South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

March 8, 2024

South Dakota Department of Social Services

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South Dakota Department of Social Services

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

March 8, 2024
1:00 – 3:00 PM CT
12:00 – 2:00 PM MT

Meeting Link:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_YWYwNGUwOTMtMWVkOC00NTU3LWI1ZjQtNDEzOWVjNzE0MDE5%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: 116 514 471 22

Join by phone
+1 952-222-7450
Phone Conference ID: 564 670 728#

Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **Selgentis & tramadol review**
- **Hep C review**
- **Opioid update**

New business
- **PMPM comparison**
- **Brand inhalers review**
- **Glucose test strip review**
- **Zoryve**
- **Zurzuvae**

Public input accepted after individual topic discussion
Next meeting date June 7, 2024 & adjournment

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

Friday, December 8, 2023
1:00 – 3:00 pm CT

Members and DSS Staff

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

Darger Retirement

Secretary of Social Services Matt Althoff read the proclamation designating December 8 as Dana Darger Day. Darger has served on this committee since its inception 20 years ago. Darger said it was his honor to serve on this committee to help the community of South Dakota.

Administrative Business

Darger called the meeting to order at 1:08 pm and handed the position of chair to Van Gilder. Van Gilder assumed chair of the meeting. The minutes of the September 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 July 1, 2023, to September 30, 2023. A total of 2,416 PAs were reviewed of which 147 requests (6%) were received via telephone, 113 requests (4.7%) were received via fax, 846 (35%) were reviewed electronically, and 1,309 (54.2%) PAs were received via ePA. There was a 30.7% increase in PAs received compared to the previous quarter. This corresponded to an increase in ePA and phone requests. The phone requests had doubled since the previous quarter and for the first time exceeded the number of fax requests. The increase in phone requests was due to requests for brand Synthroid which was the result of terming the narrow therapeutic index drug list in July.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from July 1, 2023, to September 30, 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 23.8% 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 9.1% of total claims. The drug Daybue had the highest increase due to the increase in utilizers.

Old Business

PA Approval Comparison

The committee reviewed the PA approvals of South Dakota Medicaid and other Medicaid states. South Dakota Medicaid PA approvals are higher than the three other states for comparison. The other states

have lower approval rates since many of their requests are for non-formulary drug requests compared to a clinical PA review. Jockheck expressed reviewing those PA requests with low frequency or high approval rates for cleanup. Stanley inquired about the per member per month (PMPM) figure. Jockheck stated the average is $72 PMPM and that expansion members would receive the same benefits. The PMPM comparison with other Medicaid states was requested for review.

Opioid update
The committee reviewed 3Q2023 opioid outcomes compared to previous quarters from the opioid initiatives. There was a decrease in opioid utilization and utilizers during 3Q2023 with corresponding decrease in total eligibility and utilizers. Ladwig inquired about calculating the decrease in MME over time. Stanley inquired about the change in hospitalization and/or deaths associated with opioids use. Baack noted experiencing less neonatal opioid withdrawal seen now.

New Business

Epidemiology Presentation
Angela Cascio, Infectious Disease Director from the South Dakota Department of Health, presented the Trending Epidemiology in South Dakota. The committee discussed current trends seen across the state. In addition, committee reviewed the hepatitis C PA approvals, number of patients treated, and utilization. Petrik asked how many still need treatment for hepatitis C. A review of denied claims compared to those who have been treated will be provided at the next meeting. Oehlke asked what the next steps are for treating members who may not know criteria has been expanded. DSS will explore options to notify providers.

Jornay PM & Stimulant review
The committee reviewed Jornay PM utilization. Stimulant utilization of members 21 years and older was also review compared to 4Q2020. Stimulant utilization of members taking immediate release (IR) and extended-release (ER) was also reviewed. Baack expressed concern for Jornay PM utilization in a 4-year-old member and concern for diversion. Stanley commented Vyvanse has a lower risk of diversion. Committee reviewed PA criteria of other states. Nicole Poppinga from Avera provided public comment. Stanley recommended adding PA on long-acting stimulants for children less than 6 years old unless written by a psychiatrist or behavioral specialist. After discussion, Baack made a motion to add PA to long-acting stimulants to try short acting first for children less than 6 years old unless seen by a psychiatrist or behavioral specialist. Darger seconded the motion. Van Gilder inquired if there was any public comment. There was none. The motion was approved unanimously.

FDA Advisory Letter on Stimulants
Ladwig provided commentary on the crisis seen with the ADHD shortages. Baack stated pandemic has heightened mental health concerns for children and this is going to continue to be a national issue.

Van Gilder inquired if there was any public comment. There were none.

Humira shift to Skyrizi
Committee reviewed analysis of the potential utilization shift from Humira to Skyrizi. There were none seen during the time frame reviewed.

Ilaris new indication
The committee reviewed the new indication for Ilaris for the symptomatic treatment of adult patients with gout flares and discussed adding PA criteria. Baack motioned removing the rheumatology consult

and proposed patients try NSAIDs and colchicine. Darger seconded the motion. Van Gilder inquired if there was any public comment. There was none. The motion was approved unanimously.

Nuzyra
Nuzyra clinical information was presented for review. Committee discussed adding criteria to Nuzyra. Darger made a motion to add PA criteria. Petrik seconded the motion. Van Gilder inquired if there was any public comment. There was none. The motion was approved unanimously.

Vowst
Vowst clinical information was presented for review. Committee discussed the merits of this drug. Baack recommended monitoring utilization.

Adjournment

The next meeting is scheduled on March 8, 2024. The June meeting is scheduled for June 7, 2024. Darger made the motion to adjourn the meeting and Petrik seconded the motion. The motion to adjourn the meeting was unanimous, and the meeting adjourned at 3:01 pm CT.

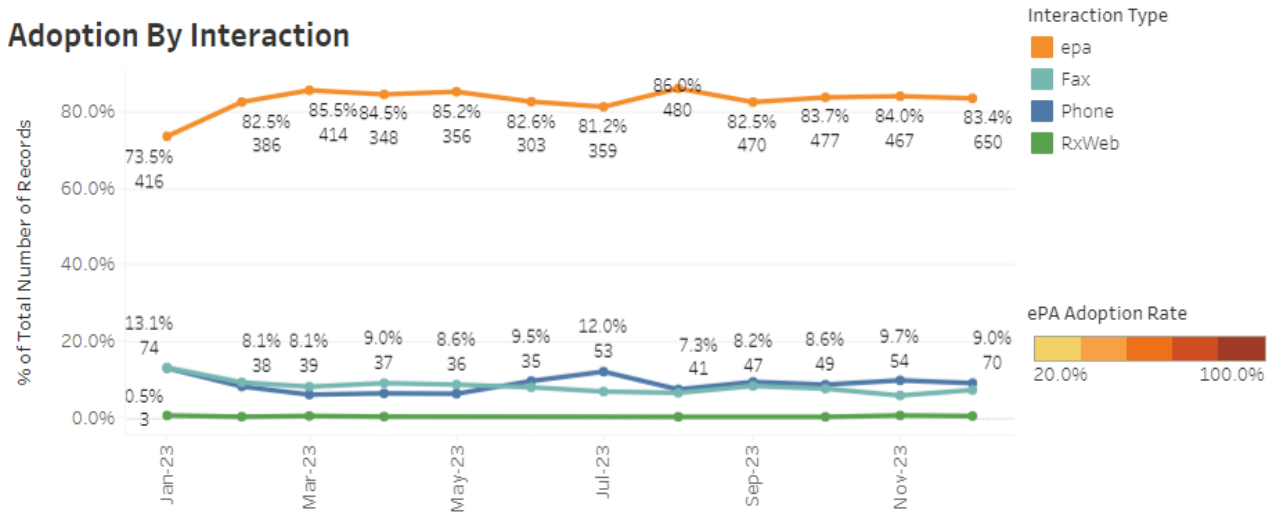
PA Report
10/1/2023 – 12/31/2023

Compliance Summary

Priority	Total PAs	PAs Compliant	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	2,495	2,495	0	100.00%	0.00%
Urgent	350	350	0	100.00%	0.00%
Grand Total	**2,845**	**2,845**	**0**		

Priority	Standard	Urgent
ePA	1,278	316
Fax	120	11
Phone	154	19
Real-Time	940	
RxWeb	3	4

Request Summary	Total # of Requests	Phone Requests		Fax Requests		Real-Time PA		ePA PA	
		#	%	#	%	#	%	#	%
Total	**2,845**	**173**	**6.1%**	**131**	**4.6%**	**940**	**33%**	**1,594**	**56%**



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
Oct-23	725	174	899
Nov-23	700	159	859
Dec-23	875	212	1,087
4Q23	**2,300**	**545**	**2,845**
Percent of Total	**80.84%**	**19.16%**	

Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
ANTIDIABETICS	435	73	508	85.63%	17.86%	, OZEMPIC
ANTIPSYCHOTICS/ANTIMANIC	451	30	481	93.76%	16.91%	, VRAYLAR
ANALGESICS - OPIOID	209	46	255	81.96%	8.96%	HYDROCODONE/APAP
DERMATOLOGICALS	162	79	241	67.22%	8.47%	DUPIXENT, EUCRISA
ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ ANOREX	125	72	197	63.45%	6.92%	QELBREE, VYVANSE
OTHERS -	918	245	1163	78.93%	40.88%	
4Q23	2,300	545	2,845	80.84%		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
27 - ANTIDIABETICS*	435	73	508	85.63%
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	451	30	481	93.76%
65 - ANALGESICS - OPIOID*	209	46	255	81.96%
90 - DERMATOLOGICALS*	162	79	241	67.22%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	125	72	197	63.45%
58 - ANTIDEPRESSANTS*	168	28	196	85.71%
67 - MIGRAINE PRODUCTS*	96	33	129	74.42%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	98	21	119	82.35%
52 - GASTROINTESTINAL AGENTS - MISC.*	86	33	119	72.27%
97 - MEDICAL DEVICES AND SUPPLIES*	101	17	118	85.59%
66 - ANALGESICS - ANTI-INFLAMMATORY*	79	7	86	91.86%
16 - ANTI-INFECTIVE AGENTS - MISC.*	41	4	45	91.11%
12 - ANTIVIRALS*	34	9	43	79.07%
54 - URINARY ANTISPASMODICS*	22	9	31	70.97%
72 - ANTICONVULSANTS*	25	5	30	83.33%
41 - ANTIHISTAMINES*	22	6	28	78.57%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	10	15	25	40.00%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	16	3	19	84.21%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	17	1	18	94.44%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	10	8	18	55.56%
39 - ANTIHYPERLIPIDEMICS*	13	2	15	86.67%
28 - THYROID AGENTS*	9	3	12	75.00%
34 - CALCIUM CHANNEL BLOCKERS*	6	5	11	54.55%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	9	2	11	81.82%
75 - MUSCULOSKELETAL THERAPY AGENTS*	6	5	11	54.55%
50 - ANTIEMETICS*	9	1	10	90.00%
83 - ANTICOAGULANTS*	5	4	9	55.56%
40 - CARDIOVASCULAR AGENTS - MISC.*	8	0	8	100.00%
33 - BETA BLOCKERS*	3	3	6	50.00%
36 - ANTIHYPERTENSIVES*	3	3	6	50.00%
02 - CEPHALOSPORINS*	3	1	4	75.00%
45 - RESPIRATORY AGENTS - MISC.*	2	2	4	50.00%
74 - NEUROMUSCULAR AGENTS*	2	2	4	50.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	2	1	3	66.67%
57 - ANTIANXIETY AGENTS*	2	1	3	66.67%
01 - PENICILLINS*	1	1	2	50.00%
03 - MACROLIDES*	2	0	2	100.00%
22 - CORTICOSTEROIDS*	1	1	2	50.00%
25 - CONTRACEPTIVES*	0	2	2	0.00%
32 - ANTIANGINAL AGENTS*	0	2	2	0.00%
79 - MINERALS & ELECTROLYTES*	1	1	2	50.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	2	0	2	100.00%
04 - TETRACYCLINES*	0	1	1	0.00%
11 - ANTIFUNGALS*	1	0	1	100.00%
15 - ANTHELMINTICS*	0	1	1	0.00%
37 - DIURETICS*	0	1	1	0.00%
51 - DIGESTIVE AIDS*	1	0	1	100.00%
82 - HEMATOPOIETIC AGENTS*	1	0	1	100.00%
85 - HEMATOLOGICAL AGENTS - MISC.*	1	0	1	100.00%
88 - MOUTH/THROAT/DENTAL AGENTS*	0	1	1	0.00%
4Q23	**2,300**	**545**	**2,845**	
Percent of Total	**80.84%**	**19.16%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Oct-23	16	80.00%	4	20.00%	20
Nov-23	23	95.83%	1	4.17%	24
Dec-23	29	69.05%	13	30.95%	42
4Q23	**68**	**79.07%**	**18**	**20.93%**	**86**

