), escitalopram (OR, 1.96; 95% CI, 1.21 to 3.17), fluvoxamine (OR, 1.89; 95% CI, 1.14 to 3.12), and sertraline (OR, 2.50; 95% CI, 1.02 to 6.15). These analyses were based on low to very low quality of evidence with the exception of paroxetine and escitalopram, which were based on moderate to high quality evidence. The authors concluded that differences between drugs and placebo were small, apart from a significant reduction in symptom severity and response for paroxetine, which they recommend as a first-line treatment.

PPD: zuranolone

- The efficacy of zuranolone in women with PPD was evaluated in 2 randomized, DB, PC studies. The studies included women with PPD who met criteria for a major depressive episode, with symptoms starting in the third trimester of pregnancy or within 4 weeks of childbirth. Included patients had HAMD-17 scores ≥ 26 at baseline and could administer existing oral antidepressants if they had been on a stable dose for > 30 days before starting the study. The primary outcome in both studies was the change from baseline in depressive symptoms, assessed using the HAMD-17 total score at Day 15. Patients were followed for 4 weeks after treatment (*Deligiannidis et al 2023[a]*, *Deligiannidis et al 2021*)
  - In the first study, patients took either 50 mg of zuranolone (n = 98) or placebo (n = 97) once daily for 14 days, with the option to reduce the dose to 40 mg if needed. Results demonstrated a HAMD-17 total score difference of -4.0 (95% CI, -6.3 to -1.7; p = 0.001) with zuranolone vs placebo (*Deligiannidis et al 2023[a]*).
  - In the second study, patients received a different capsule formulation of zuranolone (approximately equivalent to 40 mg of Zurzuvae per the prescribing information) (n = 77) or placebo (n = 76) once daily for 14 days. Results demonstrated a LSM change in HAMD-17 total score of -17.8 points (zuranolone) vs -13.6 points (difference, -4.2; 95% CI, -6.9 to -1.5; p = 0.003) (*Zurzuvae prescribing information 2023*, *Deligiannidis et al 2021*).
    - A post hoc analysis of this study evaluated women with PPD who had concomitant anxiety and insomnia symptoms. The rates of concurrent remission of depressive and anxiety symptoms were higher with zuranolone vs placebo at days 3, 15, and 45 (p < 0.05 for all). Furthermore, insomnia symptoms assessed by the HAMD-17 insomnia subscale were significantly improved with zuranolone vs placebo at days 3 (p < 0.05), 15 (p < 0.01), and 45 (p < 0.05) (*Deligiannidis et al 2023[b]*).

Clinical Guidelines

MDD

- Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of MDD (*Va/DoD 2022*)
  - As first-line treatment for uncomplicated mild to moderate MDD, either psychotherapy or pharmacotherapy should be offered. Selection should be driven by patient preference.
    - Suggested initial pharmacotherapy includes SSRIs, SNRIs, mirtazapine, bupropion, trazodone, vilazodone, or vortioxetine.
    - Among suggested initial options, no specific psychotherapy or pharmacotherapy is recommended over another.
  - In patients with severe MDD, combined psychotherapy and pharmacotherapy are suggested. No pharmacotherapeutic agents are specifically recommended in this setting.
  - In patients with persistent or recurrent MDD despite an adequate trial of initial pharmacotherapy, switching to or augmenting treatment with psychotherapy or a second-generation (atypical) antipsychotic, or switching to an alternative antidepressant (including a TCA or MAOI), is suggested.
- Nonpharmacologic and Pharmacologic Treatments of Adults in the Acute Phase of Major Depressive Disorder: A Living Clinical Guideline from the American College of Physicians (ACP) (*Qaseem et al 2023*)
  - Monotherapy with CBT is suggested as initial treatment in adults in the acute phase of mild MDD.

- Monotherapy with CBT or a SGA, including SSRIs or SNRIs, is recommended as initial treatment in adults in the acute phase of moderate to severe MDD; alternatively, the combination of CBT and a SGA, based on shared decision-making, is suggested in this setting.
- In adults in the acute phase of moderate to severe MDD who did not respond to an adequate dose of a SGA in the front-line setting, switching to or augmenting treatment with CBT or another pharmacotherapeutic agent is suggested.
- Choosing between CBT, SGA, or both, as well as choice of SGA, should be a shared decision-making process based on patient preference informed by differences in AE profiles, serious AEs, contraindications and precautions, and costs.

- The American Academy of Child and Adolescent Psychiatry (AACAP) makes the following recommendations regarding the management of children and adolescents with major and persistent depressive disorders (*Walter et al 2023*):
  - CBT and interpersonal therapy could be offered to adolescents and children with MDD or persistent depressive disorder.
  - The SSRIs, preferably fluoxetine, could be offered to adolescents and children with MDD. Paroxetine is not recommended in this population.
  - Combination CBT plus fluoxetine could be offered to adolescents and children with MDD.
  - Continued fluoxetine alone or CBT plus fluoxetine could be offered to adolescents and children responding to acute treatment with fluoxetine to prevent relapse/recurrence of MDD.

MDD with a Seasonal Pattern

- Light therapy is suggested for patients with mild to moderate MDD with or without a seasonal pattern. While there is limited evidence supporting the effectiveness of light therapy, the benefits outweigh the risks. Current guidelines do not make specific recommendations for pharmacologic management of MDD with a seasonal pattern (*Qaseem et al 2023, VA/DoD 2022*).

GAD

- According to the World Federation of Societies of Biological Psychiatry (WFSBP), the first-line pharmacologic therapies for GAD are SSRIs (specifically escitalopram, paroxetine, and sertraline) and SNRIs (specifically duloxetine and venlafaxine) *(Bandelow et al 2023)*.
  - Second-line pharmacologic options for GAD include imipramine, pregabalin, and vilazodone.
  - Benzodiazepines (alprazolam, diazepam, and lorazepam) may be considered in combination with antidepressants early in the course of treatment before antidepressant onset.
  - Olanzapine and pregabalin may be considered as add-on therapy to antidepressants in treatment-refractory cases.
  - CBT may be considered for treatment of GAD, but evidence on its effectiveness is mixed. Evidence regarding effectiveness of CBT relative to pharmacotherapy is lacking.
- The AACAP recommends that SSRIs be offered to patients 6 to 18 years of age with social anxiety, GAD, separation anxiety, or PD, and suggests that SNRIs could be offered to patients in this age group with these conditions (*Walter et al 2020*). CBT is also recommended.
  - In the corresponding systematic review, the SNRIs for which sufficient data were available for comparisons were venlafaxine and duloxetine. Although mechanisms of action vary somewhat across SNRIs, the primary mechanism was deemed to be sufficiently similar across medications to warrant extension of the findings to the medication class.
  - Duloxetine is the only SNRI to have an FDA-approved indication for the treatment of any anxiety disorder in the pediatric population. However, the choice of medication for anxiety within the SNRI class may also be governed by considerations such as pharmacokinetics, pharmacodynamics, tolerability, cost, insurance formularies, and warnings/precautions.
  - For all SNRIs, medical monitoring should include height, weight, pulse, and blood pressure.

PD

- The WFSBP recommends SSRIs (specifically citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, and sertraline) and venlafaxine as first-line agents for PD *(Bandelow et al 2023)*.
  - Clomipramine and imipramine are as effective as the first-line agents, but are less preferred due to tolerability. Phenelzine may also be considered in the third-line setting.

- Benzodiazepines may be considered in combination with antidepressants early in the course of treatment before antidepressant onset, or in severe panic attacks.
- CBT has shown inconsistent results in comparative studies, but has more often shown inferiority to drug therapy than equal efficacy. CBT in combination with pharmacotherapy is more effective than CBT alone, but not more effective than pharmacotherapy alone.

Social Anxiety Disorder

- The WFSBP recommends SSRIs (specifically escitalopram, fluvoxamine, paroxetine, and sertraline) and venlafaxine as first-line therapy for treatment of social anxiety disorder *(Bandelow et al 2023)*.
  - Pregabalin is a second-line option for social anxiety disorder.
  - Phenelzine may be considered social anxiety disorder where other standard treatments have failed.
  - Benzodiazepines may be considered in combination with antidepressants early in the course of treatment before antidepressant onset, or in severe attacks.
  - CBT is more effective for social anxiety disorder than waitlist control groups and some active controls, but may be less effective than pharmacotherapy. Evidence for combining CBT with pharmacotherapy is inconclusive.

PPD

- An ACOG practice guideline for the management of mental health conditions during pregnancy and postpartum provides recommendations for the pharmacologic management of perinatal depression (*ACOG 2023[a]*).
  - The SSRIs are recommended as first-line pharmacotherapy for perinatal depression, with SNRIs recommended as reasonable alternatives. The guideline recommends that pharmacotherapy should be individualized based on prior response to therapy, and if no prior pharmacotherapy history exists, sertraline or escitalopram are reasonable first-line medications.
  - Recommendations for the use of brexanolone (not covered in this review) are also provided.
- An ACOG practice advisory provides recommendations for the use of zuranolone for the management of PPD (*ACOG 2023[b]*).
  - Zuranolone may be considered in the postpartum period (ie, within 12 months postpartum) for depression that has onset in the third trimester or within 4 weeks after childbirth. The decision should balance the drug's benefits (rapid symptom improvement) and risks (suicidal thoughts, sedation affecting daily activities, and limited efficacy data beyond 42 days).

Safety Summary

Contraindications

- All antidepressants and dextromethorphan-bupropion are contraindicated in patients with concurrent (or within 14 days of) administration of MAOIs (nefazodone has this listed as a warning rather than a contraindication). The risk for serotonin syndrome is increased with the use of MAOIs, including linezolid and intravenous methylene blue.
- Bupropion products are additionally contraindicated in the following: seizure disorder; current or prior diagnosis of bulimia or anorexia; abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs.
- Nefazodone is additionally contraindicated in patients who were withdrawn from nefazodone due to liver injury and in patients concurrently on terfenadine, astemizole, cisapride, pimozide, carbamazepine, or triazolam.
- Gepirone is also contraindicated in patients with a prolonged QTc interval (> 450 msec) or congenital QT syndrome, those receiving concomitant strong cytochrome P450 (CYP)3A4 inhibitors, and those with severe hepatic impairment.
- Additional contraindications for dextromethorphan-bupropion include seizure disorder, current or prior diagnosis of bulimia or anorexia nervosa, and known hypersensitivity to any component.

