South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

September 27, 2019

DSS

Strong Families - South Dakota's Foundation and Our Future

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

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

September 27, 2019
1:00 – 3:00 PM

DDN Locations:
Sioux Falls
University Center
DDN Room FADM145
4801 North Career Avenue

Pierre
Capitol Building
DDN Room CAP A
500 East Capitol

Rapid City
Black Hills State University
DDN Room UC113
4300 Cheyenne Boulevard

Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **CGRP utilization**
- **Orilissa utilization**
- **ADD/ADHD utilization**
- **Opioid update**

New business
- **Albuterol utilization**
- **Buprenorphine PA**
- **Opioid prescribing guidelines for acute pain**
- **Opioid & Benzo**
- **Opioid & Antipsychotics**
- **Seysara, Nuzyra**
- **Mayzent, Mavenclad**

Public comment accepted after individual topic discussion
Next meeting date 12/13/2019 & adjournment

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

Friday, June 21, 2019
1:00 – 3:00 pm CT

Members and DSS Staff

Michelle Baack, MD	X	Kelley Oehlke, PharmD	
Dana Darger, RPh	X	Lenny Petrik, PharmD	X
James Engelbrecht, MD		Timothy Soundy, MD	
Deidre Van Gilder, PharmD	X	Mike Jockheck, DSS Staff	X
Mikal Holland, MD		Sarah Akers, DSS Staff	X
Richard Holm, MD	X	Bill Snyder, DSS Staff	X
Bill Ladwig, RPh, Chair	X		

Administrative Business
Darger called the meeting to order at 1:03 PM. The minutes of the March meeting were presented. Holm made a motion to approve and Van Gilder seconded the motion. The motion was approved unanimously.

Prior Authorization Update (PA) and Statistics
The committee reviewed the PA activity report from January 1, 2019 to March 31, 2019. A total of 2,112 PAs were reviewed of which 347 requests (16%) were received via telephone and 1,166 requests (55%) were received via fax, and 597 (22%) were reviewed electronically.

Analysis of the Top 15 Therapeutic Classes and Drug Spend
The committee reviewed the top 15 therapeutic classes by total cost of claims from January 1, 2019 to March 31, 2019. The top five therapeutic classes based on paid amount were atypical antipsychotics, amphetamines, anticonvulsants, and respiratory and CNS stimulants. The top 15 therapeutic classes make up 25.96% of total claims. The committee also reviewed the top 50 drugs based on total claims cost and number of claims. The top 50 drugs by claims cost make up 15.49% of total claims.

Old Business
Committee reviewed the calcitonin gene related peptide (CGRP) utilization comparing 4Q18 vs 1Q19. Utilization continues to increase each quarter. Committee also reviewed utilization for Orilissa for 1Q19. Committee requested to review utilization for both classes again at the next meeting.

Committee reviewed the CiproDex utilization for 1Q19. After in-depth reviews over several quarters, Committee was satisfied with the utilization.

Committee reviewed the attention-deficit-hyperactivity-disorder/attention deficit disorder (ADHD/ADD) utilization for 1Q19. Committee wanted to further explore utilization for adults 26 years of age and older only. Utilization to include prescriber specialty, diagnosis; and concurrent therapy for opioids, benzodiazepines, and stimulants.

Committee reviewed criteria consideration for Dupixent and recommended a trial and failure of ICS and controller medication for asthma diagnosis. Baack made a motion to approve and Van Gilder seconded the motion. The motion was approved unanimously.

Committee reviewed criteria consideration for Actemra and recommended to accept clinical diagnosis for Giant Cell Arteritis instead of requiring a biopsy, a trial of oral or parenteral corticosteroid, and rheumatologist consult. Baack made a motion to approve and Holm seconded the motion. The motion was approved unanimously.

New business

Committee reviewed the utilization for Hepatitis C for the time-period 2014 through May 2019. The Committee also discussed updating the criteria for coverage of hepatitis C treatments to:

1. Female patient prescribed ribavirin must have a negative pregnancy test within thirty days prior to initiation of therapy and monthly during treatment.
2. Age of patient must be equal to or greater than the age indicated for the drug requested.
3. The drug requested must match the approved genotype for that drug.
4. Treat reinfections using these same criteria.

Hannah Wenger, staff physician from Rosebud Service Unit, Indian Health Service spoke regarding her experience treating the hepatitis C population at Rosebud. Brent Hildebrand from Gilead spoke regarding the pediatric age labeling starting at 12 years of age for Harvoni and Sovaldi and no pediatric age labeling currently for Epclusa. Margaret Olmon from AbbVie spoke regarding the FDA approval for an age indication of 12 years old and older for Mavyret; and provided information on a possible new indication for treatment naïve patients with compensated cirrhosis therapy decreasing from 12 weeks to 8 weeks. Jessica Leston, HCV/HIV Clinical Programs Director of Northwest Portland Area Indian Health Board, shared a letter from a mother about her daughter on the risks of opioid addiction and contracting hepatitis C.

Jockheck clarified the recommended criteria and stated he would provide the Committee's recommendation to the Department of Social Services executive management for consideration. Holm made a motion to approve and Baack seconded the motion. The motion was approved unanimously.

Committee reviewed utilization for triptans. Some generics are still on step therapy. Jockheck clarified if the Committee wanted to remove generics from step therapy. Baack made a motion to remove generics from step therapy and Van Gilder seconded the motion. The motion was approved unanimously.

Committee reviewed outcomes reporting for the opioid initiatives implemented in 2018. In reviewing the opioids utilization snapshot, Jockheck presented outcomes comparing 1Q18 to 1Q19. The number of opioid claims, opioid utilizers, the use of poly pharmacies, and poly prescribers have all decreased. The Committee was excited and pleased with the opioid outcomes. Darger requested the opioid snapshot reports to be included at the next meeting.

The next meeting is scheduled for September 27, 2019. Tentative meeting date for December is December 13, 2019. Darger signified the meeting was adjourned by everyone leaving. The motion passed unanimously and the meeting adjourned at 3:35 PM.

PA Report

4/1/2019 to 6/30/2019

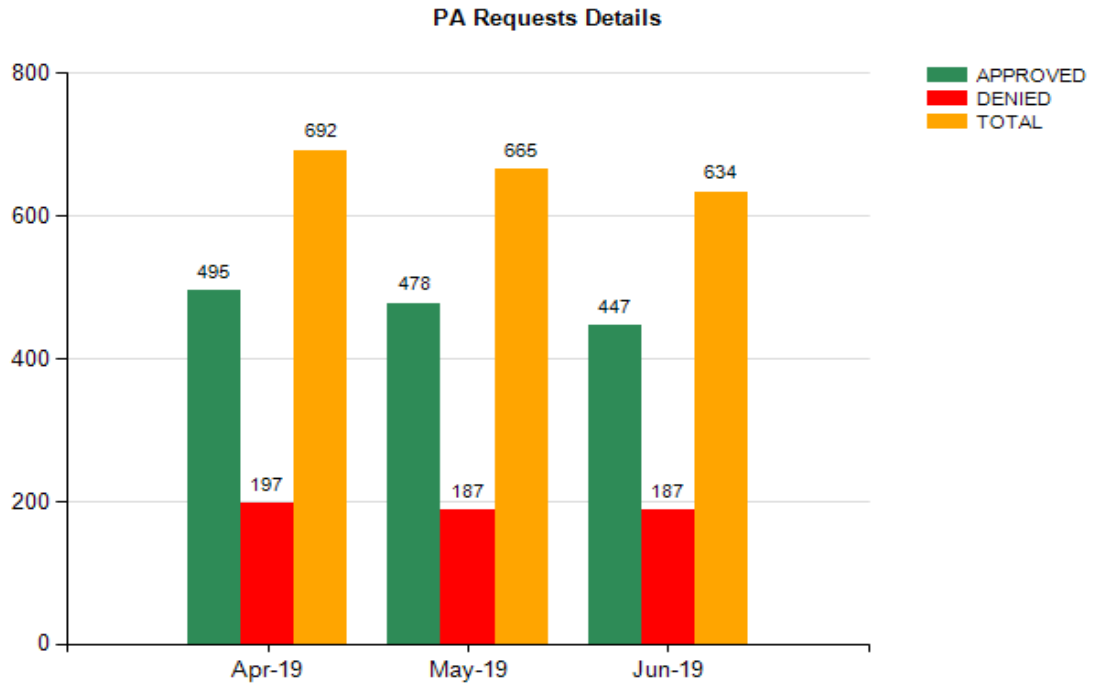
Compliance Summary

Priority	Total PAs	PAs Compliant (Standard - 72 Hrs Urgent - 24 Hrs)	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
STANDARD	1937	1937	0	100.00%	0.00%
URGENT	54	54	0	100.00%	0.00%
GRAND TOTAL	**1991**	**1991**	**0**		

	# of	Phone Requests		Fax Requests		Real-Time PA	
Drug Class	Requests	#	%	#	%	#	%
TOTAL	1991	333	16.73	1133	56.91	525	26.37

PA Initial Requests Summary

Month	Approved	Denied	Total
Apr-19	495	197	692
May-19	478	187	665
Jun-19	447	187	634
2Q19	**1420**	**571**	**1991**
Percent of Total	**71.32%**	**28.68%**	



Top 5 Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
65 - ANALGESICS - OPIOID*	222	95	317	70.03%	15.92%	HYDROCODONE/APAP, TRAMADOL
59 - ANTIPSYCHOTICS/ ANTIMANIC AGENTS*	217	22	239	90.79%	12.00%	, LATUDA
58 - ANTIDEPRESSANTS*	176	27	203	86.70%	10.20%	, DULOXETINE
72 - ANTICONVULSANTS*	116	73	189	61.38%	9.49%	LYRICA,
90 - DERMATOLOGICALS*	76	89	165	46.06%	8.29%	LIDOCAINE, CLINDAMYCIN/BENZOYL
Others -	613	265	878	69.82%	44.10%	
2Q19	**1420**	**571**	**1991**	**71.32%**		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
65 - ANALGESICS - OPIOID*	222	95	317	70.03%
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	217	22	239	90.79%
58 - ANTIDEPRESSANTS*	176	27	203	86.70%
72 - ANTICONVULSANTS*	116	73	189	61.38%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	110	53	163	67.48%
27 - ANTIDIABETICS*	85	3	88	96.59%
83 - ANTICOAGULANTS*	83	4	87	95.40%
90 - DERMATOLOGICALS*	76	89	165	46.06%
52 - GASTROINTESTINAL AGENTS - MISC.*	48	14	62	77.42%
41 - ANTIHISTAMINES*	45	4	49	91.84%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	39	13	52	75.00%
66 - ANALGESICS - ANTI-INFLAMMATORY*	33	7	40	82.50%
54 - URINARY ANTISPASMODICS	23	20	43	53.49%
16 - ANTI-INFECTIVE AGENTS - MISC.*	21	3	24	87.50%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	19	2	21	90.48%
67 - MIGRAINE PRODUCTS*	19	50	69	27.54%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	11	7	18	61.11%
50 - ANTIEMETICS*	10	2	12	83.33%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	7	5	12	58.33%
75 - MUSCULOSKELETAL THERAPY AGENTS*	7	2	9	77.78%
86 - OPHTHALMIC AGENTS*	7	35	42	16.67%
12 - ANTIVIRALS*	6	16	22	27.27%
33 - BETA BLOCKERS*	6	1	7	85.71%
36 - ANTIHYPERTENSIVES*	6	4	10	60.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	5	0	5	100.00%
02 - CEPHALOSPORINS*	3	0	3	100.00%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	3	1	4	75.00%
39 - ANTIHYPERLIPIDEMICS*	3	3	6	50.00%
34 - CALCIUM CHANNEL BLOCKERS*	2	3	5	40.00%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	2	5	7	28.57%
03 - MACROLIDES	1	0	1	100.00%
05 - FLUOROQUINOLONES*	1	0	1	100.00%
11 - ANTIFUNGALS*	1	2	3	33.33%
25 - CONTRACEPTIVES*	1	0	1	100.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	1	2	3	33.33%
45 - RESPIRATORY AGENTS - MISC.*	1	0	1	100.00%
51 - DIGESTIVE AIDS*	1	0	1	100.00%
68 - GOUT AGENTS*	1	0	1	100.00%
82 - HEMATOPOIETIC AGENTS*	1	1	2	50.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	1	0	1	100.00%
01 - PENICILLINS*	0	1	1	0.00%
23 - ANDROGENS-ANABOLIC*	0	1	1	0.00%
84 - HEMOSTATICS*	0	1	1	0.00%
2Q19	**1420**	**571**	**1991**	
Percent of Total	**71.32%**	**28.68%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Apr-19	15	71.43%	6	28.57%	21
May-19	18	75.00%	6	25.00%	24
Jun-19	14	73.68%	5	26.32%	19
2Q19	47	73.44%	17	26.56%	64

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
LYRICA	10	0	10	100.00%
CLOBAZAM	3	0	3	100.00%
AMITIZA	2	0	2	100.00%
DULOXETINE HCL	2	0	2	100.00%
DUPIXENT	2	0	2	100.00%
HYDROCODONE/ACETAMINOPHEN	2	0	2	100.00%
AIMOVIG	2	3	5	40.00%
MAVYRET	2	7	9	22.22%
ARIPIPRAZOLE	1	0	1	100.00%
BANZEL	1	0	1	100.00%
EPIDIOLEX	1	0	1	100.00%
HUMIRA PEN	1	0	1	100.00%
KINERET	1	0	1	100.00%
LANSOPRAZOLE ODT	1	0	1	100.00%
MODAFINIL	1	0	1	100.00%
MORPHINE SULFATE	1	0	1	100.00%
NEXIUM	1	0	1	100.00%
NORDITROPIN FLEXPRO	1	0	1	100.00%
NUTROPIN AQ NUSPIN 5	1	0	1	100.00%
OXYCODONE/ACETAMINOPHEN	1	0	1	100.00%
SPRYCEL	1	0	1	100.00%
STELARA	1	0	1	100.00%
SUBOXONE	1	0	1	100.00%
TIZANIDINE HCL	1	0	1	100.00%
XELJANZ	1	0	1	100.00%
AJOVY	1	1	2	50.00%
EMGALITY	1	1	2	50.00%
EPCLUSA	1	1	2	50.00%
ESOMEPRAZOLE MAGNESIUM	1	1	2	50.00%
SOFOSBUVIR/VELPATASVIR	1	2	3	33.33%
LIDOCAINE	0	1	1	0.00%
2Q19	47	17	64	

PA Approval Reviews

Approvals: 96% – 82%

Drug Class	Approved	Denied	Total	Approval Rate
ANTIDIABETICS* • DPP4 Inhibitors (Januvia – QL denied) • Incretin Mimetics (Victoza, Ozempic, Trulicity, Bydureon) • Rapid-Acting Insulin (Novolog Flexpen – QL) • Short-Acting Insulin (Humulin R U-500 Kwikpen – QL)	85	3	88	96.59%
ANTICOAGULANTS* • DIRECT FACTOR XA INHIBITORS (Eliquis, Xarelto – 4 denials) • HEPARINS (Lovenox-DAW, enoxaparin	83	4	87	95.40%
ANTIHISTAMINES* • desloratadine, cetirizine, loratadine (ST, QL) • Claritin RDT, Clariting Chew, Claritin Reditab – PA	45	4	49	91.84%
ANTIPSYCHOTICS/ANTIMANIC AGENTS* • Abilify Maintena – PA • Aripiprazole tab – QL • Aripiprazole soln – PA • Aristada Inj – PA • Clozapine ODT – PA • Invega Sust Inj – PA • Latuda tab - PA	217	22	239	90.79%
PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT • Anticonvulsant: Horizont – PA • Vesicular Monoamie Transport2 Inhibitor: Ingrezza – Claim Dollar • Immunomodulatory Agents: Tetrabenazine, Refib Rebidose, Tecfidera, Dalfampridin (claim dollare & PA)	19	2	21	90.48%
ANTI-INFECTIVE AGENTS - MISC.* • Daptomycin – Claim Dollar • Xifaxan (3 denials)	21	3	24	87.50%
ANTIDEPRESSANTS* • Bupropion & Mirtazapine QL • SNRI-QL, Pristiq/desvenlafaxine ER-PA • SSRI-QL, Lexapro-DAW, sertraline solution-PA	176	27	203	86.70%
BETA BLOCKERS* • Metoprolol ER – QL • Inderal LA – DAW PA	6	1	7	85.71%
ANTIEMETICS* • Diclegis	10	2	12	83.33%
ANALGESICS - ANTI-INFLAMMATORY* • Disease-Modifying Anti-rheumatic Agents (28 Approved; 5 Denied; 3 Overturned) • Other-Nonsteroidal Anti-Inflam Agents (meloxicam 7.5m denied #2/day)	33	7	40	82.50%

South Dakota Medicaid

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 4/1/2019 – 6/30/2019				
AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	11,962	149294.25	$12.48	6.13%
MISCELLANEOUS ANTICONVULS	10,562	1180967.82	$111.81	5.41%
ATYPICAL ANTIPSYCHOTICS	7,837	1877384.76	$239.55	4.01%
SECOND GENERATION ANTIHIS	7,739	90867.06	$11.74	3.96%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	6,797	511443.37	$75.25	3.48%
AMINOPENICILLIN ANTIBIOTICS	6,589	97908.1	$14.86	3.37%
RESPIRATORY AND CNS STIMULANTS	6,428	959129.8	$149.21	3.29%
OPIATE AGONISTS	6,155	228144.59	$37.07	3.15%
AMPHETAMINES	6,138	1041953.33	$169.75	3.14%
PROTON-PUMP INHIBITORS	5,752	213019.26	$37.03	2.95%
ADRENALS	5,359	552273.47	$103.06	2.74%
THYROID AGENTS	3,706	71140.4	$19.20	1.90%
LEUKOTRIENE MODIFIERS	3,429	49875.6	$14.55	1.76%
MISC. CENTRAL NERVOUS SYSTEM	3,298	154016.85	$46.70	1.69%
SEROTONIN MODULATORS	3,283	90683.85	$27.62	1.68%
TOTAL TOP 15 THERAPEUTIC CLASSES	**95,034**	**$7,268,102.51**	**$76.48**	**48.68%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 4/1/2019 – 6/30/2019				
AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
ATYPICAL ANTIPSYCHOTICS	7837	$1,877,384.76	$239.55	4.01%
MISCELLANEOUS ANTICONVULSANTS	10562	$1,180,967.82	$111.81	5.41%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	232	$1,137,738.41	$4,904.04	0.12%
AMPHETAMINES	6138	$1,041,953.33	$169.75	3.14%
RESPIRATORY AND CNS STIMULANTS	6428	$959,129.80	$149.21	3.29%
ANTINEOPLASTIC AGENTS	334	$745,801.74	$2,232.94	0.17%
SKIN AND MUCOUS MEMBRANE	425	$630,492.34	$1483.51	0.22%
RAPID-ACTING INSULINS	1275	$627,293.8	$492.00	0.65%
LONG-ACTING INSULINS	1420	$604,650.66	$425.81	0.73%
ADRENALS	5359	$552,273.47	$103.06	2.74%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	6797	$511,443.37	$75.25	3.48%
HEMOSTATICS	41	$442,556.22	$10,794.05	0.02%
SOMATOTROPIN AGONISTS	93	$364,281.02	$3,917.00	0.05%
CYSTIC FIBROSIS (CFTR) CORRECTORS	20	$364,156.81	$18,207.84	0.01%
HCV POLYMERASE INHIBITOR ANTIVIRALS	16	$275,005.25	$17,187.83	0.01%
TOTAL TOP 15 THERAPEUTIC CLASSES	**49,977**	**$11,315,128.80**	**$240.87**	**24.06%**