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
LINZESS	15	1	16	93.75%
QELBREE	6	3	9	66.67%
MAVYRET	5	0	5	100.00%
VRAYLAR	5	0	5	100.00%
LUBIPROSTONE	2	2	4	50.00%
AJOVY	2	1	3	66.67%
BELSOMRA	0	2	2	0.00%
CLINDAMYCIN/BENZOYL PEROXIDE	2	0	2	100.00%
DEXCOM G6 TRANSMITTER	1	1	2	50.00%
ESCITALOPRAM OXALATE	2	0	2	100.00%
JUBLIA	0	2	2	0.00%
SPINOSAD	2	0	2	100.00%
STELARA	2	0	2	100.00%
XELJANZ XR	1	1	2	50.00%
AMPHETAMINE/DEXTROAMPHETAMINE	1	0	1	100.00%
CETIRIZINE HYDROCHLORIDE	0	1	1	0.00%
COSENTYX SENSOREADY PEN	1	0	1	100.00%
EMGALITY	1	0	1	100.00%
ENOXAPARIN SODIUM	1	0	1	100.00%
ESOMEPRAZOLE MAGNESIUM	1	0	1	100.00%
ESZOPICLONE	0	1	1	0.00%
EVRYSDI	1	0	1	100.00%
GATTEX	1	0	1	100.00%
GENOTROPIN MINIQUICK	1	0	1	100.00%
HYDROCODONE/APAP	1	0	1	100.00%
IVERMECTIN	1	0	1	100.00%
KESIMPTA	1	0	1	100.00%
LISDEXAMFETAMINE DIMESYLATE	1	0	1	100.00%
METHADONE HYDROCHLORIDE	1	0	1	100.00%
MOUNJARO	0	1	1	0.00%
MYRBETRIQ	1	0	1	100.00%
NORDITROPIN FLEXPRO	1	0	1	100.00%
NUCYNTA	0	1	1	0.00%
NURTEC	1	0	1	100.00%
OPZELURA	1	0	1	100.00%
OZEMPIC	0	1	1	0.00%
QULIPTA	1	0	1	100.00%
REPATHA	1	0	1	100.00%
SKYRIZI PEN	1	0	1	100.00%
SOFOSBUVIR/VELPATASVIR	1	0	1	100.00%
TROSPIUM CHLORIDE	1	0	1	100.00%
TRULANCE	1	0	1	100.00%
4Q23	**68**	**18**	**86**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 10/1/2023 – 12/31/2023					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	14,456	$191,390.26	$13.24	6.15%
2	ANTICONVULSANTS, MISCELLANEOUS	13,236	$1,071,148.88	$80.93	5.63%
3	ATYPICAL ANTIPSYCHOTICS	9,834	$3,117,364.64	$317.00	4.18%
4	SELECTIVE BETA-2-ADRENERGIC AGONISTS	8,212	$438,572.63	$53.41	3.49%
5	AMINOPENICILLIN ANTIBIOTICS	7,752	$114,577.84	$14.78	3.30%
6	RESPIRATORY AND CNS STIMULANTS	7,271	$757,144.34	$104.13	3.09%
7	SECOND GENERATION ANTIHISTAMINES	7,240	$81,353.24	$11.24	3.08%
8	PROTON-PUMP INHIBITORS	7,148	$195,414.50	$27.34	3.04%
9	AMPHETAMINES	6,900	$709,501.20	$102.83	2.93%
10	ADRENALS	6,831	$747,002.29	$109.35	2.90%
11	OPIATE AGONISTS	6,370	$222,337.76	$34.90	2.71%
12	ANXIOLYTICS,SEDATIVES,AND HYPNOTICS,MISC	5,546	$71,821.34	$12.95	2.36%
13	HMG-COA REDUCTASE INHIBITORS	4,569	$54,149.85	$11.85	1.94%
14	SEL.SEROTONIN,NOREPI REUPTAKE INHIBITOR	4,185	$79,093.38	$18.90	1.78%
15	ANTIDEPRESSANTS, MISCELLANEOUS	4,126	$99,862.79	$24.20	1.75%
Total		**113,676**	**$7,950,734.94**	**$69.94**	**48.33%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 10/1/2023 – 12/31/2023					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	ATYPICAL ANTIPSYCHOTICS	9,834	$3,117,364.64	$317.00	4.18%
2	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	395	$2,761,893.31	$6,992.13	0.17%
3	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	791	$2,699,103.91	$3,412.27	0.34%
4	INCRETIN MIMETICS	1,809	$1,672,897.05	$924.76	0.77%
5	CYSTIC FIBROSIS (CFTR) CORRECTORS	63	$1,433,586.08	$22,755.33	0.03%
6	ANTINEOPLASTIC AGENTS	362	$1,336,023.54	$3,690.67	0.15%
7	HEMOSTATICS	47	$1,194,416.84	$25,413.12	0.02%
8	ANTICONVULSANTS, MISCELLANEOUS	13,236	$1,071,148.88	$80.93	5.63%
9	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	4,056	$882,574.16	$217.60	1.72%
10	RESPIRATORY AND CNS STIMULANTS	7,271	$757,144.34	$104.13	3.09%
11	ADRENALS	6,831	$747,002.29	$109.35	2.90%
12	AMPHETAMINES	6,900	$709,501.20	$102.83	2.93%
13	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	192	$668,394.57	$3,481.22	0.08%
14	SODIUM-GLUC COTRANSPORT 2 (SGLT2) INHIB	1,081	$590,073.45	$545.86	0.46%
15	GI DRUGS, MISCELLANEOUS	466	$556,882.23	$1,195.03	0.20%
Total		**53,334**	**$20,198,006.49**	**$378.71**	**22.67%**

Total Rx Claims from 10/1/2023 – 12/31/2023	**235,213**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 10/1/2023 – 12/31/2023						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Penicillins	AMOXICILLIN	5,635	$74,283.31	$13.18	2.40%
2	Antidepressants	FLUOXETINE	5,122	$62,399.44	$12.18	2.18%
3	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	4,613	$166,024.31	$35.99	1.96%
4	Antidepressants	SERTRALINE	4,543	$59,620.95	$13.12	1.93%
5	ADHD & Narcolepsy Medications	METHYLPHENIDATE	4,539	$272,654.78	$60.07	1.93%
6	Antihistamines	CETIRIZINE	4,224	$45,334.73	$10.73	1.80%
7	Proton Pump Inhibitors	OMEPRAZOLE	4,181	$46,778.31	$11.19	1.78%
8	Anticonvulsants - 2nd Generation	GABAPENTIN	4,084	$66,175.71	$16.20	1.74%
9	Antidepressants	TRAZODONE	3,655	$39,014.28	$10.67	1.55%
10	Thyroid Hormones	LEVOTHYROXINE SODIUM	3,555	$39,396.62	$11.08	1.51%
11	Antidepressants	ESCITALOPRAM OXALATE	3,386	$41,586.66	$12.28	1.44%
12	ADHD & Narcolepsy Medications	AMPHETAMINE/DEXTROAMP	3,127	$92,252.48	$29.50	1.33%
13	Biguanides & Combos	METFORMIN	2,860	$33,269.53	$11.63	1.22%
14	Leukotriene Modulators	MONTELUKAST SODIUM	2,854	$36,833.63	$12.91	1.21%
15	Antidepressants	BUPROPION	2,788	$49,061.50	$17.60	1.19%
16↑	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE	2,774	$387,296.80	$139.62	1.18%
17	ACE Inhibitors & Combos	LISINOPRIL	2,664	$24,922.38	$9.36	1.13%
18	Statins & Combos	ATORVASTATIN CALCIUM	2,655	$30,330.77	$11.42	1.13%
19	Opioid Agonists & Combos	HYDROCODONE BIT/AC	2,475	$37,691.78	$15.23	1.05%
20	Antiadrenergic Antihypertensives	CLONIDINE	2,448	$21,815.98	$8.91	1.04%
21	Antidepressants	DULOXETINE	2,261	$34,556.41	$15.28	0.04%
22	Antiemetics	ONDANSETRON ODT	2,248	$30,797.02	$13.70	0.96%
23	Antianxiety Agents	HYDROXYZINE	2,135	$25,316.46	$11.86	0.91%
24	Penicillins	AMOXICILLIN/CLAVULANATE	2,116	$40,270.58	$19.03	0.90%
25	Atypical Antipsychotics	ARIPIPRAZOLE	2,088	$31,596.32	$15.13	0.89%
26	Glucocorticosteroids	PREDNISONE	2,013	$19,697.07	$9.78	0.86%
27↑	Inhaled Bronchodilator	ALBUTEROL SULFATE	1,840	$35,024.58	$19.04	0.78%
28↑	Macrolides	AZITHROMYCIN	1,823	$28,556.60	$15.66	0.78%
29	Anticonvulsants - 2nd Generation	LAMOTRIGINE	1,809	$23,955.36	$13.24	0.77%
30	Cephalosporins	CEPHALEXIN	1,788	$28,221.42	$15.78	0.76%
31	Atypical Antipsychotics	RISPERIDONE	1,737	$21,277.64	$12.25	0.74%
32	Atypical Antipsychotics	QUETIAPINE FUMARATE	1,736	$22,038.66	$12.70	0.74%
33	Antianxiety Agents	BUSPIRONE	1,716	$20,841.68	$12.15	0.73%
34	Calcium Channel Blockers	AMLODIPINE BESYLATE	1,619	$15,432.61	$9.53	0.69%
35	ADHD & Narcolepsy Medications	GUANFACINE ER	1,588	$26,497.36	$16.69	0.68%
36	Muscle Relaxants & Combos	CYCLOBENZAPRINE	1,578	$15,811.05	$10.02	0.67%
37	Proton Pump Inhibitors	PANTOPRAZOLE SODIUM	1,545	$20,820.88	$13.48	0.66%
38	Antihistamines	LORATADINE	1,544	$16,344.81	$10.59	0.66%
39	Angiotensin II Receptor Antagonists & Combo	LOSARTAN POTASSIUM	1,534	$16,633.54	$10.84	0.65%
40	Anticonvulsants - 2nd Generation	CLONAZEPAM	1,530	$17,206.39	$11.25	0.65%
41↑	Cephalosporins	CEFDINIR	1,493	$31,856.32	$21.34	0.63%
42	Nasal Steroids	FLUTICASONE PROPIONATE	1,427	$22,278.02	$15.61	0.61%
43	Anticonvulsants - 2nd Generation	TOPIRAMATE	1,424	$17,657.34	$12.40	0.61%
44	Anticonvulsants - 2nd Generation	LEVETIRACETAM	1,397	$28,897.55	$20.69	0.59%
45	Beta Blockers & Combos	METOPROLOL SUCC ER	1,361	$16,507.56	$12.13	0.58%
46↓	Corticosteroids - Topical	TRIAMCINOLONE ACETONIDE	1,294	$19,351.51	$14.95	0.55%
47	Statins & Combos	ROSUVASTATIN CALCIUM	1,293	$15,680.55	$12.13	0.55%
48	Antidepressants	MIRTAZAPINE	1,274	$17,244.69	$13.54	0.54%
49	Nonsteroidal Anti-Inflammatory Agents	MELOXICAM	1,266	$11,607.77	$9.17	0.54%
50	Diuretics & Combos	FUROSEMIDE	1,253	$10,991.02	$8.77	0.53%
	Total Top 50 Drugs		**121,912**	**$2,309,712.72**	**$18.95**	**51.83%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 10/1/2023 – 12/31/2023						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Chronic Inflammatory Disease	***HUMIRA/PEN-CD/UC/HS START***	151	$1,435,216.21	$9,504.74	0.06%
2	Cystic Fibrosis	TRIKAFTA	63	$1,433,586.08	$22,755.33	0.03%
3	Chronic Inflammatory Disease	DUPIXENT	330	$1,189,723.91	$3,605.22	0.14%
4	Atypical Antipsychotics	***INVEGA SUSTENNA/TRINZA/HAFYERA***	336	$1,137,582.81	$3,385.66	0.14%
5	Chronic Inflammatory Disease	STELARA	41	$959,489.29	$23,402.18	0.02%
6	GLP-1 Receptor Agonists	OZEMPIC	939	$851,329.97	$906.63	0.40%
7	Rett Syndrome Agent	DAYBUE	17	$666,504.71	$39,206.16	0.01%
8	Atypical Antipsychotics	VRAYLAR	491	$586,196.15	$1,193.88	0.21%
9	GLP-1 Receptor Agonists	MOUNJARO	504	$491,843.58	$975.88	0.21%
10↑	HIV-Multiclass Combo	BIKTARVY	108	$398,888.53	$3,693.41	0.05%
11	Atypical Antipsychotics	***ARISTADA/INITIO***	147	$397,420.70	$2,703.54	0.06%
12↑	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE	2,774	$387,296.80	$139.62	1.18%
13	SGLT-2 Inhibitors & Combos	JARDIANCE	677	$375,564.03	$554.75	0.29%
14	Anticonvulsants - 2nd Generation	EPIDIOLEX	121	$369,345.61	$3,052.44	0.05%
15	Chronic Inflammatory Disease	***ENBREL/SURECLICK/MINI***	54	$361,741.10	$6,698.91	0.02%
16↑	Hepatitis C	MAVYRET	28	$359,080.12	$12,824.29	0.01%
17	Chronic Inflammatory Disease	TALTZ	40	$345,999.98	$8,650.00	0.02%
18	Chronic Inflammatory Disease	***COSENTYX/SENSOREADY/UNOREADY***	42	$340,231.63	$8,100.75	0.02%
19	Hepatitis C	SOFOSBUVIR/VELPATASVIR	35	$280,273.55	$8,007.82	0.01%
20	ADHD & Narcolepsy Medications	METHYLPHENIDATE	4,539	$272,654.78	$60.07	1.93%
21	Atypical Antipsychotics	REXULTI	213	$266,163.43	$1,249.59	0.09%
22	Oral Anticoagulants	***ELIQUIS/STARTER PACK***	471	$240,192.30	$509.96	0.20%
23	Oncology	KOSELUGO	14	$232,936.45	$16,638.32	0.01%
24	Antihemophilic Products	NOVOSEVEN RT	3	$231,331.65	$77,110.55	0.00%
25↓	Movement Disorder Drug Therapy	INGREZZA	30	$229,496.80	$7,649.89	0.01%
26	Glucagon-Like Peptide-2 (GLP-2) Analog	GATTEX	5	$221,057.00	$44,211.40	0.00%
27	Antihemophilic Products	HEMLIBRA	8	$218,011.52	$27,251.44	0.00%
28	Anti-Infective Agents - Misc.	XIFAXAN	74	$209,424.30	$2,830.06	0.03%
29	Cystic Fibrosis	PULMOZYME	46	$202,683.23	$4,406.16	0.02%
30	Atypical Antipsychotics	ABILIFY MAINTENA/ASIMTUFII	79	$198,936.39	$2,518.18	0.03%
31↑	Atypical Antipsychotics	CAPLYTA	141	$195,904.76	$1,389.40	0.06%
32↑	PIK3CA-Related Overgrowth Spectrum	VIJOICE	6	$195,063.30	$32,510.55	0.00%
33↑	Antihemophilic Products	XYNTHA SOLOFUSE	4	$186,765.40	$46,691.35	0.00%
34	GLP-1 Receptor Agonists	TRULICITY	204	$186,403.77	$913.74	0.09%
35	Insulin	LANTUS/SOLOSTAR	445	$182,155.79	$409.34	0.19%
36↓	ADHD & Narcolepsy Medications	VYVANSE	770	$180,834.34	$234.85	0.33%
37↓	Spinal Muscular Atrophy (SMA) Agent	EVRYSDI	7	$172,587.87	$24,655.41	0.00%
38↓	Chronic Inflammatory Disease	SKYRIZI/PEN	9	$172,441.95	$19,160.22	0.00%
39	HIV-Multiclass Combo	GENVOYA	46	$170,276.92	$3,701.67	0.02%
40↓	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	4,613	$166,024.31	$35.99	1.96%
41↑	Pulmonary Arterial Hypertension	OPSUMIT	13	$157,139.60	$12,087.66	0.01%
42	Inhaled Asthma/COPD Combo	TRELEGY ELLIPTA	250	$154,475.46	$617.90	0.11%
43↑	Chronic Inflammatory Disease	RINVOQ	23	$153,644.68	$6,680.20	0.01%
44	Antihemophilic Products	RECOMBINATE	3	$146,301.75	$48,767.25	0.00%
45	Antihemophilic Products	ADVATE	6	$144,797.70	$24,132.95	0.00%
46	Migraine Products	NURTEC	127	$144,760.62	$1,139.85	0.05%
47	Chronic Inflammatory Disease	TREMFYA	11	$141,452.85	$12,859.35	0.00%
48	Irritable Bowel Syndrome (IBS) Agents	LINZESS	277	$136,486.33	$492.73	0.12%
49↑	Psychotherapeutic And Neurological	LYBALVI	96	$132,625.86	$1,381.52	0.04%
50↑	SGLT-2 Inhibitors & Combos	FARXIGA	243	$129,719.74	$533.83	0.10%
	Total Top 50 Drugs		**19,674**	**$18,140,065.61**	**$922.03**	**8.36%**