Warnings

- All antidepressants and dextromethorphan-bupropion carry a boxed warning for suicidal thoughts and behaviors. The risk of suicidal thinking and behavior is increased in children, adolescents, and young adults taking antidepressants.
  - Zuranolone has this listed as a warning rather than a boxed warning.
- Nefazodone labeling also contains a boxed warning for life-threatening hepatic failure and recommends that prescribers consider the risk of hepatic failure associated with nefazodone treatment when deciding among the various treatment options available for MDD. In many cases, this would lead to the conclusion that other drugs should be tried first.

- Zuranolone has a boxed warning for impaired ability to drive or engage in other potentially hazardous activities due to its central nervous system (CNS) depressant effects. Patients should be advised against driving or participating in activities that require alertness for at least 12 hours after taking the medication.
- Neonates exposed to SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with venlafaxine tablets during the third trimester, the potential risks and benefits of treatment should be carefully considered.
- Zuranolone may cause fetal harm; women who may become pregnant should use effective contraception during treatment and for 1 week after the final dose of zuranolone.
- Taking SNRIs or serotonin modulators, which interfere with serotonin reuptake, may increase the risk for gastrointestinal bleeding and postpartum hemorrhage; concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants adds to the risk. SSRIs or serotonin modulators may cause serotonin syndrome and hyponatremia.
- SNRIs have been associated with increases in blood pressure, including new-onset hypertension.
- Many antidepressants cause pupillary dilation that may contribute to the development of an angle closure glaucoma.
- Additional warnings for dextromethorphan-bupropion include dose-related seizure risks, increased blood pressure and hypertension, activation of mania/hypomania, psychosis or other neuropsychiatric reactions, angle-closure glaucoma, dizziness, serotonin syndrome and embryo-fetal toxicity.

AEs

- Common AEs with most of the antidepressants included in this review are outlined in Table 6.
- The most common AEs with gepirone include dizziness, nausea, insomnia, abdominal pain, and dyspepsia.
- The most common AEs with zuranolone include somnolence, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infection.
- The most common AEs with dextromethorphan-bupropion (≥5% and more than twice as frequently as placebo) include dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis.

Table 6. AEs of Antidepressant Medications

Drug	Anticholinergic	Drowsiness	Insomnia/ agitation	Orthostatic hypotension	QTc prolongation[1]	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
Atypical agents								
Bupropion	0	0	2+ (IR) 1+ (SR)	0	1+	1+	0	0
Mirtazapine	1+	4+	0	0	1+	0	4+	1+
SNRIs[2,3]								
Desvenlafaxine[4]	0	0	1+	0	0	2+	unknown	1+
Duloxetine	0	0	1+	0	0	2+	0-1+	1+
Levomilnacipran	0[5]	0	0-1+	0-1+	0	2+	0	1+
Venlafaxine	0	1+	1+	0	1-2+	2+	0-1+	3+
Serotonin modulators								

[1] Risk of QTc prolongation or torsades de pointes is also elevated with advanced age, female sex, heart disease, congenital long QT syndrome, hypokalemia or hypomagnesemia, elevated serum drug concentrations (eg, drug overdose, interacting drugs, organ failure) and combination of drugs with QTc prolonging effects.
[2] All SSRIs and SNRIs are associated with transient nausea and gastrointestinal discomfort upon initiation or dose increase.
[3] None of the SNRIs have anticholinergic activity. However, SNRIs can produce anticholinergic-like effects (which appear to be mediated by noradrenergic effects on the autonomic nervous system) such as dry mouth and constipation, and should be used with caution in narrow angle glaucoma. In addition, levomilnacipran is associated with urinary hesitancy.
[4] May cause persistent dose-related increases in blood pressure (primarily diastolic) and heart rate. Monitor blood pressure regularly.
[5] Levomilnacipran has dose dependent effects on urinary hesitancy.

Drug	Anticholinergic	Drowsiness	Insomnia/ agitation	Orthostatic hypotension	QTc prolongation[1]	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
Nefazodone[6]	1+	2+	0	1+	0	2+	0	0
Trazodone[7]	0	4+	0	3+	1-2+	3+	1+	1+[8]
Vilazodone	0	0	2+	0	0	4+[9]	0	2+
Vortioxetine	0	0	0	0	0	3+	0	1+

Abbreviations: IR = immediate release; SNRI = serotonin-norepinephrine reuptake inhibitor; SR = sustained release.
Scale: 0 = none; 1+ = slight; 2+ = low; 3+ = moderate; 4+ = high; ND = inadequate data.

(*Hirsch and Birnbaum 2023[a], Nelson 2023*)

Dosing and Administration

Table 7. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Atypical agents				
Aplenzin (bupropion hydrobromide)	ER tablets	Oral	Daily	Increase dose gradually to reduce seizure risk. Dose adjustments may be required in renal or hepatic impairment. Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified.† Data from epidemiological studies of pregnant patients exposed to bupropion in the first trimester have not identified increased risk of congenital malformations.
Auvelity (dextromethorphan-bupropion)	ER tablets	Oral	Twice daily	Prior to initiation: assess blood pressure; screen patients for history of bipolar disorder, mania, or hypomania; and determine if patients are receiving any other medications that contain bupropion or dextromethorphan. Max once daily dosing in recommended in moderate renal impairment and CYP2D6 poor metabolizers. Not recommended during pregnancy. If a female becomes pregnant while being treated,

[6] Caution: can cause liver failure.
[7] Side effect scale is displayed for the antidepressant dose of trazodone.
[8] Trazodone is associated rarely with priapism, which is considered a medical emergency.
[9] Vilazodone is associated with higher rates of nausea, vomiting, and diarrhea.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				discontinue treatment and counsel the patient about the potential risk to a fetus.
Forgiven XL (bupropion hydrochloride)	ER tablets	Oral	Daily	Not recommended in patients with renal or hepatic impairment due to higher dose. Bupropion treatment should not be initiated with Forfivo XL. Another bupropion formulation should be used for initial dose titration. Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified.† Data from epidemiological studies of pregnant patients exposed to bupropion in the first trimester have not identified increased risk of congenital malformations.
Remeron (mirtazapine)	Tablets	Oral	Daily	Administered in the evening prior to sleep. Caution is advised in renal or hepatic insufficiency. Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified.† Observational studies and postmarketing reports have not reliably identified drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
Remeron SolTab (mirtazapine)	Orally-disintegrating tablets	Oral	Daily	
Wellbutrin (bupropion hydrochloride)	Tablets	Oral	Three times daily	Dose adjustments may be required in renal or hepatic impairment. Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified.† Data from epidemiological studies of pregnant patients exposed to bupropion in the first trimester have not identified increased risk of congenital malformations.
Wellbutrin SR (bupropion hydrochloride)	Sustained-release tablets	Oral	Twice daily	
Wellbutrin XL (bupropion hydrochloride)	ER tablets	Oral	Daily	
GABA A Modulators				
Zurzuvae (zuranolone)	Capsule	Oral	Daily	Administer with fat-containing food. Dose reductions may be necessary in patients with renal or hepatic impairment, or when co-administered with CYP3A4 inhibitors or CNS depressants. Avoid use with CYP3A4 inducers.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy: Unclassified.† Data from animal studies suggest that zuranolone may cause fetal harm.
SNRIs				
Cymbalta (duloxetine)	Delayed-release capsules	Oral	Daily or twice daily	Avoid use in patients with chronic liver disease, cirrhosis, and severe renal impairment. Safety and effectiveness have been established for treatment of GAD in pediatric patients 7 to 17 years of age. Safety and effectiveness have not been established in pediatric patients with MDD. Pregnancy: Unclassified.† A postmarketing retrospective cohort study indicated that use of duloxetine in the month before delivery may increase risk of postpartum hemorrhage. A clear drug-associated risk of major birth defects or other adverse developmental outcomes has not been established.
Effexor XR (venlafaxine)	ER capsules	Oral	Daily	Take with food. Dose adjustments may be required in renal or hepatic impairment. Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified.† Observational data suggest potential for increased risk for preeclampsia when used during mid to late pregnancy. Exposure to SNRIs near delivery may increase risk of postpartum hemorrhage. Epidemiologic studies have not identified a drug-associated risk of major birth defects, miscarriage, or adverse fetal outcomes.
Fetzima (levomilnacipran)	ER capsules	Oral	Daily	Adjust dose in moderate or severe renal impairment. Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified.†
Pristiq (desvenlafaxine succinate)	ER tablets	Oral	Daily	Dose adjustments may be required in renal or hepatic impairment. Increased risk of orthostatic hypotension for patients ≥ 65 years.
venlafaxine	Tablets	Oral	Two or 3 times daily	Take with food. Dose adjustments may be required in renal or hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified.† Observational data suggest potential for increased risk for preeclampsia when used during mid to late pregnancy. Exposure to SNRIs near delivery may increase risk of postpartum hemorrhage. Epidemiologic studies have not identified a drug-associated risk of major birth defects, miscarriage, or adverse fetal outcomes.
Serotonin modulators				
Exxua (gepirone ER)	Tablets	Oral	Daily	Do not initiate if QTc is > 450 msec. Take with food at the same time each day. Dose reductions may be necessary in older adults, patients with renal or hepatic impairment, and when co-administered with CYP3A4 inhibitors. At least 14 days must elapse between discontinuation of an MAOI intended to treat depression and initiation of therapy with gepirone. Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified.† Third trimester use may increase the risk for persistent pulmonary hypertension and symptoms of poor adaptation in the neonate.
nefazodone	Tablets	Oral	Twice daily	Not recommended in active liver disease or elevated baseline serum transaminases. Safety and effectiveness have not been established in pediatric patients. Pregnancy category C.
trazodone	Tablets	Oral	Twice daily	Take shortly after a meal or light snack. Caution is advised in renal or hepatic impairment. Occurrence of drowsiness may require administration of a major portion of the daily dose at bedtime. Safety and effectiveness have not been established in pediatric patients.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy: Unclassified.† Prospective cohort studies and case reports have not identified drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
Trintellix (vortioxetine)	Tablets	Oral	Daily	Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified.†
Viibryd (vilazodone)	Tablets	Oral	Daily	Take with food. Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified.†