Total Rx Claims from 4/1/2019 – 6/30/2019	195,233

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 4/1/2019 – 6/30/2019					
AHFS Description	**Drug Label Name**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
SECOND GENERATION ANTIHIS	CETIRIZINE TAB 10MG	3,129	$30,282.99	$9.68	1.60%
AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN SUS 400/5ML	3,113	$41,086.10	$13.20	1.59%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL AER HFA	2,601	$118,999.57	$45.75	1.33%
PROTON-PUMP INHIBITORS	OMEPRAZOLE CAP 20MG	2,483	$27,532.10	$11.09	1.27%
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE CAP 20MG	2,074	$17,834.80	$8.60	1.06%
SECOND GENERATION ANTIHIS	LORATADINE TAB 10MG	1,975	$22,473.08	$11.38	1.01%
SEROTONIN MODULATORS	TRAZODONE TAB 50MG	1,843	$16,537.73	$8.97	0.94%
CORTICOSTEROIDS	FLUTICASONE SPR 50MCG	1,827	$29,996.21	$16.42	0.94%
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE TAB 100MG	1,701	$19,786.49	$11.63	0.87%
OPIATE AGONISTS	HYDROCO/APAP TAB 5-325MG	1,591	$20,673.69	$12.99	0.81%
MISCELLANEOUS ANTICONVULS	GABAPENTIN CAP 300MG	1,590	$24,580.06	$15.46	0.81%
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE TAB 50MG	1,520	$17,243.74	$11.34	0.78%
CENTRAL ALPHA-AGONISTS	CLONIDINE TAB 0.1MG	1,459	$14,480.80	$9.93	0.75%
LEUKOTRIENE MODIFIERS	MONTELUKAST TAB 10MG	1,411	$16,585.66	$11.75	0.72%
-	COMPOUND	1,405	$52,638.63	$37.47	0.72%
LEUKOTRIENE MODIFIERS	MONTELUKAST CHW 5MG	1,348	$18,162.22	$13.47	0.69%
OPIATE AGONISTS	TRAMADOL HCL TAB 50MG	1,336	$14,585.60	$10.92	0.68%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL NEB 0.083%	1,325	$20,433.87	$15.42	0.68%
RESPIRATORY AND CNS STIMULANTS	METHYLPHENID TAB 36MG ER	1,231	$270,570.77	$219.80	0.63%
SECOND GENERATION ANTIHIS	CETIRIZINE SOL 1MG/ML	1,167	$14,748.02	$12.64	0.60%
PROTON-PUMP INHIBITORS	OMEPRAZOLE CAP 40MG	1,131	$13,166.04	$11.64	0.58%
VITAMIN D	VITAMIN D CAP 50000UNT	1,119	$11,122.59	$9.94	0.57%
ADRENALS	PREDNISOLONE SOL 15MG/5ML	1,055	$13,634.70	$12.92	0.54%
AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN CAP 500MG	999	$10,933.68	$10.94	0.51%
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	ESCITALOPRAM TAB 10MG	973	$10,565.17	$10.86	0.50%
CENTRALLY ACTING SKELETAL MUSCLE RELAXNT	CYCLOBENZAPR TAB 10MG	952	$8,840.56	$9.29	0.49%
5-HT3 RECEPTOR ANTAGONIST	ONDANSETRON TAB 4MG ODT	950	$13,597.66	$14.31	0.49%
SEROTONIN MODULATORS	TRAZODONE TAB 100MG	943	$9,919.01	$10.52	0.48%
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	ESCITALOPRAM TAB 20MG	925	$10,327.60	$11.16	0.47%
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE CAP 10MG	920	$8,480.12	$9.22	0.47%
3RD GENERATION CEPHALOSPORIN ANTIBIOTICS	CEFDINIR SUS 250/5ML	898	$19,250.09	$21.44	0.46%
BIGUANIDES	METFORMIN TAB 500MG	880	$7,298.36	$8.29	0.45%
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE CAP 40MG	876	$8,094.67	$9.24	0.45%
VITAMIN B COMPLEX	FOLIC ACID TAB 1MG	874	$7,770.78	$8.89	0.45%
1ST GENERATION CEPHALOSPORIN ANTIBIOTICS	CEPHALEXIN CAP 500MG	854	$9,531.10	$11.16	0.44%
OTHER MACROLIDE ANTIBIOTICS	AZITHROMYCIN TAB 250MG	848	$11,419.42	$13.47	0.43%
RESPIRATORY AND CNS STIMULANTS	METHYLPHENID TAB 54MG ER	840	$163,995.45	$195.23	0.43%
SEL.SEROTONIN,NOREPI REUPTAKE INHIBITOR	DULOXETINE CAP 60MG	826	$12,436.16	$15.06	0.42%
OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	IBUPROFEN TAB 800MG	813	$9,807.52	$12.06	0.42%
ANTIBACTERIALS (SKIN & MU	MUPIROCIN OINT 2%	812	$11,939.35	$14.70	0.42%
ADRENALS	PREDNISONE TAB 20MG	798	$7,351.67	$9.21	0.41%
OTHER MACROLIDE ANTIBIOTICS	AZITHROMYCIN SUS 200/5ML	779	$16,941.51	$21.75	0.40%
BENZODIAZEPINES (ANTICONV	CLONAZEPAM TAB 0.5MG	760	$7,981.84	$10.50	0.39%
HISTAMINE H2-ANTAGONISTS	RANITIDINE TAB 150MG	742	$7,723.97	$10.41	0.38%
BENZODIAZEPINES (ANTICONVULSANTS)	CLONAZEPAM TAB 1MG	740	$8,136.30	$11.00	0.38%
MISC. CENTRAL NERVOUS SYS	GUANFACINE TAB 2MG ER	731	$15,474.66	$21.17	0.37%
PROTON-PUMP INHIBITORS	PANTOPRAZOLE TAB 40MG	729	$8,738.38	$11.99	0.37%
ANTIDEPRESSANTS, MISCELLANEOUS	BUPROPN HCL TAB 150MG XL	729	$11,965.60	$16.41	0.37%
AMPHETAMINES	VYVANSE CAP 30MG	724	$195,416.17	$269.91	0.37%
CORTICOSTEROIDS (SKIN, MUCOUS MEMBRANE)	TRIAMCINOLON CRE 0.1%	714	$10,069.20	$14.10	0.37%
TOTAL TOP 50 DRUGS		**62,063**	**$1,471,161.46**	**$23.70**	**31.79%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 4/1/2019 – 6/30/2019					
AHFS Description	**Drug Label Name**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	HUMIRA PEN INJ 40MG/0.8	51	$333,215.91	$6,533.65	0.03%
RAPID-ACTING INSULINS	NOVOLOG INJ FLEXPEN	578	$310,657.65	$537.47	0.30%
ATYPICAL ANTIPSYCHOTICS	INVEGA SUST INJ 234/1.5	117	$302,123.20	$2,582.25	0.06%
RESPIRATORY AND CNS STIMULANTS	METHYLPHENID TAB 36MG ER	1,231	$270,570.77	$219.80	0.63%
ANTINEOPLASTIC AGENTS	AFINITOR DIS TAB 2MG	8	$239,145.44	$29,893.18	0.00%
MUCOLYTIC AGENTS	PULMOZYME SOL 1MG/ML	60	$222,542.82	$3,709.05	0.03%
HCV POLYMERASE INHIBITOR ANTIVIRALS	EPCLUSA TAB 400-100	9	$218,951.55	$24,327.95	0.00%
SKIN AND MUCOUS MEMBRANE	STELARA INJ 90MG/ML	11	$213,872.16	$19,442.92	0.01%
LONG-ACTING INSULINS	LANTUS SOLOS INJ 100/ML	576	$204,366.86	$354.80	0.30%
AMPHETAMINES	VYVANSE CAP 30MG	724	$195,416.17	$269.91	0.37%
AMPHETAMINES	VYVANSE CAP 40MG	658	$182,402.66	$277.21	0.34%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	HUMIRA PEN INJ 40/0.4ML	30	$181,650.72	$6,055.02	0.02%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	ENBREL SRCLK INJ 50MG/ML	33	$166,393.88	$5,042.24	0.02%
RESPIRATORY AND CNS STIMULANTS	METHYLPHENID TAB 54MG ER	840	$163,995.45	$195.23	0.43%
AMPHETAMINES	VYVANSE CAP 50MG	577	$154,361.30	$267.52	0.30%
ATYPICAL ANTIPSYCHOTICS	LATUDA TAB 40MG	145	$145,525.11	$1,003.62	0.07%
CYSTIC FIBROSIS (CFTR) POTENTIATORS	KALYDECO TAB 150MG	6	$143,429.88	$23,904.98	0.00%
ATYPICAL ANTIPSYCHOTICS	INVEGA SUST INJ 156MG/ML	77	$133,047.68	$1,727.89	0.04%
ATYPICAL ANTIPSYCHOTICS	ARISTADA INJ 882MG/3	52	$130,642.76	$2,512.36	0.03%
LONG-ACTING INSULINS	LEVEMIR INJ FLEXTOUC	284	$127,200.33	$447.89	0.15%
ADRENALS	FLOVENT HFA AER 110MCG	514	$121,413.03	$236.21	0.26%
AMPHETAMINES	VYVANSE CAP 20MG	429	$121,088.61	$282.26	0.22%
MOVEMENT DISORDER DRUG THERAPY	INGREZZA CAP 80MG	19	$120,138.10	$6,323.06	0.01%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL AER HFA	2,601	$118,999.57	$45.75	1.33%
SKIN AND MUCOUS MEMBRANE	COSENTYX PEN INJ 300DOSE	15	$115,537.83	$7,702.52	0.01%
CYSTIC FIBROSIS (CFTR) CORRECTORS	SYMDEKO TAB 100-150	8	$113,000.05	$14,125.01	0.00%
RAPID-ACTING INSULINS	NOVOLOG INJ 100/ML	236	$110,743.41	$469.25	0.12%
ATYPICAL ANTIPSYCHOTICS	LATUDA TAB 80MG	100	$109,892.82	$1,098.93	0.05%
SOMATOTROPIN AGONISTS	NORDITROPIN INJ 10/1.5ML	31	$105,479.18	$3,402.55	0.02%
CYSTIC FIBROSIS (CFTR) CORRECTORS	ORKAMBI GRA 100-125	5	$104,648.65	$20,929.73	0.00%
CYSTIC FIBROSIS (CFTR) CORRECTORS	ORKAMBI GRA 150-188	5	$104,648.65	$20,929.73	0.00%
RESPIRATORY AND CNS STIMULANTS	METHYLPHENID TAB 27MG ER	669	$101,643.22	$151.93	0.34%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	XELJANZ XR TAB 11MG	24	$100,737.30	$4,197.39	0.01%
RIFAMYCIN ANTIBIOTICS	XIFAXAN TAB 550MG	54	$99,529.56	$1,843.14	0.03%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	HUMIRA INJ 40/0.4ML	16	$97,700.66	$6,106.29	0.01%
DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS	JANUVIA TAB 100MG	229	$95,889.56	$418.73	0.12%
RESPIRATORY AND CNS STIMULANTS	METHYLPHENID TAB 18MG ER	553	$94,569.99	$171.01	0.28%
RAPID-ACTING INSULINS	NOVOLOG INJ PENFILL	225	$93,527.64	$415.68	0.12%
INCRETIN MIMETICS	VICTOZA INJ 18MG/3ML	129	$92,663.38	$718.32	0.07%
AMPHETAMINES	VYVANSE CAP 70MG	333	$90,439.94	$271.59	0.17%
ATYPICAL ANTIPSYCHOTICS	ABILIFY MAIN INJ 400MG	41	$89,691.87	$2,187.61	0.02%
HEMOSTATICS	XYNTHA SOLOF INJ 1000UNIT	4	$88,016.40	$22,004.10	0.00%
MISCELLANEOUS ANTICONVULS	EPIDIOLEX SOL 100MG/ML	49	$86,442.23	$1,764.13	0.03%
HIV INTEGRASE INHIBITORS	GENVOYA TAB	29	$85,191.32	$2,937.63	0.01%
MISCELLANEOUS ANTICONVULS	LYRICA CAP 150MG	160	$84,994.06	$531.21	0.08%
ATYPICAL ANTIPSYCHOTICS	INVEGA TRINZ INJ 819MG	11	$84,973.35	$7,724.85	0.01%
HIV INTEGRASE INHIBITORS	BIKTARVY TAB	29	$84,111.92	$2,900.41	0.01%
CORTICOSTEROIDS	CIPRODEX SUS 0.3-0.1%	370	$83,387.72	$225.37	0.19%
AMPHETAMINES	VYVANSE CAP 60MG	304	$83,053.01	$273.20	0.16%
LONG-ACTING INSULINS	TRESIBA FLEX INJ 200UNIT	124	$80,501.56	$649.21	0.06%
TOTAL TOP 50 DRUGS		**13,383**	**$7,002,166.89**	**$523.21**	**6.85%**

Utilization

Time frame: 4/1/2019 – 6/30/2019
Red font denotes drug is on Prior Authorization

CGRP Inhibitors

	1Q 2019				2Q 20109			
Drug Name	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizing Members**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizing Members**
Aimovig	48	$27,102.51	$564.64	22	53	$30,139.63	$568.67	22
Ajovy	10	$5,630.40	$565.35	6	4	$2,248.20	$562.05	2
Emgality	4	3,350.46	$837.62	3	10	$7,288.66	$728.87	6

Orilissa

	1Q 2019				2Q 20109			
Drug Name	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizing Members**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizing Members**
Orilissa	3	$2,511.49	$837.16	2	0			

*Some states are watching utilization; other states added to PA

ADD/ADHD Drugs (26 years old and older only)

Summary

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age 26-64 years
Amphetamines	1,050	$130,738.82	$124.51	362	26-64
Respiratory & CNS Stimulants	245	$31,087.49	$126.89	94	29-62
Central Alpha-Agonists	4	$273.28	$68.32	2	28, 32
Misc Central Nervous System	153	$10,074.37	$65.85	51	26-61
Wakefulness-Promoting Agents	42	$4,839.59	$115.23	18	28-64

Amphetamine

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age 26-64 years
Amphetamine-dextroamphetamine • Amphet/dextr tab • Amphet/dextr cap ER • Mydavis	694	$33,995.70	$48.99	234	26-64
Dextroamphetamine sulfate • dextroamphetamine tab • dextroamphetamine cap ER	25	$2,666.81	$106.67	12	27-58
Lisdexamfetamine dimesylate • Vyvanse cap	331	$94,076.31	$284.22	136	26-64

Respiratory & CNS Stimulants

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Dexmethylphenidate • dexmethylphenidate tab • dexmethylphenidate cap ER	27	$2,705.26	$100.19	10	28-59
Methylphenidate hcl • methylphenidate cap • methylphenidate cap ER • methylphenidate tab • methylphenidate tab ER	218	$28,482.23	$130.65	84	26-62

Misc Central Nervous System

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Atomoxetine • atomoxetine cap	112	$9,213.44	$82.26	39	26-54
Guanfacine (ADHD) • guanfacine tab ER	41	$860.93	$21.00	13	26-61

Central Alpha-Agonists

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Clonidine hcl (ADHD) • clonidine tab ER	4	$273.28	$68.32	2	28, 32

Wakefulness-Promoting Agents

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Modafinil • modafinil tab • Provigil tab	29	$4,287.51	$147.85	12	28-64
Armodafinil • armodafinil tab	13	$552.08	$42.47	6	28-62

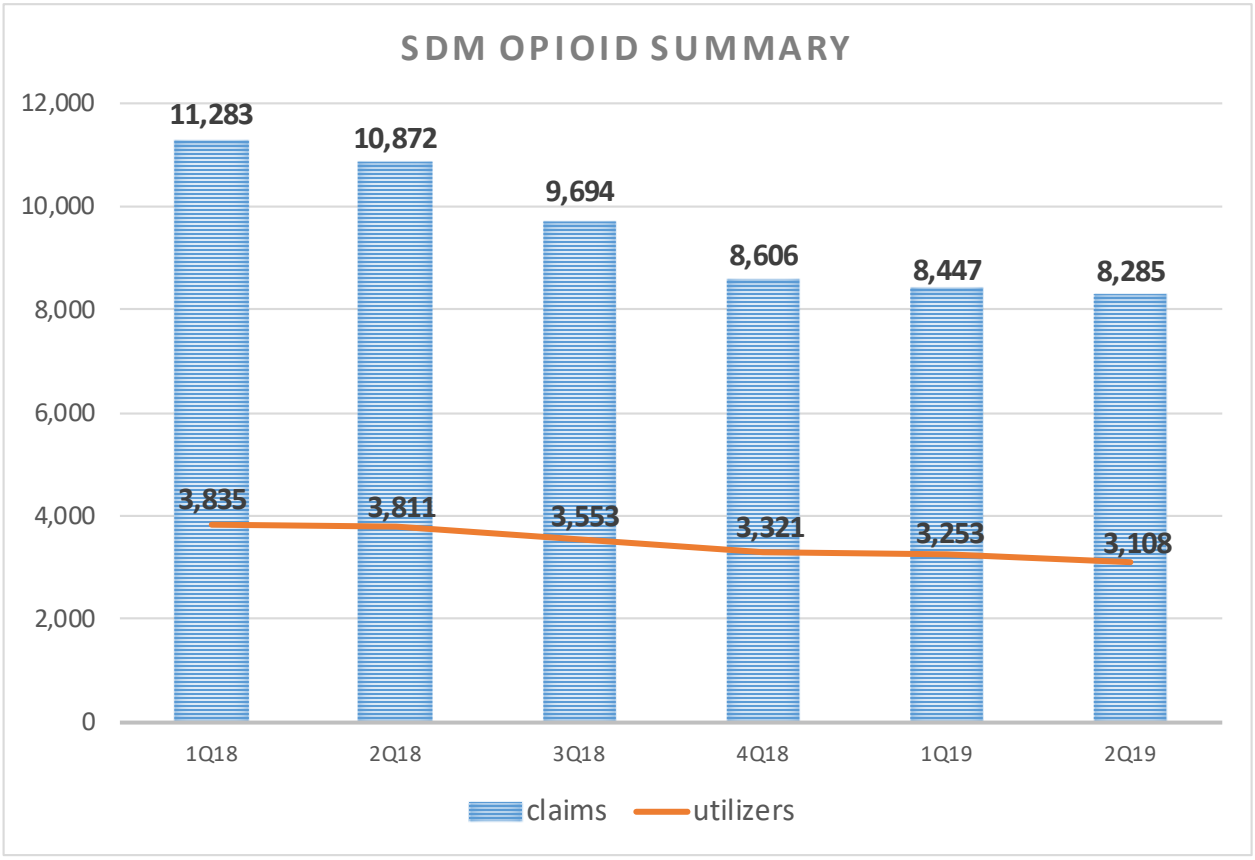
Concomitant therapy with ADD/ADHD medication:

- Antipsychotics – 133 recipients (atypical antipsychotics or phenothiazines)
- Benzodiazepines – 180 recipients
- Opioids – 112 recipients
- Benzodiazepines & opioids – 56 recipients
- Antipsychotics, benzodiazepines, & opioids – 18 recipients

Opioid Update

	Number of Unique Utilizing Members	Total # Opioid Rxs	Avg Days Supply (Total Days Supply/ Total Rxs)	Avg fill quantity (Total Quantity/ Total Rxs)	Total # Rxs	% of Opioid Rxs (Total Opioid Rxs/Total Rxs)	Clinical Edits
Jan-18	2,065	3,149	15.31	67.34	74,581	4.22%	
Feb-18	1,944	2,745	15.45	68.64	67,030	4.10%	
Mar-18	2,075	3,060	15.28	67.36	71,322	4.29%	
Apr-18	1,960	2,837	15.09	67.25	67,217	4.22%	
May-18	1,987	2,943	15.19	68.84	69,310	4.25%	
Jun-18	1,916	2,740	14.17	62.48	62,761	4.37%	Decrease refill threshold
Jul-18	1,878	2,732	15.09	64.52	63,910	4.27%	
Aug-18	1,882	2,536	15.19	64.94	68,156	3.72%	Opioid Naïve & LAO-SAO
Sep-18	1,719	2,282	15.24	63.38	64,471	3.54%	
Oct-18	1,754	2,405	14.98	62.45	71,559	3.36%	MED 300
Nov-18	1,684	2,277	15.60	65.35	67,871	3.35%	MED 270
Dec-18	1,628	2,173	15.48	66.15	64,196	3.38%	MED 240
Jan-19	1,695	2,343	15.23	61.86	72,293	3.24%	MED 220
Feb-19	1,615	2,172	14.81	60.10	67,280	3.23%	MED 200
Mar-19	1,682	2,284	15.18	61.90	68,149	3.35%	MED 180
Apr-19	1,660	2,253	15.37	62.13	67,839	3.32%	MED 160
May-19	1,637	2,272	15.74	62.00	68,112	3.34%	MED 140
Jun-19	1,547	2,073	15.27	62.27	59,282	3.50%	MED 130

MME/Day	< 90	90–179	180-240	> 240
January 2018	1,677	186	68	92
February 2018	1,592	195	58	64
March 2018	1,707	188	64	73
April 2018	1,606	196	52	62
May 2018	1,615	214	50	63
June 2018	1,592	163	48	62
July 2018	1,543	181	48	56
August 2018	1,598	138	34	55
September 2018	1,447	138	36	44
October 2018	1,483	137	32	50
November 2018	1,423	134	28	43
December 2018	1,375	125	30	44
January 2019	1,421	126	42	41
February 2019	1,355	122	28	39
March 2019	1,416	126	30	37
April 2019	1,395	125	29	33
May 2019	1,361	130	32	32
June 2019	1,299	121	24	30


SDM OPIOID SUMMARY
12,000
10,000
8,000
6,000
4,000
2,000
0
11,283
10,872
9,694
8,606
8,447
8,285
3,835
3,811
3,553
3,321
3,253
3,108
1Q18
2Q18
3Q18
4Q18
1Q19
2Q19
claims
utilizers

Opioid Utilization Snapshot

SDM 2Q2019

Mar 19 to Jun 19

Opioid Claims **8,285**

3.9% prescription claims filled for an opioid

0.4% lower than Med D benchmark

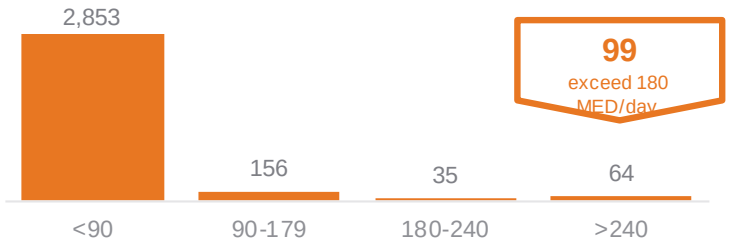
Utilizers **3,108**

34.8% are high utilizers [1]

15.2% lower than high utilizers Med D benchmark

Utilizers by Cumulative MED[4]

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



Shoppers: Poly Pharmacy

54 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

140 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

1Q2019

Dec 18 to Mar 19

Opioid Claims **8,447**

3.9% prescription claims filled for an opioid

0.5% lower than Med D benchmark

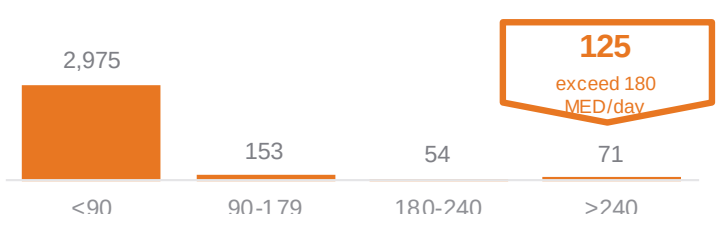
Utilizers **3,253**

33.6% are high utilizers [1]

10.3% lower than high utilizers Med D benchmark

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

56 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

169 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

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[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.