Old Business

Seglentis & tramadol

Time frame: 4Q2023

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
tramadol tab 50mg	1,306	$13,820.39	$10.59	52.2/14.6 days	649	13 – 95
tramadol tab 100mg	7	$769.84	$109.98	81.4/30 days	3	53 – 63
tramadol tab 100mg ER	14	$726.37	$51.88	36/29.8 days	5	33 – 62
tramadol tab 200mg ER	8	$455.45	$56.93	28.1/28.1 days	3	36 – 49
tramadol tab 300mg ER	4	$389.47	$97.37	30/30 days	2	42 – 47
tramadol/APAP tab 37.5-325	0					
CONZIP (tramadol SR biphasic cap)	0					
SYNAPRYN (tramadol susp)	0					
QDOLO (tramadol sol 5mg/ml)*	0					
SEGLENTIS 56-44mg (celecoxib/tramadol tab)	3	$1,489.38	$496.46	111/28.7 days	1	58
celecoxib cap 50mg	19	$296.66	$15.61	56.2/29.7 days	12	2 – 64
celecoxib cap 100mg	96	$1,450.76	$15.11	57.4/29.9 days	59	9 – 91
celecoxib cap 200mg	333	$5,048.29	$15.16	47.4/30.5 days	184	15 – 64

Red font denotes drug is on PA; *not rebateable manufacturer

celecoxib 50mg + tramadol 50mg, for 90 tablets –> $25 +$18 = ~$44

South Dakota Medicaid PA criteria: Synaprn, and tramadol ER (Ultram ER)

- 30-day trial of tramadol IR in the past 120 days

Seglentis Indication:

- **Pain, acute:** Management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

State A criteria for Seglentis:

1. *Prescriber must provide documentation that separate components are unsuitable for use*

State B PA criteria for Seglentis:

1. *Inform provider of generic celecoxib and generic tramadol*
2. *Letter of medical necessity must be submitted stating the reasons generic celecoxib and generic tramadol as separate products are not appropriate for the member*

Health Plan PA criteria for Seglentis:

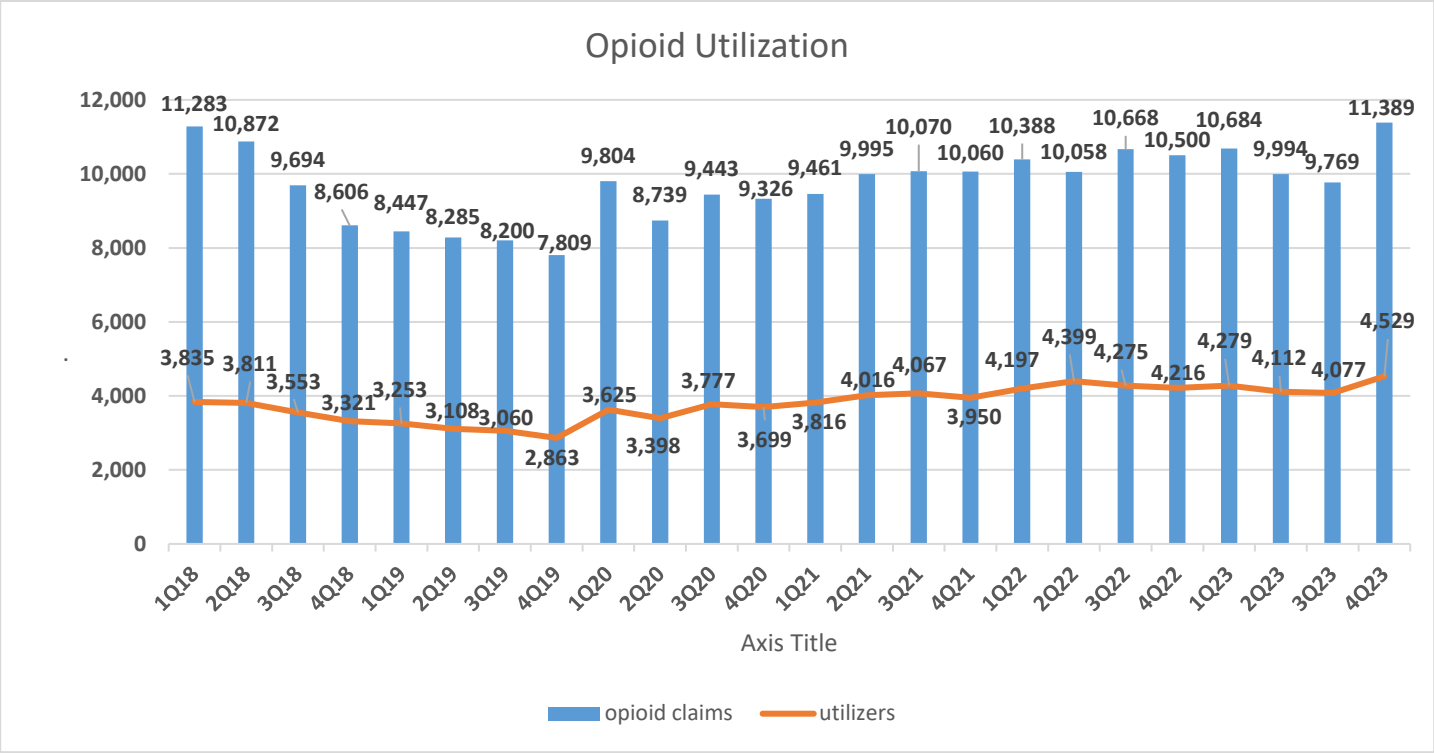
1. *Step Therapy: Patient has tried and failed, or is intolerant to three other non-opioid analgesics (e.g., meloxicam, ibuprofen) in the last 120 days*

Hepatitis C Review

Time Frame: January 2018 – January 2024

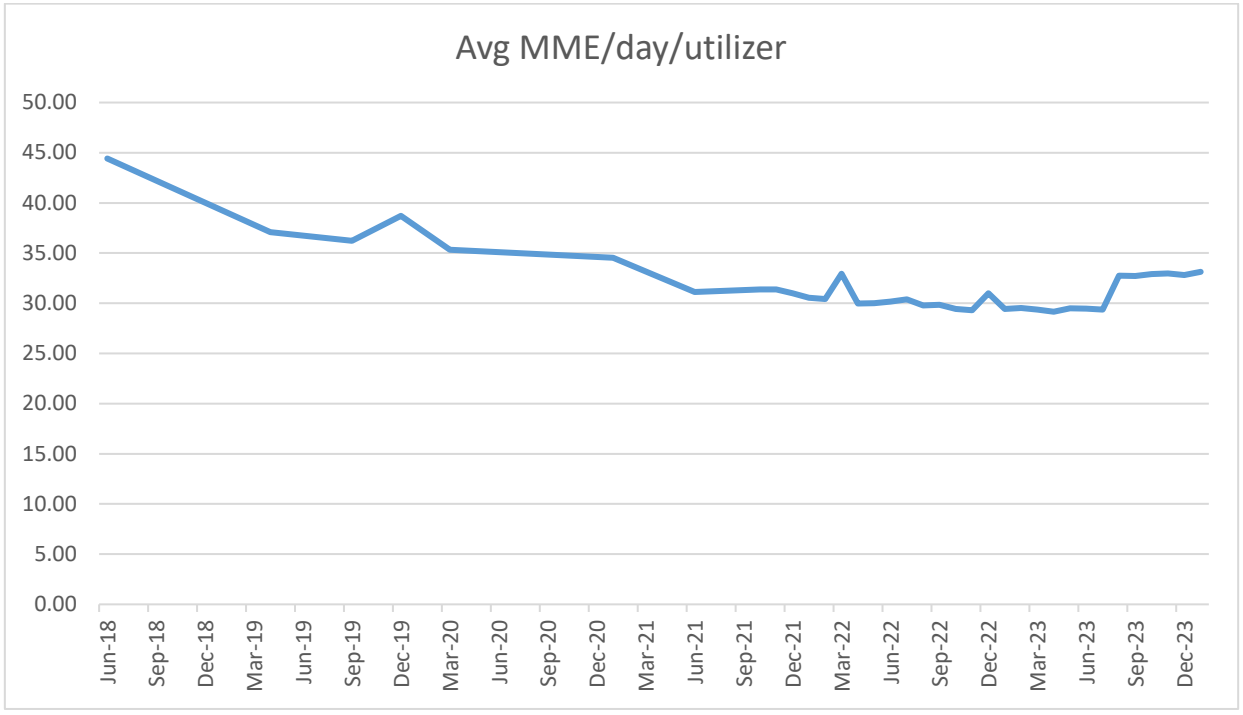
- 360 patients with rejected claims of which 159 patients were treated

Opioid Summary



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

MME



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 Eligibility 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%

