South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

March 5, 2021

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 5, 2021
1:00 – 3:00 PM

Meeting Link: https://optum.webex.com
Meeting Number (access code): 178 832 1505
Meeting Password: aYkq6bpt*93

Tap to join from a mobile device (attendees only)
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Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **90-Day Fill update**
- **Accumulation edit**
- **Atypical Antipsychotic utilization in children**
- **ADHD utilization**
- **Evrysdi PA criteria**
- **Opioid update**

New business
- **Antihistamine PA approval review**
- **Analgesic/Anti-inflammatory PA approval review**
- **SNRI/SSRI PA approval review**
- **Relexxi**

Public input accepted after individual topic discussion
Next meeting date June 11, 2021 & adjournment

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

Friday, December 11, 2020
1:00 – 3:00 pm CT

Members and DSS Staff

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

Administrative Business

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

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from July 1, 2020 to September 30, 2020. A total of 1,900 PAs were reviewed of which 178 requests (9.4%) were received via telephone and 1,051 requests (55.3%) were received via fax, and 671 (35.3%) were reviewed via electronically. This was a 40% increase of PAs received from the previous quarter.

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, 2020 to September 30, 2020. The top five therapeutic classes based on paid amount were atypical antipsychotics, amphetamines, disease-modifying anti-rheumatic agents, anticonvulsants, and cystic fibrosis correctors. The top 15 therapeutic classes make up 24.52% of total claims. It was noted that under Enzymes, Strensiq made the top 15 therapeutic class based on amount paid for the first time. 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 11.28% of total claims. New utilization for Hemlibra was noted on the top 50 drugs based on amount paid.

Old Business

90-Day Fill

An update was provided on the 90-day fill which was implemented on 10/1/2020. A 90-day supply of generic maintenance medication is allowed after member establishes three monthly fills. Most of the utilization currently were for SSRI, PPI, HMG, anticonvulsants, ACEI, and thyroid medications. Provider notification will be sent February 2021 which will increase adoption of the 90-day fill.

Nayzilam & Valtoco utilization

Committee was satisfied with the utilization for Nayziliam and Voltoco. Committee decided not to monitor quarterly. Utilization will be monitored and brought back to the Committee if it is atypical.

Humira CF PA
Proposed PA criteria for Humira citrate-free (CF) were reviewed. Jenna Gianninoto from AbbVie provided public comment on Humira CF injectables. Preuss inquired whether cost difference warranted PA criteria for CF injectables. Jockheck confirmed substantial savings to the State. Pediatric dosage of Humira CF injections are the only ones available. Preuss requested children started on citrate-free to continue CF. Committee discussed electronic compared to manual PA reviews. Ladwig made a motion to add PA to Humira CF. Van Gilder seconded the motion. The motion was unanimously approved via roll call vote.

Atypical antipsychotic utilization in children
Committee reviewed atypical antipsychotic utilization in children 17 years old and under. Members currently taking 2 or more antipsychotics were specifically reviewed. Stanley referenced best practice on utilization of two or more atypical antipsychotics especially for general health maintenance with significant potential medical ramifications for children on high dose antipsychotics. Darger suggested referring these members to DUR and conduct an in-depth analysis of the 17 members taking 3 or more atypical antipsychotics. Jockheck brought forth adding PA for members needing a third atypical antipsychotic. Stanley made a motion for members taking 3 or more atypical antipsychotics to require PA. Ladwig to second the motion. The motion was unanimously approved via roll call vote. Committee requested to review PA criteria at the next meeting. Darger inquired if there was any public comment. There were none.

Review of Reyvow, Ubrelvy, Nurtec ODT fax form
Committee reviewed the Reyvow, Ubrelvy, and Nurtec ODT fax form. Mary Jenkins from AbbVie was available for any questions on Ubrelvy. Mary Martin from Biohaven was available to address any questions on Nurtec ODT. Holland made the motion to approve PA on Reyvow, Ubrelvy and Nurtec ODT. Stanley seconded the motion. The motion was unanimously approved via roll call vote.

Opioid update
The committee reviewed 3Q20 opioid outcomes compared to previous quarters from the opioid initiatives. There was a slight increase in opioid utilization and opioid utilizers during third quarter which corresponded with the general increase in Medicaid eligible members and utilizers.

New Business

Antidiabetics PA approval review
Committee reviewed the PA approval rate for antidiabetic drugs. Based on current trend, no changes were needed.

Ulcer drugs PA approval review
Committee reviewed the PA approval rate and utilization for proton pump inhibitors. Ladwig made the motion to remove PA on esomeprazole capsule, and Petrik seconded the motion. The motion was unanimously approved via roll call vote.

Van Gilder requested to review SNRI PA approvals at the next meeting.

Accumulation edit
Jockheck discussed the accumulation edit is in preliminary stages for consideration. Preuss commented that this edit could impact the IHS community since they may have transportation issues certain days off the reservation. Darger requested quantifying this edit such as number of members and drugs.

ADHD utilization
The Committee reviewed utilization of ADHD drugs for members 21 years and younger. Preuss questioned if certain providers prescribe more than others. Darger commented that utilization is across the board. Darger asked to compare PMPM of ADHD drugs of other Medicaid States and bring proposed criteria to review at the next meeting.

Orkambi PA review
The Committee reviewed PA criteria for Orkambi and utilization of cystic fibrosis drugs. Orkambi is the only cystic fibrosis drug with clinical PA criteria. James Wallace, pediatric pulmonologist from South Dakota provided public comment. Ladwig made the motion to remove clinical PA on Orkambi. Holland seconded the motion. The motion was unanimously approved via roll call vote.

Evrysdi
Jockheck stated Evrysdi would fall under the purview of this Committee unlike other drugs currently available for spinal muscular atrophy (SMA). Jeremy Whalen from Genentech provided public comment on Evrysdi. Van Gilder suggested reviewing proposed PA criteria at the next meeting.

Adjournment
The next meeting is scheduled for March 5, 2021. The June meeting is tentatively scheduled on June 11, 2021. Petrik made a motion to adjourn the meeting and Oehlke seconded the motion. The motion passed unanimously, and the meeting adjourned at 2:55 PM.

PA Report
10/1/2020 – 12/31/2020

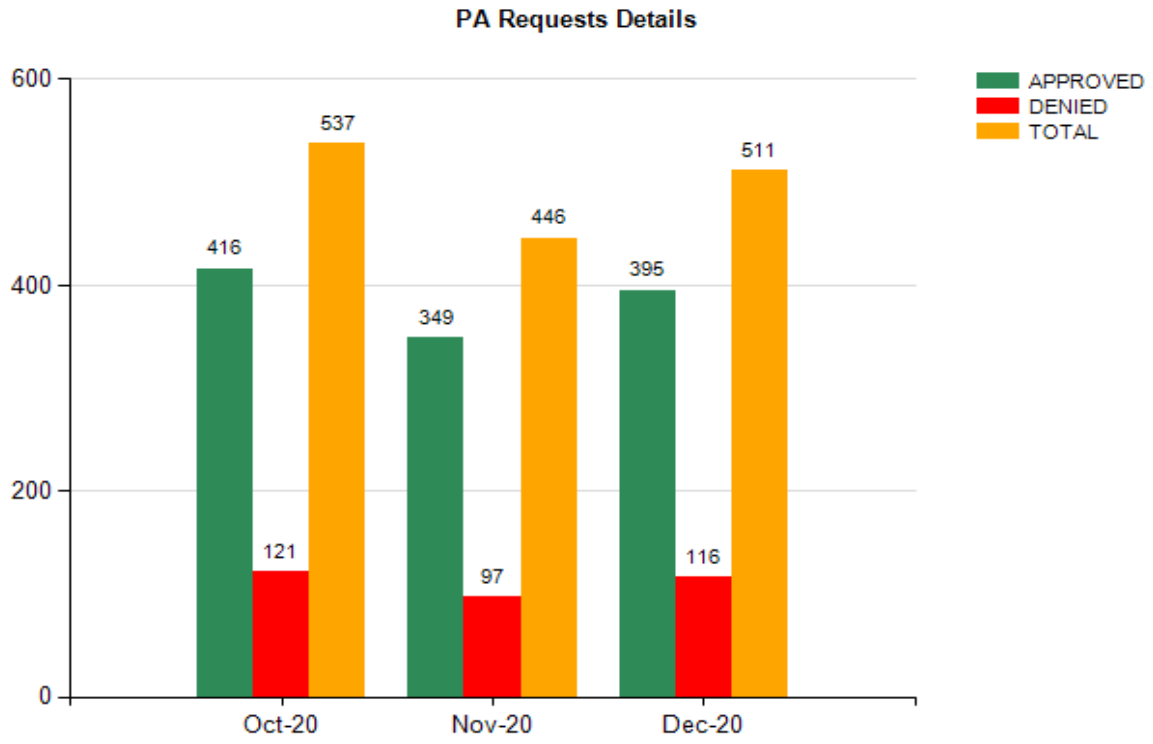
Compliance Summary

Priority	Total PAs	PAs Compliant (Standard - 72 Hrs Urgent - 24 Hrs)	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
STANDARD	1,451	1,451	0	100.00%	0.00%
URGENT	43	43	0	100.00%	0.00%
GRAND TOTAL	**1,494**	**1,494**	**0**		

	# of	Phone Requests		Fax Requests		Real-Time PA	
Drug Class	Requests	#	%	#	%	#	%
TOTAL	**1,494**	**142**	**9.5%**	**872**	**58.4%**	**480**	**32.1%**

PA Initial Requests Summary

Month	Approved	Denied	Total
Oct-20	416	121	537
Nov-20	349	97	446
Dec-20	395	116	511
4Q20	**1,160**	**334**	**1,494**
Percent of Total	**77.64%**	**22.36%**	



Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
59 - ANTIPSYCHOTICS/ANTIMANIC	247	14	261	94.64%	17.47%	, LATUDA
58 - ANTIDEPRESSANTS	154	35	189	81.48%	12.65%	, DULOXETINE
65 - ANALGESICS - OPIOID	109	62	171	63.74%	11.45%	HYDROCODONE/APAP, TRAMADOL
90 - DERMATOLOGICALS	95	71	166	57.23%	11.11%	MALATHION, METRONIDAZOLE
49 - ULCER/ANTISPASMODICS/ ANTICHOLINERGICS	91	26	117	77.78%	7.83%	ESOMEPRAZOLE MAGNESIUM
Others -	464	126	590	78.64%	39.49%	
	247	14	261	94.64%	17.47%	
4Q20	**1,160**	**334**	**1,494**	**77.64%**		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	247	14	261	94.64%
58 - ANTIDEPRESSANTS*	**154**	**35**	**189**	**81.48%**
65 - ANALGESICS - OPIOID*	109	62	171	63.74%
27 - ANTIDIABETICS*	104	2	106	98.11%
90 - DERMATOLOGICALS*	95	71	166	57.23%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	91	26	117	77.78%
52 - GASTROINTESTINAL AGENTS - MISC.*	55	10	65	84.62%
66 - ANALGESICS - ANTI-INFLAMMATORY*	**39**	**14**	**53**	**73.58%**
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	36	15	51	70.59%
67 - MIGRAINE PRODUCTS*	30	27	57	52.63%
16 - ANTI-INFECTIVE AGENTS - MISC.*	28	7	35	80.00%
72 - ANTICONVULSANTS*	26	7	33	78.79%
41 - ANTIHISTAMINES*	**23**	**4**	**27**	**85.19%**
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	20	7	27	74.07%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	18	1	19	94.74%
54 - URINARY ANTISPASMODICS*	14	7	21	66.67%
50 - ANTIEMETICS*	11	0	11	100.00%
45 - RESPIRATORY AGENTS - MISC.*	8	0	8	100.00%
83 - ANTICOAGULANTS*	7	0	7	100.00%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	6	1	7	85.71%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	5	1	6	83.33%
34 - CALCIUM CHANNEL BLOCKERS*	4	0	4	100.00%
36 - ANTIHYPERTENSIVES*	4	2	6	66.67%
75 - MUSCULOSKELETAL THERAPY AGENTS*	4	2	6	66.67%
12 - ANTIVIRALS*	4	4	8	50.00%
33 - BETA BLOCKERS*	4	5	9	44.44%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	4	5	9	44.44%
86 - OPHTHALMIC AGENTS*	3	1	4	75.00%
74 - NEUROMUSCULAR AGENTS*	2	1	3	66.67%
02 - CEPHALOSPORINS*	1	0	1	100.00%
39 - ANTIHYPERLIPIDEMICS*	1	0	1	100.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	1	0	1	100.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	1	0	1	100.00%
79 - MINERALS & ELECTROLYTES*	1	0	1	100.00%
00 - COMPOUND	0	1	1	0.00%
04 - TETRACYCLINES*	0	1	1	0.00%
28 – THRYOID AGENTS*	0	1	1	0.00%
4Q20	**1,160**	**334**	**1,494**	
Percent of Total	**77.64%**	**22.36%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
October-20	13	76.47%	4	23.53%	17
November-20	13	72.22%	5	27.78%	18
December-20	11	84.62%	2	15.38%	13
4Q20	**37**	**77.08%**	**11**	**22.92%**	**48**