SDM 2Q2019

Mar 19 to Jun 19

Opioid Utilization Snapshot

Opioid Claims

8,285

3.9% prescription claims filled for an opioid

0.4% lower than Med D benchmark

Utilizers

3,108

34.8% are high utilizers[1]

15.2% lower than high utilizers Med D benchmark

Short acting opioids **61.4%** of opioid Rxs

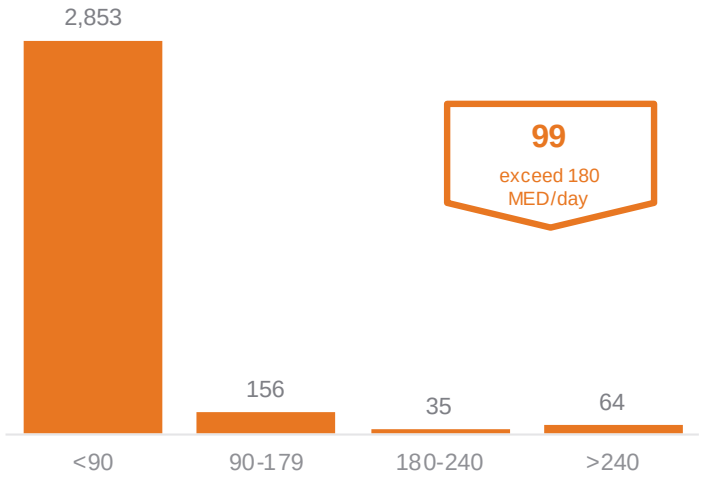
MAT[2] **538** of opioid Rxs

Rescue Therapy[3] 19 Rx(s)

CDC Guidelines advise prescribers to manage pain with lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day

Utilizers by Cumulative MED[4]

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



[1]Defined as 3+ opioid scripts within 120 days period; [2] **MAT** - Medication Assisted Therapy (e.g., buprenorphine, etc..); [3] **Overdose Rescue Therapy** – opioid overdose reversal with Narcan (naloxone), etc. [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.

SDM 2Q2019

Mar 19 to Jun 19

Opioid Utilization Opportunity Assessment

Shoppers: Poly Pharmacy

54

opioid utilizing members with 3+ pharmacies

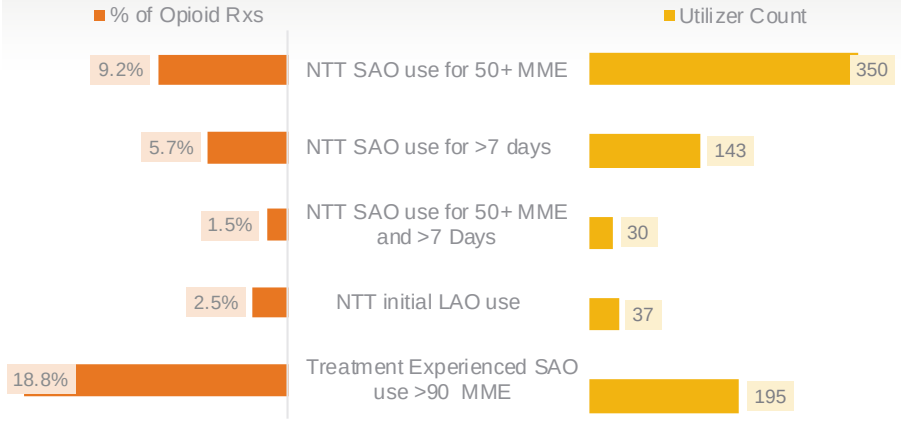
Shoppers: Poly Prescriber

140

opioid utilizing members with 3+ prescribers

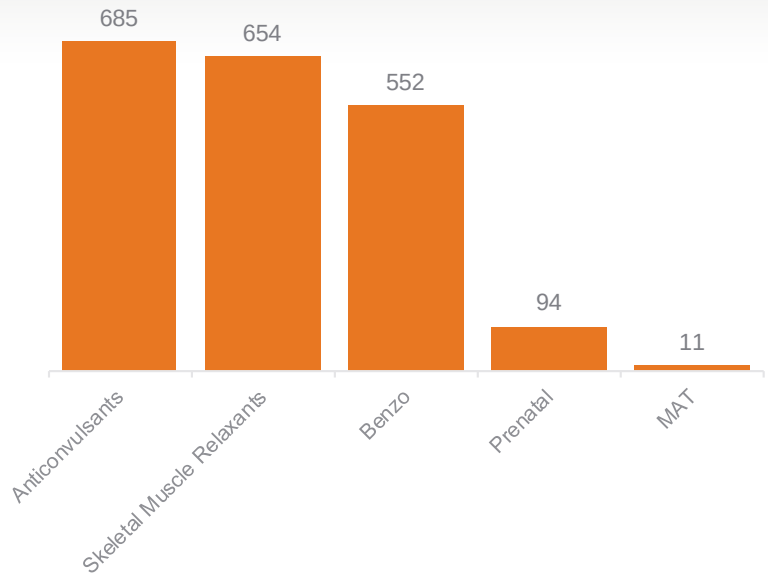
14.8%
of all Opioid Rxs

Non-Compliance to CDC Guidelines[7] for Opioid Prescriptions (NTT[8] and Chronic)



A retrospective review of claims indicates that **485 utilizing members** during this timeframe would have hit our opioid fill UM sif program was implemented.

Utilizers with Opioid Medication Combinations[9]



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[7]JAMA. 2016 Apr 19;315(15):1624-45. doi: 10.1001/jama.2016.1464; [8]NTT – New To Therapy SAO – Short Acting Opioid; LAO – Long Acting Opioid;
[9]Anticonvulsants - gabapentin, pregabalin, anticonvulsant benzodiazepines (clobazam, clonazepam, diazepam)

Field Definitions

Dashboard is based on the 120 days of most recent history claims.

Opioid Utilization Snapshot

Opioid claims – total number of opioid claims identified within most recent 120 days claims history
% of Opioid claims - % of opioid claims out of total claims with the period
Benchmark % (claims)- indicates percent difference of your prescription claims filled for an opioid in comparison to segment benchmark
% of Short Acting Opioids – percent of SAO scripts out of total opioid scripts
MAT Rxs – a number of Medication Assisted Therapy (e.g., buprenorphine, etc.) scripts out of total opioid scripts
Rescue Therapy – a number of Rxs for opioid overdose reversal with Narcan (naloxone), etc
Utilizer count – total number of utilizers with opioid Rxs within the period
% of high utilizers - % of utilizers with 3+ opioid scripts within 120 days period
Benchmark % (utilizers)- indicates percent difference of your opioid utilizers in comparison to segment benchmark
Utilizers by Cumulative MED (graph) - Morphine Equivalent Dose is relative potency of an opioid to standard of morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period; **[Total call out]** is a sum of utilizers with 180+ MED.
MME – Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose.

Opioid Utilization Opportunity Assessment

Shoppers: Poly Pharmacy – a number of opioid utilizing members with 3 or more pharmacies
Shoppers: Poly Prescriber – a number of opioid utilizing members with 3 or more prescribers
Non-Compliance to CDC Guidelines for Opioid Prescriptions (NTT and Chronic) (graph) – depicts a number of members and % opioid Rxs for New To Therapy (NTT) and chronic opioid use for each of the defined categories; **%Total** – indicates total percent of opioid scripts for the categories.
Retrospective members (call out) - a retrospective review of claims indicating the number members that would have hit Orx opioid fill UMs if program was implemented during the reporting time period.
Opioid Medication Combinations of High-Risk (graph) – depicts a number of opioid utilizers for each opioid/drug type combination.

Utilization

Albuterol Inhalers

Time frame: July 2017 to June 2019

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Albuterol AER HFA (Jan 2019)	3,712	$168,881.37	$45.49	2,334	0-68
ProAir AER HFA (July 2017)	9,462	$627,087.53	$66.27	3,696	0-92
ProAir Respi AER (Nov 2017)	207	$13,208.97	$63.81	107	2-64
Proventil HFA (Nov 2017)	1,757	$155,455.39	$88.48	710	0-89
Ventolin HFA (Aug 2017)	10,414	$629,278.88	$60.43	4,028	0-86
Total	**25,552**	**$1,593,912.14**	**$62.38**		**0-92**

Age Group	Total Rx	Paid Amount	Paid/Rx	Utilizing Members
0 years	128	$7,900.97	$61.73	89
1-4 years	1,271	$79,533.27	$62.58	675
5-12 years	6,813	$438,909.51	$64.42	2,801
13-17 years	5,208	$324,480.66	$62.30	2,043
18-24 years	1,542	$93,541.50	$60.66	683
25-39 years	3,347	$200,963.11	$60.04	1,291
40-59 years	5,594	$346,623.93	$61.96	1,261
60-92 years	1,649	$101,959.19	$61.83	329

Prescriber Description	Total Rx	Paid Amount	Utilizers	Age Range	% Utilization
None	287	$18,690.75	287	0-64	**1.13%**
Adolescent Medicine, Pediatrics	70	$4,833.57	24	3-18	
Allergy	76	$5,020.34	40	0-62	**1.51%**
Allergy & Immunology	297	$18,532.77	97	1-64	
Allergy & Immunology, Clinical & Lab Immunology	9	$516.56	1	15	
Internal Medicine, Allergy & Immunology	3	$203.09	1	7	
Anesthesiology	1	$60.52	1	54	
Cardiology	29	$1,920.90	10	9-72	
Clinical Nurse Specialty, Family Health	1	$87.64	1	18	
Clinical Nurse Specialty, Critical Care	27	$1,610.93	13	5-55	
Critical Care, Pediatrics	24	$1,543.86	19	2-17	
Dentist, General Practice	1	$116.84	1	16	
Emergency Medical Services	3	$157.64	2	12, 26	**1.16%**
Emergency Medicine	294	$17,970.36	220	0-63	
Family Practice	6,669	$409,434.69	2,214	0-91	**26.6%**
Family Practice, Adult Medicine	129	$7,540.72	44	2-63	
General Practice	4	$282.78	2	20, 22	
Geriatric Medicine	2	$127.11	1	36	
Geriatric Medicine, Family Medicine	1	$57.22	1	61	
Hematology & Oncology	4	$216.38	4	49-60	
Hematology & Oncology, Pediatric	15	$1,018.99	4	8-20	
Hospitalist	40	$2,537.06	22	1-63	

Internal Medicine	982	$60,694.54	294	3-64	**4.22%**
Internal Medicine, Critical Care	95	$5,501.03	25	14-64	
Neonatal/Perinatal Medicine	13	$1,042.78	6	4-14	
Nephrology/Renal Medicine	8	$638.91	2	51-57	
Neurodevelopmental Disabilities	1	$60.52	1	12	
Neuromusculoskeletal Medicine, Sports Medicine	2	$121.89	2	32, 35	
Nurse Midwife	19	$1205.97	13	9-57	
Nurse Practitioner	1,078	$66,732.70	548	0-74	**15.05%**
Nurse Practitioner, Adult Health	28	$1,091.37	9	38-57	
Nurse Practitioner, Family Health	2,739	$170,835.32	1,296	1-80	
Nurse Practitioner, Neonatal Care	7	$429.47	3	0-16	**2.53%**
Nurse Practitioner, Occupational Health	3	$172.98	3	11-31	
Nurse Practitioner, Pediatric Care	486	$30,942.09	217	0-37	
Nurse Practitioner, Primary Care	135	$8,475.94	66	2-61	
Nurse Practitioner, Psychiatric	1	$67.69	1	14	
Nurse Practitioner, Psychiatric/Mental Health	2	$129.66	2	19, 34	
Nurse Practitioner, Womens Health	12	$766.99	11	3-56	
Obstetrics & Gynecology	185	$11,091.75	92	15-41	
Optometrist	1	$87.09	1	56	
Orthopedic Surgery	3	$168.59	3	26-38	
Otolaryngology	30	$1,873.04	9	5-63	
Pediatrics	3,202	$205,763.74	1,467	0-64	**12.53%**
Physical Medicine & Rehabilitation	21	$1,196.57	9	14-64	
Physical Medicine & Rehabilitation, Pain Mgmt	1	$58.88	1	46	
Physician Assistant	3,165	$196,876.22	1,532	0-86	**14.71%**
Physician Assistant, Medical	592	$37,358.73	259	0-64	
Physician Assistant, Surgical	2	$117.62	2	25, 43	
Plastic Surgery, Facial	1	$62.12	1	10	
Preventive Medicine, Occupational Medicine	2	$122.61	2	9, 10	
Psychiatry	37	$2,105.54	27	9-57	
Psychiatry, Child & Adolescent	5	$300.38	2	14-17	
Pulmonary Disease	219	$15,139.30	55	18-64	**7.31%**
Pulmonology, Pediatric	1,648	$99,815.65	517	0-21	
Sleep Medicine	18	$1,007.58	4	47-61	
Sports Medicine, Family Practice	46	$3,014.64	12	8-53	
Student in an Organized Health Care Education/ Training Program/Student, Health Care	2,462	$155,060.08	955	0-92	**9.64%**
Substance Abuse Rehabilitation Facility/Substance Abuse Treatment, Children	2	$129.81	2	13, 17	
Surgery, General	28	$1,787.26	16	7-73	
Surgery, Transplant	2	$109.77	2	60, 63	
Urology	1	$116.63	1	13	

State	Quantity Limits
Georgia Medicaid	2 MDI per 30 days
Indiana Medicaid	3 MDI per 30 days for ages 18 years old and younger 2 MDI per 30 days for ages 19 years old and older
Nevada Medicaid	2 MDI per 30 days
TennCare	2 MDI per 30 days

North Dakota Medicaid	ProAir HFA – 2 MDI every 6 months (over 2 puffs per day) Ventolin HFA – 2 MDI every 4 months (over 3 puffs per day) /concurrent steroid inhaler required (can be single or combination inhaler or neb) Albuterol Nebulizers – 7 nebulizers per day Inhalers and Nebulizers are not paid together

Buprenorphine PA

Red font denotes drug is on Prior Authorization

Time frame: July 2018 to June 2019

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Belbuca MIS (buprenorphine)	60	$22,489.43	$374.82	21	26-60
Butrans DIS (buprenorphine)	24	$8,426.11	$351.09	7	37-63
buprenorphine DIS	103	$40,608.93	$394.26	24	16-64
buprenorphine SUB	509	$30,385.86	$59.70	59	20-59
Suboxone MIS (buprenorphine-naloxone)	267	$102,122.22	$382.48	38	20-50
buprenorphine-naloxone MIS	89	$28,755.61	$323.10	31	21-61
Zubsolv SUB (buprenorphine-naloxone)	28	$11,018.52	$393.52	3	27-48
buprenorphine-naloxone SUB	303	$29,530.73	$97.46	41	17-57
Total	**1,383**	**$273,337.41**	**$197.64**		**16-64**

Prescriber Description	Total Rx	Paid Amount	Utilizers	Age Range	% Utilization
Anesthesiology, Pain Management	20	$4,501.08	6	28-53	
Family Practice	347	$68,461.79	45	21-60	**25.09%**
Gastroenterology	7	$4,416.47	1	48	
Hospitalist	14	$4,298.15	10	20-50	
Internal Medicine	67	$24,384.95	15	21-64	**4.84%**
Nurse Practitioner Nurse Practitioner, Acute Care Nurse Practitioner, Family Health	137	$48,542.53	39	26-63	**9.91%**
Orthopedic Surgery	4	$179.74	3	21-44	
Physical Medicine & Rehabilitation	10	$757.98	2	28, 31	
Physician Assistant Physician Assistant, Surgical	193	$40,858.47	27	16-63	**13.96%**
Preventive Medicine, Occupational Medicine	5	$714.83	1	40	
Psychiatry	346	$36,585.70	36	20-59	**25.02%**
Student in an Organized Health Care Education/ Training Program/Student, Health Care	224	$39,073.50	36	17-57	**16.20%**
Surgery, General	9	$562.22	3	37-47	

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

Please note: All information below is required to process this request.
Fax to 1-800-527-0531
Mon-Sat: 7am to 7pm Central

Bunavail™, buprenorphine sublingual (SL) tablet, buprenorphine-naloxone SL tablet, Suboxone®, Zubsolv® Prior Authorization Request Form

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

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

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

Clinical Information (required)

Select the diagnosis below:
❑ Treatment of documented opioid dependence
❑ Other diagnosis: _____ ICD-10 Code(s): _____

Provider registration:
Is the provider registered to prescribe buprenorphine/buprenorphine-naloxone under the Substance Abuse and Mental Health Services Administration (SAMHSA)? ❑ **Yes** ❑ **No**

Clinical information:
Is the patient taking other opioids, tramadol or carisoprodol? ❑ **Yes** ❑ **No**
If **yes,** will the patient be weaned off prior to initiation of therapy of the requested medication? ❑ **Yes** ❑ **No**

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

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

_____

_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-800-527-0531.

Office use only: OpioidDependence_SouthDakotaMedicaid_2017May-P

Opioid and BZD/Antipsychotic Utilization

Time frame: July 2018 to June 2019

Opioid and benzodiazepine concomitant utilization – 943 opioid utilizers are also taking BZD

Drug	Total Rxs	Utilizing Members
ALPRAZOLAM	16,279	293
CHLORDIAZEPOXIDE HCL	326	13
CLORAZEPATE DIPOTASSIUM	17	3
DIAZEPAM	10,143	308
LORAZEPAM	21,331	415

Opioid and antipsychotics concomitant utilization: 766 opioid utilizers are also taking either phenothiazines, antipsychotics, atypical antipsychotics, or butyrophenones

Therapeutic Drug Class	Drug	Total Rxs	Utilizing Members
ATYPICAL ANTIPSYCHOTICS	ARIPIPRAZOLE TAB	6,043	187
ATYPICAL ANTIPSYCHOTICS	ARIPIPRAZOLE LAUROXIL	270	13
ATYPICAL ANTIPSYCHOTICS	ASENAPINE MALEATE	82	3
ATYPICAL ANTIPSYCHOTICS	BREXPIPRAZOLE	890	25
ATYPICAL ANTIPSYCHOTICS	CARIPRAZINE HCL	949	24
ATYPICAL ANTIPSYCHOTICS	CLOZAPINE	1,521	20
ATYPICAL ANTIPSYCHOTICS	LURASIDONE HCL	1,967	74
ATYPICAL ANTIPSYCHOTICS	OLANZAPINE	3,657	119
ATYPICAL ANTIPSYCHOTICS	PALIPERIDONE TAB	114	10
ATYPICAL ANTIPSYCHOTICS	PALIPERIDONE PALMITATE	831	21
ATYPICAL ANTIPSYCHOTICS	QUETIAPINE FUMARATE	15,453	248
ATYPICAL ANTIPSYCHOTICS	RISPERIDONE	2,609	92
ATYPICAL ANTIPSYCHOTICS	ZIPRASIDONE HCL	752	18
ANTIPSYCHOTICS, MISC	LOXAPINE SUCCINATE	198	5
BUTYROPHENONES	HALOPERIDOL TAB	431	6
BUTYROPHENONES	HALOPERIDOL DECANOATE	42	1
BUTYROPHENONES	HALOPERIDOL LACTATE	5	2
PHENOTHIAZINES	CHLORPROMAZINE HCL	107	3
PHENOTHIAZINES	FLUPHENAZINE DECANOATE	48	1
PHENOTHIAZINES	FLUPHENAZINE HCL	200	2
PHENOTHIAZINES	PROCHLORPERAZINE TAB	114	4
PHENOTHIAZINES	PROCHLORPERAZINE MALEATE	1,941	74
PHENOTHIAZINES	THIORIDAZINE HCL	7	2
PHENOTHIAZINES	TRIFLUOPERAZINE HCL	46	1

Effective Management of Acute Pain

Recommendations from the Ad Hoc Committee on Pain Management and Prescription Drug Abuse

South Dakota State Medical Association

Draft date: 06/01/2019

Participants in the Ad Hoc Committee's recommendations on acute pain management:

Nurse Practitioner Association of South Dakota
South Dakota Board of Dentistry
South Dakota Board of Medical & Osteopathic Examiners
South Dakota Board of Nursing
South Dakota Board of Pharmacy
South Dakota Dentistry Association
South Dakota Department of Health
South Dakota Department of Social Services
South Dakota Pharmacists Association

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Executive Summary

Although the focus of much public and professional attention in the past decade has been on the problems related to opioid analgesics for treating chronic non-cancer pain, the treatment and management of acute pain is an equally important topic because many of the same dynamics (e.g., prescribing opioids when non-opioids may be just as effective, or prescribing higher doses/durations than needed) are at work with acute pain as with chronic pain.

Properly and responsibly managing acute pain is desirable not only because it relieves patient suffering, but because it reduces the chances that acute pain will morph into chronic pain, and responsible prescribing can help stem the tide of opioid diversion, misuse, and abuse. Opioids do, of course, play an invaluable role in the management of acute pain, but they carry important risks, as well, and thus are generally viewed as second-line agents or to be used only as part of a multi-modal approach. The risks of opioids, even when used for acute pain and for relatively short durations, are amplified among older adults, patients with impaired renal or hepatic function, those with COPD, cardiopulmonary disorders, sleep apnea, or mental illness, and in anyone likely to combine opiates with other respiratory depressants such as alcohol or benzodiazepines.[3]

This white paper summarizes the current evidence for optimal management of acute pain, with the key recommendations being:

- *Assess the degree of expected or actual pain from an injury, surgery, or procedure*
- *Consider patient-related and drug-related factors related to pain and pain relief*
- *Use multimodal pain control methods, emphasizing, when appropriate, non-pharmacological methods and non-opioid pharmacotherapy*
- *If opioids are deemed necessary, prescribe only an amount to cover the expected pain or realistic duration of time to a follow-up appointment*
    - *Check PDMP AWARxE, South Dakota's prescription drug monitoring program.*
    - *Screen for risk factors such as history of substance abuse disorder or mental illness.*
    - *Prescribe only short-acting opioids.*
    - *Discuss with patients safe storage, use, and disposal of opioids.*
    - *Taper or discontinue opioids as soon as possible.*
    - *Re-evaluate patients if healing does not follow the expected course.*

Although the practices described in these guidelines are intended to apply broadly, they are not intended to establish a "standard of care." Providers – to include all prescribers - must exercise their own

best medical judgment when providing treatment, taking all relevant circumstances into account, including the potential for abuse, diversion and risk for addiction.