See the current prescribing information for full details.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

Conclusion

- Despite conflicting evidence, most meta-analyses and systematic reviews conclude that antidepressants have comparable efficacy across and within classes in the treatment of MDD. No robust or replicated results have established clinically meaningful differences (*Rush 2023*).
- While the AE profiles and discontinuation rates are similar among SGAs, the incidence of specific AEs varies among agents (*Gartlehner et al 2011*). The overall safety is comparable between the SNRIs, serotonin modulators, and atypical antidepressants, with the exception of nefazodone, which carries a boxed warning for life-threatening hepatic failure.
- According to clinical practice guidelines, CBT and SGAs are equally effective first-line monotherapies in the initial treatment of patients with MDD. There is insufficient evidence to recommend a specific psychotherapy or pharmacotherapy over another. The initial selection of an antidepressant medication should be based on various factors such as anticipated AEs, the safety or tolerability of these AEs for the individual patient, pharmacological properties of the medication, medication response in prior episodes, cost, and patient preference (*Qaseem et al 2023, VA/DoD 2022, Walter et al 2023*).
  - An estimated 40% of patients do not respond to initial SGA therapy; approximately 70% do not achieve remission on initial SGA therapy. For patients with an insufficient response to initial SGA monotherapy after a minimum of 4 to 6 weeks of treatment, switching to another SGA, augmenting with a second medication, or augmenting with CBT are all reasonable options (*Gartlehner et al 2015, VA/DoD 2022*).
- In 2023, 3 new agents were FDA-approved for the treatment of MDD (gepirone ER and dextromethorphan-bupropion) and PPD (zuranolone).
  - Zuranolone may be considered in the postpartum period (ie, within 12 months postpartum) for depression that has onset in the third trimester or within 4 weeks after childbirth (*ACOG 2023[b]*). However, risks (suicidal thoughts, sedation affecting daily activities, and limited efficacy data beyond 42 days) vs benefit (symptom improvement) should be considered prior starting prior to therapy.
  - Gepirone ER, a selective 5HT-1A partial agonist, has demonstrated small but statistically significant improvements in HAMD-17 scores, however clinical trials were short term (~8 weeks), thus its long-term efficacy remains unknown.
  - dextromethorphan-bupropion, the first rapid acting oral treatment for MDD, demonstrated improvements in depression symptoms starting by week 1 compared to placebo in clinical trial.

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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*).
- Antipsychotics 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 et al 2023*). The atypical antipsychotics differ from the early antipsychotics in that they have affinity for the serotonin 5-HT2 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.
- Several atypical antipsychotic formulations are available as branded and generic products. Food and Drug Administration (FDA)-approved indications for the atypical antipsychotics 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 U.S. reported a prevalence of 27.6 per 1000 children at age 8 in 2020. ASD are more common in males than females (*Centers for Disease Control [CDC] 2023*).
  - 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 [DSM] V 2013*). Based on data from 2013 to 2016, approximately 8.1% of individuals aged ≥ 20 years in the United States (U.S.) meet the criteria for depression. Women are more likely to experience symptoms of depression in their lifetime as compared to men (10.4% vs 5.5%) (*CDC 2018*).
- 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 2022*).
  - Schizophrenia is a disorder involving chronic or recurrent psychosis and is associated with significant functional impairment. Schizophrenia is believed to be caused by an increase in the cerebral 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) negative symptoms (eg, flat affect, decreased expressiveness, apathy), and cognitive symptoms (eg, impaired attention, memory, and executive functioning) (*DSM V 2013*, *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-V criteria was updated 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 V 2013*).
- 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 at least 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.

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)	-
Rexulti (brexpiprazole tablets)	-
Risperdal (risperidone tablets, oral solution)	✔
Saphris (asenapine tablets)	✔
Secuado (asenapine transdermal system)	-
Seroquel (quetiapine tablets)	✔
Seroquel XR (quetiapine ER tablets)	✔
Versacloz (clozapine oral solution)	-
Vraylar (cariprazine capsules)	-

Drug	Alternative Available (same molecular entity*)
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)	-
Invega Hafyera (paliperidone palmitate)	-
Invega Sustenna (paliperidone palmitate)	-
Invega Trinza (paliperidone palmitate)	-
Perseris (risperidone ER)	-
Risperdal Consta (risperidone microspheres)	-
Risvan (risperidone ER)	-§
Rykindo (risperidone ER)	-
Uzedy (risperidone ER)	-
Zyprexa Relprevv (olanzapine pamoate)	-
Combination Agents	
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.
§ Approved April 2024, launch is pending.

(*Drugs@FDA 2024, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2024*)

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: All oral agents in this class review are indicated for use in bipolar disorder, except clozapine, paliperidone, brexpiprazole, and pimavanserin. 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. Iloperidone is only approved for adults.
  - 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. In addition, patients must be titrated to an effective dose of iloperidone; thus, control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to other antipsychotics that do not require similar titration.
- 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 Alzheimers 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	-	-	✔	-	-	-	-	✔	-	-	-
ziprasidone mesylate (IM)	-	-	-	-	-	-	-	✔ §	-	-	-
LAI Agents											

Agent	Autism	Agitation associated with dementia due to Alzheimers 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)	-	-	-	-	-	-	-	✔	-	-	-
Invega Sustenna (paliperidone palmitate)	-	-	-	-	-	-	✔	✔	-	-	-
Invega Trinza (paliperidone palmitate)	-	-	-	-	-	-	-	✔	-	-	-
Invega Hafyera (paliperidone palmitate)	-	-	-	-	-	-	-	✔	-	-	-
Risperdal Consta (risperidone microspheres)	-	-	✔	-	-	-	-	✔	-	-	-
Risvan (risperidone ER)	-	-	-	-	-	-	-	✔	-	-	-
Rykindo (risperidone ER)	-	-	✔	-	-	-	-	✔	-	-	-
Perseris (risperidone ER)	-	-	-	-	-	-	-	✔	-	-	-
Uzedy (risperidone ER)	-	-	-	-	-	-	-	✔	-	-	-
Zyprexa Relprevv (olanzapine pamoate ER)	-	-	-	-	-	-	-	✔ ‡	-	-	-
Combination Agents											

Agent	Autism	Agitation associated with dementia due to Alzheimers 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
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 for 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.

(*Prescribing information: Abilify 2022, Abilify Asimtufii 2024, Abilify Maintena 2024, Abilify MyCite 2023, Aristada 2023, Aristada Initio 2023, Caplyta 2023, Clozaril 2023, Fanapt 2024, Geodon 2022, Invega 2023, Invega Sustenna 2022, Invega Trinza 2022, Invega Hafyera 2021, Latuda 2023, Lurasidone 2023, Lybalvi 2024, Nuplazid 2023, Perseris 2023, Rexulti 2023, Risperdal 2022, Risperdal Consta 2024, Risvan 2024, Saphris 2021, Secuado 2023, Seroquel 2022, Seroquel XR 2022, Symbyax 2023, Uzedy 2023, Versacloz 2023, Vraylar 2024, Zyprexa 2023, Zyprexa Relprevv 2023*)

- 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 review 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 the 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, taking into account 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 studies (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 safety and efficacy, and only 1 low-quality study has been conducted evaluating comparative effectiveness. The primary outcome measure in trials was the change from baseline to endpoint in the Aberrant Behavior Checklist-Irritability subscale of the ABC (ABC-I), which measured symptoms of irritability in autistic disorder. One risperidone trial measured the Clinical Global Impression (CGI)-Change scores as a co-primary outcome measure.
- The safety and efficacy of aripiprazole 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*).
- 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*).
- The safety and efficacy of risperidone was evaluated in two 8-week and one 6-week, PC pivotal trials (*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 in 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 a 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 score.

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*).

- Additional trials have been conducted measuring effects of risperidone; however, most trials included less than 50 patients. The outcomes of these trials are more sensitive to variability within the trials due to the small effect size (*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*).
- 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 discontinuations due to adverse events. Study authors concluded the safety and efficacy of both agents were comparable (*Ghanizadeh et al 2014*).
- 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 (SMD, 0.28; 95% CI, 0.08 to 0.49; p = 0.01) with modest heterogeneity (I^2 = 33.4%) (*Zhou et al 2021*).
- Another 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 decrease mania and depression symptoms slightly, and improve symptom severity and global functioning to a small extent. In addition, these agents probably increase 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 Young Mania Rating Scale (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*).

Depressive Episodes

- An SR and MA of 4 studies (2 quetiapine, 1 lurasidone, 1 olanzapine plus fluoxetine combination) evaluated SGA's 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 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*).
- A 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 Children's Depression Rating Scale-Revised (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 Children's Depression Rating Scale, Revised Version (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 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.
  - In December 2021, the FDA approved the indication of brexpiprazole for the treatment of schizophrenia in pediatric patients aged ≥ 13 years. The approval was based on safety data from an ongoing, multicenter (MC), long-term, OL, Phase 3 trial involving 194 pediatric patients aged 13 to 17 years, of which 140 patients received brexpiprazole for at

least 6 months. Adverse reactions for this age group were generally similar to those observed in adults. Among pediatric patients with normal baseline fasting glucose, 2.7% experienced a shift from normal to high (< 100 mg/dL to ≥ 126 mg/dL). A total of 7% of patients reported shifts in baseline fasting total cholesterol from normal to high (< 170 to ≥ 200 mg/dL) and 12.9% of patients reported shifts in baseline high-density lipoprotein cholesterol from normal to low (≥ 40 to < 40 mg/dL). Among patients with normal baseline triglycerides, 8.5% experienced shifts from normal to high (< 150 to ≥ 200 mg/dL) (*Rexulti prescribing information 2023*).