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
ADAPALENE/BENZOYL PEROXIDE	2	0	2	100.00%
AIMOVIG	1	1	2	50.00%
AJOVY	2	0	2	100.00%
AMITIZA	2	0	2	100.00%
BUPRENORPHINE	1	0	1	100.00%
CABERGOLINE	1	0	1	100.00%
CARISOPRODOL	1	0	1	100.00%
DUPIXENT	1	0	1	100.00%
EMGALITY	2	1	3	66.67%
EPCLUSA	1	0	1	100.00%
EPIDIOLEX	0	2	2	0.00%
ESOMEPRAZOLE MAGNESIUM	2	0	2	100.00%
FENTANYL	2	0	2	100.00%
FINTEPLA	0	1	1	0.00%
HORIZANT	1	1	2	50.00%
HUMIRA PEN	1	0	1	100.00%
HYDROCODONE/ACETAMINOPHEN	4	0	4	100.00%
HYDROMORPHONE HCL	1	0	1	100.00%
KINERET	1	0	1	100.00%
LATUDA	1	0	1	100.00%
MAVYRET	0	2	2	0.00%
METRONIDAZOLE	3	0	3	100.00%
MODAFINIL	1	0	1	100.00%
MYRBETRIQ	1	0	1	100.00%
NORDITROPIN FLEXPRO	0	2	2	0.00%
OLANZAPINE ODT	1	0	1	100.00%
OXYCODONE HYDROCHLORIDE	2	0	2	100.00%
TRAMADOL HCL	1	0	1	100.00%
XELJANZ	1	0	1	100.00%
XIFAXAN	0	1	1	0.00%
4Q20	**37**	**11**	**48**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 10/1/2020 – 12/31/2020					
	AHFS Description	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	13,148	$174,871.11	$13.30	6.74%
2	ANTICONVULSANTS, MISCELLANEOUS	11,140	$971,516.64	$87.21	5.71%
3	ATYPICAL ANTIPSYCHOTICS	8,814	$2,398,807.23	$272.16	4.52%
4	SECOND GENERATION ANTIHISTAMINES	7,094	$80,600.47	$11.36	3.64%
5	SELECTIVE BETA-2-ADRENERGIC AGONISTS	7,005	$485,231.28	$69.27	3.59%
6	RESPIRATORY AND CNS STIMULANTS	6,544	$562,098.34	$85.90	3.36%
7	AMPHETAMINES	6,349	$1,074,649.17	$169.26	3.26%
8	PROTON-PUMP INHIBITORS	6,051	$187,079.80	$30.92	3.10%
9	OPIATE AGONISTS	5,806	$181,049.87	$31.18	2.98%
10	ADRENALS	4,983	$580,797.29	$116.56	2.56%
11	AMINOPENICILLIN ANTIBIOTICS	4,287	$60,997.85	$14.23	2.20%
12	ANXIOLYTICS, SEDATIVES, & HYPNOTICS, MISC	3,916	$135,902.59	$34.70	2.01%
13	CONTRACEPTIVES	3,628	$110,982.24	$30.59	1.86%
14	SEROTONIN MODULATORS	3,516	$128,435.98	$36.53	1.80%
15	THYROID AGENTS	3,508	$70,575.94	$20.12	1.80%
Total		**95,789**	**$7,203,595.80**	**$75.20**	**49.14%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 10/1/2020 – 12/31/2020					
	AHFS Description	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	ATYPICAL ANTIPSYCHOTICS	8,814	$2,398,807.23	$272.16	4.52%
2	CYSTIC FIBROSIS (CFTR) CORRECTORS	54	$1,222,466.22	$22,638.26	0.03%
3	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	229	$1,209,362.31	$5,281.06	0.12%
4	AMPHETAMINES	6,349	$1,074,649.17	$169.26	3.26%
5	HEMOSTATICS	41	$1,073,135.60	$26,174.04	0.02%
6	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	427	$1,001,345.71	$2,345.07	0.22%
7	ANTICONVULSANTS, MISCELLANEOUS	11,140	$971,516.64	$87.21	5.71%
8	ANTINEOPLASTIC AGENTS	295	$645,978.57	$2,189.76	0.15%
9	LONG-ACTING INSULINS	1,364	$620,898.95	$455.20	0.70%
10	ADRENALS	4,983	$580,797.29	$116.56	2.56%
11	RESPIRATORY AND CNS STIMULANTS	6,544	$562,098.34	$85.90	3.36%
12	SELECTIVE BETA-2-ADRENERGIC AGONISTS	7,005	$485,231.28	$69.27	3.59%
13	RAPID-ACTING INSULINS	1,333	$443,603.01	$332.79	0.68%
14	INCRETIN MIMETICS	557	$440,539.62	$790.91	0.29%
15	GI DRUGS, MISCELLANEOUS	369	$430,794.28	$1,167.46	0.19%
Total		**49,504**	**$ 13,161,224.22**	**$265.86**	**25.39%**

Total Rx Claims from 10/1/2020 – 12/31/2020	**194,949**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 10/1/2020 – 12/31/2020						
	AHFS Description	**Drug Label Name**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE	4,726	$311,679.98	$65.95	2.42%
2	SECOND GENERATION ANTIHISTAMINES	CETIRIZINE	3,949	$41,692.07	$10.56	2.03%
3	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE HFA	3,708	$155,842.28	$42.03	1.90%
4	PROTON-PUMP INHIBITORS	OMEPRAZOLE	3,687	$42,602.62	$11.55	1.89%
5	ANTICONVULSANTS, MISCELLANEOUS	GABAPENTIN	3,405	$58,684.38	$17.23	1.75%
6	AMPHETAMINES	VYVANSE	3,301	$950,982.32	$288.09	1.69%
7	LEUKOTRIENE MODIFIERS	MONTELUKAST SODIUM	3,203	$43,376.50	$13.54	1.64%
8	SEROTONIN MODULATORS	TRAZODONE	3,202	$33,676.95	$10.52	1.64%
9	AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN	3,177	$39,762.19	$12.52	1.63%
10	AMPHETAMINES	AMPHETAMINE/DEXTROAM	2,888	$100,039.14	$34.64	1.48%
11	SELECTIVE-SEROTONIN REUPTAKE INHIB	FLUOXETINE	2,883	$38,925.48	$13.50	1.48%
12	THYROID AGENTS	LEVOTHYROXINE	2,823	$49,552.28	$17.55	1.45%
13	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	ESCITALOPRAM OXALATE	2,665	$36,322.78	$13.63	1.37%
14	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE HCL	2,379	$28,241.53	$11.87	1.22%
15	CENTRAL ALPHA-AGONISTS	CLONIDINE	2,344	$22,992.16	$9.81	1.20%
16	ANGIOTENSIN-CONVERTING ENZYME INHIBIT	LISINOPRIL	2,207	$20,539.33	$9.31	1.13%
17	ATYPICAL ANTIPSYCHOTICS	ARIPIPRAZOLE	2,155	$36,768.66	$17.06	1.11%
18	ANTIDEPRESSANTS, MISCELLANEOUS	BUPROPION	2,025	$40,607.79	$20.05	1.04%
19	HMG-COA REDUCTASE INHIBITORS	ATORVASTATIN CALCIUM	1,954	$23,161.77	$11.85	1.00%
20	OPIATE AGONISTS	HYDROCODONE/APAP	1,941	$29,254.68	$15.07	1.00%
21	SECOND GENERATION ANTIHISTAMINES	LORATADINE	1,880	$20,465.61	$10.89	0.96%
22	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE	1,878	$22,885.06	$12.19	0.96%
23	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE HCL	1,815	$22,099.11	$12.18	0.93%
24	ATYPICAL ANTIPSYCHOTICS	RISPERIDONE	1,707	$21,692.96	$12.71	0.88%
25	BIGUANIDES	METFORMIN	1,546	$14,485.91	$9.37	0.79%
26	ATYPICAL ANTIPSYCHOTICS	QUETIAPINE FUMARATE	1,543	$19,883.21	$12.89	0.79%
27	CORTICOSTEROIDS (EENT)	FLUTICASONE PROPIONAT	1,535	$23,029.05	$15.00	0.79%
28	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	GUANFACINE	1,492	$28,030.52	$18.79	0.77%
29	ANTICONVULSANTS, MISCELLANEOUS	LAMOTRIGINE	1,478	$22,688.47	$15.35	0.76%
30	SEL.SEROTONIN, NOREPI REUPTAKE INHIB	DULOXETINE	1,436	$22,772.53	$15.86	0.74%
31	1ST GENERATION CEPHALOSPORIN ANTIBIOTICS	CEPHALEXIN	1,431	$23,384.61	$16.34	0.73%
32	COMPOUNDS	-	1,417	$142,143.86	$100.31	0.73%
33	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE	1,406	$26,514.54	$18.86	0.72%
34	BENZODIAZEPINES (ANTICONVULSANTS)	CLONAZEPAM	1,404	$15,433.58	$10.99	0.72%
35	OTHER MACROLIDE ANTIBIOTICS	AZITHROMYCIN	1,319	$21,324.14	$16.17	0.68%
36	ADRENALS	PREDNISONE	1,307	$13,208.58	$10.11	0.67%
37	ANTICONVULSANTS, MISCELLANEOUS	LEVETIRACETAM	1,304	$26,966.88	$20.68	0.67%
38	CENTRALLY ACTING SKELETAL MUSCLE RELAXNT	CYCLOBENZAPRINE	1,269	$13,730.43	$10.82	0.65%
39	ANTIDEPRESSANTS, MISCELLANEOUS	MIRTAZAPINE	1,218	$17,179.92	$14.11	0.62%
40	ANTICONVULSANTS, MISCELLANEOUS	TOPIRAMATE	1,203	$17,753.42	$14.76	0.62%
41	OPIATE AGONISTS	TRAMADOL	1,183	$12,593.82	$10.65	0.61%
42	DIHYDROPYRIDINES	AMLODIPINE BESYLATE	1,170	$11,294.78	$9.65	0.60%
43	CORTICOSTEROIDS (SKIN, MUCOUS MEMBR)	TRIAMCINOLONE ACETON	1,166	$18,217.85	$15.62	0.60%
44	5-HT3 RECEPTOR ANTAGONISTS	ONDANSETRON ODT	1,115	$17,179.24	$15.41	0.57%
45	VITAMIN D	VITAMIN D	1,109	$11,238.74	$10.13	0.57%
46	AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN/CLAVULANAT	1,101	$20,821.34	$18.91	0.56%
47	OTHER NONSTEROIDAL ANTI-INFLAM. AGTS	IBUPROFEN	1,100	$13,451.66	$12.23	0.56%
48	LOOP DIURETICS	FUROSEMIDE	1,053	$9,859.05	$9.36	0.54%
49	BENZODIAZEPINES	LORAZEPAM	1,048	$11,809.61	$11.27	0.54%
50	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	GUANFACINE ER	1,033	$20,166.06	$19.52	0.53%
	TOTAL TOP 50 DRUGS		**99,288**	**$2,787,009.43**	**$28.07**	**51.21%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 10/1/2020 – 12/31/2020						
	AHFS Description	**Drug Label Name**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	AMPHETAMINES	VYVANSE	3,301	$950,982.32	$288.09	1.69%
2	CYSTIC FIBROSIS (CFTR) CORRECTORS	TRIKAFTA	31	$741,082.43	$23,905.88	0.02%
3	ATYPICAL ANTIPSYCHOTICS	INVEGA SUSTENNA	245	$559,089.24	$2,282.00	0.13%
4	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	HUMIRA PEN	74	$525,774.48	$7,105.06	0.04%
5	ATYPICAL ANTIPSYCHOTICS	LATUDA	433	$519,948.91	$1,200.81	0.22%
6	CYSTIC FIBROSIS (CFTR) CORRECTORS	ORKAMBI	23	$481,383.79	$20,929.73	0.01%
7	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	STELARA	23	$446,750.33	$19,423.93	0.01%
8	HEMOSTATICS	ADVATE	13	$388,889.07	$29,914.54	0.01%
9	ATYPICAL ANTIPSYCHOTICS	ARISTADA	143	$353,841.82	$2,474.42	0.07%
10	MUCOLYTIC AGENTS	PULMOZYME	76	$328,061.88	$4,316.60	0.04%
11	RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE	4,726	$311,679.98	$65.95	2.42%
12	ENZYMES	STRENSIQ	6	$308,923.20	$51,487.20	0.00%
13	ATYPICAL ANTIPSYCHOTICS	VRAYLAR	269	$284,389.52	$1,057.21	0.14%
14	ADRENALS	FLOVENT HFA	902	$211,313.41	$234.27	0.46%
15	LONG-ACTING INSULINS	LANTUS SOLOSTAR	544	$210,350.75	$386.67	0.28%
16	VESICULAR MONOAMINE TRANSPORT2 INHIBIT	INGREZZA	39	$209,145.14	$5,362.70	0.02%
17	OTHER MISCELLANEOUS THERAPEUTIC AGENTS	EVRYSDI	9	$201,088.74	$22,343.19	0.00%
18	SOMATOTROPIN AGONISTS	NORDITROPIN FLEXPRO	54	$194,860.19	$3,608.52	0.03%
19	ANTICONVULSANTS, MISCELLANEOUS	VIMPAT	214	$188,471.54	$880.71	0.11%
20	HEMOSTATICS	NOVOSEVEN RT	4	$186,442.00	$46,610.50	0.00%
21	HEMOSTATICS	HEMLIBRA	3	$180,371.52	$60,123.84	0.00%
22	ATYPICAL ANTIPSYCHOTICS	REXULTI	165	$166,558.49	$1,009.45	0.08%
23	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	COSENTYX SENSOREADY	27	$162,332.66	$6,012.32	0.01%
24	HEMOSTATICS	RECOMBINATE	3	$158,814.00	$52,938.00	0.00%
25	INCRETIN MIMETICS	TRULICITY	200	$156,081.73	$780.41	0.10%
26	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE HFA	3,708	$155,842.28	$42.03	1.90%
27	SODIUM-GLUC COTRANSPORT 2 (SGLT2) INHIB	JARDIANCE	294	$150,846.05	$513.08	0.15%
28	LONG-ACTING INSULINS	TRESIBA FLEXTOUCH	272	$149,675.59	$550.28	0.14%
29	GI DRUGS, MISCELLANEOUS	CHOLBAM	7	$149,323.50	$21,331.93	0.00%
30	ATYPICAL ANTIPSYCHOTICS	INVEGA TRINZA	20	$147,448.13	$7,372.41	0.01%
31	COMPOUNDS	-	1,417	$142,143.86	$100.31	0.73%
32	INCRETIN MIMETICS	OZEMPIC	173	$141,658.09	$818.83	0.09%
33	RIFAMYCIN ANTIBIOTICS	XIFAXAN	68	$139,928.39	$2,057.77	0.03%
34	RAPID-ACTING INSULINS	INSULIN ASPART FLEXPEN	401	$136,111.42	$339.43	0.21%
35	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	ENBREL SURECLICK	25	$135,666.45	$5,426.66	0.01%
36	LONG-ACTING INSULINS	LEVEMIR FLEXTOUCH	268	$128,442.51	$479.26	0.14%
37	DIGESTANTS	CREON	82	$126,359.97	$1,540.98	0.04%
38	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	DUPIXENT	42	$125,444.77	$2,986.78	0.02%
39	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	GENVOYA	39	$123,107.91	$3,156.61	0.02%
40	DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS	JANUVIA	268	$122,322.49	$456.43	0.14%
41	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	BIKTARVY	41	$122,293.70	$2,982.77	0.02%
42	GI DRUGS, MISCELLANEOUS	GATTEX	3	$121,381.62	$40,460.54	0.00%
43	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ADVAIR HFA	335	$121,346.50	$362.23	0.17%
44	ATYPICAL ANTIPSYCHOTICS	ABILIFY MAINTENA	57	$117,536.00	$2,062.04	0.03%
45	ANTICONVULSANTS, MISCELLANEOUS	BANZEL	61	$114,143.73	$1,871.21	0.03%
46	ANTITOXINS AND IMMUNE GLOBULINS	HIZENTRA	21	$112,309.40	$5,348.07	0.01%
47	ANTINEOPLASTIC AGENTS	IBRANCE	9	$112,132.23	$12,459.14	0.00%
48	ANTICONVULSANTS, MISCELLANEOUS	EPIDIOLEX	49	$110,662.01	$2,258.41	0.03%
49	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	TALTZ	15	$108,227.90	$7,215.19	0.01%
50	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	HUMIRA	17	$103,045.25	$6,061.49	0.01%
	TOTAL TOP 50 DRUGS		**19,219**	**$11,644,026.89**	**$605.86**	**9.91%**