Introduction

As unpleasant as it is, acute pain serves an important adaptive biological purpose: it alerts us to internal or external damage or dysfunction in our bodies. Acute pain can provoke a range of protective reflexes (e.g., withdrawal of a damaged limb, muscle spasm, autonomic responses) that can help the body heal. Even brief episodes of acute pain, however, can induce suffering, neuronal remodeling, and can set the stage for chronic pain.[4] Associated behaviors (e.g., bracing, abnormal postures, excessive reclining) may further contribute to the development of chronic pain. An example of this phenomenon is persistent postsurgical pain (PPP), which is pain persisting beyond the expected healing period. Many common operations (e.g., mastectomy, thoracotomy, hernia repair, coronary artery bypass surgery) are associated with an incidence of PPP of up to 30-50 percent.[5] The intensity of perioperative and postoperative pain is estimated to contribute about 20 percent of the overall risk for transition from acute pain to PPP.[6]

In addition to the purely humanitarian value of reducing or eliminating acute pain, therefore, effectively and aggressively treating acute pain may reduce complications and progression to chronic pain states.[7]

Acute pain is a multidimensional experience that usually occurs in response to tissue trauma, and although responses to acute pain may be adaptive, they can have adverse physiologic and psychological consequences (e.g., reduced tidal volume, excessive stress response, or inability to comply with rehabilitation). Acute pain is more difficult to manage if permitted to become severe, so prompt and adequate treatment of acute pain is imperative, with the basic goals of:

- Early intervention, with prompt adjustments in the regimen for inadequately controlled pain
- Reduction of pain to acceptable levels
- Facilitation of recovery from underlying disease or injury

Although much attention has been paid in the past decade to the range of problematic issues related to opioid analgesics and chronic pain, many similar issues can be at work in the treatment of acute pain. For example, a number of studies demonstrate increased risk of new persistent opioid use in opioid-naïve patients after having been prescribed opioids for acute pain.[8-11] Although the risk of opioid misuse in patients prescribed opioids for acute post-surgical or post-procedural pain is relatively small (roughly 0.6 percent), the volume of such procedures (approximately 48 million ambulatory surgeries or procedures in 2010) translates into large numbers of patients (i.e., approximately 160,000) who may develop dependence, abuse, or overdose every year.[12]

A related issue with opioid prescription for acute pain is the risk of diversion or inappropriate use from leftover pills. Approximately 40-50 percent of those who abuse opioids initially obtain the drugs

from family members or friends with pills remaining from legitimate prescriptions.[13] Many studies have found excessive levels of routine opioid prescriptions for a range of surgical procedures or emergency department visits for painful conditions.[14,15] One study of 1,416 patients in a 6-month period found that surgeons prescribed a mean of 24 pills (standardized to 5 mg oxycodone) but that patients reported using a mean of only 8.1 pills (utilization rate 34 percent).[16]

The South Dakota State Medical Association's Committee on Pain Management and Prescription Drug Abuse has reviewed current literature and existing clinical guidelines in order to articulate the following recommendations for effective and responsible treatment of acute pain, including the use of opioid analgesics. Although the practices described in these guidelines are intended to apply broadly, they are not intended to establish a "standard of care." All prescribers must exercise their own best medical judgment when providing treatment, taking all relevant circumstances into account, including the potential for abuse, diversion, and risk for addiction associated with opioid analgesics.

Types and levels of acute pain

Acute pain is typically defined as pain concordant with the degree of tissue damage and which remits with resolution of the injury. A more holistic definition is "a complex, unpleasant experience with emotional and cognitive, as well as sensory, features that occur in response to tissue trauma."[17] This definition captures the multiple levels of effects that pain can have, as well as the fact that cognitive and emotional factors can influence how pain is perceived. The subjective experience of pain (as opposed to the purely physical phenomenon of nociceptive nerve activation) varies widely in degree (from mild to severe) and quality (dull, sharp, stinging, burning, throbbing, etc.) and is significantly modulated by such factors as:

- Type of injury or surgical procedure
- Cultural or ethic factors
- History of drug or alcohol use
- History of anxiety or depression
- Anatomic location

Injuries or procedures involving bones and joints tend to be more painful than those involving soft tissues.[16] For example, in one study of 5,703 ambulatory surgical patients, those having microdiscectomy were most likely to have severe pain, followed by laparoscopic cholecystectomy, shoulder surgery, elbow or hand surgery, ankle procedures, hernia repair, and knee surgery.[18] Variations in pain levels for different procedures can also be seen in data about the amount of opioids needed to

control pain. In one study, in which opioid doses were standardized to units of 5 mg pills of oxycodone, 5 pills were adequate for patients having partial mastectomy, 10 pills for partial mastectomy with lymph node biopsy, and 15 pills for laparoscopic cholecystectomy and inguinal hernia repair.[19] (Significantly, in this study, many patients used no opioids, ranging from 22 percent after hernia repair to 82 percent after partial mastectomy.) Another study found that in the 3 days post-surgery, patients having wrist or hand surgery used about 7 pills, those having forearm or elbows procedures used an average of 11 pills, and those having upper arm or shoulder procedures used an average of 22 pills (all pills standardized to oxycodone or hydrocodone 5 mg or codeine 30 mg).[16]

Table 1. Common types of acute pain[20]

Type	Source or Examples
Acute illness	Appendicitis, renal colic, myocardial infarction
Perioperative	• Head and neck surgery • Chest and chest wall surgery • Abdominal surgery • Orthopedic and vascular surgery (back, extremities)
Major trauma	Motor vehicle accident
Minor trauma	Sprain, laceration
Burns	Fire, chemical exposure
Procedural	Bone marrow biopsy, endoscopy, catheter placement, circumcision, chest tube placement, immunization, suturing
Obstetrical	Childbirth by vaginal delivery or Cesarean section

Assessing pain

The etiology of acute pain, as opposed to chronic pain, is typically straightforward since it is usually associated with some kind of obvious injury, disease process, surgery, or procedure. Nonetheless, it can be helpful to systematically evaluate the pain using pain scales (numerical or visual-analog) to increase the precision of a patient's self-report and provide a baseline against which to evaluate analgesia and/or healing over time. Consider the following steps in assessing acute pain:[21]

Ask the patient to describe the pain using 5 characteristics:

a. What makes the pain more or less intense?

b. What does the pain feel like? (i.e., dull, throbbing, sharp, pins-and-needles)

c. Does the pain spread anywhere?
d. How severe is the pain?
e. Is the pain constant or does it come and go?

The answers to these questions can help determine if the pain is nociceptive (i.e., the result of injury to bones and muscles) or neuropathic (i.e., the result of injury to peripheral or central nerves). Making this determination is important because neuropathic pain is not particularly responsive to non-steroidal anti-inflammatory drugs (NSAIDs) or opioids. Other medications such as antidepressants or anticonvulsants may be more appropriate first-line agents for neuropathic pain.

As will be detailed later in these guidelines, opioid analgesics should not typically be considered as first-line agents for acute pain, nonetheless, just when assessing patients in chronic pain, it is important to evaluate a patient in acute pain for risk of opioid dependence or abuse. Such assessment is not completely objective, and opinions differ about which patients should be more rigorously assessed. Some favor a "universal precautions" approach, in which all pain patients are considered to have some degree of vulnerability to abuse and addiction and, hence, all patients are given the same screenings and diagnostic procedures.[22] Some patient characteristics, however, do appear to be predictive of a potential for drug abuse, misuse, or other aberrant behaviors, particularly a personal or family history of alcohol or drug abuse.[23] Some studies also show that younger age and the presence of psychiatric conditions are associated with aberrant drug-related behaviors.[23]

Relatively brief, validated tools can help formalize assessment of a patient's risk of having a substance misuse problem (Table 2) and these should be considered for routine clinical use.[23] For more information on risk reduction strategies, a free online CME is available at www.opioidprescribing.com.

The 4Ps of Screening

- Parents – Did any of your parents have a problem with alcohol or drug use?
- Partner – Does your partner have a problem with alcohol or drug use?
- Past – In the past, have you had difficulties in your life because of alcohol or other drugs, including prescription medications?
- Present – In the past month, have you drunk any alcohol or used other drugs – illicit or otherwise?

Table 2. Tools for Patient Risk Assessment

Tool	Who Administers?	Length
Diagnosis, Intractability, Risk, Efficacy (DIRE)	Clinician	7 items
Opioid Risk Tool (ORT)	Clinician or patient self-report	5 yes/no questions
Screener and Opioid Assessment for Patients with Pain, Version 1 and Revised (SOAPP, and SOAPP-R)	Patient self-report	24 items

Using state PDMP for patients with acute pain

A standard part of assessing any patient in acute pain, even if opioid analgesics are not expected to be immediately prescribed, should be accessing the South Dakota prescription drug monitoring program PDMP AWARxE. This can help identify patients at higher risk for opiate overdose or opiate use disorder, and help determine which patients may benefit from great caution and increased monitoring or interventions when risk factors are present. Research indicates that most fatal overdoses could be identified retrospectively on the basis of two pieces of information – multiple prescribers and high total daily opiate dosage – both of which are available to prescribers through the PDMP AWARxE.

PDMP AWARxE offers point-of-care access to pharmacy dispensing records of controlled substances from prescribers. From these, clinicians can quickly assess patterns of prescription drug use that can be helpful in confirming or refuting suspicions of aberrant behaviors.

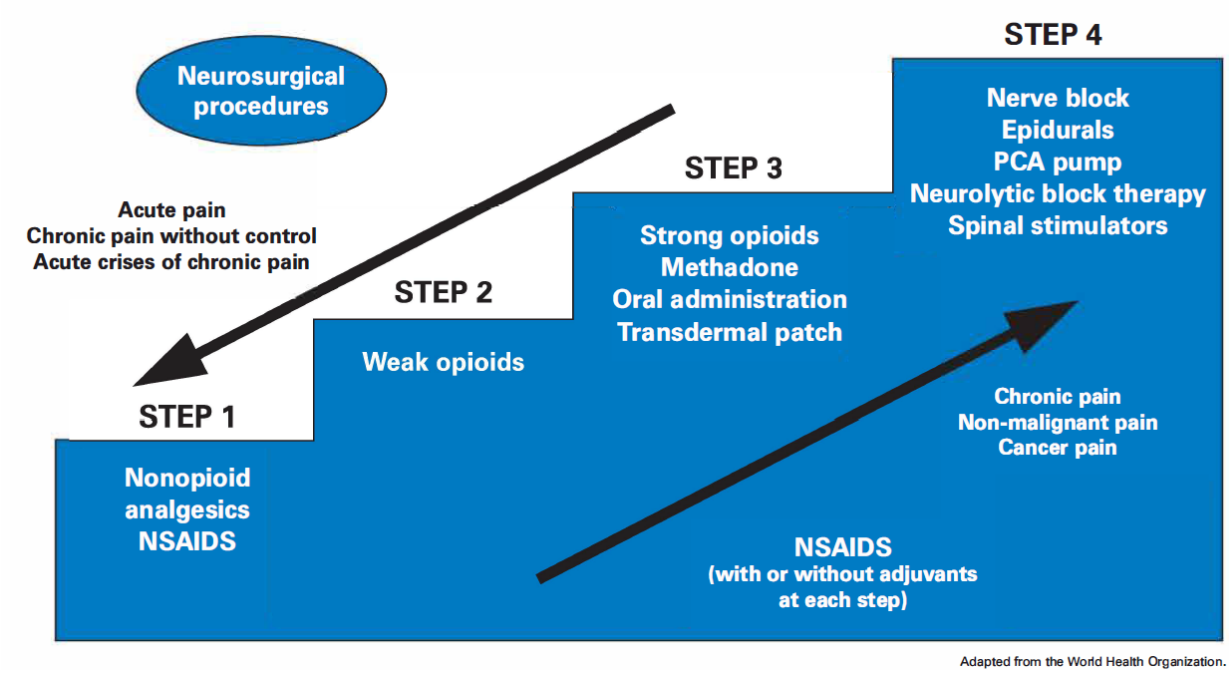
Information from PDMP AWARxE may also reveal that a patient is being prescribed medications whose combinations are contraindicated. By reviewing the PDMP each prescriber can identify other prescribers involved in the care of their patient. Pharmacies and practitioners that dispense any Schedule II, III, or IV controlled substances in South Dakota, or to an address in South Dakota, must report such dispensing to PDMP AWARxE.

Strategies for acute pain control

Ladder of pain

The World Health Organization advocates a 3-step "Pain relief ladder" model in which non-pharmacologic or non-opioid approaches are preferred as first-line pain treatment, followed by low-dose or low-potency opioids with or without adjunctive pharmacological or non-pharmacological therapies, and, for moderate to severe pain, higher doses and/or more potent opioids with or without adjunctive treatment.[24] Variations on this model include a "fast-track" approach that skips directly to step 3 for controlling intense acute pain, incorporation of "movement" on the ladder both up (when, for example, a disease process worsens) as well as down (in response to healing or remission of symptoms), and adding a 4th step that includes invasive procedures such as nerve blocks, neurolysis, epidurals, and spinal stimulators.[25]

Figure 1. 4-Step Adaptation of WHO analgesic ladder



Adapted from the World Health Organization.

Clinicians should bear in mind that the goal of pain treatment is not necessarily zero pain, but a level of pain that is tolerable and that allows the patient maximum physical and emotional functioning with the lowest risk of side effects, progression to chronic pain, or misuse or abuse. This requires an adroit balancing of many factors (both patient-related and drug-related). One way to operationalize this paradigm is with multimodal analgesia, in which several therapeutic approaches, each acting at different

sites of the pain pathway, are used, which can reduce dependence on a single medication and may reduce or eliminate the need for opioids.[26] Using both pharmacological and non-pharmacological interventions, and, if warranted, opioid and non-opioid medications can reduce overall opioid use as well as opioid-related adverse effects.

This approach involves the use of more than one method or modality of controlling pain (e.g., drugs from two or more classes, or drug plus non-drug treatment) to obtain additive beneficial effects, reduce side effects, or both. These modalities may operate through different mechanisms or at different sites (i.e., peripheral versus central actions).[26] One example of multimodal analgesia is the use of various combinations of opioids and local anesthetics to manage postoperative pain. Table 3 summarizes some specific examples of multimodal therapy; Appendix 1 provides a workflow guidline.

Some benefits of multimodal analgesia include earlier ambulation, oral intake, and hospital discharge for postoperative patients as well as higher levels of participation in activities necessary for recovery (e.g., physical therapy).[26] Some pain experts advocate revision of traditional postoperative care programs to include accelerated multimodal postoperative recovery programs.

Table 3. Examples of multimodal therapy

Combination of Agents
Systemic NSAID plus systemic opioid
Systemic NSAID plus epidural opioid and local anesthetic
Systemic NSAID plus local infiltration of anesthetic plus systemic opioid
Regional block plus systemic NSAID plus epidural opioid and local anesthetic
Ketamine plus opioid

Non-pharmacological treatments for acute pain

When possible, non-pharmacologic methods should be used, alone or combined with analgesics, to manage acute pain. The degree to which this can be done depends on the severity of pain, availability, and patient preference, but many non-pharmacological approaches can be very effective and their use avoids the potential side effects and risks associated with pharmacological interventions.

Non-pharmacologic methods for managing early-phase acute pain:[20]

- Application of cold (standard protocols are icing for 20 minutes every two hours or every 10 minutes, alternating with 10 minutes of rest)
- Compression

- Elevation
- Immobilization (although recovery from some injuries, such as ankle sprains, may be faster with graduated exercises rather than rest alone)[27]

Non-pharmacologic methods for late-phase acute pain and/or pain prophylaxis

- Physical therapy
- Yoga
- Hypnosis/guided imagery
- Massage

Physical methods of acute pain management can be helpful in all phases of care, including immediately after tissue trauma (e.g., rest, application of cold, compression, elevation) and late during the healing period (e.g., exercises to regain strength and range of motion). Mind/body or psychological therapies can encourage active patient participation in their care, address psychological or social dimensions of pain, and can support sustained improvements in pain and function with minimal risks. These therapies are not always, or fully, covered by insurance, and access and cost can be barriers, but for many patients, non-pharmacologic management can be used even with limited access to specialty care. A randomized trial comparing patients assigned to low-cost group aerobics vs. more expensive individual physiotherapy and muscle reconditioning sessions found similar reductions in low back pain intensity, frequency, or disability.[28] Low-cost options to increase physical activity include brisk walking in public spaces or use of public recreation facilities for group exercise.

Cognitive behavioral therapy (CBT) can help address psychosocial contributors to pain and has been shown to improve function.[29] Primary care clinicians can integrate elements of CBT into their practice by simply encouraging patients to take an active role in their care plan, by supporting patients in engaging in beneficial activities such as exercise, or by providing education in relaxation techniques and coping strategies. There may be free or low-cost patient support, self-help, and educational community-based programs in more populated areas of South Dakota that can provide stress reduction and other mental health benefits. Patients with more entrenched anxiety or fear related to pain, or other significant psychological distress, can be referred for formal therapy with a mental health specialist.

Multimodal therapies should be considered for patients not responding to single-modality therapy, and combinations should be tailored depending on patient needs, cost, and convenience. Additional details on some common non-pharmacological treatments shown to be effective in managing acute pain follow.

Physical therapy

Physical therapy may be useful for a range of musculoskeletal issues and can be helpful in recovering from acute pain-producing traumas initially treated with other methods. A 2018 study reported that patients with low back pain who first consulted a physical therapist were less likely to receive an opioid prescription compared to those who first saw their primary care provider.[30] Physical therapists typically create individualized exercise, stretches, and body alignment adjustments to help relax tight muscles, decrease back and joint pain, and improve range of motion. Professional guidelines have strongly recommended aerobic, aquatic, and/or resistance exercises for patients with osteoarthritis of the knee or hip[31] and maintenance of activity for patients with low back pain.[32]

Yoga

Yoga involves poses with a range of extensions and challenge, which can be tailored to an individual's level of flexibility, strength, and conditioning. Moderate evidence suggests that yoga can reduce late-stage acute pain, as well as chronic pain conditions, particularly back pain. For example, a 2017 trial randomized 131 patients (mean age 75) with lower extremity osteoarthritis to twice-weekly sessions of chair yoga vs. a health education program.[33] At 3-month follow-up, participants in the yoga group showed greater reductions in pain interferences (P=0.01) compared to control.[30] During the intervention, patients in the yoga group had reduced pain and improved gait speed compared to the control group. In addition to reducing pain, the people in the yoga group were more likely to have stopped taking pain relievers at one-year follow-up.

Massage

Massage therapy may help relieve muscular pain (acute or chronic) as well as reduce stress and anxiety. Some massage therapists specialize in working with people recovering from injuries or surgeries, or they may have focused training for treating particular conditions such as back or neck pain. A review of seven randomized trials with 352 participants suggests that massage as a stand-alone treatment may be better than no treatment for reducing pain.[34] The trials were diverse with respect to outcomes, massage techniques, and patient populations. Clinical effect sizes for pain were moderate with about a 20-point reduction in pain scores from a baseline of 50-60 points. The functional benefits were less clear; some trials showed no benefit while others showed improvement in the 50-foot walk test.

A 2011 study randomized 401 adults with back pain to two types of weekly massage (structural and relaxation) for 10 weeks vs. a usual care group. At the end of the study 36 percent of the adults having structural massage and 40 percent of the adults having relaxation massage reported that their pain was "much better" or "gone" vs. 4 percent of the control group.[35]

Hypnosis

Clinical hypnosis is a procedure in which a trained clinician or therapist gives a patient a series of verbal instructions with the goal of helping the patient enter a state of deep relaxation. In this relaxed state, the patient is aware of everything that is going on, but at the same time, becomes increasingly absorbed in using his or her imagination as directed by the therapist. Therapists often teach their patients self-hypnosis methods that they can employ on their own to reinforce and continue the process at home.

Evidence-based research on the use of hypnosis to relieve pain is limited, but a large, well-designed study, however a 2000 trial evaluated the effectiveness of hypnosis—termed "nonpharmacologic analgesia"—in easing pain and anxiety in people who were having minimally invasive surgical therapies such as angiograms, angioplasty, simple kidney procedures, or liver biopsies, during which they remained conscious.[36] Patients participated in a self-hypnosis relaxation session that involved deep-breathing and concentration techniques. The researchers found that these patients required less than half the amount of analgesic drugs compared to those receiving standard treatments. Procedures also took less time for the hypnosis group, and participants had lower levels of anxiety and pain at both one hour and four hours into the procedure.

Pharmacological management of acute pain

Most acute pain is nociceptive and responds to non-opioids and opioids. However, some adjuvant analgesics (e.g., local anesthetics) also are used to manage acute pain and medications for neuropathic pain are also important agents in the analgesic armamentarium. In general, mild-to-moderate acute pain responds well to oral non-opioids (e.g., acetaminophen, NSAIDs, and topical agents). Moderate to severe acute pain is more likely to require opioids, although, as mentioned earlier, lower doses and short durations may be appropriate.

NSAIDs and acetaminophen

NSAIDs, which include aspirin and other salicylic acid derivatives, and acetaminophen are used in the management of both acute and chronic pain such as that arising from injury, arthritis, dental procedures, swelling, or surgical procedures. Although they are weaker analgesics than opioids, acetaminophen and NSAIDs do not produce tolerance, physical dependence, or addiction and they do not induce respiratory depression or constipation. Acetaminophen and NSAIDs are often added to an opioid regimen for their opioid-sparing effect. Since non-opioids relieve pain via different mechanisms than opioids, combination therapy can provide improved relief with fewer side effects.