- An SR and network MA of 12 RCTs (N = 2158) evaluated 8 antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone) for treatment of children and adolescents with schizophrenia-spectrum disorders. Network MA found that change in Positive and Negative Syndrome Scale (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 is 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 2022*).
- 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 2022*). 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, with 43 studies comparing haloperidol with risperidone and 37 studies comparing haloperidol with olanzapine. Nevertheless, the number of studies available for each comparison and outcome was often limited. 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. Patient-important outcomes were rarely assessed. Data were sparse for the 4 key adverse events deemed to be most clinically important. 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. The evidence regarding safety, particularly those adverse events of most interest (ie, diabetes, tardive dyskinesia, metabolic syndrome, and mortality) were insufficient to draw firm conclusions about the risks among treatment groups. 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 (*Abou-Setta et al 2012*).

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*).
  - A 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/CBER summary review 2015*). 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*). 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/CBER summary review 2015*). 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 2022)*.
    - 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 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

- PC trials measuring effects for the treatment of bipolar depression have demonstrated efficacy with 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, Young et al 2010*).
  - In December 2021, lumateperone gained FDA approval for the indication of 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 (Intra-Cellular Therapies 2021). The approval 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 (LS mean difference [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 (*Caplyta prescribing information 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 (*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.

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*).
  - A 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). Compared to placebo, dropout rates due to adverse events were higher for all agents except olanzapoine and risperidone. (*Yan et al 2022*)

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% reduction in MADRS) was 10 (*Berman et al 2007, Marcus et al 2008*). Increased incidences of akathisia were seen across trials with one trial reporting a 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 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, cariprazine 1.5 mg or 3 mg and continued to receive 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 daily 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) that do not have extensive trial evidence.
- 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 2014*).

- 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*).
- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, MC study initiated by the National Institute of Mental Health 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*).
- 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/CBER 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/CBER 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 MAs 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*).

- Lumateperone was 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 mean differences [WMD],-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 (AAD). 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*).

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 2024*).
  - 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 2023).*
- 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 12 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), 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 is the only agent 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), Rykindo (risperidone once-every-2-weeks injection), and Risvan (risperidone once monthly 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 2024*).
  - 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 2023*).
  - 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 2023*)
  - 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 2023*).

- 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 FDA approval of of risperidone ER monthly injection 75 mg and 100 mg (Risvan) was based on the results of a 12-week, Phase 3, DB, PC, RCT (PRISMA-3 study) in 438 patients an acute exacerbation of schizophrenia. he primary efficacy outcome was change in PANSS total score from baseline to week 12. The PANSS total score improved significantly from baseline to day 85 with both 75 mg and 100 mg, with placebo-adjusted mean differences of -13.0 (95% CI, -17.3 to -8.8; $p < 0.0001$), and -13.3 (95% CI, -17.6 to -8.9; $p < 0.0001$), respectively. Significantly improved mean changes were also seen for CGI-S score from baseline to day 85 for both doses compared with placebo ($p < 0.0001$ for both doses) (*Correll et al 2020*).

- 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 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*).

- 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 sequience 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 2018 Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guideline recommends: lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine monotherapy or in combination as first line treatments for acute mania. Quetiapine, lurasidone plus lithium or divalproex, lithium, lamotrigine, lurasidone, or adjunctive lamotrigine are recommended first line for bipolar 1 depression. When initiating or switching during maintenance phase, lithium, quetiapine, divalproex, lamotrigine, asenapine, and aripiprazole monotherapy or combination should be considered first-line (*Yatham et al 2018*).
  - 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, 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.

- Parkinson's disease psychosis – The American Academy of Neurology (AAN) practice parameter on the treatment of depression, psychosis, and dementia in PD states that clozapine should be considered for the treatment for PD and psychosis, quetiapine may be considered, and olanzapine should not be routinely considered (*Miyasaki et al 2006 [retired February 23, 2018]*).
- 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

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (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)
  - AACAP guidelines state 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 the 2007 AACAP guidelines 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, 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. First-line agents for acute mania include lithium, risperidone, aripiprazole, asenapine, and quetiapine. Olanzapine and ziprasidone are second-line agents. For bipolar depression, lurasidone is considered a first-line agent based on extrapolated adult data and limited pediatric data. 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. Asenapine, quetiapine, risperidone, and ziprasidone can be considered for third-line treatment. (*Yatham et al 2018*).
- Schizophrenia – According to the AACAP guidelines, 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 AACAP guidelines 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

Boxed warnings

- **All** atypical antipsychotic agents, including pimavanserin: 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, cariprazine, lumateperone, lurasidone, brexpiprazole, quetiapine, 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. Lastly, clozapine-containing agents (ie, Clozaril and Versacloz) have a boxed warning for severe neutropenia, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, and cardiomyopathy.

- 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. 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. Lastly, asenapine is contraindicated in patients with severe hepatic impairment.
- 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, cognitive and motor impairment, body temperature dysregulation, and dysphagia. Additional warnings for various agents include:
  - Aripiprazole: Pathological gambling and other compulsive behaviors
  - Aripiprazole, risperidone: Cerebrovascular adverse events in elderly patients with dementia-related psychosis
  - Asenapine: QT prolongation, hyperprolactinemia, and hypersensitivity reactions
  - Brexpiprazole: Pathological gambling and other compulsive behaviors.
  - 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
- 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) 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.
- Samidorphan: may be cross-reactive with urinary immunoassay methods used for detecting opioids, resulting in false positive results
- Ziprasidone: QT prolongation, severe cutaneous reactions (eg, DRESS and Stevens-Johnson syndrome), rash, hyperprolactinemia, and priapism

- Clozapine-containing products and Zyprexa Relprevv are a part of the Risk Evaluation and Mitigation Strategies (REMS) program. Registry, training, and counseling are required as part of both programs (*REMS@FDA 2024*). Clozapine products also require certain laboratory levels prior to prescribing. Zyprexa Relprevv requires patients to be observed in clinic for 3 hours after administration.
  - In September 2015, the FDA made modifications to the clozapine REMS program. The absolute neutrophil count (ANC) requirements were modified to a lower ANC level. Benign ethnic neutropenia (BEN) patients were also included as now eligible for clozapine-treatment (*FDA safety communication [clozapine] 2015*).
  - In July 2021, the FDA approved modifications to the clozapine REMS program to ensure continuity of care for patients taking clozapine amidst the coronavirus disease (COVID) pandemic. The changes went into effect in November 2021. While this guidance is in effect, FDA does not intend to object if pharmacists dispense clozapine without a REMS dispense authorization (RDA), and if wholesalers ship clozapine to pharmacies and health care settings without confirming enrollment in the REMS.
  - In November 2022, additional guidance was published allowing inpatient pharmacies to dispense a clozapine supply to align with monitoring frequency upon discharge (*FDA Drug Safety and Availability 2022*).
- 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 postmarketing 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, amenorrhea, hirsutism, osteoporosis,	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
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	Moderate	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 et al 2023*)

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			
Abilify Mycite (aripiprazole with sensor)	Tablet with sensor			
Abilify Asimtufii (aripiprazole ER)	Injection	IM	Every 2 months	Must be administered by a healthcare professional. Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers.
Abilify Maintena (aripiprazole ER)			Monthly	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aristada (aripiprazole lauroxil)			Monthly (441 mg, 662 mg, or 882 mg) or every 6 weeks (882 mg) or every 2 months (1064 mg)	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 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 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.
Clozaril (clozapine)	Tablet			
Versacloz (clozapine)	oral suspension			

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				When restarting clozapine ODT in patients who missed 1 or more doses, the dosage must be reduced.
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. 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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				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.
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.
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 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. Not recommended in 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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
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. 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.
Perseris (risperidone ER)	Injection	SC	Monthly	
Risvan (risperidone ER)	Injection	IM	Monthly	
Rykindo (risperidone ER)	Injection	IM	Every 2 weeks	
Uzedy (risperidone ER)	Injection	SC	Monthly or every 2 months	
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 (*Miyamato et al 2005*).
- There are a number of atypical antipsychotic formulations available as both branded and generic products. These agents are available in various dosage forms including capsules, tablets, injections, oral solutions, sublingual tablets, transdermal patch, and orally disintegrating tablets.

- FDA-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, AAD, 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 products, 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, 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 AAD.
- Each atypical antipsychotic has a distinctive chemical structure, mechanism of action, and neuropharmacologic 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 et al 2023*). However, certain atypical antipsychotic agents appear to have varying levels of risk according to the side effect profile (*Jibson et al 2023*). 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. Those less likely to

cause cardiac arrhythmias include aripiprazole, lurasidone, and cariprazine; however, very few studies have been conducted with lurasidone and cariprazine.
  - 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. Incidences of seizure are most often reported with clozapine (3% to 5%), and to a lesser degree risperidone (0.3%).
  - 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 patients 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.
- 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 (*Leucht et al 2013, Lieberman et al 2005, Stroupe et al 2006, Stroupe et al 2009, Huhn et al 2019*). Clozapine is often followed by olanzapine and risperidone in terms of improved efficacy (*Leucht et al 2013, Nakajima et al 2015*).
- 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 (*Calabrese et al 2015, Durgam et al 2015[a], Durgam et al 2014, Durgam et al 2015[b], Earley et al 2020, FDA/CBER summary review 2015, Kane et al 2015[b], Sachs et al 2015*). The most common adverse events with treatment are EPS and akathisia. 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 persist on treatment maintained efficacy and tolerability at cariprazine doses of 1.5 mg to 9 mg daily during maintenance therapy (*Durgam et al 2016, Durgam et al 2017*).
- 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 (*Abilify prescribing information 2022*, *Gulisano et al 2011, Yoo et al 2013*).
- 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) (*Ghanizadeh et al 2014*). Both agents have demonstrated

safe and effective use in PC trials and MAs (*Deb et al 2023, Marcus et al 2009, McCracken et al 2002, Owen et al 2009, Shea et al 2004, McDougle et al 2005, Zhou et al 2021*).