Utilization

90 Day Fill update

Accumulation edit update

Atypical Antipsychotic Utilization in Children

June 2020 P&T: Review antipsychotic utilization in children
Atypical Antipsychotic Utilization in Children (17 years old and younger)

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

September 2020 P&T – reviewed utilization of 235 members, PAs, prescribers, etc

December 2020 P&T – reviewed utilization of 235 members utilizing 2 or more different antipsychotics
Utilization Date Range: 1/1/2020 to 10/31/2020

- 52 members taking 2 different drugs or different dosage forms
- 27 members taking 3 or more different drugs/dosage forms

March 2021 P&T – Review 79 members taking 2 or more antipsychotics
Utilization Date Range: 7/1/2020 to 1/31/2021

- 11 members taking 2 or more of same drug but different strengths
- Reviewed 19 members taking 2 or more different antipsychotics
    - 16 members taking 2 or more different drugs
        - 12 members taking 2 different drugs
        - 3 members taking 3 different drugs
        - 2 members taking 3 drugs of which 2 are same drugs but different strengths

Atypical Antipsychotic PA Criteria:

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

OR

2. Both of the following:
2.1. Patient has a diagnosis of depression **AND**
2.2. Patient has tried and failed 2 different antidepressants
AND

3. Children younger than 6 years of age must have a psychiatrist, developmental pediatrician, child/adolescent psychiatrist or pediatric neurologist involved in care
AND

4. For alternative dosage forms (e.g., rapid dissolve tablets, injectables, extended-release), one of the following criteria must be met:
4.1. The patient is unable to swallow **OR**
4.2. The patient failed a standard dosage form from this drug class in the last 30 days
AND

5. For members requesting more than 2 different antipsychotics, the following criteria must be met:
5.1. All antipsychotics involved in the therapeutic duplication are prescribed by or in consultation with a psychiatrist **AND**
5.2. History of at least 4 weeks of double agent therapy at an adequate dose **AND**
5.3. One of the following:
5.3.1. Must have diagnosis of psychoses **OR**
5.3.2. Must have a diagnosis of bipolar affective disorder, unspecified episodic mood disorder, or depressed mood disorder within the past 2 years (Depressed mood disorder applies to members taking aripiprazole, brexpiprazole, or quetiapine in conjunction with another antidepressant and olanzapine in conjunction with fluoxetine) **OR**
5.4. The medications involved in the therapeutic duplication are being cross-tapered and it is the first request for an authorization due to cross-tapering

ADHD Utilization

Time frame: 10/1/2020 – 12/31/2020

History of utilization reviews:

- March 2019 P&T meeting – reviewed utilization of all members on ADD/ADHD medications
- June 2019 P&T meeting – reviewed utilization of members aged 1-20 years old vs 21 years old & older
- September 2019 P&T meeting – reviewed utilization of members aged 26 years old & older
- December 2020 P&T meeting – reviewed utilization of members 21 years & older

State Comparison of all utilization (IHS excluded)

State Medicaid	# ADHD Claims	Plan Paid	PMPM	PUPM	PA Criteria
State A*	253,002	$30,708,197	$3.35	$96.06	PA for ≥ 21 years old
State B	19,374	$2,117,522	$1.91	$82.25	Vyvanse PA for adults & children
State C	62,001	$8,520,477	$4.42	$126.59	PA for < 6 years old, PA for ≥ 21 years old
State D**	62,920	$10,835,012	$5.23	$135.10	PA for all NP; PA for ≥ 21 years old
State E	834	$126,650	$0.07	$87.95	PA for < 6 years old for long & short acting
South Dakota	32,128	$3,527,119	$4.38	$101.30	

*PMPM may be under calculated

**PMPM may be over calculated

ADD/ADHD Drugs (21 years old and older only)

	3Q2020				4Q2020			
Class	Total Rx	Paid Amount	Paid/Rx	Utilizers	Total Rx	Paid Amount	Paid/Rx	Utilizers
Amphetamines	1,574	$206,686.60	$131.31	536	1,686	$210,736.90	$124.99	550
Respiratory & CNS Stimulants	474	$32,358.18	$68.27	148	420	$28,706.59	$68.35	148

Amphetamine

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Avg Quantity
Amphetamine-dextroamphetamine					
• Adderall tab	1	$0	$0	1	#60 per 30 days
• Adderall XR cap	12	$1,927.92	$160.66	5	#35 per 30 days
• amphet/dextroamephtamine cap ER	500	$21,227.02	$42.45	179	#38 per 29.4 days
• amphet/dextroamephtamine tab ER	563	$16,621.26	$29.52	205	#55 per 29.2 days
• Mydayis	13	$3,748.23	$288.32	4	#30 per 30 days
Dextroamphetamine sulfate					
• dextroamephtamine cap ER	6	$929.65	$154.94	2	#90 per 30 days
• dextroamephtamine tab	20	$1,260.92	$63.05	7	#136.35 per 29.6 days
Lisdexamfetamine dimesylate					
• Vyvanse cap	420	$165,021.90	$289.01	148	#129.84 per 29.76 (3 Rxs with 60 per 30 days)

Respiratory & CNS Stimulants

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Avg Quantity
Dexmethylphenidate					
• dexmethylphenidate tab	9	$217.29	$24.14	3	#50 per 30 days (2 Rxs with 120 per 30 days)
• dexmethylphenidate cap ER	28	$2,647.82	$94.57	10	#29 per 29 days
Methylphenidate hcl					
• Adhansia XR cap	2	$621.06	$78.80	1	#30 per 30 days
• methylphenidate cap ER	26	$2,048.73	$69.56	9	#31 per 29.9 days
• methylphenidate tab	117	$2747.00	$23.48	46	#59.86 per 28.85 days
• methylphenidate tab ER	238	$20,424.69	$85.82	89	#36.3 per 29.5 days (53 Rxs with 60 per 30 days)

Evrysdi

Time frame: 10/1/2020 – 1/31/2021

Month	Month	Total Rx	Paid Amount	Paid/Rx	Avg Qty/ Days Supply	Utilizers	Age Range
Evrysdi sol (risdiplam)*	October	1	$22,351.36	$22,351.36	#160/24 days	1	25
	November	3	$67,033.08	$22.344.36	#160/24 days	2	14, 25
	December	5	$111,704.30	$22,340.86	#160/24 days	3	14, 16, 25
	January	3	$67,022.58	$22,340.86	#160/24 days	3	14, 16, 26

*Hits High Dollar PA

South Dakota Department of Social Services

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EVERYSDI (risdiplam)

A. Indications – Spinal Muscular Atrophy
Indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

B. Criteria for Initial Authorization – Approval length 12 months
1. Diagnosis of spinal muscular atrophy (SMA) Type I, II, or III

2. Patient meets both of the following:
   i. The mutation or deletion of genes in chromosome 5q resulting in one of the following:
      a. Homozygous gene deletion or mutation (e.g., homozygous deletion of exon 7 at locus 5q13)
      or
      b. Compound heterozygous mutation (e.g., deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 [allele 2])
      AND
   ii. Patient has SMN2 copies of 3 or less.

3. Patient is at least 2 months of age at the initiation of treatment

4. Prescribed by or in consultation with a neurologist with expertise in the diagnosis and treatment of SMA

5. Patient is not dependent on invasive ventilation or tracheostomy

6. Patient is not dependent on use of non-invasive ventilation beyond use for naps and nighttime sleep

7. The following exam has been conducted to establish baseline motor ability*:
   - Hammersmith Functional Motor Scale Expanded (HFMSE)
8. Patient will not receive concomitant chronic survival motor neuron (SMN) modifying therapy for the treatment of SMA (e.g., Spinraza)

9. Patient meets one of the following criteria:
   i. Patient has not previously received gene replacement therapy for the treatment of SMA (e.g., Zolgensma)
   OR

ii. Both of the following:
    a. Patient has previously received gene therapy for the treatment of SMA (e.g., Zolgensma)
    b. Provider attests that there has been an inadequate response to gene therapy (e.g., sustained decrease in at least one motor test score over a period of 6 months) or worsening in clinical status since receiving gene therapy as demonstrated by a decline of minimally clinical important difference from highest score achieved on one of the following exams (based on member age and motor ability)
        - HINE-2: Decline of at least 2 points on kicking and 1 point on any other milestone (excluding voluntary grasp)
        - HFMSE: Decline of at least 3 points
        - CHOP INTEND: Decline of at least 4 points

10. Member's daily dose will not exceed the following:
    iii. Members 2 months to less than 2 years of age: 0.2mg/kg
    iv. Members 2 years of age and older weighing less than 20 kg: 0.25mg/kg
    v. Members 2 years of age and older weighing 20 kg or more: 5 mg

C. Reauthorization – Approval length 12 months

1. Documentation of positive clinical response to therapy (e.g., chart notes, laboratory values) from pretreatment baseline status as demonstrated by the most recent results (less than 1 month prior to reauthorization request) from the following exam:
    i. One of the following HFMSE milestones:
        a. Improvement or maintenance of a previous improvement of at least a 3 point increase in score from pretreatment baseline
        b. Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so (e.g., sit unassisted, stand, walk)