These agents are not without risk, however. Potential adverse effects of NSAIDs include gastrointestinal problems (e.g., stomach upset, ulcers, perforation, bleeding, liver dysfunction), bleeding (i.e., antiplatelet effects), kidney dysfunction, hypersensitivity reactions and cardiovascular concerns, particularly in the elderly.[37] The threshold dose for acetaminophen liver toxicity has not been established; however, the SDSMA recommends that the total adult daily dose should not exceed 3,000 mg in patients without liver disease (although the ceiling may be lower for older adults).[38]

The Food and Drug Administration (FDA) currently sets a maximum limit of 325 mg of acetaminophen in prescription combination products (e.g., hydrocodone and acetaminophen) in an attempt to limit liver damage and other potential ill effects of these products.[32]

Topical agents

Topical capsaicin and salicylates can both be effective for short term pain relief and generally have fewer side effects than oral analgesics, but their long-term efficacy is not well studied.[39,40] Topical NSAIDs and lidocaine have been reported to be effective for short-term relief of superficial pain with minimal side effects, although both are more expensive than topical capsaicin and salicylates. None of the topical agents are useful for non-superficial pain.

Anticonvulsants

Antiepileptic drugs (AEDs) are increasingly used for treating neuropathic pain because they can reduce membrane excitability and suppress abnormal discharges in pathologically altered neurons.[41] The exact mechanism of action for their analgesic effects, however, is unclear. It does not appear to be specifically related to their antiepileptic activity. Other drugs that suppress seizures (e.g., barbiturates) do not relieve pain, and some AEDs with effective antiepileptic activity do not necessarily have good analgesic activity.[42] Few trials have evaluated AEDs in acute pain conditions, so the evidence base is weak.[43] A 2017 trial, for example, randomized 209 patients with acute or chronic sciatica to pregabalin 150 mg/day vs. placebo and found no significant differences in leg pain or functional outcomes.[44]

Ketamine

Ketamine has been used as a general anesthetic since the 1960s, but its use in subanesthetic concentrations for analgesia has grown rapidly in recent years, due, in part, to efforts to reduce the risks of chronic opioid use.[45] Ketamine has been successfully used to treat such acute pain conditions as sickle cell crises, renal colic, and trauma.[45]

Opioids for acute pain in opioid-naïve patients

If an opioid is deemed necessary to treat acute pain, oxycodone, hydrocodone, or tramadol in short-acting formulations are commonly used. Guidelines from the Centers for Disease Control and other organizations strongly recommend that only short-acting opioids be prescribed for acute pain because they reach peak effect more quickly than extended-release formulations and the risk of unintentional overdose is reduced.[46] (One study looking at the prescription of opioids in about 840,000 opioid-naïve patients over 10 years found that unintentional overdose was 5 times more likely in patients prescribed extended-release opioids compared to immediate-release opioids.[47])

Research shows general equivalency of efficacy and tolerability between different opioids. Hydrocodone 5 mg, oxycodone 5 mg, and tramadol 50 mg alone or in combination with acetaminophen or ibuprofen have similar analgesic power to treat acute pain.[48-50] Oxycodone and hydromorphone are available as pure drugs, whereas hydrocodone (in the United States) is only available co-formulated with acetaminophen or ibuprofen, therefore oxycodone or hydromorphone might be preferred if a patient is already taking acetaminophen or NSAIDs, or if those drugs are prescribed simultaneously with the opioid as part of multi-modal therapy.

Legal limits on opioid prescribing

A number of states have passed laws in recent years regulating the prescription of opioids for acute pain, with allowed durations of prescriptions for opioid-naïve patients ranging from 5-10 days.[1] To date, South Dakota does not have similar regulations, although the South Dakota Department of Health has appointed a Prescription Opioid Abuse Advisory Committee (to which SDSMA has a representative) to review opioid use in the state and develop strategies for preventing opioid misuse and abuse.[2]

Dose and duration of opioid therapy

Only enough opioids should be prescribed to address the expected duration and severity of pain from an injury or procedure (or to cover pain relief until a follow-up appointment). Several guidelines about opioid prescribing for acute pain from emergency departments[51,52] and other settings[3,53] have recommended prescribing ≤ 3 days of opioids in most cases, whereas others have recommended ≤ 7 days,[54] or ≤ 14 days.[55] CDC guidelines suggest that for most painful conditions (barring major surgery or trauma) a 3-day supply should be enough, although many factors must be taken into account (for example, some patients in South Dakota might live so far away from a health care facility or pharmacy that somewhat larger supplies might be justified).[46]

Clinician discretion in choosing an opioid and deciding how much to prescribe is always necessary because so many factors influence how a patient will respond to both pain and an analgesic. These factors include:

- Age
- Hepatic or renal impairment
- Genetic polymorphisms
- Comorbid conditions
- History of substance abuse
- Potential drug-drug interaction
- Co-administration with other central nervous system depressants

Opioid-induced hyperalgesia

Basic science and clinical data suggest that patients receiving opioids can actually become more sensitive to painful stimuli.[56] This opioid-induced hyperalgesia is probably due to upregulation of pro-nociceptive pathways in the peripheral and central nervous systems.[57] Although hyperalgesia has traditionally been associated with chronic pain, it can also occur after intraoperative or postoperative administration of high-dose opioids as well as in low-dose or maintenance-dose regimens.[58] Opioid-induced hyperalgesia is different pharmacologically from the phenomenon of opioid tolerance, although both can lead to an increased need for opioids and disentangling the two, clinically, can be difficult.

Calculating morphine equivalents

Calculating a patient's total daily dose of opioids is important to appropriately and effectively prescribe, manage, and taper opioid medications use for both acute and chronic pain. This can be done with printed or online equianalgesic charts, which provide conversion factors and dose equivalents of all available opioid medications relative to a standard dose of morphine.

Care must be taken in using such charts because dose is not the only relevant variable. Clinicians must also consider the route of administration, cross tolerance, half-life, and the bioavailability of a drug. In addition, the patient's existing level of opioid tolerance must be taken into account. Printed equianalgesic charts are common, and online calculators are also freely available (a common one can be accessed at clincalc.com/Opioids). The CDC provides a helpful guide to opioid conversions available at: www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf

Pain medicine specialists

Integrated pain management requires coordination of medical, psychological, and social aspects of health care and includes primary care, mental health care, and specialist services when needed Consultation with an addiction medicine specialist or psychiatrist may be necessary if an episode of acute

pain involves many complicating variables (such as multiple comorbidities) or if opioids are needed but the patient is already using an opioid for chronic pain and/or opioid maintenance therapy.

Patient education

Before prescribing an opioid for acute pain, providers should discuss the known risks and benefits of such therapy. Providers should talk openly and honestly to patients in order to arrive at informed decisions about opioid therapy. Here are some suggestions:

- Be explicit and realistic about expected benefits, including the fact that complete pain relief is unlikely and not necessarily desired
- Emphasize improvement in function as a primary goal and that function can improve even when some pain in present
- Advise patients about potential serious adverse effects including respiratory depression, constipation, and development of an opioid use disorder
- Review common effects such as dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms when stopping opioids
- Discuss effects that opioids might have on one's ability to operate a vehicle, particularly when opioids are initiated, when dosages are increased, or when other central nervous system depressants, such as benzodiazepines or alcohol are used concurrently
- Review increased risks for respiratory depression when opioids are taken with benzodiazepines, other sedatives, alcohol, illicit drugs such as heroin, or other opioids
- Discuss risks to household members and other individuals if opioids are intentionally or unintentionally shared with others from whom they are not prescribed.
- Consider whether cognitive limitations might interfere with management of opioid therapy, and if so, determine whether a caregiver can responsibly co-manage the therapy

In addition, whenever an opioid is prescribed, the patient should be educated about the safe storage and disposal of opioid medications. This can be done by a non-physician/provider, if desired, and the key points can be included in patient-provider agreements or treatment plans. Safe use means following clinician instructions about dosing, avoiding potentially dangerous drug interactions, and assuring full understanding of how the medication should be consumed or applied.

Remind patients that pain medications are sought after by many people, and, thus it is best if opioids are stored in a locked cabinet or other secure storage unit. If a locked unit is not available, patients should, at least, not keep opioids in a place that is obvious to, or easily accessed by others, since theft by

friends, relatives, and guests is a known route by which opioids become diverted.[59] Storage areas should be cool, dry, and out of direct sunlight.

Proper disposal methods should be explained:

- Follow any specific disposal instructions on the prescription drug labeling or patient information that accompanies the medication
- Do not flush medicines down the sink or toilet unless this information specifically instructs to do so
- Return medications to a pharmacy, health center, or other organization with a take-back program
- Mix the medication with an undesirable substance (e.g., coffee grounds or kitty litter) and put it in the trash

Specific acute pain populations

Management of acute perioperative pain

A full discussion of ways to manage perioperative pain is beyond the scope of this document because it can involve a diverse array of pharmacological and invasive measures administered by hospital-based anesthesiologists or pain specialists in order to relieve suffering, achieve early mobilization post-surgery, and reduce hospital stay. It is worth noting, however, that a multimodal approach to acute pain management is the primary model for dealing with perioperative pain as it is, more generally, for the treatment of acute pain in primary care settings. Also, just as competent and responsible treatment of acute pain in primary care can help prevent the development of chronic pain and attendant morbidities, research has shown an array of adverse outcomes associated with the under-treatment of perioperative pain, including thromboembolic and pulmonary complications, additional time spent in an intensive care unit or hospital, hospital readmission for further pain management, needless suffering, impairment of health-related quality of life, and development of chronic pain.[60]

In addition, the issue of opioid analgesic over prescription is as important an issue in the perioperative arena as it is anywhere in medicine. A 2018 cohort study of 2,392 adults having a range of surgeries found that, overall, a median of 30 pills of hydrocodone/acetaminophen (5/325 mg) were prescribed for postsurgical pain, but patients only used a median of 9 pills.[61] The study also found that the strongest association with higher use of opioids was not level of pain, but the quantity of opioids prescribed: 0.53 more pills used (95 percent CI 0.4-0.65 $p < 0.001$) for every additional pill prescribed.[62]

Table 4 summarizes a set of 2019 recommendations from the Michigan Opioid Prescribing Engagement Network.

Table 4. Opioid Dose Recommendations for Post-procedural Pain[63]

Procedure	**Number of Oxcodone 5 mg tablets (or equivalent)**
Dental extraction	0
Thyroidectomy	5
Breast biopsy or lumpectomy	5
Lumpectomy plus sentinel lymph node biopsy	5
Sentinel lymph node biopsy only	5
Laparoscopic anti-reflux (Nissen procedure)	10
Hernia repair (minor or major)	10
Sleeve gastrectomy	10
Laparoscopic cholecystectomy	10
Carotid endarterectomy	10
Prostatectomy	10
Open cholecystectomy	15
Colectomy (laparoscopic or open)	15
Cesarean delivery	15
Hysterectomy (all types)	15
Cardiac surgery via median sternotomy	15
Open small bowel resection	20
Simple mastectomy with or without sentinel lymph node biopsy	20
Total hip arthroplasty	30
Total knee arthroplasty	50

Of note, professional opinions on this topic will continue to evolve and while this paper summarizes current findings and provides South Dakota prescribers with clear, evidence-based guidance about the appropriate prescription of opiate analgesics and the treatment of acute pain, these guidelines are intended to apply broadly, they are not intended to establish a "standard of care." Providers – to

include all prescribers - must exercise their own best medical judgment when providing treatment, taking all relevant circumstances into account, including the potential for abuse, diversion and risk for addiction.

Management of acute pain in patients already using opioids or on Medication-Assisted Treatment

When caring for patients who are physically dependent on opioids—whether because of ongoing chronic pain or opioids used as part of treating opioid use disorder (OUD)—clinicians must know the type and quantity of opioid the patient is currently using so that an equivalent (equianalgesic) dose can be administered by an appropriate route to cover their baseline opioid requirement as well as the additional medication required for the acute pain.

Some clinicians mistakenly believe that the opioid agonist therapy (methadone) or partial agonist therapy (buprenorphine) used for medication-assisted therapy (MAT) provides enough analgesia to "cover" acute pain.[64] In fact, the doses of methadone and buprenorphine typically used in MAT do not provide sustained analgesic effects and are insufficient to treat acute pain.[62] Patients on opioid agonist therapy also develop cross-tolerance, which means they require higher and more frequent doses of short- or long-acting opioids to provide analgesia for episodes of acute pain. Because buprenorphine binds to mu-receptors with much higher affinity than other opioid agonists, pain management in patients using buprenorphine can be complicated. Several types of regimens using both buprenorphine and other opioids for acute pain have been described in the literature with choices of regimen guided by the specifics of a patient's existing regimen, presence of comorbid conditions, setting, and degree of acute pain.[64]

Patients Served by Multiple Providers

Ideally, patients in pain, whether acute or chronic, would receive prescriptions for analgesic prescriptions or other pain treatments from a single provider. In the real world, this is often neither possible nor feasible. Unfortunately, the risks of overdose and overdose-related death rise steeply as the number of prescribers increases. For example, the risk of overdose (from prescribed opioids or sedatives) is 3.5 times higher for patient with 4-5 prescribers compared to patients seeing a single prescriber.[65] Increasing numbers of prescribers is a potential indicator of opioid misuse or abuse, but it can also be related to non-problematic causes such as high use of emergency room services, suboptimal medical care, "nomadic" or "migrant" populations, or of populations in which providers rotate through clinics on a short-term, regular basis (as can be the case in areas serviced by the Indian Health Service). It is not always easy to determine whether a patient with multiple providers is obtaining overlapping prescriptions in an attempt to obtain more medication than a single provider would give. But the existence of multiple

providers should be a "red flag" warranting investigation, starting with conversations with the patient, but always including use of a PDMP.

Emergency department considerations

Although emergency departments prescribe only a fraction of opioid analgesics prescribed nationwide, ED prescriptions for opioids are reported to account for about 45 percent of the opioids diverted for non-medical use.[52] Guidelines from the American Academy of Emergency Medicine and other groups have attempted to reduce the variability in pain management and prescribing practices that has been evident in past decades. These guidelines mirror recommendations by the CDC and other organizations, with the following key provisions:[52]

- Give short-acting opioids as second-line treatment to other analgesics unless there is clear indication for opioid (e.g., acute abdominal pain or long bone fracture)
- Start with lowest effective dose
- Prescribe no more than a 3-day course of opioid for most acute pain conditions
- Address exacerbations of chronic pain with non-opioid analgesics, non-pharmacological therapies, or referral to pain specialists for follow-up
- Assess for opioid misuse or addiction using validated screening tools
- Access PDMPs when available
- Avoid long-acting or extended-release opioids
- Refrain from refilling chronic opioid prescriptions—refer to treating clinician who provided original prescription
- Refrain from replacing lost, stolen, or destroyed opioid prescriptions
- Understand that the federal Emergency Medical Treatment and Labor Act (EMTALA) does not state that severe pain is an emergency medical condition, and that EMTALA allows emergency medical providers to withhold opioid treatment if in their professional judgment such withholding is clinically justified

Older adults

Older patients are at increased risk of acute pain related to trauma, surgery or procedures, or degenerative conditions such as osteoarthritis. The elderly undergo surgery four times more often than other age groups, and are therefore more likely to suffer from associated pain.[66] In those 65 years and older, acute pain leads to about 4 million U.S. emergency department visits each year.[67]

Assessing and treating pain in older patients can be complicated by issues such as age-related physiologic changes, physical accessibility to treatment, cognitive impairment, coexisting illnesses, and

polypharmacy. Elderly patients may under- or over-report their experience of pain due to functional impairment or psychological distress. Doses of NSAIDs often need to be reduced to avoid hepatic or kidney damage, and opioids may induce unacceptable risks related to falls, constipation, or respiratory depression. Clinical decision-making must take into account all of these considerations, each of which can increase the risk for adverse outcomes.

Pregnancy

In general, and whenever possible, opioids should be avoided in pregnancy due to associations between opioid use and adverse fetal outcomes such as stillbirth, poor fetal growth, pre-term delivery, and neonatal opioid withdrawal syndrome.[46] If a opioid is indicated however, don't hesitate to prescribe based on concern for neonatal abstinence syndrome alone (NAS).

Before prescribing opioids in pregnancy:

- Ensure opioids are indicated
- Maximize non-opioid therapy, including exercise, physical therapy, behavioral approaches, and non-opioid medications
- Discuss the risks and benefits of opioids, including the risk of physiologic dependence and the risk of NAS
- Take a thorough history of substance use and review the PDMP AWARxE.

For reproductive age women who are not pregnant, discuss family planning and effects on pregnancy.

Conclusions

Although the focus of much public and professional attention in the past decade has been on the problems related to opioid analgesic prescribing for chronic pain, as this report had demonstrated, the treatment and management of acute pain is an equally important topic because many of the same dynamics (e.g., prescribing opioids when non-opioids may be just as effective, or prescribing higher doses/durations than needed) are at work with acute pain as with chronic pain.

Properly and responsibly managing acute pain is desirable not only because it relieves patient suffering, but because it reduces the chances that acute pain will morph into chronic pain, and it can help stem the tide of opioid diversion, misuse, and abuse. Opioids can, of course, play an invaluable role in the pain management armamentarium, but they carry important risks, as well, and thus should be generally viewed as second-line agents or as part of a multi-modal approach. The risks of opioids, even when used for acute pain and for relatively short durations, are amplified among older adults, patients with impaired renal or hepatic function, those with COPD, cardiopulmonary disorders, sleep apnea, or mental illness, and in anyone likely to combine opiates with other respiratory depressants such as alcohol or benzodiazepines.

These guidelines present evidence-based recommendations for treating acute pain with a range of pharmacological and non-pharmacological strategies to be administered usually in a step-like fashion, with opioids only used when necessary and then at the lowest dose and shortest duration deemed clinically beneficial. As with treating chronic pain, the appropriate deployment of opioids for chronic pain can be challenging, but it is not inherently different from using any other treatment option with significant risks of harm. With proper pain assessment, primary reliance on non-pharmacologic and non-opioid analgesics, and a view that includes critical emotional, psychological, and social dimensions of pain, clinicians can both relieve immediate suffering and maximize their patients' long-term health.

Appendix 1. Acute Pain Workflow Guideline

Patient presents with acute pain or anticipated postoperative pain

Brief Pain Assessment:

In the emergency setting use opioids judiciously to alleviate pain when it overwhelms the patient's ability to contribute to the assessment.

Comprehensive Pain Assessment:

Inclusive of the following:
- Etiology and nature of the pain
- Appropriate diagnostics
- Medication history, including past and current opioid use
- Check PDMP (Prescription Drug Monitoring Program)

Acute Exacerbation of Chronic Pain

Treatment Options:

- Avoid prescribing increased dosage or additional opioids because of potential risks and adverse effect.
- Check prescription monitoring program (PDMP) for history of opioid prescriptions.
- Consult the patient's pain care agreement prior to prescribing any medications.
- Consider collaborating with the clinician managing the patient's chronic pain care plan, an interdisciplinary team or available resources to provide appropriate chronic pain management.
- Assess the patient's mental health status and social situation to determine if additional resources, e.g. social services, behavioral health, pain management or addiction medicine consult may be appropriate.

Non-traumatic tooth pain

Symptom Management could include:

Symptom Management could include:
- Long-acting local anesthetic.
- NSAID and/or acetaminophen.
- Topical anesthetic rinse for stomatitis or mouth ulcers.
- Antibiotics with presence of swelling or exudates in cheek or jaw.
- Chlorhexidine mouth wash for localized gum inflammation/infection.
- Stress need for dental follow up and avoid prescribing opioids without examination and diagnosis of the underlying reason for tooth pain, including appropriate tests and X-rays.

Other Acute Pain

See Page 2

Acute Pain Workflow Guideline

Other Acute Pain

Severe Pain that may require opioid:
(i.e. fracture, post operative pain, severe injury)

Determine if prescribing opioid Is appropriate.

Assess for risk:

- Personal or Family History of Substance abuse?
- Personal History of misuse of prescription controlled substance?
- Concurrent sedative, alcohol, muscle relaxant use?
- Respiratory insufficiency or sleep apnea?
- Identify risk factors such as age, delirium, dementia, and fall risk.
- Check PDMP

Is the answer yes to any of the above?

YES

High Risk Patients:

- Avoid prescribing opioid and use alternative if at all possible and refer to PCP or to pain specialist or provider experienced in case of opioid at risk patients.
- If must prescribe such as in severe injury.
  - Use lowest dose for shortest period of time.
  - Educate and document risks with patient
  - Monitor closely.
- Consider naloxone prescription
  - Particularly for total daily dosage > 50 mg Morphine Equivalents (MME).

NO

Does potential benefit of opioids outweigh potential risk?

YES

Prescription of Opioids:

- Educate patient on opioid risks/benefits to make informed decision and review side effects.
- If opioids are deemed necessary, prescribe only an amount to cover the expected pain or realistic duration of time to a follow-up appointment. (Tramadol is an atypical opioid and should be managed appropriately).
- Never prescribe long-acting/extended–release for acute pain.
- Caution using opioids in the elderly.
- Review safe driving, work, storage, and disposal.
- Follow-up with patient within 3-5 days.
- Maximize appropriate non-opioid therapies.

NO

Common pain conditions that are almost never indicated for opioids (non-inclusive):

- Fibromyalgia
- Headache
- Self-limited illness, i.e., sore throat
- Uncomplicated back and neck pain
- Uncomplicated musculoskeletal pain

Appropriate therapy and/or referral:

- Treat with other analgesics or NSAIDs, physical, psychological , interventional, or other appropriate non-opioid therapies.
- Reassure and provide patient education, include expected duration of pain episode and warning signs that would require immediate medical attention.
- Arrange appropriate follow-up.