- 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 *(Cummings et al 2014, Yasue et al 2016, Bozymski et al 2017).*
- For treatment of AAD, only 1 of the 2 studies conducted demonstrated a benefit in reduction of agitation with use of brexpiprazole 2 mg daily compared to placebo. (*Grossberg et al 2020*)
- 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 (*Thase et al 2015[a], Thase et al 2015[b]*, *Yoon et al 2017*). The efficacy of cariprazine compared to placebo has also been established in 2 RCTs and an MA. (*Durgam et al 2016, Sachs et al 2023, Yan et al 2022).* One MA found all agents were more effective than antidepressant monotherapy in improving response and remission rates, while adjunctive atypical antidepressant therapy was associated with a higher discontinuation rate due to adverse effects (*Wen et al 2014*). Another MA concluded aripiprazole and quetiapine may have an advantage in reducing remission (NNT, 9) compared to olanzapine/fluoxetine (NNT, 19) (*Spielmans et al 2013*). Another MA found significant response rates with olanazapine, cariprazine, brexpiprazole, quetiapine, aripiprazole, and risperidone compared to placebo. No difference was found with ziprasidone compared to placebo. (*Yan et al 2022*).
- For the treatment of bipolar disorder, several atypical antipsychotics have demonstrated effective use for managing symptoms associated with manic or mixed episodes; however, only a few agents have demonstrated efficacy 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. An 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 (*Pillay et al 2017*). For depressive episodes in youth, 2 MAs demonstrated a response with lurasidone and olanzapine/fluoxetine but not with quetiapine when compared to placebo (*Patel et al 2021*, *DelBello et al 2022*). Support for use of atypical antipsychotics in adult patients with bipolar disorder has been demonstrated in several MAs (*Abou-Setta et al 2012, Muralidharan et al 2013, Lindström et al 2017*). Risperdal Consta (risperidone microspheres) and Abilify Maintena are the only LAIs in this class that have demonstrated safe and effective use (*Calabrese et al 2017, Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*). Although only lurasidone, lumateperone, quetiapine (immediate- and extended-release), and olanzapine/fluoxetine have demonstrated efficacy for depressive episodes, MAs have concluded that olanzapine/fluoxetine may be the optimal treatment compared to other treatment options for depressive episodes (*Fornaro et al 2016, Silva et al 2013, Taylor et al 2014, Vieta et al 2010*).
- 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 (*Abou-Setta et al 2012, Asenjo Lobos et al 2010, Asmal et al 2013, Cipriani et al 2011, Citrome et al 2009, Durgam et al 2014, Durgam et al 2015[b], Glick et al 2011, Jones et al 2010, Kane et al 2015[b], Khanna et al 2014, Klemp et al 2011, Komossa et al 2009[a], Komossa et al 2010[a], Komossa et al 2009[b], Komossa et al 2010[b], Komossa et al 2011, Kumar et al 2013, Leucht et al 2009[a], Leucht et al 2009[b], Leucht et al 2013, Leucht et al 2023, Lieberman et al 2005, Pagsberg et al 2017, Perlis et al 2006[b], Pillay et al 2017, Riedel et al 2010, Stroupe et al 2006, Stroupe et al 2009, Tarr et al 2011, Vieta et al 2010, Wang et al 2024a, Wang 2024b, Yildiz et al 2011*).
- 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 (*APA 2010, Qaseem et al 2023, Va/DoD 2022*).

- 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 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 (*Keepers et al 2020*). 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.
- Parkinson's disease psychosis – The American Academy of Neurology Practice Parameter on the treatment of depression, psychosis, and dementia in PD states that clozapine should be considered for the treatment for PD and psychosis, quetiapine may be considered, and olanzapine should not be routinely considered (*Miyasaki et al 2006*).

Children and Adolescents

- Autism Spectrum Disorders (ASD) –The AACAP 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 (Hyman et al 2020, *Volkmar et al 2014)*
- Bipolar disorder – According to AACAP guidelines 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 indicated (*McClellan et al 2007, Yatham et al 2018*). For maintenance treatment of bipolar depression, the CANMAT/ISBD guidelines recommend aripiprazole, lithium, and divalproex as first-line agents. (*Yatham et al 2018*). An updated 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 episode is lurasidone monotherapy (*Hobbs et al 2022*).
- 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 (*McClellan et al 2013*).
- 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 (*Murphy et al 2013*).

- Pharmacologic therapy treatment is highly individualized and dependent on a number of patient characteristics and response to treatment. 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 in order to tailor therapies to individual patients.

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Optum Rx®

Therapeutic Class Overview

Estrogens, progestins and related products

Introduction

- Estrogens, progestins, and related products are commonly used in the treatment of symptoms related to menopause and are often referred to as hormone therapy (HT) or hormone replacement therapy (HRT).
- Many estrogen products are Food and Drug Administration (FDA)-approved to treat moderate to severe vasomotor symptoms (VMS) and/or moderate to severe vulvar and vaginal atrophy associated with menopause. Some estrogen products are also approved for the prevention of postmenopausal osteoporosis.
  - Other FDA-approved indications for estrogens include the palliative treatment of advanced prostate or breast cancer, treatment of abnormal uterine bleeding, and the treatment of hypoestrogenism.
  - Progestin products are FDA-approved in combination with estrogen products to prevent endometrial hyperplasia in non-hysterectomized postmenopausal women.
  - Some progestins are also FDA-approved to treat secondary amenorrhea, abnormal uterine bleeding, and endometriosis.
- Long-term use of unopposed estrogen therapy (ET), or estrogen monotherapy, is associated with an increased risk of endometrial hyperplasia and/or carcinoma in postmenopausal women; however, the addition of a progestin substantially reduces this risk (*de Villiers et al 2016, North American Menopause Society [NAMS] 2022, NAMS 2020*).
  - Therefore, postmenopausal women with an intact uterus must receive estrogen/progestin therapy (EPT) to avoid the increased risk of endometrial carcinoma, unless conjugated estrogens are given with bazedoxifene (*NAMS 2022*).
  - Micronized progesterone may be preferred when progesterone is necessary due to a reduced risk of breast cancer in observational trials (*NAMS 2022*).
  - For postmenopausal women who are appropriate candidates for HT, ET is appropriate in those who have undergone a hysterectomy.
  - Use of a progestogen is not recommended with low-dose vaginal ET, although women at increased risk of endometrial cancer may warrant endometrial surveillance (*NAMS 2020*).
- Both ET and EPT are associated with potential risks; therefore, the benefits and risks of each therapy should be assessed for individual patients (*Camacho et al 2020, de Villiers et al 2016, NAMS 2022, NAMS 2020, NAMS 2021, Shoback et al 2020, United States Preventive Services Task Force [USPSTF] 2022*).
  - Historically, ET was used for the prevention of cardiovascular disease in postmenopausal women; however, more recent data indicate that ET and EPT do not decrease the incidence of cardiovascular disease. Based on this data, ET and EPT are no longer recommended for the prevention of cardiovascular disease.
  - Specifically, results of the Women's Health Initiative (WHI) trial have indicated that ET is associated with increased risks of stroke and deep vein thrombosis (DVT), and EPT is associated with increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary embolism (PE), and DVT. Results of the WHI trial also demonstrated that ET and EPT had no clinically important effect on health-related quality of life measures (eg, depression, insomnia, sexual function, cognition). Although current recommendations are based on the results of the WHI trial that evaluated one specific ET (estrogen, conjugated equine 0.625 mg) and EPT (estrogen, conjugated equine [CEE]/medroxyprogesterone acetate [MPA] 0.625/2.5 mg), the risks should be assumed to be similar with other hormone therapies, including different dosages of these drugs as well as other EPT regimens not evaluated in the WHI trial, in the absence of comparable data to the contrary.
  - HT for the prevention of osteoporosis in postmenopausal women should be used within the context of the overall benefit-vs-risk analysis of each patient (*Camacho et al 2020, NAMS 2021, Shoback et al 2020*).
  - HT for osteoporosis prevention has dose-related effects on bone density. The discontinuation of treatment can result in rapid bone loss; however, no excess fractures were observed in the WHI trial (*NAMS 2022*).
- Despite the demonstrated risks associated with the use of ET and EPT for the prevention of chronic diseases in postmenopausal women, the long-term safety of short-term use of HT for the management of menopausal symptoms is well established (*NAMS 2022, NAMS 2020*).
  - Both ET and EPT are the most effective therapies for the relief of VMS (eg, hot flashes, sleep disturbances) (*de Villiers et al 2016*).
  - The decision between the use of ET or EPT for the management of menopausal symptoms should be individualized and based on patient preference, chronic comorbidities, risk factors, age, and the presence and severity of menopausal symptoms (*NAMS 2020*).

  - In general, use of ET and EPT for the management of menopausal symptoms should be prescribed at the lowest effective dosage and for the shortest duration consistent with treatment goals and risks for the individual patient (*American College of Obstetricians and Gynecologists [ACOG] 2014, NAMS 2022*).
  - Brisdelle (low-dose paroxetine) and Veozah (fezolinetant) are non-HT options used to treat VMS associated with menopause *(Clinical Pharmacology 2024).*
- Agents in this review are outlined in Table 1 and include the currently available oral, injectable, and transdermal estrogens, progestins, combination products, and Veozah (fezolinetant). Fezolinetant is a novel, non-hormonal, neurokinin 3 (NK3) receptor antagonist to treat moderate to severe hot flashes.
- Since there are multiple branded agents that contain the same generic component (eg, estradiol products), tables in the review may be organized alphabetically by generic name.
  - The combination products included in this review are EPTs, with the exception of Duavee (conjugated estrogens/bazedoxifene), which is a combination of estrogen with a selective estrogen receptor modulator.
- Medispan class: Estrogens; Progestins; Estrogen Combinations