SDM 4Q2023
Sep 23 to Dec 23

Opioid Utilization Snapshot

3Q2023
Jun 23 to Sep 23

Opioid Claims **11,389**

3.1% prescription claims filled for an opioid

1.3% higher than Medicaid FFS benchmark

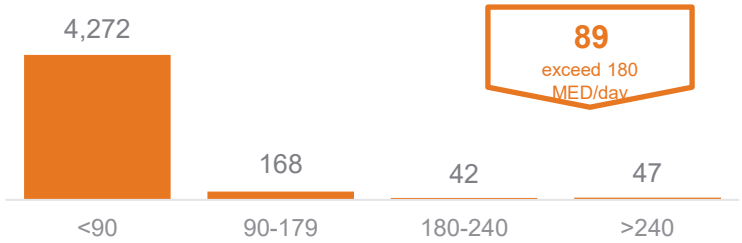
Utilizers **4,529**

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

Opioid Claims **9,769**

3.0% prescription claims filled for an opioid

0.2% higher than Medicaid FFS benchmark

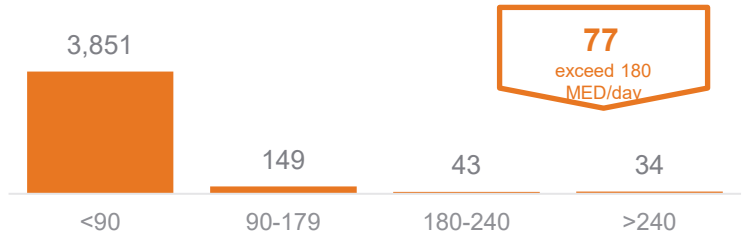
Utilizers **4,077**

28.6% are high utilizers [1]

1.0% 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

46 opioid utilizing members with 3+ pharmacies

292 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 4Q2023
Opportunities date range: Sep - Dec 2023
Benchmark: MEDICAID FEE FOR SERVICE

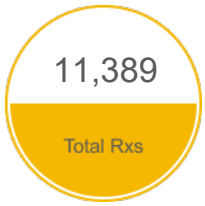
Utilizers: 4,529

3.1% of all Rx claims are filled for an Opioid

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

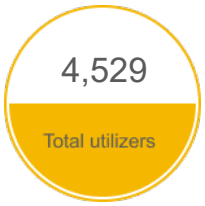
- Opioid prescriptions account for 3.1% of all prescriptions this period, which is 1.3% higher than the benchmark
- 1,397 high opioid utilizers were identified this period, which is 2.8% higher than the benchmark

Opioid claims



PERCENT NON-COMPLIANT
17.2%

Opioid utilizers

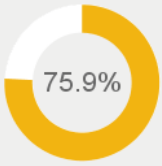


HIGH UTILIZERS
30.8%
1,397 high utilizers

2.8% over benchmark

High utilizers – 3+ opioid scripts within 120 days period

Claim breakdown



short acting opioids

75.9% of all opioid Rxs were filled for short acting opioids. **2,002** Rxs were for medication assisted therapy (MAT) and **151** 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 – Medication Assisted Therapy (buprenorphine, etc)
Overdose rescue therapy – opioid overdose reversals w/naloxone
MME – relative potency of an opioid to a morphine dose

Utilizers by cumulative MED

89 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	4,272	168	42	47

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

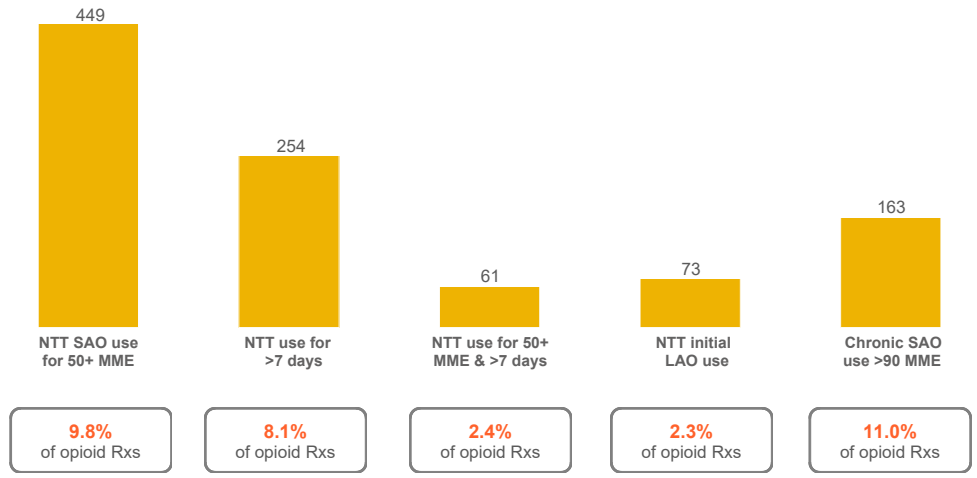
Opioid Opportunity Assessment

SDM 4Q2023
Opportunities date range: Sep - Dec 2023
Benchmark: MEDICAID FEE FOR SERVICE

Percent non-compliant: 17.2%

Utilizers non-compliant to opioid Rx CDC guidelines

(new to therapy and chronic use)



NTT - New to Therapy | *SAO* - Short Acting Opioid | *LAO* - Long Acting Opioid | *MME - Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose*

DID YOU KNOW?

62 opioid utilizing members use 3 or more pharmacies and 371 opioid utilizing members use 3 or more prescribers.

Opioid utilizers with potentially contraindicated medication use

SKELETAL MUSCLE RELAXANTS	BENZODIAZEPINES	ANTICONVULSANTS	MEDICATION ASSISTED THERAPY	PRENATAL
893	621	855	388	143

Anticonvulsants – gabapentin, pregabalin, anticonvulsant benzodiazepines, (clobazam, clonazepam, diazepam)

Hospitalization Rates due to Opioids

Some patients had more than one hospitalization; if they had a stay in 2016 and 2018 they were counted each year, but if they had two stays in 2018 they were only counted once.

Year	Distinct Opioid Hospitalizations	Enrollment	Percent
2016	49	153,378	0.03%
2017	66	153,341	0.04%
2018	53	151,001	0.04%
2019	46	148,239	0.03%
2020	30	144,913	0.02%
2021	28	154,160	0.02%
2022	37	164,187	0.02%
2023	35	185,585	0.02%

Use of Opioids at High Dosage in Persons Without Cancer

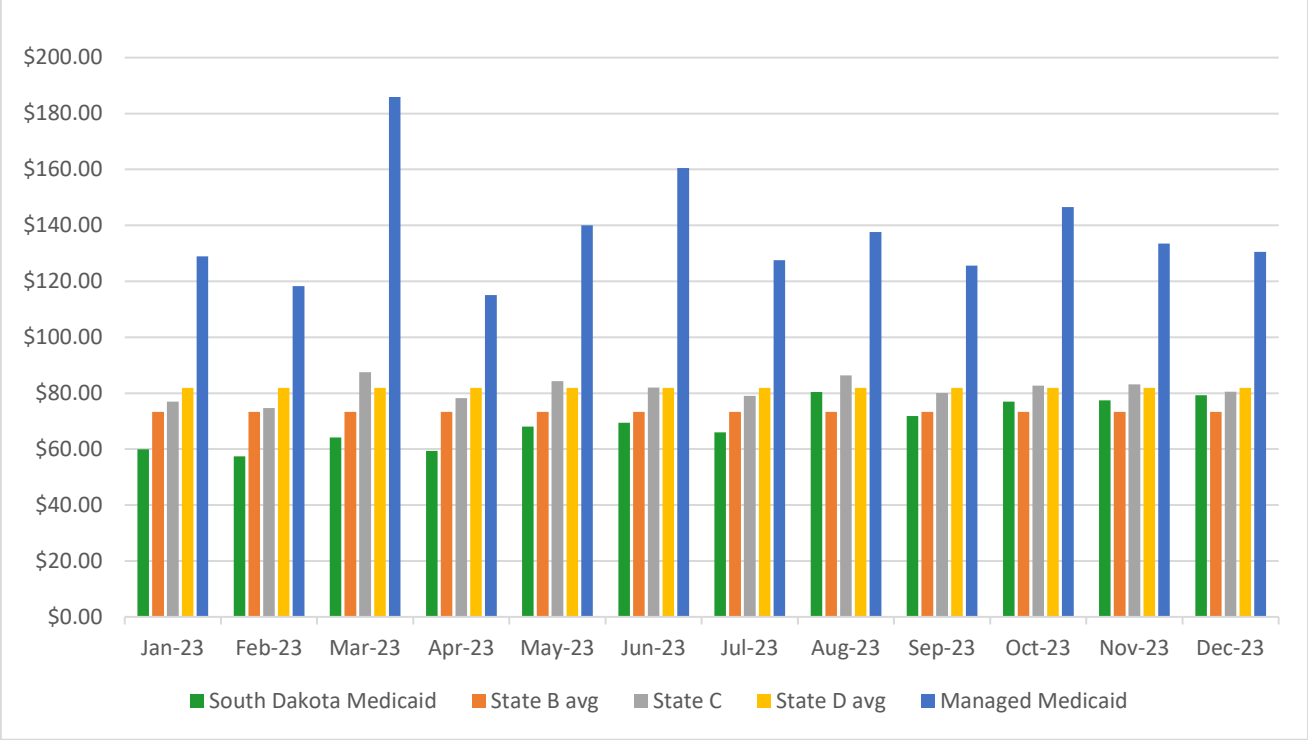
Use of opioids, at high dose in persons without cancer, where lower is better. Note: the year at the top is the reporting year, which reflects services for the year prior (ex: 2023 is for CY 2022). The measure only includes paid claims.

Reporting Year	**2023**	2022	2021	2020	2019	2018	2017	
Data Collection Method	Administrative	Administrative	Administrative	Administrative	Administrative	Administrative	Administrative	
							New Method	Reported
Eligible Population (anyone who had at least 2 opioid prescriptions with a sum of days' supply >= 15)								
18-64 years	1,163	1,139	1,105	1,212	1,324	1,683	2,032	2,050
65+ years	6	2	3	4	23	33	25	45
Total	1,169	1,144	1,108	1,216	1,347	1,716	2,057	2,095
Numerator events (anyone with 90 continuous days of opioid prescriptions >= 90 MME)								
18-64 years	52	56	63	81	116	156	194	40
65+ years	0	0	0	0	2	4	3	1
Total	52	56	63	81	118	160	197	41
Response Rate								
18-64 years	4.47%	4.92%	5.70%	6.68%	8.75%	9.27%	9.55%	1.30%
65+ years	0.00%	0.00%	0.00%	0.00%	8.70%	12.12%	12.00%	2.22%
Total	4.45%	4.90%	5.69%	6.66%	8.76%	9.32%	9.58%	1.96%
Lower 95% confidence interval	N/A							
Upper 95% confidence interval	N/A							

New Business

PMPM comparison

Time frame: Year 2023



Brand Inhalers Review

Time frame: 4Q2023

Drug Name	Rxs per Quarter	Brand Cheaper Net?	Yearly Savings
ADVAIR HFA	160	YES	$$$
fluticasone-salmeterol HFA	226		
ADVAIR DISKUS	8	YES	$
fluticasone-salmeterol DISKUS	315		
AIRDUO RESPICLICK	2	YES	$
fluticasone-salmeterol RESPICLICK	19		
SYMBICORT HFA	13	YES	$$$$
budesonide-formoterol HFA	462		
BREO	83	YES	$$
fluticasone-vilanterol	107		
COMBIVENT *RESPIMAT*	68	NO	Not equivalent products
ipratropium-albuterol ***NEB***	422		
ATROVENT *HFA*	22	NO	Not equivalent products
ipratropium ***NEB***	24		
PERFOROMIST NEB	0	NO	
formoterol NEB	8		
BROVANA NEB	0	NO	
arformoterol NEB	28		
XOPENEX HFA	1	YES	$
levalbuterol HFA	103		
PROVENTIL HFA	0	YES	$$$$
albuterol HFA	4,612		
VENTOLIN	101	YES	$
albuterol HFA	4,612		
		Total	$982,000