Clinical Pearls

1. Over 5 million Americans report that they currently (within 30 days) abuse prescription opioids and 10.3 million have abused them at some point in their lifetime. It has been noted that although most of these pills originated from a licensed prescriber, only 20% of users were the legitimate recipient of the initial prescription, with 71% of users having received the drug through methods of diversion. In addition, it is reported that 55% of these people received pills for free from a family member or friends who had excess pills.[2,3,4]
2. In one study of 642 general surgery patients it was found that opioid pills are greatly over-prescribed for the treatment of acute postoperative pain in general surgery patients: over 70% of the prescribed pills were never taken. In this study, depending on the procedure, 22-82% of patients never took any opioid following surgery.[1]

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Tetracycline Utilization

Time frame: July 2018 to June 2019
Red font denotes drug is on Step Therapy

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members
doxycycline monohydrate capsules	474	$8,905.02	$18.79	317
doxycycline monohydrate tablets	92	$2,931.39	$31.86	43
doxycycline monohydrate suspension	36	$4,951.80	$137.55	9
Vibramycin suspension (doxycycline calcium)	2	$711.32	$355.66	2
doxycycline hyclate capsules	1,139	$18,819.20	$16.52	722
doxycycline hyclate capsules DR	1	$84.68	$84.68	1
doxycycline hyclate capsules	946	$15,472.70	$16,36	611
minocycline capsules	1,655	$38,451.43	$23.23	472
minocycline tablets	59	$5,018.66	$85.06	22
tetracycline capsules	20	$3,116.17	$155.81	17
Oracea (doxycycline monohydrate DR) cap	0			
Solodyn (minocycline ER) tab	0			

INTRODUCTION

- The tetracycline class of antibiotics, discovered in the 1940s, has been widely used for its broad-spectrum bacteriostatic activity (*Nelson and Levy 2011*).
  - The tetracyclines are useful in treating aerobic gram-positive, gram-negative bacteria, and atypical pathogens (eg, *Rickettsia* species [*spp*], *Borrelia spp*, *Treponema spp*, *Chlamydia spp*). However, these drugs have little activity against fungi and viruses (*May 2019*).
  - The tetracyclines have a number of indications, some of which include acne, rosacea, sexually-transmitted diseases, acute bacterial skin and skin structure infections (ABSSSIs), urinary tract infections, respiratory tract infections, and various other infections (see Table 2 for the labelled indications for the individual agents) *(May 2019).*
  - The antimicrobial activity is generally similar between the tetracyclines, although some differences in the relative degree of activity against certain pathogens do exist among the various agents (*May 2019*).
- Tetracyclines function by binding reversibly to the 30S ribosomal subunit at a position that blocks the binding of the aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex. Protein synthesis is ultimately inhibited, leading to a bacteriostatic effect (*May 2019*).
- With regard to resistance, once resistance develops to one of the drugs in this class, it is typically conferred to all tetracyclines. However, there are differences in resistance among species of bacteria *(May 2019).*
- Doxycycline and minocycline are the most frequently prescribed drugs in this class (*May 2019*).
- Newer oral tetracyclines approved in 2018 by the Food and Drug Administration (FDA) include Nuzyra (omadacycline) and Seysara (sarecycline). Omadacycline was approved for community-acquired bacterial pneumonia (CABP) and ABSSSIs (including cellulitis, wound infection, and major cutaneous abscess); while sarecycline was approved for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients ≥ 9 years of age (*Drugs@FDA 2019, FDA multi-discipline review [Nuzyra] 2018*).
  - Community-acquired pneumonia (CAP) is an acute infection of the pulmonary parenchyma in a patient who has acquired the infection in the community. CAP is a common and potentially serious illness, and is associated with considerable morbidity and mortality, particularly in older adults and those with major comorbidities (*File 2018*).
    - *Streptococcus pneumoniae* is the most commonly identified bacterial cause of CABP worldwide. Other common pathogens identified in CABP include *Haemophilus influenzae*; atypical bacteria *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella spp.*; and oropharyngeal aerobes and anaerobes (in the setting of aspiration). Viruses are also common causes of CAP (*FDA multi-discipline review [Nuzyra] 2018, Marrie and File 2018*).
  - Systemic antibiotics are recommended in the management of moderate and severe acne and forms of inflammatory acne that are resistant to topical treatments (*Zaenglein et al 2016*).
    - The tetracycline class of antibiotics should be considered first-line therapy in moderate to severe acne, except when contraindicated (*Zaenglein et al 2016)*. In addition to sarecycline, other products in this class that are utilized for acne treatment include tetracycline, doxycycline, and minocycline (*Graber 2018*).
- Medispan class: Antibiotic; Tetracycline Derivative

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Acticlate (doxycycline) tablets	✔
Adoxa (doxycycline)* capsules	✔
CoreMino (minocycline) extended-release tablets	✔
Demeclocycline tablets	✔
Doryx, Doryx MPC (doxycycline) delayed-release tablets	✔
Dynacin (minocycline)* capsules, tablets	✔
Minocin (minocycline) capsules, tablets	✔

Drug	Generic Availability
Minolira (minocycline) extended-release tablets	-
Mondoxyne NL (doxycycline) capsules	✔
Morgidox (doxycycline) capsules	✔
Nuzyra (omadacycline) tablets, injection	-
Okebo (doxycycline) capsules	✔
Oracea (doxycycline monohydrate) delayed-release capsules	✔
Periostat (doxycycline) tablets*	✔
Seysara (sarecycline) tablets	-
Solodyn (minocycline) extended-release tablets	✔
Soloxide (doxycycline) delayed-release tablets	✔
TargaDOX (doxycycline) tablets	✔
Tetracycline	✔
Vibramycin (doxycycline) capsules, tablets	✔
Vibramycin (doxycycline calcium) syrup	✔
Ximino (minocycline) extended-release capsules	-

*This brand product has been discontinued

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Demeclocycline	Doxycycline	Minocycline	Omadacycline	Sarecycline	Tetracycline
Alternative Treatment for Selected Infections When Penicillin is Contraindicated						
Gonococcal infections, uncomplicated	✔	✔ *	✔ *			
Listeriosis	✔		✔ *			
Syphilis	✔	✔	✔ *			✔
Vincent's infection	✔	✔	✔ *			✔
Yaws	✔	✔	✔ *			✔
Central Nervous System						
Treatment of asymptomatic meningococcal carriers			✔ *			
Dermatological						
Acne	✔ †	✔ †	✔ ‡		✔ #	✔ †
Skin and soft tissue infections	✔		✔ *	✔		✔
Gastrointestinal						
Acute intestinal amebiasis	✔	✔	✔ *			✔
Cholera	✔	✔	✔ *			✔
Genitourinary conditions						
Chancroid	✔	✔	✔ *			✔
Urinary tract infections	✔	✔	✔ *			✔

Indication	Demeclocycline	Doxycycline	Minocycline	Omadacycline	Sarecycline	Tetracycline
Ophthalmic Infections						
Conjunctivitis (inclusion)	✔	✔	✔ *			✔
Trachoma	✔	✔	✔ *			✔
Respiratory Infections						
Anthrax	✔ §	✔	✔ *§			✔ §
Psittacosis	✔	✔	✔ *			✔
Respiratory tract infection	✔	✔	✔ *			✔
CABP				✔		
Rickettsial Infections						
Disease caused by rickettsiae	✔	✔	✔ *			✔
Q fever	✔	✔	✔ *			✔
Rickettsialpox	✔	✔	✔ *			✔
Rocky Mountain spotted fever	✔	✔	✔ *			✔
Typhus	✔	✔	✔ *			✔
Sexually Transmitted Infections						
Endocervical infections			✔ *			✔
Granuloma inguinale	✔	✔	✔ *			✔
Lymphogranuloma venereum	✔	✔	✔ *			✔
Nongonococcal urethritis	✔	✔	✔ *			
Rectal infections			✔ *			✔
Urethritis, uncomplicated	✔ §		✔ *§			✔
Miscellaneous						
Malaria prophylaxis		✔				
Periodontitis		✔ ‖				
Plague	✔	✔	✔ *			✔
Relapsing fever	✔	✔	✔ *			✔
Tularemia	✔	✔	✔ *			✔

*Immediate-release only.
†May be useful as adjunctive therapy.
‡Solodyn® (minocycline extended-release tablets) are indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients ≥ 12 years of age. Minocycline immediate-release may be useful as adjunctive therapy.
§ When penicillin is contraindicated.
‖ Periostat® (doxycycline hyclate immediate-release tablets), which has now been discontinued, was indicated as adjunct to scaling and root planning to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.
Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients ≥ 9 years of age.

(*Prescribing information: Acticlate 2018, Demeclocycline 2017, Doryx 2007, Minocin 2019, Minolira 2018, Mondoxyne 2018, Morgidox 2018, Nuzyra 2018, Okebo 2017, Oracea 2017, Seysara 2018, Solodyn 2017, TargaDOX 2019, Tetracycline 2018, Vibramycin 2017, Ximino 2018*)

- 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

- There are numerous clinical trials that have demonstrated the safety and efficacy of the tetracyclines for their respective FDA-approved indications, with no significant differences observed among the agents in this class. The focus of this section, however, will be the clinical trials for omadacycline and sarecycline *(Fleischer et al 2006, Garner et al 2003, Hubbell et al 1982, Lauharanta et al 1993, Lister et al 1993, Parish et al 2005, Rosentock et al 1985).*
- For the treatment of CABP, the efficacy of omadacycline was evaluated in a phase 3, double-blind (DB), active-control (AC), parallel-group (PG), multi-center (MC), randomized controlled trial (RCT), known as the OPTIC trial. The trial included 774 patients ≥ 18 years of age with radiographically-confirmed pneumonia and a pneumonia severity index/Patient Outcomes Research Team (PORT) Risk Class II, III, or IV (ie, low- to moderate-risk). Patients were treated for 7 to 14 days with omadacycline 100 mg intravenous (IV) infusion every 12 hours for 2 doses on Day 1, followed by 100 mg IV infusion once daily for ≥ 3 days, with an option to switch to 300 mg orally once daily on Day 4 (n = 386); or moxifloxacin 400 mg IV infusion once daily for ≥ 3 days, with an option to switch to 400 mg orally once daily on Day 4 (n = 388). Of note, the efficacy and safety of an oral loading dose was not evaluated in CABP (*FDA multi-discipline review [Nuzyra] 2018, Stets et al 2019*).
  - The primary endpoint was clinical success (early clinical response [ECR]) at 72 to 120 hours after the first dose, defined as survival with improvement in ≥ 2 of 4 symptoms (cough, sputum production, chest pain, dyspnea) without deterioration.
    - Clinical success was demonstrated in 81.1% of omadacycline-treated patients vs 82.7% of moxifloxacin-treated patients, with a treatment difference of -1.6% (95% confidence interval [CI], -7.1 to 3.8).
    - For the clinical success endpoint, omadacycline met an efficacy finding of noninferiority vs moxifloxacin with the lower bound of the 2-sided 95% CI being greater than the pre-specified 10% noninferiority margin (80% power).
  - The secondary endpoint of clinical response at 5 to 10 days after the last study dose was defined as improvement in signs and symptoms of CABP with no further antibacterial therapy needed.
    - Clinical response was demonstrated in 87.6% of omadacycline-treated patients vs 85.1% of moxifloxacin-treated patients, with a treatment difference of 2.5% (95% CI, -2.4 to 7.4).
- For the treatment of ABSSSI, the efficacy of omadacycline was evaluated in 2 Phase 3, DB, AC, PG, MC, RCTs, known as the OASIS-1 and OASIS-2 trials. The trials included a total of 1012 patients ≥ 18 years of age with ABSSSI and evidence of a systemic inflammatory response. Of note, both trials excluded patients with necrotizing fasciitis or diabetic foot infections (*FDA multi-discipline review [Nuzyra] 2018, McGovern 2018, O'Riordan et al 2019*).
  - In OASIS-1, patients were treated with omadacycline 100 mg IV infusion every 12 hours for 2 doses on day 1, followed by 100 mg IV infusion once daily for ≥ 3 days, with an option to switch to 300 mg orally once daily on Day 4 (n = 386); or linezolid 600 mg IV infusion twice daily for ≥ 3 days, with an option to switch to 600 mg orally every 12 hours on Day 4 (n = 322). In OASIS-2, patients were treated with omadacycline 450 mg orally once daily for 2 days, followed by 300 mg orally once daily (n = 368); or linezolid 600 mg orally every 12 hours (n = 367). Patients in both trials were treated for 7 to 14 days.
  - In both studies, the primary endpoint was clinical success (ECR) at 48 to 72 hours after the first study dose, defined as a ≥ 20% decrease in lesion size without clinical failure.
    - In OASIS-1, clinical success was demonstrated in 84.8% of omadacycline-treated patients vs 85.5% of linezolid-treated patients, with a treatment difference of -0.7% (95% CI, -6.3 to 4.9); in OASIS-2, clinical success was demonstrated in 87.3% of omadacycline-treated patients vs 82.2% of linezolid-treated patients, with a treatment difference of 5.1% (95% CI, -0.2 to 10.5).
    - In both trials, omadacycline met an efficacy finding of noninferiority for clinical success vs linezolid with the lower bound of the 2-sided 95% CI being greater than the pre-specified 10% noninferiority margin (90% power).
  - The secondary endpoint of clinical response at 7 to 14 days after the last dose was defined as survival with resolution or improvement in signs or symptoms of infection without receiving alternative antibacterial therapy and/or unplanned major surgical intervention, and sufficient resolution of infection.
    - In OASIS-1, clinical response was demonstrated in 86.1% of the omadacycline-treated patients vs 83.6% of linezolid-treated patients, with a treatment difference of 2.5% (95% CI, -3.2 to 8.2); in OASIS-2, clinical response was demonstrated in 83.9% of the omadacycline-treated patients vs 80.5% of linezolid-treated patients, with a treatment difference of 3.4% (95% CI, -2.3 to 9.1).
- The efficacy and tolerability of sarecycline 1.5 mg/kg daily (administered as 60 mg, 100 mg, or 150 mg) were evaluated in 2 phase 3, DB, PC, RCTs (*Moore et al 2018, Seysara prescribing information 2018*). Patients 9 to 45 years of age with moderate to severe acne were randomized to sarecycline or placebo once daily for 12 weeks. At baseline, the

mean facial inflammatory and noninflammatory lesion counts were approximately 30 and 43, respectively. The trials assessed the proportion of patients with success on the facial investigator's global assessment (IGA) (scores range from 0 [clear] to 4 [severe]), as well as assessing lesion counts.

- In the first trial, the proportions of patients achieving IGA success (defined as clear or almost clear and a ≥ 2-grade improvement from baseline) were 21.9% and 10.5% in the sarecycline and placebo groups, respectively ($p < 0.0001$). In the second trial, proportions were 22.6% and 15.3%, respectively ($p = 0.0038$).
- In the first trial, the mean absolute changes in inflammatory lesion counts were -15.3 and -10.2 for sarecycline and placebo, respectively ($p < 0.001$). In the second trial, changes were -15.5 and -11.1, respectively ($p < 0.001$).
- Improvements were also demonstrated for reductions in noninflammatory lesions and for IGA success on chest and back acne.

CLINICAL GUIDELINES

CABP

- Treatment recommendations from the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) recommend selection of empiric antimicrobial regimens based on prediction of the most likely pathogen(s) and knowledge of local susceptibility patterns. Once the etiology of CABP has been identified via microbiological testing, antimicrobial therapy should be directed at that pathogen (*FDA multi-discipline review [Nuzyra] 2018, Mandell et al 2007*).
  - Regimens chosen by the IDSA/ATS guidelines mainly rely on macrolides (with or without a β-lactam) or fluoroquinolones for outpatient therapy (*File 2018*). The guidelines promote the use of macrolides to provide coverage for both *S. pneumoniae* and atypical pathogens (particularly, *M. pneumoniae* and *C. pneumoniae*), which account for the majority of cases of CAP in ambulatory patients.
  - The IDSA recommends IV vancomycin, oral or IV linezolid, or oral or IV clindamycin for community-acquired (CA)-methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia if the strain is susceptible (*Liu et al 2011*).

ABSSSI

- The IDSA recommended the following in their 2014 practice guidelines for the diagnosis and management of skin and soft tissue infections (*Stevens et al 2014*):
  - Nonpurulent skin and soft tissue infections (SSTIs): cellulitis/erysipelas/necrotizing infection
    - Mild infection (ie, typical cellulitis/erysipelas with no focus of purulence)
      - Patients with typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against *streptococci* such as oral penicillin or amoxicillin, cephalosporin, dicloxacillin, or clindamycin.
    - Moderate infection (ie, typical cellulitis/erysipelas with systemic signs of infection)
      - For cellulitis with systemic signs of infection, IV antibiotics such as penicillin, ceftriaxone, cefazolin, or clindamycin are indicated. Coverage against methicillin-susceptible *S. aureus* (MSSA) can be considered.
    - Severe infection (ie, oral antibiotic failure, systemic signs of infection, immunocompromised patients, clinical signs of deeper infection [bullae, skin sloughing, hypotension, or evidence of organ dysfunction])
      - For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or systemic inflammatory response syndrome (SIRS), vancomycin or another antimicrobial effective against both MRSA and *streptococci* is recommended.
      - In severely compromised patients, broad-spectrum antimicrobial coverage may be considered.
      - Vancomycin plus either piperacillin/tazobactam or imipenem/cilastin, or meropenem is recommended as a reasonable empiric regimen for severe nonpurulent infections.
  - Purulent SSTIs: furuncle/carbuncle/abscess
    - Mild infection (ie, inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles)
      - Incision and drainage is the recommended treatment.
    - Moderate infection (ie, purulent infection with systemic signs of infection)
      - The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of SIRS.
      - Empiric treatment options include sulfamethoxazole/trimethoprim (SMX/TMP) and doxycycline.
      - MRSA: SMX/TMP
      - MSSA: Dicloxacillin or cephalexin

- Severe infection (ie, failure of incision and drainage plus oral antibiotics, systemic signs of infection, immunocompromised patients)
  - An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension.
  - Empiric treatment options include vancomycin, daptomycin, linezolid, telavancin, and ceftaroline.
  - MRSA: any of the empiric treatments may be considered.
  - MSSA: nafcillin, cefazolin, or clindamycin.

- The Clinical practice guidelines by the IDSA for the treatment of MRSA infections recommend the following in adults and children (*Liu et al 2011*):
  - The following recommendations pertain only to the management of SSTI and pneumonia associated with MRSA disease.
  - SSTIs
    - For a cutaneous abscess, incision and drainage is the primary treatment.
      - Antibiotic therapy is recommended for abscesses associated with conditions such as severe or extensive disease or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, abscess in an area difficult to drain (eg, face and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone.
    - For outpatients with purulent cellulitis, empiric therapy for community acquired MRSA (CA-MRSA) is recommended pending culture results. Empiric therapy for infection due to β-hemolytic *streptococci* is likely to be unnecessary.
    - For outpatients with nonpurulent cellulitis, empiric therapy for infection due to β-hemolytic *streptococci* is recommended. Empiric coverage for CA-MRSA is recommended in patients who do not respond to β-lactam therapy and may be considered in those with systemic toxicity.
    - For empiric coverage of CA-MRSA in outpatients with SSTI, oral antibiotic options include clindamycin, SMX/TMP, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both β-hemolytic *streptococci* and CA-MRSA is desired, options include clindamycin alone, SMX/TMP or a tetracycline in combination with a β-lactam (eg, amoxicillin), or linezolid alone.
    - For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used.
      - Tetracyclines should not be used in children < 8 years of age.

Acne

- The American Academy of Dermatology published guidelines for the management of acne vulgaris in 2015. The recommendations are as follows (*Zaenglein et al 2016*):
  - Systemic antibiotics are recommended in the management of moderate and severe acne, and forms of inflammatory acne that are resistant to topical treatments.
    - Doxycycline and minocycline are considered more effective than tetracycline, but neither agent is considered superior over the other.
    - Oral erythromycin and azithromycin can be effective; however, their use should be limited to patients who cannot use tetracyclines (eg, pregnant women or children < 8 years of age). Of note, erythromycin should be used carefully, due to the increased risk of bacterial resistance.
    - Systemic antibiotic use should be limited to the shortest possible duration, usually 3 months, in order to minimize the risk of bacterial resistance.
    - Monotherapy with systemic antibiotics is not recommended. Concomitant topical therapy (eg, benzoyl peroxide and/or retinoid) should be used with systemic antibiotics, as well as maintenance after completion of systemic antibiotic therapy.

Sexually-transmitted diseases (STDs)

- The Centers for Disease Control (CDC) published treatment guidelines for the management of STDs in 2015. The recommendations are listed below (*CDC 2015*).
  - Chancroid
    - Azithromcyin, ceftriaxone, ciprofloxacin (contraindicated in pregnant or lactating women) or erythromycin are recommended treatment strategies.
  - Granuloma inguinale

- Doxycycline is recommended.
- Alternative agents include azithromycin, ciprofloxacin, erythromycin or SMX/TMP.