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)*
Estrogen Single Entity Agents	
Alora (estradiol transdermal system)	✔
Climara (estradiol transdermal system)	✔
Delestrogen (estradiol valerate injection)	✔
Depo-Estradiol (estradiol cypionate injection)	-
Divigel (estradiol gel)	✔
Dotti (estradiol transdermal patch)	✔
Elestrin (estradiol gel)	-
Estrace (estradiol) tablet	✔
Estrogel (estradiol gel)	-
Evamist (estradiol transdermal spray)	-
Lyllana (estradiol transdermal patch)	✔
Menest (estrogens, esterified tablet)	-
Menostar (estradiol transdermal system)	-
Minivelle (estradiol transdermal system)	✔
Premarin (conjugated estrogens, equine)	-
Vivelle-Dot (estradiol transdermal system)	✔
Progestin Single Entity Agents	
norethindrone acetate tablet	✔
Prometrium (progesterone, micronized capsule)	✔
Provera (medroxyprogesterone acetate tablet)	✔
Combination Products	
Activella, Amabelz, Mimvey (estradiol/norethindrone acetate tablet)	✔
Angeliq (estradiol/drospirenone tablet)	-
Bijuva (estradiol/progesterone tablet)	-
Climara Pro (estradiol/levonorgestrel transdermal system)	-
CombiPatch (estradiol/norethindrone acetate transdermal system)	-
Duavee (conjugated estrogens/bazedoxifene tablet)	-
Fyavolv, Jinteli (ethinyl estradiol/norethindrone acetate tablet)	✔
Premphase (conjugated estrogens/medroxyprogesterone acetate tablet)	-

Drug	Alternative Available (same molecular entity)*
Prempro (conjugated estrogens/medroxyprogesterone acetate tablet)	-
Non-hormonal agents	
Veozah (fezolinetant) tablet	-

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

(*Clinical Pharmacology 2024, Drugs@FDA 2024, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2024*)

Indications

Table 2. Food and Drug Administration Approved Indications - Estrogen Single Entity Agents

Indication	Delestrogen (estradiol valerate)	Depo-Estradiol (estradiol cypionate)	Estradiol Products (Alora, Climara, Divigel, Dotti, Elestrin, estradiol tablet, Estrogel, Evamist, Menostar, Minivelle, Vivelle-Dot)	Menest (estrogens, esterified)	Premarin (conjugated estrogens, equine)
Palliative treatment of advanced prostate cancer	✔		✔ (estradiol tablet)	✔	✔ (oral)
Palliative treatment of metastatic breast cancer			✔ (estradiol tablet)	✔	✔ (oral)
Prevention of postmenopausal osteoporosis†			✔ (Alora, Climara, Dotti, estradiol tablet, Lyllana, Menostar, Minivelle, Vivelle-Dot)		✔ (oral)
Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure	✔	✔	✔ (Alora, Climara, Dotti, estradiol tablet, Vivelle-Dot)	✔	✔ (oral)
Treatment of moderate to severe vasomotor symptoms associated with menopause	✔	✔	✔ (Alora, Climara, Divigel, Dotti, Lyllana, Elestrin, estradiol tablet, Estrogel, Evamist, Minivelle, Vivelle-Dot)	✔	✔ (oral)
Treatment of moderate to severe vulvar and vaginal atrophy associated with menopause*	✔		✔ (Alora, Climara, Dotti, estradiol tablet, Estrogel, Vivelle-Dot)	✔	✔ (oral)
Abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology (for short-term use only)					✔ (injection)

†When prescribing solely for the prevention of postmenopausal osteoporosis, first consider the use of non-estrogen medications. Consider estrogen therapy only for women at significant risk of osteoporosis.
*When prescribing solely for this purpose, first consider the use of topical vaginal products.

(*Prescribing information: Alora 2020, Climara 2023, Delestrogen 2022, Depo-Estradiol 2022, Divigel 2023, Dotti 2022, Elestrin 2023, estradiol tablet 2021, Estrogel 2023, Evamist 2023, Lyllana 2022, Menest 2020, Menostar 2023, Minivelle 2021, Premarin injection 2022, Premarin tablet 2023, Vivelle-Dot 2022*)

Table 1. FDA-Approved Indications - Progestin Single Entity Agents

Indication	norethindrone acetate	Prometrium (progesterone, micronized)	Provera (medroxyprogesterone acetate)
Prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women receiving conjugated estrogen tablets		✔	
Treatment of secondary amenorrhea	✔	✔	✔
Reduce the incidence of endometrial hyperplasia in nonhysterectomized postmenopausal women receiving daily oral conjugated estrogen 0.625 mg tablets			✔
Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology	✔		✔
Treatment of endometriosis †	✔		

† Not approved to be used with concomitant estrogen therapy in postmenopausal women for endometrial protection.

(*Prescribing information: norethindrone acetate 2022, Prometrium 2022, Provera 2021*)

Table 2. FDA-Approved Indications for the Estrogen Combination Products

Indication	Angeliq (estradiol/ drospirenone)	Bijuva (estradiol/ progesterone)	Climara Pro (estradiol/ levonorgestrel)	CombiPatch (estradiol/ norethindrone acetate transdermal)	Conjugated estrogens/ medroxy-progesterone acetate (Premphase, Prempro)	Duavee (conjugated estrogens/ bazedoxifene)	Estradiol/ norethindrone acetate tablets (Activella, Amabelz, Mimvey)	Ethinyl estradiol/ norethindrone (Fyavolv, Jinteli)
Prevention of postmenopausal osteoporosis†			✔		✔	✔	✔	✔
Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure				✔				
Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause*	✔ (1/0.5 mg)			✔	✔		✔ (1/0.5 mg)	
Treatment of moderate to severe vasomotor symptoms due to menopause	✔	✔	✔	✔	✔	✔	✔	✔

†When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.
*When prescribing solely for this purpose, topical vaginal products should be considered.

(*Prescribing information: Activella 2021, Amabelz 2024, Angeliq 2023, Bijuva 2023, Climara Pro 2023, CombiPatch 2022, Duavee 2023, Fyavolv 2023, Jinteli 2016, Mimvey 2022, Premphase and Prempro 2023*)

Table 5. FDA-Approved Indications – Non-Hormonal Agents

Indication	Veozah (fezolinetant)
Treatment of moderate to severe vasomotor symptoms due to menopause.	✔

(*prescribing information: Veozah 2023*)

- 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

- Clinical trials demonstrating the safety and efficacy of the oral, injectable, and transdermal estrogens for FDA-approved indications are discussed below. Overall, the efficacy of estrogen products alone or in combination with progesterone for FDA-approved indications is well established.
  - In general, clinical trials with estrogen support the use of these agents for the treatment of symptoms associated with menopause, such as vulvar or vaginal atrophy and VMS (*Al-Azzawi et al 2003, Archer et al 1994, Archer et al 1999, Archer et al 2012, Bachmann et al 2010, Blanc et al 1998, Buster et al 2008, Cortellaro et al 1991, Cravioto et al 2011, Chunha et al 2010, Good et al 1996, Good et al 1999, Gordon et al 1995, Haines et al 2009, Hays et al 2003, Hilditch et al 1996, Hirvonen et al 1987, Kagan et al 2010, Lara et al 2023, Lin et al 2011, Lobo et al 2018, MacLennan et al 2004, Meziou et al 2023, Nelson HD 2004, Pattison et al 1989, Pinkerton et al 2009, Pinkerton et al 2013, Pinkerton et al 2014[a], Pinkerton et al 2014[b], Place et al 1985, Polvani et al 1991, Pornel B 1996, Rowan et al 2006, Schurmann et al 2004, Simon et al 2001, Simon et al 2003[a], Studd et al 1995, Studd et al 1996, Van de Weijer et al 2002, Yu et al 2013*).
  - Multiple clinical trials also support the role of these agents for postmenopausal osteoporosis (*Jackson et al 2006, Mirkin et al 2013, Mizunuma et al 2010, Yang et al 2007*).
- Results from multiple clinical trials do not support the use of HT for prevention of cardiovascular disease; some trials even demonstrated an increased risk of stroke, PE, and DVT in postmenopausal women on HT (*Anderson et al 2004, Gartlehner et al 2022, Grady et al 2002, Hsia et al 2006, Hulley et al 1998, Hulley et al 2002, LaCroix et al 2011, Manson et al 2003, Marjoribanks et al 2017, Rossouw et al 2002, Rossouw et al 2007*).
  - However, trials have demonstrated that these agents may be safe in patients with recent myocardial infarctions and may not increase risks of myocardial infarction or heart failure (*Cherry et al 2014, Schierbeck et al 2012*).
- Multiple trials have evaluated the role of estrogens in various cancers, including breast cancer. While data are conflicting, results of some trials demonstrated an increased incidence of breast cancer with HT (*Chen et al 2006, Chlebowski et al 2003, Chlebowski et al 2013, Gartlehner et al 2022, Marjoribanks et al 2017, Reeves et al 2006, Stefanick et al 2006*).
  - A meta-analysis concluded that estradiol conferred no increased risk for breast cancer; however, the risk of breast cancer did vary with the type of progestogen used. Medroxyprogesterone, norethisterone, and levonorgestrel were associated with an increased risk for breast cancer, while dydrogesterone and progesterone were not (*Yang et al 2017*).
  - One trial also demonstrated an increased risk of ovarian cancer with HT (*Morch et al 2009*).
  - Despite these risks, evidence from clinical trials supports the use of a progestin in combination with an estrogen for endometrial protection (*Archer et al 2005, Archer et al 2009, Furness et al 2012, Lindsay et al 2009, Lobo et al 2009, Mirkin et al 2013, Pickar et al 2009*).
- An observational follow-up of 2 WHI HT trials evaluated all-cause and cause-specific mortality in postmenopausal women who received HT vs placebo. Of the 27,347 women who were randomized in 2 WHI clinical trials between 1993 and 1998, mortality follow-up through the end of 2014 was available for more than 98%. HT was not associated with increased risk for all-cause, cardiovascular, or cancer mortality during a cumulative follow up of 18 years (*Manson et al 2017*).

- All-cause mortality was 27.1% in the HT group vs 27.6% in the placebo group (hazard ratio [HR], 0.99; 95% confidence interval [CI], 0.94 to 1.03) in the overall pooled cohort.
- Similarly, no significant difference between HT and placebo was detected for cardiovascular mortality (8.9% vs 9.0%; HR, 1.00; 95% CI, 0.92 to 1.08) or cancer mortality (8.2% vs 8.0%; HR, 1.03; 95% CI, 0.95 to 1.12).