2. Patient continues to not be dependent on invasive ventilation or tracheostomy

3. Patient continues to not be dependent on the use of non-invasive ventilation beyond use for naps and nighttime sleep

4. Prescribed by or in consultation with a neurologist with expertise in the diagnosis and treatment of SMA

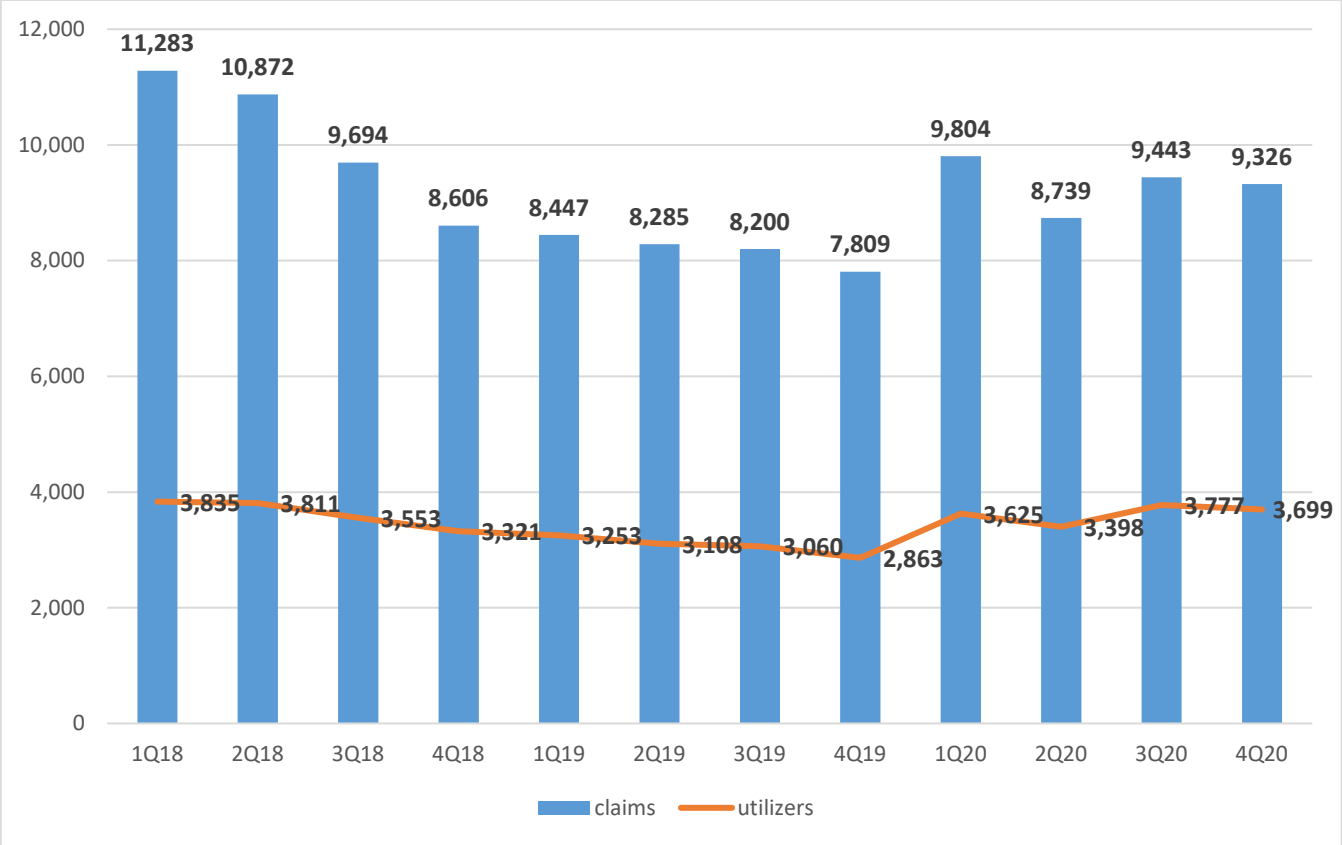
5. Patient is not to receive concomitant chronic survival motor neuron (SMN) modifying therapy for the treatment of SMA (e.g., Spinraza)

6. One of the following
    i. Patient has not previously received gene replacement therapy for the treatment of SMA (e.g., Zolgensma)
    OR
    ii. Both of the following:
        a. Patient has previously received gene therapy for the treatment of SMA (e.g., Zolgensma)

b. Submission of medical records (e.g., chart notes) documenting that there has been an inadequate response to gene therapy (e.g., sustained decrease in at least one motor test score over a period of 6 months)

7. Member's daily dose will not exceed the following:
    i. Members 2 months to less than 2 years of age: 0.2mg/kg
    ii. Members 2 years of age and older weighing less than 20 kg: 0.25mg/kg
    iii. Members 2 years of age and older weighing 20 kg or more: 5 mg

Opioid Summary



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

Total Eligibility

Quarter	Avg eligible members	Total utilizing members of all drugs	% utilizing members of all drugs
1Q2020	123,552	27,893	22.6%
2Q2020	126,777	20,747	16.4%
3Q2020	132,373	23,388	17.7%
4Q2020	136,262	21,785	15.9%

Opioid Utilization Snapshot

SDM 4Q2020

Sep 20 to Dec 20

Opioid Claims **9,326**

3.2% prescription claims filled for an opioid

0.5% lower than Medicaid FFS benchmark

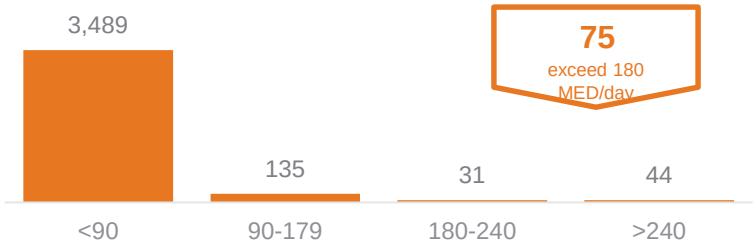
Utilizers **3,699**

31.3% are high utilizers [1]

-19.5% lower than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

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



Shoppers: Poly Pharmacy

37 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

232 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

3Q2020

Jun 20 to Sep 20

Opioid Claims **9,443**

3.3% prescription claims filled for an opioid

0.4% lower than Medicaid FFS benchmark

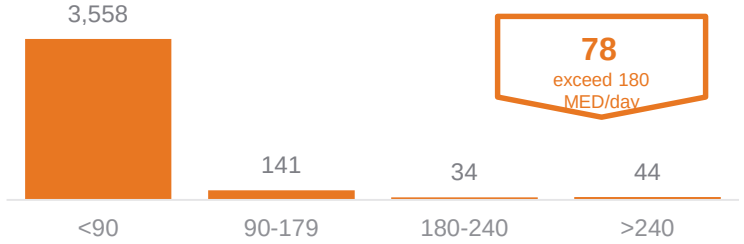
Utilizers **3,777**

31.1% are high utilizers [1]

-19.4% lower than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

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



Shoppers: Poly Pharmacy

50 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

254 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 4Q2020
Opportunities date range: Sep - Dec 2020
Benchmark: MEDICAID FEE FOR SERVICE

Utilizers: 3,699

3.2% of all Rx claims are filled for an Opioid

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

- Opioid prescriptions account for 3.2% of all prescriptions this period, which is 0.5% lower than the benchmark
- 1,159 high opioid utilizers were identified this period, which is -19.5% lower than the benchmark

Opioid claims

PERCENT OPIOID CLAIMS
3.2%

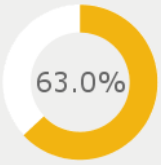
Opioid utilizers

HIGH UTILIZERS
31.3%
1,159 high utilizers

-19.5% under benchmark

High utilizers – 3+ opioid scripts within 120 days

Claim breakdown



short acting opioids

63.0% of all opioid Rxs were filled for short acting opioids. **1,053** Rxs were for medication assisted therapy (MAT) and **47** 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 reversal w/naloxone
MME – relative potency of an opioid to a morphine dose

Utilizers by cumulative MED

75 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	3,489	135	31	44

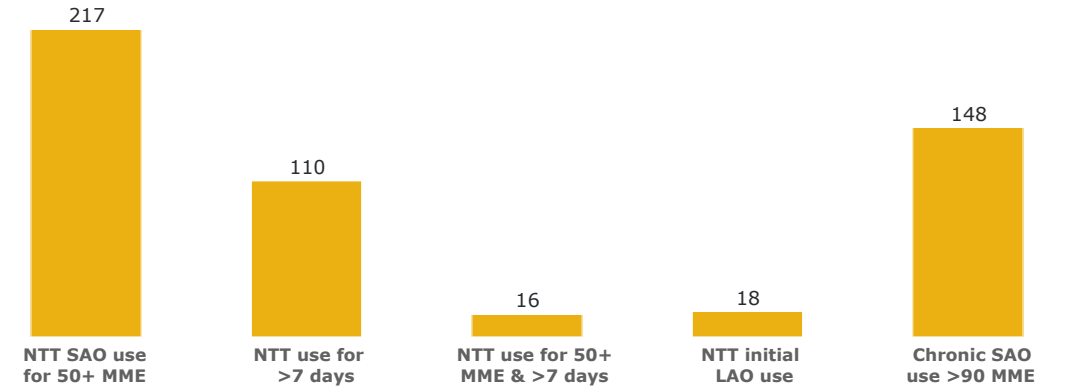
MED – Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period

Opioid Opportunity Assessment

SDM 4Q2020
Opportunities date range: Sep - Dec 2020
Benchmark: MEDICAID FEE FOR SERVICE

Utilizers

new to therapy and chronic use



6.0% of opioid Rxs	4.5% of opioid Rxs	1.0% of opioid Rxs	0.7% of opioid Rxs	12.3% of opioid Rxs

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

37 opioid utilizing members use 3 or more pharmacies and 232 opioid utilizing members use 3 or more prescribers.

NNT - 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

Opioid utilizers with potentially contraindicated medication use

SKELETAL MUSCLE RELAXANTS	BENZODIAZEPINES	ANTICONVULSANTS	MEDICATION ASSISTED THERAPY	PRENATAL
686	537	736	N/A	99

Anticonvulsants –view definition

PA Reviews & Utilization

PA Drug Class Summary 4Q2020

Drug Class	Approved	Denied	Total	Approval Rate
ANTIHISTAMINES*	23	4	27	85.19%
ANALGESICS - ANTI-INFLAMMATORY*	39	14	53	73.58%
ANTIDEPRESSANTS*	154	35	189	81.48%

Antihistamines PA Approval Review

Non-Sedating Antihistamine Criteria:

1. Patient is younger than 13 years of age OR
2. Has documented difficulty in swallowing diagnosis

Drug Name	Total Manual Reviews	Approvals	Denials
cetirizine ODT 5mg or 10mg – qll 1 per day	6	ST – 1 QTY – 2 (5mg – qll 2 per day)	QTY – 3 (10mg – qll 2 per day)
desloratadine ODT 5mg – qll 1 per day	1		ST – 1
loratadine chew or reditab 10mg – qll 1 per day	1	QTY – 1 (10mg – qll 4 per day)	

19 PA reviewed via electronic
8 reviewed manually

Analgesic/Anti-inflammatory PA Approval Review

Vimovo/Duexis on PA

Drug Name	Total Manual Reviews	Approvals	Denials
Duexis	1		PA – #1
diclofenac patch • 2 patches per day	1		QTY • #1 – 3 per day
ketorolac tab • max days supply of 5	1		QTY • #1 – 90 per days
meloxicam tab • 7.5mg – 1 per day • 15mg – 2 per day	3		QTY • #3 – 7.5mg, 2 per day

Red font denotes drug is on Prior Authorization

Antidepressants PA Approval Review

Drug Name	Total Manual Reviews	Approvals	Denials
Effexor XR	1	P – #1	
venlafaxine • 25mg – qll 3 per day • 37.5mg – qll 3 per day • 50mg – qll 3 per day • 75mg – qll 3 per day • 100mg – qll 3 per day	1	QTY – #1	
venlafaxine ER • 37.5mg – qll 1 per day • 75mg – qll 1 per day • 150mg – qll 2 per day	5	QTY – #4 • #1 – 75mg, 3 per day only for 1 month • #2 – 37.5mg, 2 per day • #2 – 37.5mg, 3 per day	QTY • #1 – 75mg, 2 per day
desvenlafaxine ER • 50mg – qll 1 per day • 100mg – qll 1 per day	4	ST – #4	
duloxetine • 20mg – qll 2 per day • 30mg – qll 2 per day • 60mg – qll 1 per day	34	QTY – #28 • #5 – 30mg, 3 per day • #23 – 60mg, 2 per day	QTY – #6 • #2 – 30mg, 3 per day • #1 – 30mg, 4 per day • #3 – 60mg, 2 per day
escitalopram • 5mg – qll 1 per day • 10mg – qll 1.5 per day • 20mg – qll 1.5 per day • 5mg/5ml – 20mg per day	10	QTY – #2 • #1 – 5mg, 1.5 per day • #1 – 20mg, 2 per day PA – #1 solution approved	QTY – #7 • #2 – 5mg, 1.5 per day • #3 – 20mg, 2 per day • #1 – 20mg, 4 per day • #1 – 5mg/ml – 40mg per day
Prozac	2	PA – #1	PA – #1
fluoxetine • 10mg – qll 2 per day • 20mg – qll 8 per day • 40mg – qll 1 per day • 60mg – qll 1 per day	18	QTY – #13 • #10 – 40mg, 2 per day PA – #2, solution	QTY – #5 • #2 – 10mg, 3 per day • #1 – 20mg, 2 per day (no rejected claim for 20mg) • #2 – 40mg, 2 per day
fluvoxamine • 50mg – qll 2 per day • 100mg – qll 3 per day • 100mg XR – qll 1 per day	1	QTY – #1 #1 – 50mg, 3 per day	
olanzapine/fluoxetine • qll 1 per day	1	PA – #1	
paroxetine ER • 12.5mg – qll 1 per day • 25mg – qll 2 per day • 37.5mg – qll 1 per day	2	PA – #1	PA – #1
paroxetine • 10 mg – qll 1 per day • 20mg – qll 1 per day • 30mg – qll 1 per day • 40mg – qll 2 per day	1	QTY – #1 #1 – 10mg, 1.5 per day	
sertraline	12	QTY – #7 • #2 - 25mg, 1.5 per day	QTY – #3 • #1 – 25mg, 1.5 per day