- Lymphogranuloma venereum
  - Doxycycline for 21 days is recommended.
  - Erythromycin for 21 days is an alternative treatment option.
- Syphilis
  - Penicillin G is the preferred drug for all stages of syphilis. Alternative agents include doxycycline and tetracycline.
  - Azithromycin may be effective in early syphilis but should only be used when treatment with penicillin G or doxycycline is not feasible.
  - Penicillin G is the only therapy recommended during pregnancy. Pregnant women with an allergy to penicillin should be desensitized.
  - Benzathine penicillin G is recommended for primary and secondary syphilis.
  - Infants >1 month of age with primary or secondary syphilis should be treated with benzathine penicillin G.
  - Patients with neurosyphilis should be treated with aqueous crystalline penicillin G. An alternative regimen in patients in whom compliance can be assured is procaine penicillin plus probenecid
- Urethritis
  - Azithromycin or doxycycline is recommended. Alternative regimens include erythromycin, levofloxacin or ofloxacin.
- Cervicitis
  - Azithromycin or doxycycline is recommended.
- Chlamydia
  - Azithromycin or doxycycline is recommended.
  - Alternative agents include erythromycin, levofloxacin or ofloxacin.
  - Azithromycin or amoxicillin is recommended in pregnant patients. An alternative agent is erythromycin.
- Gonococcal infections
  - Dual therapy with ceftriaxone and azithromycin is preferred. If ceftriaxone is unavailable, then cefixime + azithromycin are an option.
- Pelvic inflammatory disease
  - Recommended parenteral regimen A: cefotetan or cefoxitin plus doxycycline (oral or IV).
  - Recommended parenteral regimen B: clindamycin plus gentamicin.
  - Alternative parenteral regimens are ampicillin/sulbactam plus doxycycline (oral or IV).
  - Outpatient oral therapy may be considered in patients with mild to moderate disease. Recommended regimens include ceftriaxone plus doxycycline with or without metronidazole, cefoxitin and probenecid plus doxycycline with or without metronidazole, or another parenteral third generation cephalosporin plus doxycycline with or without metronidazole.
- Epididymitis
  - Ceftriaxone plus doxycycline is recommended. For acute infections most likely caused by enteric organisms, ceftriaxone + levofloxacin or ofloxacin are recommended.
- Proctitis
  - Ceftriaxone + doxycycline are recommended.

SAFETY SUMMARY

- The tetracyclines are contraindicated in patients hypersensitive to tetracyclines or any component in the formulations.
- Key warnings and precautions for tetracyclines:
  - Tooth discoloration and enamel hypoplasia: Use during tooth development (ie, during the last half of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown) and enamel hypoplasia.
  - Inhibition of bone growth: Use during the second and third trimester of pregnancy, infancy, and childhood up to the age of 8 years may cause reversible inhibition of bone growth.
  - *C. difficile*-associated diarrhea
  - Photosensitivity: Skin protection and sun avoidance is recommended.
- Tetracyclines are generally considered safe; the most common adverse effects associated with this class are gastrointestinal in nature, eg, epigastric pain, anorexia, diarrhea, nausea, and vomiting.
- Key drug interactions with the tetracycline class include:

- ○ Antacids and iron preparations: Dosing should be spaced apart
- ○ Methoxyflurane: Fatal renal toxicity has been reported
- ○ Anticoagulants: Anticoagulant levels may increase
- ○ Retinoids: Increased risk of pseudotumor cerebri (benign intracranial hypertension)
- ○ Urinary alkalinizers and zinc salts: Serum levels of tetracyclines may decrease

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Acticlate, Doryx, Doryx MPC, Okebo, Mondoxyne NL, Morgidox, Soloxide, TargaDOX, Vibramycin (doxycycline)	Capsules, suspension, syrup, tablets	Oral	More severe or life-threatening infections Once or twice daily Prophylaxis of malaria Once daily, starting 1 to 2 days before travel and for 4 weeks after return from travel Inhalation anthrax Twice daily for 60 days	Pediatric dosing in patients who weigh < 45 kg is weight-based; patients weighing ≥ 45 kg should receive the adult dose, which may differ based on the indication. Should be administered with adequate amounts of fluid to reduce risk of esophageal irritation/ulcer May be given with food or milk if gastric irritation occurs Tablets may be broken into thirds to provide the appropriate strength
Oracea, Oracea (doxycycline)	Capsules, delayed-release beads	Oral	Once daily in the morning	Should be taken on an empty stomach, preferably ≥ 1 prior or 2 hours after meals The dose of Oracea differs from other doxycycline formulations that are used to treat infections
Demeclocycline	Tablets	Oral	Adults: twice daily Pediatric patients > 8 years of age: 2 to 4 times daily	Pediatric dosing in weight-based Should be used cautiously in patients with impaired renal or hepatic function (dose may need to be decreased or dosing interval extended) Should be given at least 1 hour before or 2 hours after meals Should be administered with adequate amounts of fluid to reduce risk of esophageal irritation/ulcer
CoreMino, Dynacin, Minocin,	Capsules, tablets	Oral	Adults: Immediate release: 2 to 4 times daily	Pediatric dosing is weight-based.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Minolira, Solodyn, Ximino (minocycline)			Pediatric patients > 8 years of age: 2 times daily	Can be given with or without food Should be administered with adequate amounts of fluid to reduce risk of esophageal irritation/ulcer Current data are insufficient to determine if a dosage adjustment is warranted in patients with creatinine clearance (CLcr) < 80 ml/min, therefore the total daily dosage should not exceed 200 mg in 24 hours in these patients (blood urea nitrogen [BUN] and serum creatinine should be monitored)
Nuzyra (omadacycline)	Tablets, injection	IV, oral	IV: once daily infusion over 30 minutes for 7 to 14 days Oral: once daily for 7 to 14 days	A higher dose is recommended for ABSSSI Fasting is recommended for at least 4 hours prior to oral omadacycline administration; with the exception of water, food and drink should be avoided for 2 hours and dairy products, antacids, or multivitamins for 4 hours post oral omadacycline administration Safety and efficacy have not been established in pediatric patients < 18 years of age. Omadacycline should be avoided in patients < 8 years of age, due to potential adverse effects related to tooth development and bone growth
Seysara (sarecycline)	Tablets	Oral	Once daily	Weight-based dosing Efficacy beyond 12 weeks and safety beyond 12 months has not been tested
Solodyn, Ximino (minocycline)	Extended-release tablets	Oral	Once daily for 12 weeks	May be taken with or without food, however food may help reduce risk of esophageal irritation A dose decrease or extend dosing interval is recommended

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				in patients with renal impairment. Safety beyond 12 weeks has not been established
Tetracycline	Capsule	Oral	Adults: 2 to 4 times daily Pediatric patients > 8 years of age: 4 times daily	Pediatric dosing is weight-based Should be used cautiously in patients with impaired renal function (a dose decrease or extend dosing interval is recommended) Should be administered with adequate amounts of fluid to reduce risk of esophageal irritation/ulcer

See the current prescribing information for full details

CONCLUSION

- The tetracyclines are broad-spectrum bacteriostatic antibiotics with activity against many aerobic gram-positive and gram-negative bacteria and atypical pathogens, such as *mycoplasma* and *chlamydia*.
- Based on various treatment guidelines, the tetracyclines potentially play a role in the treatment of various infectious diseases based on their established susceptibility to certain microorganisms and FDA-approved indications.
- Within the class no major clinically significant differences exist among the various agents; however, doxycycline and minocycline appear to be the most highly utilized.
- Tetracyclines have been associated with permanent tooth discoloration in children < 8 years of age if used repeatedly or for prolonged courses, and with accumulation in fetal bones and teeth when administered to pregnant women.
  - The newer generation tetracyclines (eg, doxycycline) are associated with a lower risk of dental staining when used ≤ 21 days in children.
  - Doxycycline has not been correlated with teratogenic effects during pregnancy and is a treatment option when other agents appear less effective.
- Tetracycline antibiotics are relatively safe, with the most common adverse events relating to gastrointestinal symptoms.
- Omadacycline, FDA-approved in 2018, provides an additional oral option for the treatment of ABSSSI due to MRSA, as well as a non-fluoroquinolone monotherapy option for CABP.
  - In CABP, a phase 3 RCT demonstrated non-inferiority with omadacycline treatment vs an appropriate comparator (ie, moxifloxacin) for clinical success (ie, ECR) in patients with low- to moderate-risk pneumonia.
  - In ABSSSI, 2 phase 3 RCTs demonstrated non-inferiority with omadacycline treatment vs an appropriate comparator (ie, linezolid) for clinical success (ie, ECR) in patients with moderate to severe skin infections.
- Sarecycline, also FDA-approved in 2018, is specifically indicated for inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients ≥ 9 years of age.
  - Sarecycline has demonstrated efficacy vs placebo for improving the severity of acne and decreasing lesion counts, and is well tolerated.

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

Please note: All information below is required to process this request.
Fax to 1-800-527-0531
Mon-Sat: 7am to 7pm Central

Oracea® and Solodyn® Prior Authorization Request Form

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

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

Medication Information (required)

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

Clinical Information (required)

Select the diagnosis below:

- ❑ Inflammatory lesions of non-nodular moderate to severe acne vulgaris [**Solodyn** only]
- ❑ Inflammatory lesions (papules and pustules) of rosacea [**Oracea** only]
- ❑ Other diagnosis: _____ ICD-10 Code(s): _____

Clinical information:

Has the patient had a trial and failure (a minimum of 90 day trial) of doxycycline monohydrate, doxycycline hyclate, minocycline IR, or tetracycline in the last180 days? ❑ **Yes** ❑ **No**

Quantity limit requests:

What is the quantity requested per DAY? _____

What is the reason for exceeding the plan limitations?

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

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

_____

_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-800-527-0531.

MS Utilization

Red font denotes PA
Time frame: July 2018 to June 2019

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
AMPYRA	10	$27,123.14	$2,712.31	2	39, 51
dalfampridin ER	16	$9,211.92	$575.75	4	39-51
AUBAGIO	39	$259,587.70	$6,656.09	5	40-57
COPAXONE	27	$155,904.26	$5,774.23	5	29-66
glatiramer	36	$80,975.62	$2,249.32	7	25-57
GILENYA	24	$187,662.62	$7,819.28	3	28-53
GLATOPA	2	$10,087.56	$5,043.78	1	31
PLEGRIDY	8	$55,098.32	$6,887.29	1	27
REBIF	3	$14,133.78	$4,711.26	1	55
REBIF REBIDO	2	$14,908.68	$7,454.34	1	55
TECFIDERA	22	$168,148.83	$7,643.13	5	27-53
MAYZENT					
MAVENCLAD					
TOTAL	**189**	**$982,842.43**		**29**	**25-66**

Prescriber Description	Total Rx	Paid Amount	Utilizers	Age Range	% Utilization
Family Practice	3	$14,517.84	1	56	
Internal Medicine	10	$64,790.90	4	28-37	
Neurology	120	$599,712.20	19	25-66	**63%**
Nurse Practitioner Nurse Practitioner, Family Health	30	$210,843.58	5	27-53	
Physician Assistant, Medical	16	$78,296.36	2	39, 41	
Psychiatry & Neurology, Behavioral Neurology & Neuropsychiatry	9	$7,775.07	1	42	
**Student in an Organized Health Care Education/ Training Program/Student, Health Care	1	$6,906.48	1	55	

**Patient also seen by Family Practitioner and Neurology

INTRODUCTION

- Multiple Sclerosis (MS), a chronic, immune-mediated disease of the central nervous system (CNS), is the leading cause of disability in young and middle-aged people in developed areas of the world *(MS Coalition 2018)*. MS is characterized by repeated episodes of inflammation within the brain and spinal cord, resulting in injury to the myelin sheaths that surround and insulate nerves, and subsequently the nerve cell axons *(Goodin et al 2002)*. There are 4 clinical subtypes of MS:
  - Relapsing-remitting MS (RRMS), which is characterized by acute attacks followed by partial or full recovery. This is the most common form of MS, accounting for 80 to 85% of cases.
  - Secondary progressive MS (SPMS) begins as RRMS; however, the attack rate declines over time. Patients experience a gradual deterioration. Patients with RRMS for more than 10 years may transition to SPMS.
  - Primary progressive MS (PPMS) occurs in approximately 10% of patients with MS. Patients have a continuous and gradual decline in function without evidence of acute attacks.
  - Clinically isolated syndrome (CIS) refers to the first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the CNS *(Goodin et al 2002, Sanvito et al 2011, National MS Society 2019[a])*.
- A more recent revision of the MS clinical course descriptions recommended that the core MS phenotype descriptions of relapsing and progressive disease be retained with some of the following modifications: (1) an important modifier of these core phenotypes is an assessment of disease activity, as defined by clinical assessment of relapse occurrence or lesion activity detected by CNS imaging; (2) the second important modifier of these phenotypes is a determination of whether progression of disability has occurred over a given time period; and (3) the prior category of PRMS can be eliminated since subjects so categorized would now be classified as PPMS patients with disease activity *(Lublin et al 2014)*.
- An estimated 1 million adults in the United States have been diagnosed with MS. Most patients are diagnosed between the ages of 20 and 50 years, and MS is reported more frequently in women than in men *(National MS Society 2019[b])*.
- Diagnosis of MS requires evidence of damage in at least 2 separate areas of the CNS, evidence of damage that occurred at 2 separate time points at least 1 month apart, and that other possible diagnoses have been ruled out. The clinically isolated syndrome (CIS) includes 1 attack and objective evidence of 1 lesion *(Thompson et al 2018)*. Following CIS, the course of MS is variable. The inclusion of CIS in the spectrum of MS phenotypes with prospective follow-up of most such patients determining their subsequent disease phenotype was also recommended in the recent revision of the MS clinical course descriptions *(Lublin et al 2014)*.
- Disease-modifying therapies (DMTs) delay the development from CIS to clinically definite MS (CDMS) *(Miller et al 2012, Armoiry et al 2018)*. Evaluation includes an extensive patient history, neurological examination, laboratory tests to rule out other possible causes, magnetic resonance imaging (MRI) to evaluate for new disease and signs of more chronic damage, and possibly lumbar puncture (*Thompson et al 2018*).
- Exacerbations, also known as flares, relapses, or attacks of MS are caused by inflammation in the CNS that leads to damage to the myelin and slows or blocks transmission of nerve impulses. An exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. Exacerbations can be mild or severe. Intravenous (IV) corticosteroids may be used to treat severe exacerbations of MS. Corticosteroids decrease acute inflammation in the CNS but do not provide any long-term benefits *(Frohman et al 2007)*.

  The approach to treating MS includes the management of symptoms, treatment of acute relapses and utilization of DMTs to reduce the frequency and severity of relapses, reduce lesions on MRI scans, and possibly delay disease and disability progression *(Rae-Grant et al 2018[b])*. The American Academy of Neurology (AAN), the European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) recently updated their guidelines on MS. Both guidelines recommend initiation of DMTs treatment early on in the patient's disease course (*Rae Grant et al 2018[b], Montalban et al 2018*). The MS Coalition, the AAN, and the Association of

British Neurologists guidelines support access to the available DMTs for patients with MS. While there are no precise algorithms to determine the order of product selection, therapy should be individualized and patients' clinical response and tolerability to medications should be monitored (Corboy et al 2015, Goodin et al 2002, MS Coalition 2017, Scolding et al 2015).

- Pediatric-onset MS is rare, with the vast majority of cases demonstrating a relapsing remitting disease course (*Otallah et al 2018*). Gilenya (fingolimod) is the first FDA-approved agent for pediatric patients. Its approval was based on the PARADIGMS trial (*Chitnis et al 2018*). Tecfidera (dimethyl fumarate), Aubagio (teriflunomide), and Lemtrada (alemtuzumab) are all currently being evaluated in pediatric patients in Phase 3 trials.
- Cladribine injection is indicated for the treatment of active hairy-cell leukemia (*Clinical Pharmacology 2019*). This oncology indication is not related to the treatment of MS and will not be discussed in this review.
- All agents in this class review are listed as Multiple Sclerosis Agents in Medispan; the exceptions are mitoxantrone (listed as an antineoplastic antibiotic) and Ampyra (dalfampridine) (listed as a potassium channel blocker).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Ampyra (dalfampridine)	✔
Aubagio (teriflunomide)	✔ *
Avonex (interferon β-1a)	-
Betaseron (interferon β-1b)	-
Copaxone, Glatopa† (glatiramer acetate)	✔
Extavia (interferon β-1b)	-
Gilenya (fingolimod)	-
Lemtrada (alemtuzumab)	-
Mavenclad (cladribine)	-
Mayzent (siponimod)	-
mitoxantrone‡	✔
Ocrevus (ocrelizumab)	-
Plegridy (peginterferon β-1a)	-
Rebif (interferon β-1a)	-
Tecfidera (dimethyl fumarate)	-
Tysabri (natalizumab)	-

*A generic of teriflunomide received FDA-approval in 2018; however, a settlement agreement will delay launch.
†Glatopa by Sandoz is an FDA-approved generic for Copaxone (glatiramer acetate); it is available in 20 mg/mL and 40 mg/mL injections. Mylan launched generic versions of the 20 mg/mL and the 40 mg/mL strengths of Copaxone on October 5, 2017.
‡Although brand Novantrone has been discontinued, generic mitoxantrone remains available.
§As of April 30, 2018, Zinbryta (daclizumab) has been voluntarily withdrawn from the market by the manufacturer; cases of encephalitis and meningoencephalitis have been reported in patients treated with Zinbryta. All references to the drug have been removed from this document.

(*Drugs@FDA 2019, FDA Web Site 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019, Purple Book 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Improve walking in MS‡	Relapsing forms of MS	Slow accumulation of physical disability	Decrease frequency of clinical exacerbations	First clinical episode	Progressive forms of MS
Ampyra (dalfampridine)	✔ *	-	-	-	-	-
Aubagio (teriflunomide)	-	✔	-	-	-	-
Avonex (IM interferon β-1a)	-	✔	✔	✔	✔	-

Drug	Improve walking in MS‡	Relapsing forms of MS	Slow accumulation of physical disability	Decrease frequency of clinical exacerbations	First clinical episode	Progressive forms of MS
Betaseron/Extavia (interferon β-1b)	-	✔	-	✔	✔	-
Copaxone/Glatopa (glatiramer acetate)	-	✔	-	-	-	-
Gilenya (fingolimod)	-	✔ †	-	-	-	-
Lemtrada (alemtuzumab)	-	✔ ‡ (3rd line)	-	-	-	-
Mavenclad (cladribine)		✔				✔ §
Mayzent (siponimod)		✔			✔ ‖	✔ ‖
mitoxantrone	-	✔ (2nd line)	✔ (neurologic disability)	✔	-	✔ ¶
Ocrevus (ocrelizumab)	-	✔	-	-	-	✔ #
Plegridy (peginterferon β-1a)	-	✔	-	-	-	-
Rebif (interferon β-1a)	-	✔	✔	✔	-	-
Tecfidera (dimethyl fumarate)	-	✔	-	-	-	-
Tysabri (natalizumab)	-	✔ **	-	-	-	-

IM=intramuscular; SC=subcutaneous
*Ampyra is indicated as a treatment to improve walking in patients with MS. This was demonstrated by an increase in walking speed.
†Approved in patients 10 years of age and older.
‡Because of its safety profile, Lemtrada should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS
§ Because of its safety profile, use of Mavenclad is generally recommended for patients who have had an inadequate response, or are unable to tolerate, an alternate drug indicated for the treatment of MS. Mavenclad is not recommended for use in patients with CIS because of its safety profile.
‖ Mayzent is a sphingosine-phosphate receptor modulator indicated for the treatment of relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults.
¶Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening RRMS (ie, patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated for the treatment of patients with PPMS. The product has additionally been approved for several cancer indications.
#Ocrevus is approved for PPMS.
**Tysabri increases the risk of Progressive Multifocal Leukoencephalopathy (PML) (a rare, but often fatal demyelinating disease of the central nervous system caused by the John Cunningham virus [JCV]). When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. Tysabri is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation that have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. In CD, Tysabri should not be used in combination with immunosuppressants or inhibitors of TNF-α.

(Prescribing information: Ampyra 2017, Aubagio 2016, Avonex 2016, Betaseron 2018, Copaxone 2018, Extavia 2016, Gilenya 2018, Glatopa 2018, Lemtrada 2017, Mavenclad 2019, Mayzent 2019, mitoxantrone 2018, Novantrone 2012, Ocrevus 2017, Plegridy 2018, Rebif 2015, Tecfidera 2018, Tysabri 2018,)

- 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

- In the management of MS, numerous clinical trials have established the safety and efficacy of the biologic response modifiers in reducing the frequency of relapses lesions on MRI scans, and possibly delaying disease progression and disability.