*Total excludes Ventolin HFA savings

Glucose Test Strip Review

Time period: 4Q2023

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
ACCU-CHEK TEST AVIVA PL	23	$3,957.01	$172.04	104.3 per 27.2 days	12	28 – 62
ACCU-CHEK TEST GUIDE	111	$5,005.06	$45.09	98.6 per 25.9 days	64	5 – 64
ACCU-CHEK TEST SMART	1	$163.39	$163.39	100 per 25 days	1	51
CONTOUR TEST BLD GLUC	3	$361.65	$120.55	100 per 30 days	1	49
CONTOUR TEST NEXT	189	$22,747.49	$120.36	104.6 per 26.4 days	112	3 – 64
EASY TOUCH TEST STRIPS	2	$30.48	$15.24	50 per 25 days	2	43
EMBRACE PRO TEST	1	$10.49	$10.49	50 per 25 days	1	43
EMBRACE TALK TEST STRIPS	21	$300.64	$14.32	66.7 per 25.8 days	13	20 – 59
FREESTYLE TEST	14	$1,990.31	$142.17	92.9 per 26.1 days	8	8 – 63
FREESTYLE TEST INSULINX	1	$158.21	$158.21	100 per 25 days	1	39
FREESTYLE TEST LITE	46	$6,618.38	$143.88	95.7 per 25.9 days	21	16 – 64
FREESTYLE TEST PREC NEO	3	$136.65	$45.55	100 per 25 days	1	61
GLUCOCARD TEST EXPRESSI	6	$103.60	$17.27	83.3 per 26.7 days	2	44, 58
GLUCOCARD TEST SHINE	68	$977.75	$14.38	72.8 per 26 days	44	10 – 64
ONETOUCH TEST ULTRA	94	$11,731.81	$124.81	89.1 per 25.8 days	49	8 – 64
ONETOUCH TEST VERIO	573	$51,499.15	$89.88	111.6 per 25.9 days	338	0 – 64
PRODIGY NO TEST CODING	11	$264.75	$24.07	77.3 per 24.3 days	7	40 – 63
RELION PREMI TEST GLUCOSE	16	$171.30	$10.71	76.6 per 26.1 days	8	32 – 62
RELION PRIME TEST	1	$27.00	$27.00	150 per 25 days	1	32
RELION PRIME TEST GLUCOSE	8	$180.18	$22.52	137.5 per 28.8 days	3	32 – 59
RELION TRUE TEST METRIX	1	$58.55	$58.55	100 per 30 days	1	56
TRUE METRIX TEST GLUCOSE	127	$6,771.50	$53.32	86.8 per 27.4 days	75	3 – 64
TRUE METRIX TEST PRO TEST	1	$11.68	$11.68	100 per 20 days	1	62

*Excludes IHS

South Dakota Medicaid: Test strip quantity limit #300 per 30 days

- 57 members using 300 test strips per 30 days
    - 6 members aged 5 years and younger
    - 46 members aged 6 – 18 years old
    - 5 members aged 22 years and older

State A: 200 per 30 days (CGM covered at POS)
State B: 306 per 30 days Age ≤ 5 and 204 per 30 days Age > 6 (preferred CGM covered at POS)
State C: 8 per day, up to a maximum of 200 per fill (CGM covered at POS)
State D: 150 per 30 days (CGM not covered at POS)

Glucose Test Strip Allowance for CGM Utilizers

Some states are reducing the quantity limit of glucose test strips if patient is using a continuous glucose monitor (CGM)

Test strip limits if using CGM:

- States A and C: 200 per 30 days
- State E: 200 per year
- State F: 100 per 75 days
- State G: 50 per month
- State H: 50 per 30 days

Zoryve (roflumilast) – 0.3% cream and foam; for the topical treatment of plaque psoriasis, including intertriginous areas, in patients 6 years of age and older

State A:
Initial Authorization – 6 months

- Member is 6 years of age or older AND one of the following:
    - ≥90 days of topical drug therapy with each of the following: topical corticosteroids AND calcineurin inhibitors (pimecrolimus OR tacrolimus)
    - Prescriber has provided valid medical justification for the use of Zoryve (roflumilast) over topical corticosteroids, tacrolimus, and pimecrolimus

Reauthorization – 12 months

- History of the requested agent within the past 180 days

State B:
Initial Authorization – 6 months

- Submission of medical records (e.g., chart notes, lab work, imaging, paid claims history) documenting a diagnosis of plaque psoriasis
- Patient is 5 years of age or older
- Prescribed by or in consultation with a dermatologist
- chart notes, lab work, imaging, paid claims history) documenting a minimum duration of a 4-week trial and failure, contraindication, or intolerance to TWO of the following topical therapies:
    - Corticosteroids (e.g., betamethasone, clobetasol)
    - Vitamin D analogs (e.g., calcitriol, calcipotriene)
    - Tazarotene
    - Calcineurin inhibitors (e.g., tacrolimus, pimecrolimus)
    - Anthralin
    - Coal tar

Reauthorization – 12 months

- Submission of medical records (e.g., chart notes, lab work, imaging, paid claims history) documenting positive clinical response to therapy as evidenced by one of the following:
    - Reduction in the body surface area (BSA) involvement from baseline
    - Improvement in symptoms (e.g., pruritus, inflammation) from baseline

State C:
Initial Authorization – 3-month duration

- Diagnosis of seborrheic dermatitis
- Patient is 9 years of age or older
- Patient does not have moderate to severe liver impairment (Child-Pugh B or C)
- Trial and failure, contraindication, or intolerance to BOTH of the following:
    - Topical antifungals (ketoconazole, ciclopirox, miconazole, clotrimazole)
    - Topical corticosteroids

Renewal criteria – 12 months

- Patient continues to be monitored for liver impairment
- Documented clinical improvement in response to treatment (eg., decreased erythemal, scaling, inflammation, size of patches)
- Patient does not have treatment limiting adverse effects

State D:

- diagnosis of plaque psoriasis
- Member must be 12 years of age or older
- Member must have a body surface area (BSA) involvement of ≤20%
- Member must not have moderate-to-severe hepatic impairment (Child-Pugh B or C)
- Must be prescribed by, or in consultation with, a dermatologist (or an advanced care practitioner with a supervising physician who is a dermatologist)
- Member must have documented trials within the last 6 months for a minimum of 2 weeks that resulted in failure with at least 2 of the following therapies (or have a contraindication or documented intolerance)
    - An ultra-high to high potency topical corticosteroid (TCS); OR
    - A generic topical calcipotriene product; OR
    - A topical tazarotene product; AND
- Initial approvals will be for the duration of 1 month. Reauthorization may be granted if the prescriber documents the member is responding well to treatment
- A quantity limit of 60 grams per 30 days will apply

Commercial:
Initial Authorization – 6 months

- Diagnosis of plaque psoriasis
- Minimum duration of a 4-week trial and failure, contraindication, or intolerance to one of the following topical therapies:
    - Corticosteroids (e.g., betamethasone, clobetasol, desonide)
    - Vitamin D analogs (e.g., calcitriol, calcipotriene)
    - Tazarotene
    - Calcineurin inhibitors (e.g., tacrolimus, pimecrolimus)
    - Anthralin
    - Coal tar
- Patient is not receiving Zoryve in combination with a Targeted Immunomodulator [e.g., Enbrel (etanercept), Cimzia (certolizumab), Simponi (golimumab), Orencia (abatacept), adalimumab, Stelara (ustekinumab), Skyrizi (risankizumab), Tremfya (guselkumab), Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), Ilumya (tildrakizumab), Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib), Otezla (apremilast)]
- Prescribed by, or in consultation with, a dermatologist

Reauthorization – 12 months

- Documentation of positive clinical response to therapy AND
- Patient is not receiving Zoryve in combination with a Targeted Immunomodulator [e.g., Enbrel (etanercept), Cimzia (certolizumab), Simponi (golimumab), Orencia (abatacept), adalimumab, Stelara (ustekinumab), Skyrizi (risankizumab), Tremfya (guselkumab), Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), Ilumya (tildrakizumab), Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib), Otezla (apremilast)

Zurzuvae (zuranolone) – first oral medication for the treatment of postpartum depression (PPD) in adults

State A:

- Diagnosis of postpartum depression
- Member is 18 years old and older
- Member is within 12 months of being postpartum (date of delivery required)
- Dose requested does not exceed one of the following
    - 20mg capsule – 28 capsules for 14-day period
    - 25mg capsule – 28 capsules for 14-day period
    - 30mg capsule – 14 capsules for 14-day period and one of the following:
        - Prescriber has submitted documentation of severe hepatic impairment (Child-Pugh C)
        - Prescriber has submitted documentation of moderate to severe impairment (eGFR <60mL/min/1.73m^2)
- Approvals will be granted for ONE treatment course (14 days of therapy) per 365 days

State B:

- Diagnosis:
    - Diagnosis of severe postpartum depression OR
    - Diagnosis of mild to moderate postpartum depression AND trial and failure, contraindication or intolerance to at least one oral SSRI or SNRI (e.g., escitalopram, duloxetine, etc)
- Patient is 18 years of age or older
- Onset of symptoms in the third trimester or within 4 weeks of delivery
- Prescriber attests that the patient has been counseled and has agreed to adhere to the following: Will follow instructions to not drive or operate machinery until at least 12 hours after taking each dose of Zurzuvae for the duration of the 14-day treatment course and that patients are informed that they may not be able to assess their own driving competence, or the degree of driving impairment caused by Zurzuvae
- Approval length: 14 days

State C:

- Patient is 18 years of age or older
- Diagnosis of severe depression and symptoms began in the 3rd trimester or within 4 weeks of delivery
- Patient is ≤ 12 months postpartum (provide delivery date)
- Prescriber attests to ALL of the following:
    - Patient has been advised not to drive or operate machinery until at least 12 hours after administration due to central nervous system (CNS) depressant effects such as somnolence and confusion
    - Females of reproductive potential should be advised to use effective contraception during treatment and for 1 week after the final dose

State D:

1. An FDA approved diagnosis of moderate to severe postpartum depression
2. Member must be ≤12 months postpartum and the date of delivery must be provided
3. Member must be a female 18 years of age or older
4. Prescriber must verify the following:
    a. Member is not currently pregnant and will use effective contraception while receiving treatment and for 7 days after the last dose of Zurzuvae
    b. Member is not breastfeeding or has agreed to temporarily hold breastfeeding during Zurzuvae therapy and for 7 days after the last dose; and
    c. If the member does not agree to cease breastfeeding, please provide the following:
        i. The provider attests that the benefits of Zurzuvae therapy while breastfeeding outweigh the risks to the infant due to studies showing that Zurzuvae is present in the breastmilk
        ii. The member has been counseled on the potential risks of CNS depression effects that may occur to the infant
    d. Member has been counseled on the proper administration of Zurzuvae including taking with a fat-containing meal
    e. Member has been counseled on the central nervous system (CNS) depression effects of Zurzuvae and the member agrees not to drive or engage in other potentially hazardous activities until at least 12 hours after administration
5. Dosing and approval duration will be limited to the following:
    a. 50mg once daily for 14 days; or
    b. For members with severe hepatic impairment, moderate to severe renal impairment, or concomitant use with CYP3A4 inhibitors:
        i. 30mg once daily for 14 days; and
    c. If a dose reduction to 40mg once daily is required due to CNS depression effects, the prescriber should contact the specialty pharmacy that filled the member's initial Zurzuvae prescription to obtain the 20mg capsules from the manufacturer for the remainder of the member's treatment course; and
6. Approvals will be for 1 treatment course.

State E:

Proposed criteria:

- Patient is ≥ 18 years of age
- Diagnosis of postpartum/peripartum depression based on Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for a major depressive episode (DSM-5
- Symptom onset began during the third trimester of pregnancy or up to 4 weeks post-delivery
- Other medical conditions that may contribute to a depressive disorder, e.g., thyroid dysfunction, have been ruled out
- Patient is ≤ 12 months postpartum
- Patient is not currently pregnant
- Patient has ceased lactating or breastmilk produced will not be used for feedings during treatment and up to 7 days following last dose
- Prescribed by or in consultation with a psychiatrist or an obstetrician-gynecologist
- Length of approval: One 14-day course of treatment

Commercial:
Initial Approval Criteria

A. Postpartum Depression
    1. Diagnosis of a major depressive episode that began no earlier than the third trimester and no later than the first 4 weeks following delivery, as diagnosed by Structured Clinical Interview for DSM-5
    2. Prescribed by or in consultation with psychiatrist
    3. Age ≥ 18 years
    4. Member meets one of the following (a, b, c, d, or e):
        a. HAMD score is ≥ 17 (moderate/severe depression) (see Appendix D)
        b. MADRS score is ≥ 20 (moderate/severe depression) (see Appendix D)
        c. PHQ-9 score is ≥ 15 (moderate/severe depression) (see Appendix D)
        d. If member does not have moderate/severe depression as demonstrated by at least one of the depression scores above (a, b, or c), documentation of severe depression as evidenced by a psychiatrist clinical interview
        e. Failure of a 4-week trial of one of the following oral antidepressants at up to maximally indicated dose but no less than the commonly recognized minimum therapeutic dose, unless clinically significant adverse effects are experienced or all are contraindicated: selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressant (TCA), bupropion, mirtazapine (see Appendix B)
    5. No more than 12 months have passed since member has given birth
    6. Member has not received prior treatment with Zulresso or Zurzuvae for the current pregnancy
    7. Dose does not exceed a 14-day treatment course and both of the following (a and b):
        a. 50 mg per day
        b. 2 capsules per day

    Approval duration: 30 days (one 14-day treatment course per pregnancy)