• 25mg – qll 1 per day • 50mg – qll 1.5 per day		• #2 – 25mg, 3 per day • #2 – 50mg, 2 per day • #1 – 50mg, 3 per day PA – #1	• #1 – 25mg, 2 per day • #1 – 50mg, 2 per day PA – #1 solution
bupropion ER • 150mg 12HR – qll 2/day • 150mg 24HR – qll 1/day	1		QTY • #1 – 150mg, 3 per day
bupropion XL • 150mg 12HR – qll 2/day • 150mg 24HR – qll 1/day	5	QTY – #2 #1 – 150mg, 2 per day #1 – 300mg, 2 per day	QTY – #3 #3 – 150mg, 2 per day
Wellbutrin XL	2	PA – #2	
mirtazapine • 15mg – qll, 1 per day • 30mg – qll, 1 per day • 45mg – qll, 1 per day	3	QTY – #1 #1 – 15mg, 1.5 per day	QTY – #2 #1 – 30mg, 2 per day #1 – 45mg, 1.5 per day

Red font denotes drug is on Prior Authorization

Time frame: 10/1/2020 to 12/31/2020

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Avg Quantity
Desvenlafax ER tab	3	$376.80	$125.60	1	#30 per 30 days
Khedezla (desvenlfaxine)	0				
desvenlafax succinate ER tab	211	$6,178.10	$29.28	80	#28.5 per 28.4 days
Pristiq	6	$2,437.92	$406.32	2	#30 per 30 days
venlafaxine tab	97	$1,549.29	$15.97	44	#49.5 per 30.9 days
venlafaxine ER tab	48	$7,448.29	$155.17	23	#32.5 per 32.5
venlafaxine ER cap	1,024	$15,819.27	$15.45	375	#34.9 per 30.5 days
Effexor XR cap	10	$10,087.86	$1,008.79	3	#66 per 33 days
duloxetine	1,629	$26,594.68	$16.33	608	#37.2 per 30.9 days
Cymbalta	3	$1,496.95	$498.98	1	#60 per 30 days
Drizalma DR (duloxetine)	0				
Fetzima (levomilnacipran)	17	$6,832.54	$401.91	6	#30 per 30 days
citalopram tab	1,056	$9,312.03	$8.88	466	#32.2 per 31 days
escitalopram tab	2,632	$32,179.93	$12.23	1,162	#31.7 per 30.6 days
Lexapro tab	10	$3,981.58	$398.16	4	#33 per 33 days
Lexapro solution	0				
fluoxetine cap	4,720	$63,686.78	$13.49	1,910	#36.5 per 30.5 days
fluoxetine cap 90 mg	21	$2,651.48	$126.26	8	#4 per 28 days
fluoxetine solution	112	$6,882.19	$61.45	49	#125.5 per 28.5 days
fluoxetine tab	453	$11,384.88	$25.13	236	#35 per 32 days
fluoxetine PMDD tab	0				
fluvoxamine	51	$1,540.85	$30.21	20	#43 per 29.9 days
paroxetine	353	$3,831.63	$10.85	138	#31.6 per 31.2 days
paroxetine ER	21	$1,009.99	$48.09	9	#30 per 30 days
paroxetine mesylate	1	$141.39	$141.39	1	#30 per 30 days
paroxetine suspension	0				
sertraline tab	4,215	$49,273.58	$11.69	1,842	#35.4 per 30.9 days
sertraline conc	42	$1,853.01	$44.12	17	#82 per 27.4 days
olanzapine-fluoxetine	9	$3,811.95	$423.55	5	#33 per 33 days

bupropion tab	110	$2,140.23	$19.46	51	#58 per 29.6 days
bupropion tab SR	392	$6,404.13	$16.34	173	#52.2 per 31 days
bupropion tab XL	1,614	$33,620.82	$20.83	657	#31.3 per 31 days
Wellbutrin tab XL 300mg	5	$9,333.56	$1,866.71	2	#30 per 30 days
Aplenzin	0				
Forfivo XL	0				
mirtazapine	1,218	$17,179.92	$14.11	479	#27 per 28.5 days
mirtazapine ODT	17	$455.21	$26.78	7	#29 per 30 days
mirtazapine solution	0				
Ensam (selegiline)	0				
Oleptro (trazodone)	0				
Viibryd (vilazodone)	174	$43,936.72	$252.17	64	#27.3 per 26.2 days
Trintellix (vortioxetine)	140	$50,822.31	$363.02	46	28 per 26.9 days

Red font denotes drug is on Prior Authorization

Therapeutic Class Overview
Attention-Deficit/Hyperactivity Disorder (ADHD) Agents

INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder among children, with an estimated prevalence of up to 10% of school-age children in the United States (U.S.). It is more common in boys than girls and frequently persists into adulthood (*Feldman et al 2014*). Epidemiologic studies of adult ADHD have estimated the current prevalence to be 4.4% in the U.S. (*Bukstein 2018*).
  - In children, this chronic disorder is characterized by symptoms of hyperactivity, impulsivity, and/or inattention. These symptoms affect cognitive, academic, behavioral, emotional, and social functioning (*Krull 2019a*). Common comorbid psychiatric disorders include oppositional defiant disorder, conduct disorder, depression, anxiety disorder, and learning disabilities (*Krull 2019b*). Approximately 20% of children with ADHD develop chronic tic disorders and approximately 50% of children with chronic tics or Tourette syndrome have comorbid ADHD (*Krull 2020b*).
  - ADHD in adults is characterized by symptoms of inattention, impulsivity, and restlessness. Impairment in executive function and emotional dysregulation frequently occur. Common comorbid psychiatric disorders include mood and anxiety disorders, substance use disorder, and intermittent explosive disorder (*Bukstein 2018*).
- For children < 17 years of age, the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) diagnosis of ADHD requires ≥ 6 symptoms of hyperactivity and impulsivity or ≥ 6 symptoms of inattention. For adolescents ≥ 17 years of age and adults, ≥ 5 symptoms of hyperactivity and impulsivity or ≥ 5 symptoms of inattention are required.
  - The symptoms of hyperactivity/impulsivity or inattention must occur often; be present in more than 1 setting; persist for at least 6 months; be present before the age of 12 years; impair function in academic, social, or occupational activities; and be excessive for the developmental level of the child.
  - Other physical, situational, or mental health conditions that could account for the symptoms must be excluded.
- Treatment of ADHD may involve behavioral/psychologic interventions, medication, and/or educational interventions, alone or in combination (*Krull 2019c*).
  - For preschool children (age 4 through 5 years), behavioral therapy is considered the first-line treatment; when medication is necessary, methylphenidate is generally recommended.
  - For children and adolescents with moderate to severe ADHD, medication and behavioral therapy are recommended. In general, stimulants are the first-line agents; however, non-stimulant medications may be more appropriate for certain children.
    - About 30% of patients do not respond to or may not tolerate the initial stimulant treatment. At least one-half of children who do not respond to one type of stimulant will respond to the other. If there is still no improvement, consideration should be given to switching to or adding a non-stimulant ADHD medication (*Pharmacist's Letter 2015, Krull 2020a*).
- Multiple agents are currently approved by the Food and Drug Administration (FDA) for the treatment of ADHD. They include central nervous system (CNS) stimulants (amphetamine- and methylphenidate-based formulations), as well as non-stimulants: a selective norepinephrine reuptake inhibitor (SNRI), atomoxetine, and 2 alpha$_2$-adrenergic agonists, clonidine extended-release (ER) and guanfacine ER.
  - Due to the potential for abuse, the stimulant agents are classified as Schedule II controlled substances.
  - Several stimulants are also approved for the treatment of narcolepsy and exogenous obesity; the use of stimulants for the treatment of obesity will not be covered in this review. Lisdexamfetamine dimesylate is the only FDA-approved drug for the treatment of binge eating disorder (BED).
- Medispan Classes: ADHD Agents – Amphetamines, Dexmethylphenidate, Methylphenidate, Selective Alpha Adrenergic Agonists, Selective Norepinephrine Reuptake Inhibitor

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Stimulants	
Evekeo (amphetamine sulfate)	✔
Evekeo ODT (amphetamine sulfate)	-
Adderall (mixed amphetamine salts)	✔
Focalin (dexmethylphenidate hydrochloride [HCl])	✔
ProCentra (dextroamphetamine sulfate)	✔
Zenzedi (dextroamphetamine sulfate)	✔
Desoxyn (methamphetamine HCl)	✔
methylphenidate HCl chewable tablets	✔
Methylin Oral Solution (methylphenidate HCl)	✔
Ritalin (methylphenidate HCl)	✔
Dexedrine Spansule (dextroamphetamine sulfate sustained-release)	✔
Adzenys ER (amphetamine ER)	✔
Adzenys XR-ODT (amphetamine ER)	-
Dyanavel XR (amphetamine ER)	-
Adderall XR (mixed amphetamine salts ER)	✔
Mydayis (mixed amphetamine salts ER)	-
Focalin XR (dexmethylphenidate HCl ER)	✔
Vyvanse (lisdexamfetamine dimesylate)	-
Adhansia XR (methylphenidate HCl ER)	-
Aptensio XR (methylphenidate HCl ER)	✔
Concerta (methylphenidate HCl ER)	✔
Cotempla XR-ODT (methylphenidate ER)	-
Jornay PM (methylphenidate HCl ER)	-
methylphenidate HCl ER (CD)	✔
methylphenidate HCl ER	✔
QuilliChew ER (methylphenidate HCl ER)	-
Quillivant XR (methylphenidate HCl ER)	-
Relexxii (methylphenidate HCl ER)	✔
Ritalin LA (methylphenidate HCl ER)	✔
Daytrana (methylphenidate transdermal system)	-
Non-stimulants	
Strattera (atomoxetine HCl)	✔
Kapvay (clonidine HCl ER)	✔
Intuniv (guanfacine HCl ER)	✔

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Evekeo (amphetamine sulfate)	Evekeo ODT (amphetamine sulfate)	Adzenys ER, Adzenys XR-ODT, Dyanavel XR (amphetamine ER)	Adderall (mixed amphetamine salts)	Adderall XR, Mydayis (mixed amphetamine salts ER)	Strattera (atomoxetine HCl)	Kapvay (clonidine HCl ER)	Focalin (dexmethylphenidate IR); Focalin XR (dexmethylphenidate ER)	ProCentra, Zenzedi (dextroamphetamine sulfate IR); Dexedrine Spansule (dextroamphetamine sulfate SR)	Intuniv (guanfacine HCl ER)	Vyvanse (lisdexamfetamine dimesylate)	Desoxyn (methamphetamine HCl)	Methylin Oral Solution, Ritalin (methylphenidate HCl IR); methylphenidate HCl chewable tablets; methylphenidate ER tablets	Adhansia XR, Aptensio XR, Concerta , Cotempla XR-ODT, Daytrana, methylphenidate ER (CD), Jornay PM, QuilliChew ER, Quillivant XR, Relexxii, Ritalin LA (methylphenidate ER)
ADHD*		✓	✓	✓	✓	✓		✓			✓			✓
ADHD, as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, and social) for a stabilizing effect in pediatric patients with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal electroencephalogram (EEG) may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted.*	✓								✓			✓	✓	
Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications							✓			✓				
Narcolepsy**	✓			✓					✓				✓	
Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction for patients refractory to alternative therapy	✓													

(eg, repeated diets, group programs, and other drugs).†														
Moderate to severe BED in adults											✓			

(*Prescribing Information*: *Adderall 2020*, *Adderall XR 2020*, *Adhansia XR 2019*, *Adzenys ER 2017*, *Adzenys XR-ODT 2018*, *Aptensio XR 2019*, *Concerta 2017*, *Cotempla XR-ODT 2017*, *Daytrana 2019, Desoxyn 2019, Dexedrine Spansule 2019*, *Dyanavel XR 2019*, *Evekeo 2019*, *Evekeo ODT 2019*, *Focalin 2019*, *Focalin XR 2019*, *Intuniv 2019, Jornay PM 2019, Kapvay 2020, Mydayis 2019, Methylin Oral Solution 2017, methylphenidate chewable tablets 2019, methylphenidate ER 2019, methylphenidate ER (CD) 2018, ProCentra 2017*, *QuilliChew ER 2018*, *Quillivant XR 2018*, *Relexxii 2019,* *Ritalin 2019*, *Ritalin LA 2019*, *Strattera 2020*, *Vyvanse 2018, Zenzedi 2019*)

* Adderall, Evekeo, ProCentra, and Zenzedi are approved for use in children 3 years of age and older. Daytrana, Desoxyn, Dexedrine Spansule, Intuniv, and Kapvay are approved for use in children 6 years of age and older. Adderall XR, Adhansia XR, Adzenys ER, Adzenys XR-ODT, Aptensio XR, Dyanavel XR, Focalin, Focalin XR, Jornay PM, methylphenidate ER (CD), methylphenidate ER, Methylin Oral Solution, methylphenidate chewable tablets, QuilliChew ER, Quillivant XR, Ritalin, Strattera, and Vyvanse are approved for use in patients 6 years of age and older. Cotempla XR-ODT and Evekeo ODT are approved for use in pediatric patients 6 to 17 years of age. Ritalin LA is approved for use in pediatric patients 6 to 12 years of age. Concerta and Relexxii are approved for use in children 6 years of age and older, adolescents, and adults up to 65 years of age. Mydayis is approved for use in patients 13 years of age and older.
**These drugs are approved for use in patients 6 years of age and older.
†These drugs are not recommended for use in children under 12 years of age for treatment of exogenous obesity. The limited usefulness of these products should be weighed against possible risks inherent in use of the drugs.