- Another observational follow-up of the 2 WHI HT trials evaluated the incidence of breast cancer in women (N=27,347) with or without a hysterectomy who received HT or placebo. In one trial, 8506 women with an intact uterus received 0.625 mg/day of CEE + 2.5 mg/d of MPA and 8102 received placebo. Patients received treatment for a median duration of 5.6 years. In the other trial of women who underwent a hysterectomy, 5310 received 0.625 mg CEE alone and 5429 received placebo for a median duration of 7.2 years. The breast cancer incidence after a median cumulative follow-up of 20 years was statistically significantly lower in women who underwent a hysterectomy who received CEE alone (annualized rate, 0.3%) compared to placebo (annualized rate, 0.37%; HR, 0.78; 95% CI, 0.65 to 0.93; p = 0.005). Mortality due to breast cancer was also significantly lower with CEE alone (annualized rate, 0.031%) compared to placebo (annualized rate, 0.046%; HR, 0.60; 95% CI, 0.37 to 0.97; p = 0.04). However, breast cancer incidence was found to be statistically significantly higher in women with an intact uterus who received CEE + MPA (annualized rate, 0.45%) compared to placebo (annualized rate, 0.36%; HR, 1.28; 95% CI, 1.13 to 1.45; p < 0.001) but no significant difference in mortality due to breast cancer was observed between the 2 groups (*Chlebowski et al 2020*).
- Other trials have evaluated other potential concerns with HT, including mental function, with mixed results (*Espeland et al 2004, Maki et al 2007, Shumaker et al 2003*).
- A Cochrane review of 22 studies (N = 43,637) evaluated the effect of long-term (> 1 year) HT on mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture, and cognition in postmenopausal women (*Marjoribanks et al 2017*).
  - In relatively healthy postmenopausal women, long-term use of EPT increased the risk of a coronary event, venous thromboembolism (VTE), stroke, breast cancer, gallbladder disease, death from lung cancer, and dementia (in women > 65 years). EPT use was associated with a significantly decreased risk of fracture.
  - ET alone increased the risk of VTE, stroke, and gallbladder disease; reduced the risk of breast cancer and clinical fracture; and did not increase the risk of coronary events at any follow-up time.
- A systematic review and meta-analysis of 20 randomized controlled trials (N =39,145) and 3 cohort studies (N = 1,155,410) performed by the USPSTF examined the risks and benefits associated with HT for primary prevention of chronic conditions in postmenopausal women. Risks for diabetes and fractures were significantly decreased with estrogen-only therapy compared to placebo, but risks of gallbladder disease, stroke, VTE, and urinary incontinence were increased. With EPT, risks of colorectal cancer, diabetes, and fractures were decreased compared to placebo, but risks of invasive breast cancer, probable dementia, gallbladder disease, stroke, urinary incontinence, and VTE were significantly increased (*Gartlehner et al 2022*).
- A systematic review and meta-analysis of 12 studies (N = 4474) performed by the McMaster Institute for Research on Aging examined the association between HT and lean body mass (LBM). This analysis did not show a significant beneficial or detrimental association of HT with muscle mass (*Javed et al 2019*).
- Head-to-head trials comparing single entity estrogen products do not consistently demonstrate the superiority of one formulation over the other for the management of symptoms of menopause; oral, injectable, transdermal, and vaginal formulations of estrogen all provide improvement and relief in symptoms (*Al-Azzawi et al 2003, Andersson et al 2000, Archer et al 1999, Blanc et al 1998, Bowen et al 1998, Canonico et al 2008, Chetkowski et al 1986, Cortellaro et al 1991, Erianne et al 1997, Good et al 1999, Gordon et al 1995, Harrison et al 2002, Hilditch et al 1996, Ibarra de Palacios et al 2002, Jarvinen et al 2001, Nelson HD 2004, Pattison et al 1989, Place et al 1985, Pornel et al 1995, Pornel B 1996, Slater et al 2001, Studd et al 1995, Studd et al 1996, Toole et al 2002*).
  - Compared with oral estrogen, transdermal estrogen may be considered less likely to produce thrombotic risk and may be associated with a lower risk of stroke and coronary artery disease, although clinical trials have not been adequately powered to confirm this benefit (*NAMS 2022*).
- Trials focused on progestins support the use of these agents for the treatment of symptoms associated with menopause. Many of these trials also included an estrogen component (*Hitchcock et al 2012, Nand et al 1998, Ozdegirmenci et al 2011, Shangold et al 1991*). A systematic review of 7 randomized trials found conflicting results for improvement in VMS with progestin-only HT compared to placebo and tolerability concerns in 5 trials (*Dolitsky et al 2020*).
- Conjugated estrogens/bazedoxifene is the first HT without a progestin indicated for VMS in women with a uterus. In 5 large randomized controlled trials, conjugated estrogens/bazedoxifene demonstrated reductions in hot flashes, bone

loss, bone turnover, and vaginal dryness without a significant increase in endometrial hyperplasia after 2 years compared with placebo (*Parish and Gillespie 2017*).

- Head-to-head trials comparing EPT products are rare. In a 9-month retrospective analysis of pharmacy claims for women receiving HT, continuation rates were significantly higher with ethinyl estradiol/norethindrone compared to CEE/MPA (*Simon et al 2003[bj]*). In a head-to-head trial comparing CEE/MPA with estradiol/norethindrone in healthy postmenopausal women, a significantly larger proportion of patients receiving estradiol/norethindrone reported no bleeding or spotting (*Johnson et al 2002*).
- A network meta-analysis of 47 trials (N = 8326) examined the efficacy of different treatments for VMS in menopausal women without hysterectomy. In this analysis, transdermal EPT had the highest probability of being the most effective treatment. Transdermal EPT was ranked higher than oral EPT, but oral EPT was not significantly worse than transdermal EPT in terms of vasomotor symptom relief (*Sarri et al 2017*). A meta-analysis of 22 studies showed an increased risk for VTE with oral HT, while non-oral HT did not affect the risk (*Rovinski et al 2018*).
- A meta-analysis of 31 studies (N = 40,521) revealed that HT initiation with increasing age increased the risk for stroke, transient ischemic stroke, and systemic embolism (*Nudy et al 2019*).
- The efficacy and safety of fezolinetant were demonstrated in 2, identically designed 12-week, Phase 3, double-blind, multi-center, placebo-controlled, randomized controlled trials, SKYLIGHT-1 and SKYLIGHT-2 (*Johnson et al 2023, Lederman et al 2023*). The studies evaluated fezolinetant vs placebo in females aged 40 to 65 years who were seeking relief from moderate to severe VMS associated with menopause. Patients had a minimum average of 7 to 8 daily moderate to severe VMS (ie, “hot flashes”) or 50 to 60 VMS per week. Patients were randomized to fezolinetant 30 mg or 45 mg orally daily or placebo for 12 weeks. The primary endpoints were the change from baseline in the frequency and severity of VMS at weeks 4 and 12. Patients electronically recorded daily VMS episodes.
  - Fezolinetant met both co-primary endpoints at weeks 4 and 12 in both trials.
    - Fezolinetant 30 mg and 45 mg groups demonstrated statistically significant reductions in the frequency of moderate to severe VMS vs placebo at weeks 4 and 12 in both trials.
      - Per the FDA, the fezolinetant 45 mg group met the clinical threshold of superiority in reduction of VMS by > 2 per day or 14 per week vs placebo at week 4 and was sustained through week 12 (*FDA summary review 2023*).
  - In both trials, both doses of fezolinetant also demonstrated statistically significant reductions in the severity of moderate to severe VMS vs placebo at weeks 4 and 12.

Clinical Guidelines

- According to current guidelines, HT is the most effective treatment for the relief of severe menopausal symptoms, including VMS (and shown to prevent bone loss and fracture). It may be used in select postmenopausal women on the basis of individually determined benefit-vs-risk profile (*NAMS 2020, NAMS 2022, NAMS 2023*).
  - Benefits are most likely to outweigh risks in symptomatic women who are younger than 60 years or who are within 10 years of menopause onset (*NAMS 2022*).
  - Transdermal hormonal preparations may be associated with a lower risk of stroke than oral estrogen preparations, although no head-to-head data comparing oral to transdermal hormone therapy are available (*NAMS 2022*). Vaginal estrogen preparations may provide local effects with less systemic absorption compared to oral estrogen (*NAMS 2020*).
  - Furthermore, when HT is considered solely for vulvar and vaginal atrophy, vaginal estrogen preparations are recommended over other routes of administration (*ACOG 2014, NAMS 2022, NAMS 2020*).
  - Use of a progestogen is not recommended with low-dose vaginal ET, although women at increased risk of endometrial cancer may warrant endometrial surveillance (*NAMS 2020*).
- HT for the prevention of osteoporosis in postmenopausal women should be used within the context of the overall benefit-vs-risk analysis of each patient. Data from clinical trials substantiate the efficacy of ET in preserving bone mass, and less consistently, preventing fractures, but nonhormonal therapeutic options for bone health exist and should be considered (*ACOG 2022, Camacho et al 2020, Humphrey et al 2023, NAMS 2021, Shoback et al 2020*). The Endocrine Society suggests HT for postmenopausal women at a high risk of fracture with the following characteristics: under 60 years of age or < 10 years post menopause; at low risk of DVT; those in whom bisphosphonates or denosumab are not appropriate; with bothersome VMS; with additional climacteric symptoms; without contraindications; without prior myocardial infarction or stroke; without breast cancer; willing to take menopausal HT (*Shoback et al 2020*).
  - The American Association of Clinical Endocrinologists (AACE), ES, and ACOG guidelines and the NAMS position statement indicate that lifestyle modifications are fundamental measures in all postmenopausal women for bone

health and decreasing the risk of postmenopausal osteoporosis or fractures. They include adequate calcium and vitamin D intake, weight bearing exercise, balance improvement, avoidance of tobacco and avoidance of excessive alcohol (*ACOG 2022*, *Camacho et al 2020*, *NAMS 2021*, *Shoback et al 2020).*

- When HT is prescribed to manage menopausal symptoms, the lowest effective dosage should be used for the shortest duration consistent with treatment goals and risks for the individual patient (*ACOG 2014*). Additionally, treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation (*NAMS 2022*).
- Finally, the AACE and NAMS do not support the use of HT in postmenopausal women as a sole or primary indication for prevention (primary or secondary) of cardiovascular disease (*NAMS 2022*). Similarly, USPSTF recommends against the use of HT for the primary prevention of chronic conditions in postmenopausal individuals (*USPSTF 2022*).