Continued Therapy

B. Postpartum Depression
    1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Optum Rx®

Therapeutic Class Overview

Antipsoriatic agents

Introduction

- The goal of treatment for patients with psoriasis is to control the disease. There are 3 main treatment modalities available for the treatment of psoriasis including topical agents, phototherapy, and systemic agents. Topical therapies are the mainstay for mild or moderate disease, and are frequently used in conjunction with phototherapy, traditional systemic agents, or biologic agents. Phototherapy, photochemotherapy, and traditional systemic agents are generally used for moderate or severe disease and in situations in which topical therapy is ineffective or otherwise contraindicated (*Elmets et al 2021, Feldman 2023*).
- Topical corticosteroids (eg, betamethasone, clobetasol, triamcinolone, etc.) are the cornerstone of treatment for the majority of patients with psoriasis. Their effectiveness in treating psoriasis is due to anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive effects. Drawbacks associated with topical corticosteroid treatment are local cutaneous side effects and more serious systemic side effects that are associated with long-term use over a large body surface area (*Elmets et al 2021*). Due to these side effects, several agents have been developed and tested as monotherapy or in combination with topical corticosteroids in the hopes of reducing the duration of corticosteroid treatment.
- Other topical antipsoriatic agents include anthralin, calcitriol, calcipotriene, and tazarotene. These agents are available in a variety of vehicles. A topical phosphodiesterase 4 inhibitor, roflumilast cream, is approved by the Food and Drug Administration (FDA) for treatment of plaque psoriasis, including intertriginous areas, in patients 6 years of age and older. Tapinarof, a topical aryl hydrocarbon receptor agonist, was FDA-approved for the treatment of psoriasis in adults in 2022. Early forms of treatment also included coal tar. In the United States, coal tar use has declined due to lack of standardization of available compounds and the development of other agents with less cosmetic issues such as odor and staining.
- Oral antipsoriatic systemic agents are typically reserved for moderate to severe psoriasis and are often combined with other therapies. Acitretin, an oral retinoid, modulates the cellular differentiation of the epidermis and is known to have immunomodulatory and anti-inflammatory activity (*Menter et al 2020).* Acitretin is most effective as a maintenance therapy, usually after the disease has been stabilized, or in combination with other treatments such as phototherapy (*Villasenor-Park et al 2012*). Methoxsalen is a naturally occurring photosensitivity agent (psoralen) that enhances skin reactivity to ultraviolet light A (UVA). The combination of psoralen and UVA is referred to as photochemotherapy or PUVA. PUVA (with methoxsalen) is recommended for treatment of psoriasis in adults and is most often used for psoriasis that is moderate to severe and does not respond to topical therapy *(Elmets et al 2019, Richard 2022).*
- Agents included in this review are the topical and oral antipsoriatic agents, which are listed in Table 1. Biologics, their respective biosimilars, and targeted agents (eg, adalimumab, apremilast, brodalumab, certolizumab pegol, etanercept, guselkumab, infliximab, ixekizumab, risankizumab-rzaa, secukinumab, tildrakizumab-asmn, and ustekinumab) that are used to treat psoriasis and other inflammatory/immunologic diseases are not included in this review. Topical corticosteroids are also not included in this review.
- Medispan Class: Antipsoriatics, Antipsoriatic – Systemic, and Topical Steroid Combinations

Table 1. Medications Included Within Class Review

Generic name	Brand name	Alternative available (same molecular entity)*
Topical Agents		
Anthralin†	Zithranol shampoo	-
Calcipotriene	topical cream	✔
	Sorilux foam	✔
	topical ointment	✔
	topical scalp solution	✔
Calcitriol	Vectical ointment	✔
Roflumilast	Zoryve cream	-
Tapinarof	Vtama cream	-
Tazarotene ‡	Tazorac cream	✔

Generic name	Brand name	Alternative available (same molecular entity)*
	Tazorac gel	✔
Calcipotriene/ Betamethasone dipropionate	Enstilar foam	✔
	Taclonex suspension	✔
	Taclonex ointment	✔
	Wynzora cream	-
Tazarotene/ Halobetasol propionate	Duobrii lotion	-
Oral Systemic Agents		
Acitretin	--	✔
Methoxsalen	--	✔

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

†Anthralin products are unapproved marketed drugs that have not been formally evaluated by the FDA as they were initially marketed before the Federal, Food, Drug, and Cosmetic Act was passed.

‡ Tazarotene 0.1% topical foam (Fabior) and 0.045% topical lotion (Arazlo) are approved for the treatment of acne. The Avage brand of tazarotene 0.1% topical cream is approved for cosmetic indications.

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

Indications

Table 2. Food and Drug Administration Approved Indications

Drugs	Psoriasis (quiescent or chronic)	Severe Psoriasis	Plaque Psoriasis	Acne Vulgaris
Topical Agents				
Anthralin (Zithranol)	✔			
Calcipotriene (calipotriene cream, Sorilux, calcipotriene ointment, calcipotriene scalp solution)			✔ *	
Calcitriol (Vectical)			✔ †	
Roflumilast (Zoryve)			✔ ‖	
Tapinarof (Vtama)			✔	
Tazarotene (Tazorac)			✔ ‡	✔ ‡
Calcipotriene/ betamethasone dipropionate (Enstilar foam)			✔ £	
Calcipotriene/ betamethasone dipropionate (Taclonex suspension)			✔ §	
Calcipotriene/ betamethasone dipropionate (Taclonex ointment)			✔ £	
Calcipotriene/ betamethasone dipropionate (Wynzora cream)			✔	
Tazarotene/ halobetasol propionate (Duobrii lotion)			✔	

Drugs	Psoriasis (quiescent or chronic)	Severe Psoriasis	Plaque Psoriasis	Acne Vulgaris
Oral Systemic Agents				
Acitretin capsules		✔		
Methoxsalen capsules		✔ ¶		

*Sorilux is indicated for plaque psoriasis of scalp and body in adults and pediatric patients 4 years or older; calcipotriene topical solution, 0.005% (Scalp Solution) is indicated for the treatment of chronic, moderately severe psoriasis of the scalp.
†Mild to moderate plaque psoriasis in adults and pediatric patients 2 years and older.
‡Tazorac 0.05% and 0.1% cream are indicated for treatment of adult patients with plaque psoriasis. Tazorac 0.05% and 0.1% gel are indicated for treatment of patients 12 years and older with plaque psoriasis of up to 20% body surface area involvement. Tazorac 0.1% cream and gel are also indicated for acne.
§Taclonex suspension is indicated for plaque psoriasis of the scalp and body in patients 12 years and older.
‖Indicated for plaque psoriasis, including intertriginous areas, in patients 6 years and older.
£ Indicated for plaque psoriasis in patients 12 years and older.
¶Combination of methoxsalen with long-wave UV radiation (photochemotherapy) is indicated for control of severe, recalcitrant, disabling psoriasis not adequately responsive to other forms of therapy and when the diagnosis has been supported by biopsy.

(Prescribing Information: *Acitretin 2023, Calcipotriene cream 2023*, *Calcipotriene ointment 2020, Calcipotriene solution 2022, Duobrii 2020, Enstilar 2022, Methoxsalen 2019, Sorilux 2023, Taclonex ointment 2023, Taclonex suspension 2020, Tazorac cream 2022, Tazorac gel 2020, Vectical 2022, Vtama 2023, Wynzora 2023, Zithranol shampoo 2014, Zoryve 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

- Various strengths and formulations of anthralin or dithranol have been evaluated (*Fredriksson 1983, Jones et al 1985*). Results from these trials support efficacy of anthralin in the treatment of psoriasis with no significant differences identified between dosage strength, formulation, or administration.
- Topical calcipotriene has demonstrated favorable efficacy in treating psoriasis in several studies with marked improvements in clearing of psoriatic lesions occurring in approximately 50% to 70% of patients (*Highton et al 1995, Dubertret et al 1992, Thaci et al 2001*). Treatment success was reported in patients 12 years and older with psoriasis who were treated with topical calcipotriene foam in two 8-week, multicenter, randomized, double-blind, vehicle-controlled clinical trials (*Feldman et al 2012, Feldman et al 2013*). The topical calcipotriene foam has been approved in pediatric patients 4 years and older based on two 8-week studies in addition to a 15-day open-label pharmacokinetic study in patients 12 to < 17 years old and an 8-week open-label safety and pharmacokinetic study in patients 4 to 11 years old *(Sorilux prescribing information 2023).*
- For the treatment of plaque psoriasis, topical calcipotriene has demonstrated favorable efficacy when combined with betamethasone, PUVA, and methotrexate (*Buckley et al 2008, De Jong et al 2003, Kragballe et al 2009, Luger et al 2008, Ortonne et al 2009, Ozkan et al 2012, Torras et al 2004, van de Kerkhof et al 2009*). The combination of calcipotriene plus betamethasone has demonstrated superior efficacy when compared to monotherapy with either calcipotriene or betamethasone or placebo in several clinical trials (*Buckley et al 2008, Douglas et al 2002, Guenther et al 2002, Jemec et al 2008, Kaufman et al 2002, Kragballe et al 2004, Kragballe et al 2009, Luger et al 2008, Ortonne et al 2009, Papp et al 2003, Parslew et al 2005, Singh et al 2000, van de Kerkhof et al 2005, van de Kerkhof et al 2009, van de Kerkhoff et al 2004; Lebwohl et al 2021a*). Compared to the calcipotriene plus betamethasone topical suspension, the calcipotriene plus betamethasone cream was superior in achieving treatment success at week 8. Treatment success was achieved in 37.4% and 22.8% of patients receiving the cream and topical solution, respectively ($p < 0.0001$) (*Gold et al 2021).*
- The efficacy of calcitriol ointment for the treatment of mild to moderate plaque psoriasis was demonstrated in 2 double-blind, randomized controlled studies involving 839 patients. Calcitriol applied twice daily for 8 weeks was significantly more effective than the vehicle. Additionally, there were no clinically relevant changes in calcium homeostasis or other routine laboratory parameters in calcitriol-treated patients (*Lebwohl et al 2007*). Calcitriol ointment was FDA-approved for use in pediatric patients aged 2 years and older for the treatment of mild to moderate psoriasis based on the results of adult and pediatric studies. The pediatric studies included an 8-week vehicle-controlled study in patients aged 2 to 12

years old and 3 open-label safety and pharmacokinetic studies in patients aged 12 to 17 years, 2 to 12 years, and 2 to 17 years. These studies found that systemic exposure of calcitriol was generally similar to the baseline, endogenous levels *(Vectical prescribing information 2022)*.

- Head-to-head trials comparing the vitamin D analogues have been conducted. Ortonne et al found calcitriol to be significantly better tolerated than calcipotriol in sensitive skin fold areas (*Ortonne et al 2003*). In another 12-week, randomized trial in patients with chronic plaque psoriasis, calcitriol demonstrated similar efficacy to calcipotriol and had a significantly better safety profile (*Zhu et al 2007*).
- Head-to-head trials comparing therapies from different medication classes for the treatment of psoriasis also exist. Veronikis et al compared calcipotriene to coal tar and found that both agents were effective in the treatment of plaque psoriasis with no significant differences found between treatment groups (p value not reported) (*Veronikis et al 1999*). Calcipotriol solution has been compared to clobetasol shampoo, with clobetasol found to be significantly more efficacious in terms of total severity score measures as well as global severity score ($p < 0.05$ for all) (*Reygagne et al 2005*).
- Roflumilast cream demonstrated efficacy against placebo in the treatment of plaque psoriasis in adult and pediatric patients (ages 6 to 88 years old) in 2 multicenter, randomized, double-blind, vehicle-controlled trials, DERMIS-1 and DERMIS-2. In these trials, 881 patients with mild to severe plaque psoriasis and an affected body surface area of 2% to 20% were randomized 2:1 to receive either roflumilast cream or placebo vehicle, applied once daily for 8 weeks. The primary outcome was the proportion of patients who achieved an Investigator's Global Assessment (IGA) score of "clear" (0) or "almost clear" (1), plus a 2-point improvement from baseline, at week 8. In DERMIS-1, 42.4% of patients using roflumilast compared to 6.1% of patients using vehicle achieved the primary outcome (difference from vehicle, 39.6%; 95% confidence interval [CI], 32.3 to 46.9; $p < 0.001$). Similarly, in DERMIS-2, 37.5% of patients using roflumilast vs 6.9% of patients using vehicle achieved the primary outcome (difference, 28.9%; 95% CI, 20.8% to 36.9%; $p < 0.001$). Among patients with a baseline IGA score of at least 2 (mild) across both studies, there was a higher percentage of patients achieving IGA success at week 8 in the group using roflumilast vs the group using vehicle (*Lebwohl et al 2022*).
- The expanded indication of roflumilast cream in patients 6 to 11 years old was based on data from a Phase 2, 4-week Maximal Usage Systemic Exposure (MUSE) study which fulfilled post-marking requirements (*FDA approval letter 2023*).
- Tapinarof cream demonstrated superiority over placebo vehicle in the PSOARING 1 and PSOARING 2 trials, 2 identical Phase 3 trials that included 510 and 515 adult patients with mild to severe plaque psoriasis, respectively. By trial design, the majority of patients had moderate psoriasis. Patients were randomized 2:1 to receive with tapinarof 1% cream or placebo vehicle cream once daily for 12 weeks. At week 12, patients receiving tapinarof were more likely to achieve the primary endpoint of a Physician Global Assessment (PGA) score of "clear" (0) or "almost clear" (1) and at least a 2-point decrease in the 5-point PGA scale vs patients receiving placebo vehicle (PSOARING 1: 35.4% vs 6.0%; adjusted difference, 29.4%; relative rate, 5.8; 95% CI, 2.9 to 11.6; PSOARING 2: 40.2% vs 6.3%; adjusted difference, 33.9%; relative rate, 6.1; 95% CI, 3.3 to 11.4; $p < 0.001$ for both comparisons). Adverse effects of tapinarof included folliculitis, nasopharyngitis, contact dermatitis, pruritus, upper respiratory tract infection, and headache (*Lebwohl et al 2021c*). The PSOARING 3 trial evaluated long-term safety and efficacy over a 40-week open-label treatment period with 4-weeks' follow-up after the initial 12-week randomized trial inclusion. Patients with a PGA score of 0 upon entry discontinued tapinarof and were monitored to ensure remission. Patients who had a PGA score ≥ 1 upon entry received tapinarof until the PGA score was 0. Patients with PGA ≥ 2 were re-treated until the PGA score was 0. Of eligible patients, 763 patients enrolled in the open-label safety study: 40.9% of patients achieved complete disease clearance (PGA = 0) at least once during the trial, and 58.2% entering with PGA ≥ 2 achieved a PGA score of 0 or 1. Among patients entering with or achieving PGA = 0 at any time during the study, the mean total duration of remittive effect off therapy was 130.1 days. Adverse events were similar to those observed in PSOARING 1 and PSOARING 2 (*Strober et al 2022).*
- Tazarotene was shown to be more effective than placebo in treating plaque psoriasis (*Weinstein et al 1997*). Results demonstrated that both tazarotene 0.1% and 0.5% gel were significantly more effective than placebo in reducing the severity of signs and symptoms of target lesions ($p < 0.05$). A second, placebo-controlled trial with the same methodology found similar results (*Weinstein et al 2003*). Topical tazarotene in combination with a low-, medium-, and high-potency topical corticosteroid has been evaluated in patients with mild to moderate plaque psoriasis (*Guenther et al 2000, Lebwohl et al 1998*). While all treatments were effective, the tazarotene and topical corticosteroid combination produced significantly higher treatment success rates at weeks 2, 8, and 12 vs tazarotene monotherapy (all $p < 0.05$). Bowman et al compared the combination of tazarotene gel plus calcipotriene ointment to clobetasol ointment in patients with stable psoriasis and found that both treatments were effective in reducing scaling, plaque elevation, and overall