- Limitation of use:
  - Lisdexamfetamine: Lisdexamfetamine is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular (CV) adverse events (AEs). The safety and effectiveness of this drug for the treatment of obesity have not been established.
  - Mydayis: Pediatric patients 12 years and younger experienced higher plasma exposure than patients 13 years and older at the same dose and experienced higher rates of AEs, mainly insomnia and decreased appetite.

- 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

- Randomized trials, systematic reviews, and meta-analyses have found stimulants, atomoxetine, and alpha$_2$-adrenergic agonists to be more efficacious than placebo in reducing the core symptoms of ADHD in children and adolescents.
  - Adzenys ER, an amphetamine ER oral suspension, was approved under the 505(b)(2) regulatory pathway and was found to be bioequivalent to Adderall XR. No clinical efficacy studies were conducted.
  - Evekeo (amphetamine sulfate) was approved based on a randomized, double-blind (DB), multicenter (MC), placebo-controlled (PC) laboratory classroom study that was conducted in 107 children between the ages of 6 and 12 years (*Childress et al 2015*). The study found Evekeo to be associated with significant improvements in the average Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) combined score compared to placebo (least squares [LS] mean difference -7.9; 95% CI, -10.1 to -5.6; $p < 0.0001$).
    - Evekeo ODT, an orally disintegrating amphetamine tablet, was approved under the 505(b)(2) regulatory pathway. The safety and effectiveness of Evekeo ODT for the treatment of ADHD was established based on an adequate and well-controlled study of Evekeo (*Childress et al 2015*).
  - Cotempla XR-ODT, a new methylphenidate ER orally disintegrating tablet formulation, was approved based on a randomized, DB, MC, PC laboratory classroom study (*Childress et al 2017*) (N = 87) which found that the average SKAMP-combined score was significantly better for Cotempla XR-ODT than for placebo (LS mean 14.3 [95% CI, 12.2 to 16.4] vs 25.3 [9% CI, 23.0 to 27.6], respectively, $p < 0.0001$).
  - Adhansia XR, a recently approved methylphenidate ER capsule, was approved via the 505(b)(2) regulatory pathway, and its efficacy was supported by 4 clinical studies in patients with ADHD including 2 studies conducted in adults, 1

study in adolescents 12 to 17 years of age, and 1 study in pediatric patients 6 to 12 years of age (*Adhansia XR FDA Clinical Review 2019):*

- One randomized, DB, MC, PC 4-week study conducted in 368 adult patients with ADHD evaluated the safety and efficacy of 4 doses of Adhansia XR (25 mg, 45 mg, 70 mg, and 100 mg) compared to placebo. The primary endpoint, change in the ADHD-Rating Scale (ADHD-RS)-5 total score from baseline to Week 5, was significantly improved compared to placebo in the Adhansia XR 45 mg group (LS mean difference, -6.9; 95% CI, -11.5 to -2.2; p = 0.0013), 100 mg group (LS mean difference, -8.1; 95% CI, -12.9 to -3.2; p = 0.0002), and when combining all dosage groups compared to placebo (LS mean difference, -4.7; 95% CI, -7.7 to -1.6; p = 0.0026). No significant difference was seen in the 25 mg or 70 mg groups compared to placebo.
- A second randomized, DB, crossover, PC study was conducted in 45 adults in an adult workplace environment (*Adhansia XR FDA Clinical Review 2019, Wigal et al 2020*). The study aimed to assess efficacy parameters for Adhansia XR vs placebo over 16 hours post-dose. Patients were titrated to an optimal dose of Adhansia XR (either 25, 35, 45, 55, 70, 85, or 100 mg) during an open-label (OL) treatment period between 2 and 7 weeks, then entered into a 1-week PC, DB treatment phase prior to the adult workplace environment session, followed by a 7-day washout period between crossover periods, then another 1-week treatment phase followed by another adult workplace environment session. The primary endpoint was the average Permanent Product Measure of Performance (PERMP) score for various time points up to 16 hours post-dose. When combining data from all time points, patients treated with Adhansia XR had significant improvements in the PERMP score compared to placebo (LS mean difference, 13.05; 95% CI, 3.88 to 22.23; p = 0.0064).
  A 4-week randomized, DB, PC trial assessed efficacy of Adhansia XR in 354 adolescent patients 12 to 17 years of age (*Adhansia XR FDA Clinical Review 2019)*. The study compared Adhansia XR 25, 45, 70, and 85 mg to placebo and found significant improvements in the ADHD-5-RS score from baseline to Week 5 in adolescents treated with Adhansia XR 45 mg (LS mean difference, -5.4; 95% CI, -9.2 to -1.6; p = 0.0052), 70 mg (LS mean difference, -5.2; 95% CI, -9.0 to -1.4; p = 0.0069), and when combining all dosage groups compared to placebo (LS mean difference, -4.3; 95% CI, -7.3 to -1.3; p = 0.0049). Adolescents treated with Adhansia XR 25 or 85 mg did not achieve significant improvements in the ADHD-5-RS score compared to placebo.
- A fourth study, which included a 6-week OL dose optimization period (majority of patients received between 45 and 55 mg of Adhansia XR) followed by a 1- week DB PC study, was conducted to assess the efficacy of Adhansia XR in 147 children 6 to 12 years of age in an analog classroom setting. The primary endpoint, average SKAMP-C score (taken at various time points up to 13 hours post-dose), was significantly improved in children treated with Adhansia XR compared to placebo (LS mean difference, -8.6; 95% CI, -10.6 to -6.6).

- Jornay PM, an ER methylphenidate capsule formulation, was approved based on the results of 2 clinical studies conducted in patients 6 to 12 years of age with ADHD:
  - The first study was a 6-week OL dose-optimization study, followed by a 1-week DB, PC withdrawal phase where patients were randomized to continue treatment with Jornay PM or switch to placebo (*Jornay PM Prescribing Information 2019*). The study, which was conducted in an analog classroom setting and included 117 children aged 6 to 12 years, found that Jornay PM was associated with a significant reduction in the SKAMP symptom score over a 12-hour period (LS mean difference -5.9; 95% CI, -9.1 to -2.7).
  - A randomized, DB, MC, PC, parallel group, forced-dose titration trial was conducted over 3 weeks in 161 children 6 to 12 years of age with ADHD (*Pliszka et al 2017*). The study found that 40 to 80 mg/day of Jornay PM achieved significant improvements vs placebo in ADHD symptoms (LS mean ADHD rating scale-IV 24.1 vs 31.2; p = 0.002) at 3 weeks. Significant improvements were also seen vs placebo in key secondary outcomes including at-home early morning and late afternoon/evening functional impairment at 3 weeks. The most commonly reported treatment-emergent AEs were insomnia and decreased appetite.
- Mydayis, a mixed amphetamine salts product, was approved for the treatment of ADHD based on the results of 5 MC, DB, PC, randomized controlled trials (RCTs): 3 in adults and 2 in pediatric patients 13 to 17 years of age. The studies found that Mydayis demonstrated a statistically significant treatment effect compared with placebo on various ADHD outcomes measures (eg, ADHD-RS score, PERMP score) (*Mydayis Prescribing Information 2019, Weisler et al 2017, Wigal et al 2018a, Wigal et al 2018b, Wigal et al 2019*) (see results below in Table 3 below). An additional 6-week, randomized, placebo-controlled, double-blind, forced dose titration trial in 411 adults with ADHD similarly found that Mydayis significantly improved ADHD-RS-IV scores compared to placebo (LS mean treatment difference for all Mydayis doses combined vs placebo, -10.6; 95% CI, -13.2 to -8.0; p < 0.0001) (*Frick et al 2020*).

Table 3. Summary of Primary Efficacy Results for Mydayis

Study Number (Age range)	Primary Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline	Placebo-subtracted Difference (95% CI)
Adult Studies					
Study 1 (18 to 55 years)	ADHD-RS	Mydayis 12.5 mg/day§ Mydayis 37.5 mg/day§ Placebo	39.8 (6.38) 39.9 (7.07) 40.5 (6.52)	-18.5 -23.8 -10.4	-8.1 (-11.7 to -4.4) -13.4 (-17.1 to -9.7)
Study 2 (18 to 55 years)	Average PERMP	Mydayis 50 mg/day§ Placebo	239.2 (75.6)† 249.6 (76.7)†	293.23* 274.85*	18.38 (11.28 to 25.47)
Study 3 (18 to 55 years)	Average PERMP	Mydayis 25 mg/day§ Placebo	217.5 (59.6)† 226.9 (61.7)†	267.96* 248.67*	19.29 (10.95 to 27.63)
Pediatric Studies					
Study 4 (13 to 17 years)‡	ADHD-RS-IV	Mydayis 12.5 to 25 mg/day§ Placebo	36.7 (6.15) 38.3 (6.67)	-20.3 -11.6	-8.7 (-12.6 to -4.8)
Study 5 (13 to 17 years)	Average PERMP	Mydayis 25 mg/day§ Placebo	214.5 (87.8)† 228.7 (101)†	272.67* 231.41*	41.26 (32.24 to 50.29)

SD= standard deviation; LS = least squares; CI = confidence interval
†Pre-dose PERMP total score
*LS mean for PERMP is post-dose average score over all sessions of the treatment day, rather than change from baseline
‡Results are for a subgroup of study 4 and not the total population
§Doses statistically significant for placebo

- A systematic (Cochrane) review of 185 RCTs (*Storebø et al 2015*) (N = 12,245) in children and adolescents with ADHD found that methylphenidate may improve teacher-rated ADHD symptoms, teacher-reported general behavior, and parent-reported quality of life (QOL) vs placebo. However, the evidence was of low quality.
- An RCT called the Preschool ADHD Treatment Study (PATS) (*Greenhill et al 2006*) evaluated the efficacy of methylphenidate immediate-release (IR) in 303 preschool children with ADHD and found that it demonstrated significant reductions on ADHD symptom scales; however, the effect sizes (0.4 to 0.8) were smaller than those generally reported for school-age children.
- A systematic (Cochrane) review of 23 PC, RCTs (*Punja et al 2016*) (N = 2675) found that amphetamines were effective at improving the core symptoms of ADHD, but they were also associated with a higher risk of AEs compared to placebo. There was no evidence that one kind of amphetamine was better than another and there was no difference between short-acting and long-acting formulations.
- A meta-analysis of 25 DB, PC, RCTs (*Schwartz et al 2014*) (N = 3928) in children and adolescents with ADHD found atomoxetine to be superior to placebo for overall ADHD symptoms, with a medium effect size (-0.64).
- A meta-analysis of 12 RCTs (*Hirota et al 2014*) (N = 2276) in pediatric patients with ADHD found that alpha$_2$-adrenergic agonists were significantly superior to placebo for overall ADHD symptoms both as monotherapy and, to a lesser extent, as augmentation therapy to stimulants.
  - Meta-analytic results failed to demonstrate a significant difference in efficacy between alpha$_2$-adrenergic agonists. In sub-analyses of individual formulations, the ER formulations separated robustly from placebo whereas the IR formulations did not separate from placebo.
- A systematic review of 16 RCTs and 1 meta-analysis (*Chan et al 2016*) (N = 2668) found evidence supporting the use of methylphenidate ER and amphetamine ER formulations, atomoxetine, and guanfacine ER for the treatment of ADHD in adolescents. For the primary outcome measure of mean change in ADHD-RS total symptom score, both stimulant and non-stimulant medications led to clinically significant reductions of 14.93 to 24.60 points.