Safety Summary

- While not every agent carries the same contraindications, contraindications are generally related to estrogen pharmacology rather than the specific chemical entity or route of administration.
  - Contraindications to estrogens and progestins include active or recent arterial thromboembolic disease, DVT, PE, or history of these conditions; known hypersensitivity; known thrombophilic disorders; known cancers, specifically breast cancer or estrogen-dependent neoplasms; liver dysfunction or disease; and undiagnosed genital bleeding.
  - Notably, Prometrium contains peanut oil and should not be used in those with a peanut allergy.
  - HT should not be used in women who are pregnant or nursing.
- All estrogen and progestin products carry boxed warnings.
  - These include warnings for endometrial cancer in patients with a uterus on unopposed estrogen; cardiovascular disorders and a risk of probable dementia, as demonstrated in the WHI and WHI Memory Study (WHIMS); and breast cancer in patients on estrogen/progestin combination products.
  - Evamist also carries a boxed warning for unintentional secondary exposure to estrogen.
- Other warnings and precautions with these products include flammability with alcohol-based products; photosensitivity, and possibly increased exposure with sunscreen (most topical products); elevated blood pressure; exacerbation of endometriosis or other conditions; increased risk of ovarian cancer; fluid retention; gallbladder disease; hypo- or hypercalcemia; exacerbation of symptoms of angioedema in women with hereditary angioedema; hypothyroidism; severe hypertriglyceridemia; cholestatic jaundice; and visual abnormalities. Additional warnings for topical products include potential for increased estradiol gel absorption with use of moisturizing lotion within 1 hour of gel use (Estrogel), possible transfer of estradiol gel if skin contact with another before the application area is dry (Divigel), and reduction of estradiol gel absorption if application area is washed within 1 hour of gel application (Divigel).
- Reported adverse events with these products are extensive. Common adverse events include gastrointestinal effects, such as nausea, abdominal pain, and flatulence; infections; general pain and/or arthralgia; breast pain and tenderness; headache; insomnia; weight changes; emotional lability; postmenopausal bleeding; and ovarian cysts.
- Drug interactions with these agents are typically associated with other medications that may induce or inhibit their hepatic metabolism.
- Fezolinetant is contraindicated in patients with known cirrhosis, severe renal impairment, end-stage renal disease and with concomitant use of cytochrome P450 (CYP) 1A2 inhibitors. A key warning/precaution is risk of hepatic transaminase elevation. The most common adverse events include abdominal pain, diarrhea, insomnia, back pain, hot flush and hepatic transaminase elevation.

Dosing and Administration

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Estrogen Single Entity Agents				
Alora (estradiol transdermal system)	Patch	Transdermal	Twice weekly	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Climara (estradiol transdermal system)	Patch	Transdermal	Once weekly	
Delestrogen (estradiol valerate injection)	Injection	Intramuscular	Every 4 weeks	
Depo-Estradiol (estradiol cypionate injection)	Injection	Intramuscular	Every 3 to 4 weeks	
Divigel (estradiol gel)	Gel	Transdermal	Once daily	
Dotti (estradiol transdermal system)	Patch	Transdermal	Twice weekly	
Elestrin (estradiol gel)	Gel	Transdermal	Once daily	
estradiol tablet	Tablet	Oral	Once daily, or 3 times daily for cancer indications	Cyclic administration (eg, 3 weeks on and 1 week off)
Estrogel (estradiol gel)	Gel	Transdermal	Once daily	
Evamist (estradiol transdermal spray)	Spray	Transdermal	Once daily	
Lyllana (estradiol transdermal system)	Patch	Transdermal	Twice weekly	
Menest (estrogens, esterified tablet)	Tablet	Oral	Once daily, or in divided doses for some indications	Cyclic administration
Menostar (estradiol transdermal system)	Patch	Transdermal	Once weekly	
Minivelle (estradiol transdermal system)	Patch	Transdermal	Twice weekly	
Premarin (conjugated estrogens, equine)	Tablet; Injection	Oral; Intramuscular or intravenous	Tablet: once daily, or 3 times daily for cancer indications Injection: one dose, may repeat in 6 to 12 hours	Tablet: continuously or cyclically
Vivelle-Dot (estradiol transdermal system)	Patch	Transdermal	Twice weekly	
Progestin Single Entity Agents				
norethindrone acetate	Tablet	Oral	Once daily	
Prometrium (progesterone, micronized capsule)	Capsule	Oral	Once daily	Administer at bedtime
Provera (medroxyprogesterone acetate tablet)	Tablet	Oral	Once daily	Administer for 12 to 14 consecutive days per month in women receiving daily 0.625 mg conjugated estrogens
Combination Products				
Activella, Amabelz, Mimvey (estradiol/norethindrone acetate tablet)	Tablet	Oral	Once daily	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Angeliq (estradiol/drospirenone tablet)	Tablet	Oral	Once daily	Taken at the same time each day
Bijuva (estradiol/progesterone capsule)	Capsule	Oral	Once daily	Administer in the evening with food
Climara Pro (estradiol/levonorgestrel transdermal system)	Patch	Transdermal	Once weekly	
CombiPatch (estradiol/norethindrone acetate transdermal system)	Patch	Transdermal	Twice weekly	
Duavee (conjugated estrogens/ bazedoxifene tablet)	Tablet	Oral	Once daily	Not recommended in renal impairment or age > 75 years
Fyavolv, Jinteli (ethinyl estradiol/norethindrone acetate tablet)	Tablet	Oral	Once daily	
Premphase, Prempro (conjugated estrogens/medroxyprogesterone acetate tablet)	Tablet	Oral	Once daily	Premphase: medroxyprogesterone component is only included on days 15 through 28
Non-Hormonal Agents				
Veozah (fezolinetant) tablet	Tablet	Oral	Once daily	Bloodwork at baseline, 3, 6 and 9 months to monitor hepatic function and injury.

Abbreviation: ESRD = end-stage renal disease.
See the current prescribing information for full details.

Conclusion

- Included in this review are the oral, injectable, and transdermal estrogen products, progestin products, combination estrogen products, and Veozah (fezolinetant) for menopausal symptoms. In general, estrogen products are FDA-approved for the prevention of postmenopausal osteoporosis, treatment of VMS due to menopause, treatment of vulvar and vaginal atrophy due to menopause, and treatment of hypoestrogenism. Progestin products are primarily FDA-approved for the prevention of endometrial hyperplasia when used in combination with estrogen products.
- Veozah (fezolinetant) is a first-in-class NK3 receptor antagonist which is indicated for the treatment of moderate to severe VMS due to menopause. In 2, identically designed, Phase 3, randomized controlled trials, fezolinetant 45 mg had a statistically significant reduction in the frequency and severity of VMS at weeks 4 and 12 vs placebo in postmenopausal females with moderate to severe VMS. The FDA determined that the clinical threshold of superiority of fezolinetant 45 mg in frequency reduction was by > 2 per day or > 14 per week when compared to placebo at weeks 4 and 12. Fezolinetant offers a new non-hormonal treatment option for females seeking treatment for moderate to severe VMS associated with menopause.
- The efficacy of estrogens (in combination with progestins for women with an intact uterus) for the treatment of moderate to severe VMS or vulvar and vaginal atrophy associated with menopause is well established and supported by current treatment guidelines (*ACOG 2014, de Villiers et al 2016, Goodman et al 2011, NAMS 2020, NAMS 2022*).
  - Specifically, ET and EPT are the most effective therapies for the relief of menopausal symptoms such as hot flashes, sleep disturbances, and vaginal dryness.
  - When patients are receiving hormonal therapy solely for the management of vulvar and vaginal symptoms, topical vaginal hormone preparations should be considered.

  - The decision on whether to use HT for management of menopausal symptoms and selection of a specific HT product should be individualized based on patient preference, chronic comorbidities, risk factors, age, and the presence and severity of menopausal symptoms.
  - Long-term use of ET is associated with an increased risk of endometrial hyperplasia and/or carcinoma in postmenopausal women; however, the addition of a progestin substantially reduces this risk. Therefore, postmenopausal women with an intact uterus should receive EPT to avoid the increased risk of endometrial carcinoma. However, long-term observational data from women in the WHI trials have demonstrated that EPT is associated with increased risks of myocardial infarction, stroke, invasive breast cancer, PE, and DVT. Micronized progesterone may be preferred when progesterone is necessary due to a reduced risk of breast cancer in observational trials. For postmenopausal women who are appropriate candidates for HT, ET is appropriate in those who have undergone a hysterectomy. Use of a progestogen is not recommended with low-dose vaginal ET, although women at increased risk of endometrial cancer may warrant endometrial surveillance (*NAMS 2020*).
  - In general, ET and EPT for the management of menopausal symptoms should be prescribed at the lowest effective dosage and for the shortest duration consistent with treatment goals and risks for the individual patient.
  - Benefits of HT are most likely to outweigh risks in symptomatic women who are younger than 60 years or who are within 10 years of menopause onset (*NAMS 2022*).
- The use of estrogens (with progestins for women with an intact uterus) for prevention of postmenopausal osteoporosis is also supported by clinical trials; however, they are not considered first-line treatments in clinical guidelines. Data from clinical trials substantiate the efficacy of ET in preserving bone mass, and less consistently, preventing fractures; however, nonhormonal therapeutic options (ie, bisphosphonates) should be considered first-line (*Camacho et al 2020, Cosman et al 2014, Humphrey et al 2023, Shoback et al 2020*).
- Furthermore, clinical guidelines do not distinguish or make a preference for one agent over another; treatment decisions should be individualized. Transdermal and vaginal hormonal preparations may be preferred over oral formulations for safety considerations.
- Overall, HT is considered the most effective treatment for the relief of severe menopausal symptoms, including VMS and should be used in select postmenopausal females based on individually determined benefit-vs-risk profile (*NAMS 2022, NAMS 2023*).

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