lesion severity with no significant differences between the 2 groups (p = 0.93, p = 0.76, and p = 0.29, respectively) (*Bowman et al 2002*).

- The efficacy of topical tazarotene and halobetasol propionate fixed combination was evaluated in 2 Phase 3, multicenter, double-blind randomized controlled trials in 418 patients with moderate-to-severe plaque psoriasis. More patients treated with topical tazarotene 0.045%/halobetasol propionate 0.01% lotion achieved treatment success at 8 weeks compared to patients who received vehicle in both studies *(Gold et al 2018).* Similarly, in a double-blind, multicenter Phase 2 trial, more patients who received combination tazarotene/halobetasol propionate achieved treatment success after 8 weeks compared to halobetasol propionate 0.01%, tazarotene 0.045%, or vehicle *(Sugarman et al 2017).* Tazarotene/halobetasol propionate lotion was also compared to halobetasol propionate 0.05% cream and vehicle in patients with moderate-to-severe plaque psoriasis. Treatment success was achieved in 32.8% of patients with tazarotene/halobetasol propionate, 34.0% of patients with halobetasol propionate 0.05%, and 3.3% of patients with vehicle *(Bhatia et al 2018).* The long-term safety and efficacy of tazarotene 0.045%/halobetasol propionate 0.01% lotion was evaluated in a 1-year, open-label study in 555 adults with psoriasis. Overall, 57.8% of patients achieved treatment success during the study. The most common treatment-related adverse events were dermatitis, pruritus, pain, and irritation (*Lebwohl et al 2021b*).
- Acitretin has been shown to be effective in the treatment of patients with moderate to severe psoriasis in open-label studies and controlled clinical trials (*Olsen et al 1989, Tosti et al 2009*). In combination with calcipotriol, acitretin demonstrated improved clinical outcomes compared to acitretin alone or placebo (*Rim et al 2003, van de Kerkhof et al 1998*). Acitretin in combination with phototherapy can enhance treatment efficacy for patients with moderate to severe chronic plaque psoriasis that does not clear using UVB, PUVA, or acitretin alone. Compared with acitretin or UV light monotherapy, the combination regimen enhances efficacy and limits treatment frequency, duration, and cumulative doses (*Lebwohl et al 2001*). A network meta-analysis found conventional agents (including acitretin) to be superior to placebo for Psoriasis Area and Severity Index (PASI) 90 but found biologic agents to be more effective than conventional agents for PASI 90. However, the authors cautioned that the results with acitretin were based on few trials *(Sbidian et al 2021)*.
- Several large multicenter trials have demonstrated the efficacy of oral methoxsalen with UVA (PUVA) in psoriasis, indicating clearance of lesions in 70% to 89% of patients (*Henseler et al 1981, Roenigk et al 1979, Melski et al 1977*). Two systematic reviews of the large majority of PUVA studies verified these findings demonstrating that between 70% and 100% of patients treated with PUVA achieved clearing of psoriasis lesions (*Griffiths et al 2000, Spuls et al 1997*).
- A Cochrane Review was conducted to compare the effectiveness, tolerability, and safety of topical treatments for chronic plaque psoriasis, relative to placebo, and to similarly compare vitamin D analogues (alone or in combination) with other topical treatments. A total of 177 randomized controlled trials with 34,808 participants were included. When used on the body, most vitamin D analogues were significantly more effective than placebo. Dithranol, combined treatment with vitamin D/corticosteroid, and tazarotene all performed significantly better than placebo. Head-to-head comparisons of vitamin D for psoriasis of the body against potent or very potent corticosteroids had mixed findings. For both the body and scalp psoriasis, combined vitamin D and corticosteroid treatment performed significantly better than vitamin D alone or corticosteroid alone. When applied to psoriasis of the scalp, vitamin D was significantly less effective than both potent corticosteroids and very potent corticosteroids. Vitamin D generally performed better than coal tar, but findings compared to dithranol were mixed. For both body and scalp psoriasis, potent corticosteroids were less likely than vitamin D to cause local adverse events, such as burning or irritation. No comparison of topical agents found a significant difference in systemic adverse effects (*Mason et al 2013*).
- In addition to its FDA approval for the treatment of psoriasis, tazarotene, a topical retinoid agent, is also FDA-approved for the treatment of acne vulgaris. In a placebo-controlled trial by Bershad et al, tazarotene 0.1% gel was compared with tazarotene 0.1% gel plus a vehicle gel, or vehicle gel alone (*Bershad et al 2002*). The primary efficacy endpoint, reduction in acne vulgaris lesions, was significant in both tazarotene treatment groups compared to the vehicle group (p = 0.002). Clinical trials comparing tazarotene to other topical retinoid agents have shown conflicting results, with tazarotene being equally or more effective than other topical retinoids (*Pariser et al 2008, Tanghetti et al 2010*).

Clinical Guidelines

- Joint guidelines for the management of psoriasis from the American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) recommend topical agents for mild to moderate psoriasis. Topical agents are also used adjunctively with ultraviolet light or systemic medications for resistant lesions or more severe disease. Topical corticosteroids are recommended as first-line treatment for most patients. Other topical agents included in the guidelines

are vitamin D analogues (calcipotriene and calcitriol), topical retinoids (tazarotene), calcineurin inhibitors (tacrolimus and pimecrolimus), anthralin, emollients, salicylic acid, and coal tar. The guideline recommends use of calcipotriene, calcitriol, or tazarotene for treatment of mild to moderate psoriasis. The guideline also recommends use of calcipotriene or tazarotene in combination with corticosteroids. Topical anthralin is recommended for mild to moderate psoriasis for 8 to 12 weeks; however, it is recommended to limit contact up to 2 hours per day to reduce adverse events. Topical steroids alone or in combination with vitamin D analogues may be used with various biologic agents for treatment of moderate to severe plaque psoriasis. Acitretin can be used as monotherapy, in combination with calcipotriene, in combination with PUVA phototherapy, or with broadband ultraviolet B. Acitretin is often used in patients on highly active antiretroviral therapy for treatment of human immunodeficiency virus (HIV) due to its lack of immunosuppression. Agents approved in 2022, roflumilast cream and tapinarof cream, have yet to be addressed in published clinical practice guidelines (*Elmets et al 2019, Elmets et al 2021, Menter et al 2019, Menter et al 2020*).

- In a 2013 position paper published by the AAD, psoriasis patients with moderate to severe psoriasis may avoid stepwise-therapy (ie, first phototherapy, then oral systemic therapies, followed by biologic therapies) and be moved to later line therapy based on disease severity (*AAD 2013*). Treatment needs vary depending on the severity of disease, body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences.
- Topical retinoids such as tazarotene are also effective in the treatment of acne vulgaris. Guidelines do not recommend one retinoid over another but do generally recommend these agents as a first-line combination option (*Eichenfield et al 2013, Thiboutot et al 2018, Reynolds et al 2024*).
  - According to the AAD, topical retinoids (eg, tretinoin, adapalene, tazarotene, trifarotene) are recommended among the first-line treatment options for the management of acne (strength of recommendation: strong; certainty of evidence: moderate) (*Reynolds et al 2024*). Topical retinoids are important in addressing the development and maintenance of acne and are recommended as monotherapy in primarily comedonal acne, or in combination with topical or oral antimicrobials in patients with mixed or primarily inflammatory acne lesions. The guidelines do not prefer one topical retinoid over another.
    - There are several head-to-head studies with retinoid products. Some support greater efficacy of tazarotene over adapalene and tretinoin, and adapalene over tretinoin, but the concentrations and formulations were varied. Overall, the limitations of the existing studies prohibit direct efficacy comparisons of topical retinoids.
  - According to the Medical Letter, a topical retinoid, alone or in combination with benzoyl peroxide and/or a topical antibiotic, is often used for first-line treatment of inflammatory and noninflammatory acne (*Medical Letter 2020*). Retinoid/antimicrobial combinations are more effective than either component alone, especially in patients with inflammatory acne.

Safety Summary

- Topical calcipotriene is contraindicated in individuals with hypersensitivity to any components of the preparation. Additionally, calcipotriene administration in patients with vitamin D toxicity or hypercalcemia is also contraindicated. Calcipotriene should not be used for the treatment of the face, and the scalp solution is contraindicated in acute psoriatic eruptions. The most common adverse effects of calcipotriene are local effects including burning, pruritus, peeling, stinging, dryness, skin irritation, rash, and erythema. Contact dermatitis has been reported to occur with use of topical calcipotriene. Systemic side effects of vitamin D analogues, including hypercalcemia, are rare unless patients apply more than the recommended dosage of 100 g per week (*Clinical Pharmacology 2023*).
- There are no known contraindications to topical calcitriol. Hypercalcemia was observed in clinical trials with use of topical calcitriol. The safety and efficacy of topical calcitriol in patients with disorders of calcium metabolism have not been evaluated. The most common adverse effects include hypercalciuria, hypercalcemia, and skin discomfort.
- There are no known contraindications to calcipotriene/betamethasone cream, suspension, ointment, or foam. Caution should be used with all formulations in patients with elevated serum calcium levels. Additionally, hypothalamic-pituitary-adrenal axis suppression has occurred due to systemic absorption of the topical corticosteroid. Topical steroids may increase the risk of cataracts and glaucoma. Avoid exposure of treated areas to artificial or natural sunlight. Local adverse reactions such as atrophy, irritation, and allergic contact dermatitis are more likely to occur with occlusive use. Common adverse effects include pruritus, worsening of psoriasis, erythema, and burning sensation.
- Topical roflumilast is contraindicated in individuals with moderate to severe liver impairment (Child-Pugh Class B or C). Coadministration of roflumilast with systemic cytochrome P450 3A4 (CYP3A4) inhibitors or oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure, resulting in increased adverse

reactions; the risk of increased exposure should be weighed against the benefit. The most common adverse reactions seen in clinical trials include diarrhea, headache, insomnia, application site pain, upper respiratory tract infections, and urinary tract infections.