- For the treatment of ADHD in children and adolescents, stimulants typically have a slightly larger treatment effect size (standardized mean difference [SMD]) than non-stimulants (approximately 1.0 vs approximately 0.7 for both atomoxetine and alpha$_2$-adrenergic agonists). However, there is insufficient evidence to definitively conclude that one stimulant is more efficacious than another (*Krull 2020a*, *AAP 2019).*

- An Agency for Healthcare Research and Quality (AHRQ) review of 78 studies (*Jadad et al 1999*) evaluating the efficacy of various interventions for the treatment of ADHD in children and adults found few, if any, differences between methylphenidate and dextroamphetamine.
- A meta-analysis of 23 DB, PC trials (*Faraone 2010a*) comparing the efficacy of methylphenidate and amphetamine formulations found that amphetamine products may be moderately more efficacious than methylphenidate products.
- A DB, PC, RCT (*Newcorn et al 2008*) (N = 516) comparing the efficacy of atomoxetine vs methylphenidate ER (osmotic-release formulation) in patients 6 to 16 years of age with ADHD found that both drugs were superior to placebo in terms of response rate, and that methylphenidate ER was superior to atomoxetine.
- A meta-analysis of 29 DB, PC trials (*Faraone et al 2006*) evaluated the efficacy of various medications (methylphenidate and amphetamine compounds, atomoxetine, pemoline [no longer available in the U.S.], bupropion, and modafinil) for the treatment of ADHD. The effect sizes for non-stimulant medications were significantly less than those for IR stimulants or long-acting stimulants. The 2 classes of stimulant medications did not differ significantly from one another.
- A meta-analysis of 28 DB, PC, RCTs (*Stuhec et al 2015*) (N = 4699) compared the efficacy of various medications for the treatment of ADHD in children and adolescents. Efficacy in reducing ADHD symptoms compared to placebo was small for bupropion (SMD = -0.32; 95% confidence interval [CI], -0.69 to 0.05), modest for atomoxetine (SMD = -0.68; 95% CI, -0.76 to -0.59) and methylphenidate (SMD = -0.75; 95% CI, -0.98 to -0.52), and highest for lisdexamfetamine (SMD = -1.28; 95% CI, -1.84 to -0.71).
- A network meta-analysis and mixed treatment comparison of 36 RCTs (*Joseph et al 2017*) evaluating the comparative efficacy and safety of ADHD pharmacotherapies in children and adolescents found that lisdexamfetamine had greater efficacy than guanfacine ER, atomoxetine, and methylphenidate ER. Guanfacine ER had a high posterior probability of being more efficacious than atomoxetine, but their credible intervals overlapped.
- A network meta-analysis of 48 DB, RCTs (*Padilha et al 2018*) compared the safety and efficacy of various ADHD medications in children and adolescents. Of the 12 trials that were evaluated for efficacy, analysis was performed using the Clinical Global Impression Improvement (CGI-I) scale for 3 drugs, which showed that methylphenidate was more effective than atomoxetine (MD, 3.15; 95% CI, 0.75 to 13.71) and guanfacine (MD, 1.92; 95% CI, 0.64 to 5.94). Thirty-three trials were evaluated for safety. Ranking of AEs showed that lisdexamfetamine was more likely to cause sleep disorders, loss of appetite, and behavior problems compared to other treatments.

- Alpha$_2$-adrenergic agonists have been associated with improvements in ADHD symptoms and comorbid tics.
  - A meta-analysis of 9 DB, PC, RCTs (*Bloch et al 2009*) (N = 477) was conducted to determine the relative efficacy of different medications in treating ADHD and tic symptoms in children with both Tourette syndrome and ADHD.
  - Methylphenidate seemed to offer the greatest improvement of ADHD symptoms and did not seem to worsen tic symptoms.
  - Alpha$_2$-adrenergic agonists offered the best combined improvement in both tic and ADHD symptoms.
  - Atomoxetine significantly improved both tic and ADHD severity compared to placebo.
  - One small study found that tic severity was significantly increased with higher doses of dextroamphetamine treatment.
  - A Cochrane review of 8 RCTs (*Osland et al 2018*) including 510 children with both ADHD and a chronic tic disorder found low-quality evidence for improvement of ADHD symptoms with methylphenidate, atomoxetine, and clonidine, and very low-quality evidence for desipramine, dextroamphetamine, guanfacine, and deprenyl. Tic symptoms improved with guanfacine, desipramine, methylphenidate, clonidine, and a combination of methylphenidate and clonidine. The authors noted that in 1 study with a short duration (3 weeks), high doses of dextroamphetamine worsened tics.
- There are limited efficacy data regarding the treatment of ADHD in the adult population. Comparison of effect sizes in clinical trials suggests that stimulant medications are more efficacious in adult ADHD than non-stimulants.
  - In a meta-analysis of 12 clinical trials (*Cunill et al 2013*) (N = 3375) comparing atomoxetine with placebo in adult ADHD, atomoxetine led to a modestly greater reduction in ADHD symptom severity, but was associated with higher all-cause discontinuation.
  - A meta-analysis (*Faraone 2010b*) of 19 randomized trials of 13 medications for adult ADHD found a greater average effect size for reduction in ADHD symptoms in patients receiving short- and long-acting stimulant medications (vs placebo; 0.86 and 0.73, respectively) compared with patients receiving non-stimulant medication (vs placebo; 0.39). No difference in effect size was found between short- and long-acting stimulants.
  - A meta-analysis of 20 randomized trials (*Stuhec et al 2019*) compared the efficacy, acceptability, and tolerability of lisdexamfetamine, mixed amphetamine salts, methylphenidate, and modafinil in the treatment of ADHD in adults. The highest effect size in reducing ADHD symptoms was found with lisdexamfetamine (SMD -0.89; 95% CI, -1.09 to

-0.70), while moderate reductions in symptoms were seen with mixed amphetamine salts (SMD -0.64; 95% CI, -0.83 to -0.45) and methylphenidate (SMD -0.50; 95% CI, -0.58 to -0.41). No efficacy was reported with modafinil.
  - A Cochrane review of 19 studies (*Castells et al 2018*, N = 2521) comparing dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts for the treatment of ADHD in adults found that overall, amphetamines reduced the patient- and clinician-rated severity of ADHD symptoms compared to placebo; however, they did not improve retention in treatment. Amphetamines were associated with an increased proportion of patients who withdrew because of AEs. When comparing different types of amphetamines, lisdexamfetamine and mixed amphetamine salts reduced the severity of ADHD symptoms as rated by clinicians, but dextroamphetamine did not. No differences in any outcome were found when comparing immediate- and sustained-release formulations.
  - A systematic review and network meta-analysis (*Elliot et al 2020*) of 81 RCTs compared methylphenidate, atomoxetine, dexamfetamine, lisdexamfetamine, guanfacine, mixed amphetamine salts, modafinil, and bupropion for the treatment of ADHD in adults. Treatment with any ADHD pharmacotherapy was associated with statistically significant improvement in patient-reported clinical response vs placebo. When drugs were analyzed individually, only atomoxetine was found to significantly improve patient-reported clinical response compared to placebo (mean difference, -5.9; 95% CI, -12.6 to -0.4). Atomoxetine (mean difference, -3.7; 95% CI, -6.7 to -0.9), sustained-release methylphenidate (mean difference, -5.7; 95% CI, -11.2 to -0.3), and low-dose methylphenidate (mean difference, -10.4; 95% CI, -19.0 to -2.1) were found to improve clinician-assessed clinical response compared to placebo. No significant differences were observed between individual medications when response was considered as a continuous outcome.
  - Another meta-analysis (*Cortese et al 2018*) of 133 RCTs comparing the use of amphetamines, atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil for the treatment of ADHD found that all drugs were superior to placebo for ADHD core symptoms as rated by clinicians in children and adolescents, and all drugs except for modafinil were more efficacious than placebo in adults.
    - When comparing the various drugs based on teachers' ratings in children and adolescents, only methylphenidate and modafinil were found to be more efficacious than placebo.
    - In head-to-head comparisons, differences in efficacy based on clinicians' ratings were found, favoring amphetamines over modafinil (SMD -0.39; 95% CI -0.67 to -0.12), atomoxetine (SMD -0.46; 95% CI, -0.65 to -0.27), and methylphenidate (SMD -0.24; 95% CI, -0.44 to -0.05) in children and adolescents. Efficacy results based on clinicians' ratings were similar for adults, and favored amphetamines over modafinil (SMD -0.94; 95% CI -1.43 to -0.46), atomoxetine (SMD -0.34; 95% CI, -0.58 to -0.10), and methylphenidate (SMD-0.29; 95% CI, -0.54 to -0.05).
- Lisdexamfetamine dimesylate has demonstrated efficacy in the treatment of BED. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.
  - In 2 Phase 3, 12-week, randomized, DB, PC trials (*McElroy et al 2016*) (N = 773) in patients with moderate to severe BED, lisdexamfetamine-treated patients had a statistically significantly greater reduction from baseline in mean number of binge days per week at week 12 vs placebo (treatment difference in study 1: -1.35 [-1.70 to -1.01]; study 2: -1.66 [-2.04 to -1.28]; both $p < 0.001$).
    - A 12-month, OL extension study (*Gasior et al 2017*) (N = 599) in adults with BED found that the long-term safety and tolerability of lisdexamfetamine were generally consistent with the safety profile observed in 3 previous short-term trials in BED as well as its established profile for ADHD. Common treatment-emergent AEs included dry mouth, headache, insomnia, and upper respiratory tract infection. Weight loss and increases in blood pressure and pulse rate were also observed.
  - In a phase 3, DB, randomized, PC, withdrawal study (*Hudson et al 2017*) (N = 418) in adults with moderate to severe BED, responders to lisdexamfetamine during a 12-week OL phase were randomized to placebo or continued lisdexamfetamine during a 26-week, DB phase. The percentage of patients meeting relapse criteria was 3.7% with lisdexamfetamine vs 32.1% with placebo; time to relapse statistically favored lisdexamfetamine ($p < 0.001$). The hazard ratio (HR) was 0.09 (95% CI, 0.04 to 0.23).
    A systematic review and meta-analysis of 9 waitlist-controlled psychological trials and 25 PC trials evaluating pharmacologic (n = 19) or combination (n = 6) treatment for BED (*Brownley et al 2016*) found that therapist-led cognitive behavioral therapy (CBT), lisdexamfetamine, and second-generation antidepressants (SGAs) increased binge-eating abstinence (relative risk [RR], 4.95 [95% CI, 3.06 to 8.00], 2.61 [CI, 2.04 to 3.33], and 1.67 [CI, 1.24 to 2.26], respectively), while lisdexamfetamine and SGAs decreased binge-eating frequency (mean difference in days/week, -1.35 [CI, -1.77 to -0.93] and -0.67 [CI, -1.26 to -0.09], respectively). Topiramate and other forms of CBT also increased abstinence and reduced binge-eating frequency.

- A 2018 systematic review and meta-analysis of 45 RCTs (*Ghaderi et al 2018*) compared various psychological, pharmacological, and combined treatments for BED, and found moderate support for the efficacy of CBT and CBT-guided self-help (moderate quality of evidence), and low quality evidence to support interpersonal psychotherapy, selective serotonin reuptake inhibitors, and lisdexamfetamine for the cessation of or reduction in the frequency of binge eating. Only lisdexamfetamine showed a modest effect on weight loss (SMD for body mass index -5.23; 95% CI, -6.52 to -3.94).

CLINICAL GUIDELINES

ADHD

- Several clinical guidelines have provided recommendations on the treatment of ADHD in children and adolescents.
  - According to the American Academy of Pediatrics (AAP) guidelines (2019), the evidence is particularly strong for stimulant medications, and sufficient but less strong for atomoxetine, guanfacine ER, and clonidine ER (in that order). Guanfacine ER and clonidine ER have evidence to support their use as adjunctive therapy with stimulant medications. Methylphenidate is recommended for preschool-aged children who have had an inadequate response to behavioral interventions.
  - The American Academy of Child and Adolescent Psychiatry (AACAP) guidelines (*Pliszka et al 2007*) state that both methylphenidate and amphetamines are equally efficacious in the treatment of ADHD. The long-acting formulations are equally efficacious as the IR formulations and may be used as initial therapy. Short-acting stimulants are often used as initial treatment in small children (< 16 kg in weight), for whom there are no long-acting preparations in a sufficiently low dose. Some patients may respond similarly to different stimulant classes, whereas other patients may respond preferentially to only 1 of the classes of stimulants. Although stimulants have demonstrated greater efficacy compared to atomoxetine in published studies, atomoxetine may be used first-line in patients with an active substance abuse problem, comorbid anxiety or tics, and in those who experience severe AEs with stimulants.
  - The Medical Letter (2020) recommends that treatment of ADHD in school-age children or adults should begin with an oral stimulant, either a methylphenidate- or amphetamine-based formulation. Mixing short- and long-acting stimulants can be helpful to achieve an immediate effect for early-morning school classes or for reducing rebound irritability or overactivity, especially in the evening. An ER alpha$_2$-adrenergic agonist may be helpful as adjunctive therapy with a stimulant in patients who cannot tolerate usual doses of the stimulant, particularly those with tics. Atomoxetine is an alternative for patients who cannot tolerate stimulants or for whom treatment with a controlled substance is undesirable.
  - The AACAP practice parameter for the treatment of children and adolescents with tic disorders (2013) states that alpha$_2$-adrenergic agonists have demonstrated an effect size of 0.5 for the amelioration of tics and may be preferred by some prescribers over antipsychotics due to their relatively favorable AE profile.