- There are no known contraindications to topical tapinarof. Safety and efficacy have not been established in pediatric patients with psoriasis under 18 years of age. The most common adverse reactions seen in clinical trials include folliculitis, nasopharyngitis, contact dermatitis, headache, pruritus, and influenza.
- Topical tazarotene is contraindicated in patients who are pregnant or who have a documented hypersensitivity reaction to any component of the formulation. Tazarotene should not be used on eczematous skin as severe irritation may occur. Additionally, increased photosensitivity may occur with concurrent administration of fluoroquinolones, phenothiazines, sulfonamides, tetracyclines, and thiazides. Patients should be cautioned to take protective measures (eg, sunscreens, protective clothing) against exposure to sunlight or ultraviolet light (eg, tanning beds) until tolerance is determined. Excessive pruritus, burning, skin redness, or peeling may occur. Discontinue tazarotene until skin integrity is restored or reduce the dosing interval or switch to a lower concentration. The most common adverse effects include burning, erythema, and pruritus.
- Topical tazarotene/halobetasol propionate lotion is contraindicated in pregnancy. Warnings include hypothalamic-pituitary-adrenal axis suppression, photosensitivity, and risk of cataracts and glaucoma. Common adverse effects include contact dermatitis, application site pain, folliculitis, skin atrophy, and excoriation. Local adverse reactions are more likely to occur with occlusive dressings.
- Topical anthralin is contraindicated in acute or actively inflamed psoriatic eruptions. Additionally, the agent should not be used if there is a hypersensitivity to the active ingredient or any of its components. The most common side effects of anthralin are skin irritation and staining of lesions and adjoining skin, nails, and clothing.
- Acitretin is teratogenic and its use, therefore, is limited to male and female patients of nonchildbearing potential. Acitretin should only be considered for women of childbearing potential with severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments. Other contraindications for acitretin include severe liver or kidney impairment, chronic elevation of lipid profile, and use in combination with methotrexate or tetracyclines. Potential adverse effects of acitretin include dry skin and mucus membranes, alopecia, skin peeling, pruritus, cheilitis, rhinitis, hyperlipidemia, liver toxicity, and teratogenicity. Periodic monitoring of bones, lipid profile, liver function, and eyes is recommended.
- Methoxsalen is contraindicated with a history of light sensitivity, melanoma, invasive squamous cell carcinoma or aphakia. Skin irritation, including severe edema, erythema, blistering, and exfoliative dermatitis, can occur during PUVA therapy. Pruritus and other dermatological effects may occur as well. Nausea occurs in 10% of patients receiving methoxsalen, and central nervous system effects including depression, dizziness, and headache have been reported. Patients who have received PUVA therapy should be monitored throughout their lives for the development of cutaneous malignancies.
- Pregnancy and lactation:
  - Anthralin: Pregnancy Category C. It is not known if anthralin is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of treatment to the mother.
  - Calcipotriene: Unclassified in accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR) for Sorilux and calcipotriene cream. It is not known if calcipotriene is excreted in breast milk; caution is advised.
  - Calcitriol: Unclassified in accordance with the FDA's PLLR. It is not known if calcitriol is excreted in breast milk; caution is advised. It should not be applied to the breast if breast-feeding.
  - Calcipotriene/betamethasone: Unclassified in accordance with the FDA's PLLR. It is not known if calcipotriene/betamethasone is excreted in breast milk; caution is advised. It should not be applied to the breast if breast-feeding.
  - Roflumilast: Unclassified in accordance with the FDA's PLLR. Roflumilast cream should not be used during labor and delivery. Although there are no human studies investigating the effects of roflumilast cream on preterm labor or labor at term, animal studies showed that oral roflumilast disrupted the labor and delivery process in mice. It is not known if roflumilast cream is excreted in breast milk. To minimize potential exposure, roflumilast cream should be used on the smallest area of skin for the shortest duration possible while breastfeeding. It should not be applied to the breast if breast-feeding.
  - Tapinarof: Unclassified in accordance with the FDA's PLLR. It is not known if tapinarof cream is excreted in breast milk; caution is advised and the risks should be weighed against the benefits.

- Tazarotene and tazarotene/halobetasol: Use in pregnancy is contraindicated. It is not known if tazarotene and/or halobetasol are excreted in breast milk. The decision to continue or discontinue breastfeeding during therapy should take into account the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
- Acitretin: Acitretin is a known teratogen. Pregnancy must be excluded prior to therapy; it must not be used in females who intend to become pregnant during therapy or at any time for at least 3 years after discontinuation. Acitretin is excreted in breast milk. Due to the potential for serious adverse reactions in the breastfeeding infant, the manufacturer does not recommend acitretin prior to or during breastfeeding.
- Methoxsalen: Unclassified in accordance with the FDA's PLLR. It is not known if methoxsalen (systemic) is excreted in breast milk; either methoxsalen ingestion or nursing should be discontinued.

Dosing and Administration

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
Topical Agents			
Zithranol (anthralin)	Shampoo	Apply onto wet scalp 3 to 4 times per week.	Leave on scalp for 3 to 5 minutes and then rinse thoroughly.
Calcipotriene cream	Cream	Apply a thin layer to affected area twice daily and rub in gently and completely.	
Sorilux (calcipotriene)	Foam	Apply a thin layer twice daily to the affected areas and rub in gently and completely.	Avoid contact with the face and eyes. Not for oral, ophthalmic, or intravaginal use.
Calcipotriene ointment	Ointment	Apply a thin layer to affected area 1 to 2 times per day and rub in gently and completely.	
Calcipotriene scalp solution	Solution	Comb hair to remove scaly debris and apply twice daily, only to lesions, and rub in gently and completely.	Do not spread to forehead. Keep well away from eyes. Avoid applying to uninvolved scalp margins.
Vectical (calcitriol)	Ointment	Apply to affected areas twice daily, morning and evening.	The maximum weekly dose should not exceed 200 g in patients ≥ 7 years of age or 100 g in patients 2 to 6 years of age. Not for oral, ophthalmic, or intravaginal use. Avoid use on eyes, lips, or facial skin.
Enstilar (calcipotriene/ betamethasone dipropionate)	Foam	Apply to affected areas once daily for up to 4 weeks.	Do not use more than 60 g every 4 days. Do not use with occlusive dressings unless directed by a physician. Not for oral, ophthalmic, or intravaginal use. Avoid use on face, groin, axillae, or if skin atrophy is present at treatment site.

Drug	Available Formulations	Usual Recommended Frequency	Comments
Taclonex (calcipotriene/ betamethasone dipropionate)	Ointment, Topical Suspension	Ointment: Apply to affected areas once daily for up to 4 weeks. Topical Suspension: Apply to affected areas once daily for up to 8 weeks.	Maximum weekly dose should not exceed 100 g for patients ≥ 18 years of age. For patients 12 to 17 years of age, maximum weekly use should not exceed 60 g. Treatment of > 30% of body surface area is not recommended (ointment). Do not use on face, axillae, or groin. Do not use with occlusive dressings unless directed by a physician. Do not use if skin atrophy is present at treatment site. Shake topical suspension before use. Not for oral, ophthalmic, or intravaginal use.
Wynzora (calcipotriene/ betamethasone dipropionate)	Cream	Apply to affected areas once daily for up to 8 weeks. Rub in gently.	The maximum weekly dose should not exceed 100 g. Do not use on face, axillae, or groin. Do not use with occlusive dressings unless directed by a physician. Do not use if skin atrophy is present at treatment site. Not for oral, ophthalmic, or intravaginal use.
Zoryve (roflumilast)	Cream	Apply to affected areas once daily and rub in completely.	Wash hands after application, unless roflumilast is used for treatment of the hands. Not for oral, ophthalmic, or intravaginal use.
Vtama (tapinarof)	Cream	Apply a thin layer of cream to affected areas once daily.	Wash hands after application, unless tapinarof is used for treatment of the hands. Not for oral, ophthalmic, or intravaginal use.
Tazorac (tazarotene)	Cream, gel	Psoriasis for ages ≥ 12 years old (gel) and ≥ 18 years old (cream): Apply a thin film to affected area once daily in the evening.	Psoriasis: Start with 0.05% cream/gel, then increase to 0.1% if tolerated and medically indicated. Treatment of > 20% of body surface area is not recommended (gel only).

Drug	Available Formulations	Usual Recommended Frequency	Comments
		Acne vulgaris for ages ≥ 12 years old: Apply a thin film to affected area once daily in the evening.	Not for oral, ophthalmic, or intravaginal use. Avoid contact with eyes, mouth, or other mucous membranes. Apply to dry skin and at least an hour after using emollients.
Duobrii (tazarotene/ halobetasol propionate)	Lotion	Apply a thin layer to affected area once daily.	Maximum weekly dosage should not exceed approximately 50 g. Not for oral, ophthalmic, or intravaginal use. Do not use on face, axillae, or groin. Apply to dry skin.
Oral Systemic Agents			
Acitretin	Capsules	Take by mouth once daily with the main meal	Must be dispensed in no more than a 1-month supply. A medication guide must be given to the patient each time it is dispensed.
Methoxsalen	Capsules	Take 1.5 to 2 hours before UVA exposure with low-fat food or milk (see prescribing information for weight-based dosing instructions)	The number of doses per week will be determined by the schedule of UVA exposures.

See the current prescribing information for full details.

Conclusion

- Numerous topical and systemic therapies are available for the treatment of psoriasis. Topical treatment is considered to be the safest option and is widely used for mild or moderate psoriasis, followed by systemic and phototherapies, which are used for moderate to severe psoriasis. Selection of medication must take into account severity of disease, thickness and scaling of the lesions, relevant comorbidities, patient preference, efficacy, and evaluation of individual patient response (*AAD 2013, Elmets et al 2019, Elmets et al 2021, Menter et al 2020).*
- Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. Drawbacks associated with topical corticosteroid treatment are local cutaneous side effects and more serious systemic side effects that are associated with long-term use over a large body surface area (*Elmets et al 2021*). Several agents have been developed and tested as monotherapy or in combination with topical corticosteroids in the hopes of reducing the duration of corticosteroid treatment.
- The vitamin D analogues, calcipotriene and calcitriol, are other first-line topical agents with proven efficacy in the treatment of psoriasis. Although less effective than topical corticosteroids, they are often used in combination with topical corticosteroids to enhance efficacy and reduce the risk of atrophy, especially over the long term. One potential advantage of calcitriol is that there are no known contraindications for use, whereas calcipotriene (alone, but not in combination with betamethasone) is contraindicated in patients with hypercalcemia and vitamin D toxicity and in acute or actively inflamed psoriatic lesions. Another possible advantage of calcitriol is that it has been shown to be better tolerated in sensitive skin fold areas as well as associated with less stinging, burning, edema and erythema (*Weinstein et al 2003, Zhu et al 2007*).

- The combination of calcipotriene and betamethasone (Enstilar, Taclonex, and Wynzora) has been evaluated in several studies for the treatment of psoriasis compared to placebo and to its individual components. Overall, results indicated that the combination product was more effective in reducing psoriasis area and severity index scores, and it increased the percentage of patients with clear or almost clear disease compared to either agent alone or placebo (*Douglas et al 2002, Guenthe et al 2002, Kaufman et al 2002, Kragballe et al 2004, Papp et al 2003, Parslew et al 2005, Singh et al 2000, van de Kerkhof et al 2004, van de Kerkhof et al 2005, Wynzora prescribing information 2023*). The combination is available as a suspension, ointment, foam, and cream.
- In 2022, a topical phosphodiesterase 4 inhibitor, roflumilast cream, and a topical aryl hydrocarbon receptor agonist, tapinarof, were approved by the FDA for treatment of plaque psoriasis based on the results of clinical trials demonstrating superior efficacy vs placebo (*Lebwohl et al 2021c, Vtama prescribing information 2023, Zoryve prescribing information 2023*). These agents and their place in therapy have yet to be addressed in clinical guidelines.
- Tazarotene is the only topical retinoid agent that is FDA-approved for the treatment of psoriasis. Clinical trials have demonstrated its efficacy alone as well as in combination with other antipsoriatic agents. Guidelines recommend its use as an adjunct to topical corticosteroids to increase its effectiveness (*Elmets et al 2021*). No significant differences were observed between calcipotriene or calcitriol and tazarotene in several head-to-head studies (*Guenther et al 2000, Schiener et al 2000, Tzung et al 2005*). Tazarotene is also available in fixed combination with halobetasol propionate. The combination has shown efficacy compared to its individual components *(Sugarman et al 2017).* Other topical preparations, including anthralin, have taken on more secondary roles and are particularly challenging as they stain clothing and skin.
- Of the systemic therapies, acitretin is the least effective as monotherapy and is therefore often used in conjunction with ultraviolet B or PUVA phototherapy. Acitretin does not lead to immunosuppression or the associated risk of infection like biologic agents. Acitretin is recommended as monotherapy or in combination with PUVA or broadband UVB for psoriasis (*Lebwohl 2001, Elmets et al 2019, Menter et al 2020)*. Acitretin should not be used in women of childbearing potential.
- Methoxsalen and ultraviolet light (PUVA) is an effective method of treating psoriasis and is most often used for psoriasis that is moderate to severe and does not respond to topical therapy *(Elmets et al 2019, Richard 2022).*
- In a position paper published by the AAD, psoriasis patients with moderate to severe psoriasis may avoid stepwise-therapy (i.e., first phototherapy, then oral systemic therapies, followed by biologic therapies) and be moved to later line therapy based on disease severity. Consensus guidelines agree that the decision for treatment should be based on efficacy, potential adverse effects, prior treatments, patient preference, duration and severity of disease, medical risk factors**,** co-morbidities, and potential impact on quality of life (*AAD 2013*).
- Topical retinoids such as tazarotene are also effective in the treatment of acne vulgaris. Guidelines do not recommend one retinoid over another but do generally recommend these agents as a first-line combination option (*Thiboutot et al 2018, Reynolds et al 2024, Eichenfield et al 2013*).

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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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