Narcolepsy

- The American Academy of Sleep Medicine (AASM) practice parameters (*Morgenthaler et al 2007*) recommend various drugs for the treatment of daytime sleepiness due to narcolepsy including modafinil (high degree of clinical certainty); amphetamine, methamphetamine, dextroamphetamine, and methylphenidate (moderate degree of clinical certainty); sodium oxybate (high degree of clinical certainty); and selegiline (uncertain clinical certainty).

BED

- According to the American Psychiatric Association (APA) practice guidelines on eating disorders (*Yager et al 2006*, *Yager et al 2012* [guideline watch update]), treatment of BED may include the following:
  - Nutritional rehabilitation and counseling
  - Psychosocial treatment
    - CBT, behavior therapy, dialectical behavior therapy (DBT), and interpersonal therapy (IPT) have all been associated with binge frequency reduction rates of 67% or more and significant abstinence rates during active treatment.
    - Self-help programs using self-guided, professionally designed manuals have been effective in reducing the symptoms of BED in the short-run for some patients and may have long-term benefit.
  - Medications
    - Antidepressant treatment is associated with short-term reductions in binge-eating but generally does not result in substantial weight loss. Selective serotonin reuptake inhibitors (SSRIs) have the fewest difficulties with AEs and the most evidence for efficacy when used at the high end of the recommended dose range.
    - Topiramate can reduce bingeing and decrease weight, but its use may be limited by AEs.

- Combination psychotherapy and pharmacotherapy
  - For most patients, adding antidepressant therapy to a behavioral weight control and/or CBT regimen does not have a significant effect on binge suppression.
  - Although limited evidence is available, combined treatment is frequently used in clinical practice.
- The American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) guidelines for medical care of patients with obesity (*Garvey et al 2016*) recommend the following for patients with overweight or obesity who have BED:
  - Patients should be treated with a structured behavioral/lifestyle program, combined with CBT or other psychological interventions
  - Treatment with orlistat or approved medications containing topiramate or bupropion may be considered in conjunction with structured lifestyle therapy, CBT, and/or psychological interventions
- The Task Force on Eating Disorders of the World Federation of Societies of Biological Psychiatry (*Aigner et al 2011*) concluded that for the treatment of BED, grade A evidence supports the use of imipramine (moderate risk-benefit ratio), sertraline (good risk-benefit ratio), citalopram/escitalopram (good risk-benefit ratio), orlistat (low to moderate risk-benefit ratio), and topiramate (moderate risk-benefit ratio). Atomoxetine has grade B evidence supporting its use.

SAFETY SUMMARY

- Due to the potential for abuse, the stimulants are classified as Schedule II controlled substances. Atomoxetine, clonidine ER, and guanfacine ER are not classified as controlled substances.
- Various stimulants are contraindicated for use in patients with advanced arteriosclerosis, symptomatic CV disease, moderate to severe hypertension, hyperthyroidism, hypersensitivity to sympathomimetic amines, glaucoma, agitated states, history of drug abuse, tics, and in those using monoamine oxidase inhibitors (MAOIs). The stimulants carry a boxed warning for potential drug abuse and dependence. They also have warnings for increased risks of serious CV reactions, psychiatric AEs, suppression of growth, peripheral vasculopathy, and priapism. Amphetamines have a warning for risk of serotonin syndrome when used in combination with other drugs affecting the serotonergic neurotransmitter systems.
  - Common AEs of stimulants include anorexia, decreased weight, tachycardia, anxiety, irritability, and insomnia.
  - Refer to the prescribing information for details on warnings, precautions, and AEs for individual products. For example:
    - QuilliChew ER can be harmful to patients with phenylketonuria (PKU) since it contains phenylalanine.
    - Because Concerta and Relexxii tablets are nondeformable and do not appreciably change in shape in the gastrointestinal tract, they should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing.
    - The use of Daytrana may result in chemical leukoderma and contact sensitization; in addition, exposure of the application site to external heat sources should be avoided due to increased absorption of the drug.
    - Adhansia XR capsules contain FD&C yellow No. 5 dye (tartrazine), which may cause allergic-type reactions in susceptible patients.
- Atomoxetine is contraindicated for use in patients with narrow angle glaucoma, pheochromocytoma, severe CV disorders, hypersensitivity to any component of the product, and in those taking MAOIs. It carries a boxed warning for a rare increased risk of suicidal ideation in children and adolescents. It also has warnings for serious CV events, effects on blood pressure and heart rate, effects on growth, psychiatric AEs, rare cases of severe liver injury, and priapism.
  - Common AEs associated with atomoxetine include somnolence, nausea, and vomiting.
- The alpha$_2$-adrenergic agonists are contraindicated in patients known to be hypersensitive to any constituent of the product. They carry warnings for increased risk of hypotension, bradycardia, and syncope; sedation and somnolence; rebound hypertension; and cardiac conduction abnormalities.
  - Common AEs associated with clonidine ER include somnolence, fatigue, and irritability while common AEs with guanfacine ER include somnolence, fatigue, and hypotension.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Stimulants					
Evekeo (amphetamine)	10 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily *Exogenous obesity*: Divided doses daily	*ADHD and narcolepsy* The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours.
Evekeo ODT (amphetamine)	10 h	Orally disintegrating tablets	Oral	Once or twice daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Adzenys ER (amphetamine ER)	10 to 12 h	Suspension	Oral	Daily in the morning	The bottle should be shaken before administration.
Adzenys XR-ODT (amphetamine ER)	10 to 12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Dyanavel XR (amphetamine ER)	Up to 13 h	Suspension	Oral	Daily in the morning	The bottle should be shaken before administration.
Adderall (mixed amphetamine salts)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given on awakening, then additional doses at intervals of 4 to 6 hours.
Adderall XR (mixed amphetamine salts ER)	10 to 12 h	Capsules	Oral	Daily in the morning	Capsules may be taken whole, or the capsule may be opened and the entire contents

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					sprinkled on applesauce and consumed immediately. The dose of a single capsule should not be divided.
Mydayis (mixed amphetamine salts ER)	16 h	Capsules	Oral	Daily in the morning	Dosage adjustment is needed for severe renal impairment. Use in end stage renal disease (ESRD) is not recommended. Capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately in its entirety without chewing. The dose of a single capsule should not be divided.
Focalin (dexmethylphenidate)	5 to 6 h	Tablets	Oral	Twice daily	
Focalin XR (dexmethylphenidate ER)	10 to 12 h	Capsules	Oral	Daily in the morning	ER capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce.
ProCentra, Zenzedi (dextroamphetamine)	4 to 6 h	Solution (ProCentra) Tablets (Zenzedi)	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours
Dexedrine Spansule (dextroamphetamine SR)	6 to 8 h	Capsules	Oral	*ADHD* Daily or twice daily Narcolepsy Daily	

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Vyvanse (lisdexamfetamine)	10 to 12 h	Capsules, chewable tablets	Oral	*ADHD, BED*: Daily in the morning	Dosage adjustment is needed for renal impairment/ESRD. The capsules may be swallowed whole or can be opened, emptied, and mixed with yogurt, water, or orange juice and consumed immediately. A single capsule should not be divided. The chewable tablets must be chewed thoroughly before swallowing. A single dose should not be divided.
Desoxyn (methamphetamine)	3 to 5 h	Tablets	Oral	Daily to twice daily	
Methylin, Ritalin (methylphenidate)	3 to 5 h	Chewable tablets, tablets (Ritalin), solution (Methylin)	Oral	Twice daily to 3 times daily	The chewable tablets should be taken with at least 8 ounces (a full glass) of water or other fluid. The liquid should be given 30 to 45 minutes before meals. The ER tablets may be used in place of the IR tablets when the 8-hour dosage of the ER product corresponds to the titrated 8-hour dosage of the IR products. The ER tablets must be swallowed whole and never crushed or chewed.
Methylphenidate ER	3 to 8 h	Tablets			

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Adhansia XR (methylphenidate ER)	13 to 16 h	Capsules	Oral	Daily in the morning	The capsules may be taken whole or they can be opened and sprinkled onto applesauce or yogurt; the entire contents of the mixture should be consumed within 10 minutes, and should not be chewed. The dose of a single capsule should not be divided.
Aptensio XR (methylphenidate ER)	12 h	Capsules	Oral	Daily in the morning	The capsules may be taken whole or they can be opened and sprinkled onto applesauce; the applesauce should be consumed immediately and it should not be chewed. The dose of a single capsule should not be divided.
Concerta (methylphenidate ER)	10 to 12 h	Tablets	Oral	Daily in the morning	The tablets should not be chewed or crushed. Note: An FDA analysis of methylphenidate ER products manufactured by UCB/Kremers (formerly Kudco) and Mallinckrodt indicated that in some individuals, they may deliver the drug in the body at a

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Methylphenidate ER					slower rate during the 7- to 12-hour range. As a result, the FDA changed the therapeutic equivalence of these products from AB to BX. Because these manufacturers have subsequently failed to demonstrate that their products are bioequivalent to the brand-name reference drug, the FDA proposes to withdraw their approval (*FDA 2016*).
Cotempla XR-ODT (methylphenidate ER)	12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Jornay PM (methylphenidate ER)	Peak concentration occurs 14 hours after dose with gradual decline thereafter.	Capsules	Oral	Daily in the evening	The capsule may be swallowed whole or it may be opened and the contents sprinkled onto applesauce and given immediately. The capsule contents must not be crushed or chewed, the dose of a single capsule should not be divided, and the contents of the entire capsule should be taken at the same time.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Methylphenidate ER (CD)	8 to 12 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or it may be opened and the contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately. The capsule contents must not be crushed or chewed.
QuilliChew ER (methylphenidate ER)	12 h	Chewable tablets	Oral	Daily in the morning	A 10 mg or 15 mg dose can be achieved by breaking in half the functionally scored 20 mg and 30 mg tablets, respectively.
Quillivant XR (methylphenidate ER)	12 h	Suspension	Oral	Daily in the morning	The bottle of Quillivant XR should be shaken vigorously for 10 seconds prior to administration. The suspension is stable for up to 4 months once reconstituted.
Relexxii (methylphenidate ER)	12 h	Tablet	Oral	Daily in the morning	The tablet must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.
Ritalin LA (methylphenidate ER)	8 to 12 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or may be administered by sprinkling the capsule contents on a small amount of applesauce; the contents should not be crushed, chewed, or divided. The mixture should

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					be consumed immediately.
Daytrana (methylphenidate transdermal system)	10 to 12 h	Transdermal system	Transdermal	The patch should be applied 2 hours before an effect is needed and removed within 9 hours. It may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear.	
Non-stimulants					
Strattera (atomoxetine)	24 h	Capsules	Oral	Daily in the morning or divided dose in the morning and late/afternoon early evening	Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency. The capsules are not intended to be opened and should be taken whole.
Kapvay (clonidine ER)	12 h	Tablets	Oral	Daily at bedtime or twice daily divided doses.	With twice daily dosing, either an equal or higher split dosage should be given at bedtime. The tablets should not be crushed, chewed, or broken prior to swallowing. The initial dosage should be based on the degree of renal impairment.
Intuniv (guanfacine ER)	8 to 24 h	Tablets	Oral	Daily in the morning or evening	The tablets should not be crushed, chewed, or broken prior to swallowing; they should not be administered with high fat meals, due to increased exposure

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					It may be necessary to reduce the dosage in patients with significant renal and hepatic impairment.

See the current prescribing information for full details
*References: Prescribing information for individual products, *Medical Letter 2020, Pharmacist's Letter 2016, Krull 2020a*

CONCLUSION

- Both CNS stimulants and non-stimulants may be used for the treatment of ADHD. In general, stimulants are first-line treatment due to their superior efficacy. Clinical evidence suggests that methylphenidate and amphetamines are equally efficacious, but some patients may respond to one stimulant and not the other. Various short-, intermediate- and long-acting formulations (eg, tablets/capsules, chewable/orally disintegrating tablets, solution/suspension, transdermal patch) are available to provide a range of dosing options. Although non-stimulants such as atomoxetine and alpha$_2$-adrenergic agonists have smaller effect sizes, they may be used in patients who have failed or are intolerant to stimulants or when there is concern about possible abuse or diversion. The alpha$_2$-adrenergic agonists are approved both as monotherapy and as adjunctive therapy to stimulants, and they have been shown to improve both tic and ADHD symptoms in patients with comorbid tic disorder.
  - Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children (*AACAP 2007*; *AAP 2019*).
- Ultimately, the choice of the initial agent for treatment of ADHD depends upon various factors such as: duration of desired coverage; ability of the child to swallow pills; coexisting tic disorder (use of alpha$_2$-adrenergic agonists may be warranted); potential AEs, history of substance abuse in the patient or household member (eg, avoid stimulants or use stimulants with less potential for abuse [eg, lisdexamfetamine, osmotic-release preparation, methylphenidate patch]); and preference of the patient and parent/guardian (*Krull 2020a*).
- Various stimulants are indicated for treatment of narcolepsy and are generally considered to be second-line agents after modafinil/armodafinil due to their sympathomimetic AEs (*Scammell 2020*).
- Lisdexamfetamine is the only FDA-approved drug indicated for the treatment of moderate to severe BED, with demonstrated efficacy in reduction of mean binge days per week vs placebo. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.

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