Interferons and glatiramer acetate

- Pivotal clinical trials demonstrating efficacy in reducing the rate of relapses, burden of disease on MRI, and disability progression for the interferons and glatiramer acetate were published in the 1990's *(Jacobs et al 1996, Johnson et al, 1995, The interferon beta [IFNβ] Multiple Sclerosis Study Group 1993, The IFNβ Multiple Sclerosis Study Group 1995)*. Long-term follow-up data for IFN β-1b show that overall survival in MS is improved *(Goodin et al 2012)*.
- Head-to-head trials have found Copaxone (glatiramer acetate), Rebif (IFNβ-1a SC), and Betaseron (IFNβ-1b) to be comparable in terms of relapse rate reduction and disease and disability progression *(PRISMS 1998, Kappos et al 2006, Mikol et al 2008, Flechter et al 2002, Cadavid et al 2009, O'Connor et al 2009)*. The results of several studies suggest that lower dose Avonex (IFNβ-1a 30 mcg intramuscular [IM] once weekly) may be less efficacious while being more tolerable compared to higher dose Rebif (IFNβ-1a subcutaneous [SC] 3 times weekly or every other day) or glatiramer acetate *(Khan et al 2001[a], Khan et al 2001[b], Barbero et al 2006, Durelli et al 2002, Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*.
- In a meta-analysis of 5 randomized studies comparing IFNs with glatiramer acetate, there were no significant differences between IFNs and glatiramer acetate in terms of the number of patients with relapses, confirmed progression, or discontinuation due to adverse events at 24 months *(La Mantia et al 2016)*.
  - At 36 months, however, evidence from a single study suggested that relapse rates were higher in the group given IFNs than in the glatiramer acetate group (risk ratio [RR] 1.40, 95% confidence interval [CI]: 1.13 to 1.74; p = 0.002). While MRI outcomes analysis showed that effects on newer enlarging T2 or new contrast-enhancing T1 lesions at 24 months were similar, the reduction in T2- and T1-weighted lesion volume was significantly greater in the groups given IFNs than in the glatiramer acetate groups (mean difference [MD] −0.58, 95% CI: −0.99 to −0.18; p = 0.004, and MD −0.20, 95% CI: −0.33 to −0.07; p = 0.003, respectively).
- In a network meta-analysis of 24 studies comparing IFNs and glatiramer acetate, both drugs were found to reduce the annualized relapse rate (ARR) as compared to placebo but did not differ statistically from each other (*Melendez-Torres et al 2018*). Ranking of the drugs based on SUCRA (surface under the cumulative ranking curve) indicated that glatiramer acetate 20 mg once daily had the highest probability for superiority, followed by peginterferon β-1a 125 mcg every 2 weeks.
- A meta-analysis of 6 placebo-controlled trials failed to find a significant advantage of Avonex (IFNβ-1a) 30 mcg IM once weekly compared to placebo in the number of relapse-free patients after 1 year of therapy (*Freedman et al 2008*). In contrast, other studies found Avonex (IFNβ-1a) 30 mcg IM once weekly to be comparable to the other IFNβ products in terms of relapse rate reduction, disability progression, and SPMS development *(Carra et al 2008, Limmroth et al 2007, Minagara et al 2008, Rio et al 2005, Trojano et al 2003, Trojano et al 2007)*. Moreover, IFN therapy, especially the higher dose products, is associated with the production of neutralizing antibodies (NAb), which may result in decreased radiographic and clinical effectiveness of treatment *(Goodin et al 2007, Sorensen et al 2005)*. Exploratory post-hoc analyses of the PRISMS trial linked the development of NAb with reduced efficacy *(Alsop et al 2005)*. Development of NAb among patients (N = 368) randomized to receive Rebif (IFNβ-1a) 44 or 22 mcg SC 3 times weekly for 4 years was associated with higher relapse rates (adjusted relapse rate ratio, 1.41; 95% CI: 1.12 to 1.78; p = 0.004), a greater number of active lesions, and percentage change in T2 lesion burden from baseline on MRI scan (p < 0.001). In a systematic review of 40 studies of MS agents including IFNβ-1a and IFNβ-1b, the primary outcome measure was the frequency of IFN NAb *(Govindappa et al 2015)*. NAb development was most frequent with IFN β-1b, followed by IFN β-1a SC, and lowest with IFN β-1a IM. Higher doses were associated with a higher rate of NAb development.
- The CombiRx trial evaluated the combination of Copaxone (glatiramer acetate) and Avonex (IFNβ-1a IM) over 3 years. The ARR for the combination therapy (IFNβ-1a + glatiramer) was not statistically superior to the better of the 2 single treatment arms (glatiramer) (p = 0.27). The ARRs were 0.12 for the combination therapy, 0.16 for IFNβ-1a, and 0.11 for glatiramer acetate. Glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 31% (p = 0.027), and IFNβ-1a + glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 25% (p = 0.022). The 3 treatment groups did not show a significant difference in disability progression over 6 months. Combination therapy was superior to either monotherapy in reducing new lesion activity and accumulation of total lesion volume *(Lublin et al 2013)*.
- It is estimated that within a few years of initiating treatment, at least 30 and 15% of patients discontinue MS biological response modifiers due to perceived lack of efficacy or side effects, respectively *(Coyle 2008, Portaccio et al 2008)*. According to several observational studies, switching patients who have failed to adequately respond to initial treatment to another first-line therapy is safe and effective *(Caon et al 2006, Zwibel 2006, Carra et al 2008)*. Patients switching to glatiramer acetate after experiencing inadequate response to IFNβ-1a therapy experienced a reduction in relapse rates and disability progression. Likewise, switching to IFNβ-1a therapy after suboptimal efficacy with glatiramer acetate

increased the number of relapse-free patients in 1 study *(Carra et al 2008)*. The smallest reduction in the ARR was seen in patients who had switched from one IFNβ-1a preparation to another.

- The GALA study evaluated glatiramer acetate SC 40 mg 3 times weekly compared to placebo in 1404 patients with relapsing MS over 12 months. Results demonstrated that glatiramer acetate 40 mg 3 times weekly, compared to placebo, reduced the ARR and MRI endpoints *(Khan et al 2013)*.
- Glatiramer acetate 20 mg daily and 40 mg 3 times weekly have not been directly compared for efficacy. A Phase 3 dose comparison study evaluated glatiramer acetate 20 mg and 40 mg each given daily in 1155 patients with MS. The primary endpoint, mean ARR, was similar in both groups: ARR = 0.33 (20 mg group) vs ARR = 0.35 (40 mg group). For patients from both groups who completed the entire 1-year treatment period, the mean ARR = 0.27 *(Comi et al 2011)*.
- The efficacy and safety of Plegridy (peginterferon β-1a) in adult patients with MS (N = 1516) were evaluated in ADVANCE, a Phase 3, multicenter, randomized, placebo-controlled trial. Eligible adult patients had RRMS with baseline Expanded Disability Status Scale (EDSS) score ≤ 5 and 2 clinically documented relapses in the previous 3 years with at least 1 relapse in the previous 12 months. Patients were randomized to placebo or SC peginterferon β-1a 125 mcg every 2 weeks or every 4 weeks for 48 weeks. Approximately 81% of patients were treatment naïve.
  - At week 48, ARRs were significantly lower in the peginterferon β-1a every 2 week group (ARR = 0.256; p = 0.0007) and peginterferon β-1a every 4 week group (ARR = 0.288; p = 0.0114) compared to placebo (ARR = 0.397).
  - There were also significant differences between the peginterferon β-1a every 2 weeks and every 4 weeks groups compared to placebo in the proportion of patients with relapse at week 48 (p = 0.0003 and p = 0.02, respectively). The proportions of patients with 12 weeks of sustained disability progression at the end of the 48 week study period were significantly lower in the peginterferon β-1a groups (both 6.8%; p = 0.0383 for every 2 weeks group; p = 0.038 for every 4 weeks group) compared to placebo (10.5%).
  - The mean number of new or newly enlarging T2 hyperintense lesions on MRI were significantly reduced in the peginterferon β-1a every 2 weeks group compared to placebo (3.6 lesions vs 10.9 lesions, respectively; p < 0.0001). Significant beneficial effects on the mean number of Gadolinium (Gd)-enhancing lesions were also observed with peginterferon β-1a every 2 weeks compared to placebo (p < 0.0001).
  - During the 48 weeks of treatment, the most commonly reported adverse effects included influenza-like illness and injection site erythema. Discontinuations due to adverse effects were higher in the peginterferon β-1a groups compared to placebo *(Calabresi et al 2014b)*.
  - NAb to interferon β-1a were identified in < 1% of all groups after 1 year (peginterferon β-1a every 2 weeks, 4 patients; peginterferon β-1a every 4 weeks, 2 patients; placebo, 2 patients) *(Calabresi et al 2014b)*. Preliminary data on NAb development to peginterferon β-1a over 2 years showed < 1% for all groups *(White et al 2014)*.
- The ADVANCE study continued into a second year. Patients originally randomized to placebo were re-randomized to peginterferon β-1a (the "placebo-switch group"). Peginterferon β-1a patients were continued on their original assigned therapy. A total of 1332 patients entered the second year of the study. After 96 weeks, the ARR was significantly lower in the peginterferon β-1a every 2 weeks group (ARR 0.221; p = 0.0001 vs placebo-switch group; p = 0.0209 vs every 4 week regimen) compared to both the placebo-switch group (ARR 0.351) and the peginterferon β-1a every 4 week group (ARR 0.291). The peginterferon β-1a every 4 week group (ARR 0.291; p = NS vs placebo-switch group) was not significantly different than the placebo-switch group (ARR 0.351) after 96 weeks based on the intent-to-treat (ITT) analysis. Peginterferon β-1a every 2 weeks was also associated with a lower proportion of patients who had relapse and a lower proportion of patients who had disability progression. Mean number of new or newly enlarging T2-weight hyperintense MRI lesions over 2 years was numerically lower with the peginterferon β-1a every 2 weeks group compared to the placebo-switch group *(Calabresi et al 2014b, Kieseier et al 2015)*.
- The ATTAIN study was an open-label extension of the ADVANCE study, where patients were followed for an additional 2 years (*Newsome et al 2018*). Of the original ADVANCE patients, 71% continued into the ATTAIN study, and 78% of those patients completed the extension study. The primary objective of the study was to evaluate the long-term safety of peginterferon β-1a. During the study, the common adverse events were influenza-like illness (43%), injection site erythema (41%), and headache (29%). The rate of treatment-related serious adverse events was 1%. The adjusted ARR and risk of relapse was reduced significantly with the every 2 weeks compared to the every 4 weeks dosing group (0.188 vs 0.263 and 36% vs 49%, respectively).

Gilenya (fingolimod)

- Gilenya (fingolimod) has been evaluated in 2 large, randomized controlled trials (RCTs) in adults against placebo and against Avonex (IFNβ-1a IM). In FREEDOMS, a 24-month placebo-controlled trial, fingolimod (0.5 and 1.25 mg once daily) was associated with significant reductions in ARR compared to placebo (54 and 60%, respectively; p < 0.001 for

both). Moreover, fingolimod was associated with reductions in disability progression and a prolonged time to first relapse compared to placebo *(Kappos et al 2010)*. In the 12-month TRANSFORMS trial, fingolimod 0.5 and 1.25 mg once daily significantly reduced ARR by 52 and 40%, respectively, compared to IFNβ-1a 30 mcg IM once weekly ($p < 0.001$ for both) *(Cohen et al 2010)*. In a 12-month extension of TRANSFORMS, patients initially randomized to IFNβ-1a IM were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IFNβ-1a IM. Patients switched from IFNβ-1a IM to fingolimod experienced fewer adverse events compared to treatment with IFNβ-1a IM in the core study (86 vs 91% and 91 vs 94% for the 0.5 and 1.25 mg groups, respectively; p values not reported). Fewer patients continuing fingolimod from the core study reported adverse events in the extension period compared to the core study (72 vs 86% and 71 vs 90% for the 0.5 and 1.25 mg doses, respectively; p values not reported) *(Khatri et al 2011)*. The TRANSFORMS extension study followed patients for up to 4.5 years with results consistent with those observed in the first 12 months of the extension study; however, there was significant attrition bias with very few patients enrolled past 36 months *(Cohen et al 2015)*.

- In the FREEDOMS II study, a 24-month placebo-controlled study, fingolimod (0.5 mg and 1.25 mg) significantly reduced ARR compared to placebo (48 and 50%, respectively; both $p < 0.0001$) *(Calabresi et al 2014a)*. Mean percentage brain volume change was lower with both fingolimod doses compared to placebo. Fingolimod did not show a significant effect on time to disability progression at 3 months compared to placebo.
- Fingolimod has also been evaluated in pediatric patients with relapsing MS (*Chitnis et al 2018*). The PARADIGMS trial randomized patients between 10 and 17 years of age to fingolimod 0.5 mg daily (0.25 mg for patients ≤ 40 kg) or IFNβ-1a IM 30 mcg weekly for up to 2 years. Fingolimod significantly reduced ARR compared to IFNβ-1a IM (adjusted rates, 0.12 vs 0.67; relative difference of 82%; $p < 0.001$). Fingolimod was also associated with a 53% relative reduction in the annualized rate of new or newly enlarged lesions. However, serious adverse events occurred more frequently with fingolimod than IFNβ-1a IM (16.8% vs 6.5%).

Aubagio (teriflunomide)

- Efficacy and safety of Aubagio were evaluated in two Phase 3, randomized, double-blind, placebo-controlled trials – the TEMSO trial (*O'Connor et al, 2011*) and the TOWER trial *(Confavreux et al 2014)*. In the TEMSO trial, 1088 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for a total of 108 weeks. Results demonstrated that compared to placebo, teriflunomide at both doses, reduced the ARR.
  - The percentage of patients with confirmed disability progression (CDP) was significantly lower only in the teriflunomide 14 mg group (20.2%) compared to placebo (27.3%; $p = 0.03$) *(O'Connor et al 2011)*.
- Teriflunomide has demonstrated beneficial effects on MRI scans in a Phase 2, randomized, double-blind, clinical trial. A total of 179 patients with MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for 36 weeks and were followed every 6 weeks with MRI scans during the treatment period. The teriflunomide groups had significant reductions in the average number of unique active lesions per MRI scan *(O'Connor et al 2006)*.
- In the TOWER trial, 1165 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for at least 48 weeks of therapy. The study ended 48 weeks after the last patient was randomized. Results demonstrated that, compared to placebo, teriflunomide 14 mg significantly reduced the ARR and the risk of sustained accumulation of disability *(Confavreux et al 2014)*.
- Teriflunomide and Rebif were compared in the 48-week TENERE study evaluating 324 patients with relapsing MS. The primary outcome, time to failure defined as a confirmed relapse or permanent discontinuation for any cause, was comparable for teriflunomide 7 mg and 14 mg and Rebif *(Vermersch et al 2014)*.

Tecfidera (dimethyl fumarate)

- Tecfidera (dimethyl fumarate) was evaluated in two Phase 3 studies: DEFINE and CONFIRM *(Gold et al 2012, Fox et al 2012, Xu et al 2015)*. DEFINE was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo in patients with RRMS. There were 1237 patients enrolled, and the trial duration was 96 weeks. Results demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, the number of lesions on MRI, and the proportion of patients with disability progression *(Gold et al 2012)*.
- CONFIRM was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo, with an additional, open-label study arm evaluating glatiramer acetate 20 mg SC daily. Glatiramer acetate was included as a reference comparator, but the study was not designed to test the superiority or non-inferiority of dimethyl fumarate vs glatiramer acetate. There were 1430 patients enrolled, and the trial duration was 96 weeks. Results of CONFIRM were similar to DEFINE, with the exception that there was no significant difference

between groups in the likelihood of disability progression. The CONFIRM trial demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, and the number of lesions on MRI *(Fox et al 2012)*.

Tysabri (natalizumab)

- Tysabri (natalizumab) reduced the risk of experiencing at least 1 new exacerbation at 2 years and reduced the risk of experiencing progression at 2 years *(Polman et al 2006, Pucci et al 2011, Rudick et al 2006)*. The AFFIRM trial compared natalizumab to placebo in patients with MS with less than 6 months of treatment experience with any DMT. Natalizumab reduced the ARR at 1 and 2 years compared to placebo. The cumulative probability of sustained disability progression and lesion burden on MRI were significantly reduced with natalizumab compared to placebo *(Polman et al 2006)*. In the SENTINEL trial, natalizumab was compared to placebo in patients who were receiving IFNβ-1a IM 30 mcg once weekly for at least 1 year. The combination of natalizumab plus IFNβ-1a IM resulted in a significant reduction in ARR at year 1 and 2 and significant reduction in cumulative probability of sustained disability progression at year 2. Lesion burden on MRI was also significantly reduced with the combination therapy. Two cases of PML were reported in the SENTINEL patient population resulting in the early termination of the trial *(Rudick et al 2006)*.

Lemtrada (alemtuzumab)

- The efficacy and safety of alemtuzumab were compared to Rebif (IFNβ-1a SC) in two randomized, Phase 3, open-label trials in patients with relapsing forms of MS – CARE-MS I and CARE-MS II (*Cohen et al 2012, Coles et al 2012)*. In the 2-year studies, patients were randomized to alemtuzumab infused for 5 consecutive days followed by a 3 consecutive day treatment course 12 months later or to Rebif (IFNβ-1a SC) 44 mcg 3 times weekly after an initial dosage titration. All patients received methylprednisolone 1 g IV for 3 consecutive days at the initiation of treatment and at month 12.
  - The CARE-MS I trial enrolled treatment-naïve patients with MS (n = 581) who were high functioning based on the requirement of a score of 3 or lower on the EDSS.
  - Patients (n = 840) enrolled in the CARE-MS II trial had experienced at least 1 relapse while on IFNβ or glatiramer acetate after at least 6 months of treatment. Patients were required to have an EDSS score of ≤ 5.
  - The co-primary endpoints for both trials were the relapse rate and the time to 6-month sustained accumulation of disability.
  - In the CARE-MS I trial, alemtuzumab reduced the risk of relapse by 55% compared to IFNβ-1a SC ($p < 0.0001$). Relapses were reported in 22% of alemtuzumab-treated patients and 40% of IFNβ-1a SC patients over 2 years. The proportion of patients having sustained accumulation of disability over 6 months was not significantly different between alemtuzumab (8%) vs IFNβ-1a SC (11%) ($p = 0.22$).
  - In the CARE-MS II trial, alemtuzumab significantly reduced relapse rate and sustained accumulation of disability compared to IFNβ-1a SC. The relapse rate at 2 years was reduced by 49% with alemtuzumab ($p < 0.0001$). The percent of patients with sustained accumulation of disability confirmed over 6 months was 13% with alemtuzumab and 20% with IFNβ-1a SC, representing a 42% risk reduction with alemtuzumab ($p = 0.0084$).
  - Both studies evaluated MRI outcomes, specifically the median percent change in T2 hyperintense lesion volume from baseline. Neither study found a significant difference between the 2 drugs for this measure.
  - During extension studies of CARE-MS I and CARE-MS II, approximately 80% of patients previously treated with alemtuzumab did not require additional treatment during the first year *(Garnock-Jones 2014)*.
- A Cochrane review by Zhang et al (2017) that compared the efficacy, tolerability, and safety of alemtuzumab vs IFNβ-1a in the treatment of RRMS identified 3 RCTs in 1694 total patients from the CARE-MS I, CARE-MS II, and CAMMS223 studies. In the alemtuzumab 12 mg/day group, the results showed statistically significant differences in reducing relapses (RR = 0.60, 95% CI: 0.52 to 0.70); preventing disease progression (RR = 0.60, 95% CI: 0.45 to 0.79); and developing new T2 lesions on MRI (RR = 0.75, 95% CI: 0.61 to 0.93) after 24 and 36 months' follow-up, but found no statistically significant difference in the changes of EDSS score (MD = -0.35, 95% CI: -0.73 to 0.03). In the alemtuzumab 24 mg/day group, the results showed statistically significant differences in reducing relapses (RR = 0.38, 95% CI: 0.23 to 0.62); preventing disease progression (RR = 0.42, 95% CI: 0.21 to 0.84); and the changes of EDSS score (MD = -0.83, 95% CI: -1.17 to -0.49) after 36 months' follow-up. The most frequently reported adverse effects with alemtuzumab were infusion-associated reactions, infections, and autoimmune events.

Ocrevus (ocrelizumab)

- The Phase 3 clinical development program for ocrelizumab (ORCHESTRA) included 3 studies: OPERA I, OPERA II, and ORATORIO *(Hauser et al 2017[a], Montalban et al 2017)*.

- OPERA I and OPERA II were 2 identically-designed, 96-week, Phase 3, active-controlled, double-blind, double-dummy, multicenter, parallel-group, RCTs that evaluated the efficacy and safety of ocrelizumab (600 mg administered as an IV infusion given as 2-300 mg infusions separated by 2 weeks for dose 1 and then as a single 600 mg infusion every 6 months for subsequent doses) compared with Rebif (IFNβ-1a; 44 mcg administered by SC injection 3 times per week) in 1656 patients with RMS *(Hauser et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*.
  - Across both studies, the majority of patients had not been treated with a DMT in the 2 years before screening (range: 71.4% to 75.3%); of those patients that had received a previous DMT as allowed by the protocol, most received IFN (18.0% to 21.0%) or glatiramer acetate (9.0% to 10.6%). Two patients previously treated with natalizumab for < 1 year were included, while 5 patients previously treated with fingolimod and 1 patient previously treated with dimethyl fumarate (both not within 6 months of screening) were also included.
  - Ocrelizumab achieved statistically significant reductions in the ARR vs Rebif across both trials (primary endpoint).
    - OPERA I (0.16 vs 0.29; 46% lower rate with ocrelizumab; $p < 0.001$)
    - OPERA II (0.16 vs 0.29; 47% lower rate; $p < 0.001$)
  - In pre-specified pooled analyses (secondary endpoints), the percentage of patients with disability progression confirmed at 12 weeks was statistically significantly lower with ocrelizumab vs Rebif (9.1% vs 13.6%; hazard ratio [HR] = 0.60, 95% CI: 0.45 to 0.81; $p < 0.001$). The results were similar for disability progression confirmed at 24 weeks: 6.9% vs 10.5%; HR = 0.60, 95% CI: 0.43 to 0.84; $p = 0.003$. The percentages of patients with disability improvement confirmed at 12 weeks were 20.7% in the ocrelizumab group vs 15.6% in the Rebif group (33% higher rate of improvement with ocrelizumab; $p = 0.02$).
  - The mean numbers of Gd-enhancing lesions per T1-weighted MRI scan were statistically significantly reduced with ocrelizumab vs Rebif (secondary endpoint).
    - OPERA I: 0.02 vs 0.29 (rate ratio = 0.06, 95% CI: 0.03 to 0.10; 94% lower number of lesions with ocrelizumab; $p < 0.001$)
    - OPERA II: 0.02 vs 0.42 (rate ratio = 0.05, 95% CI: 0.03 to 0.09; 95% lower number of lesions; $p < 0.001$)
  - The most common adverse events were infusion-related reactions and infections.
- No opportunistic infections, including PML, were reported in any group over the duration of either trial.
  - An imbalance of malignancies was observed with ocrelizumab; across both studies and through 96 weeks, neoplasms occurred in 0.5% (4/825) of ocrelizumab-treated patients vs 0.2% (2/826) of Rebif-treated patients.
  - Among the ocrelizumab-treated patients that developed neoplasms, there were 2 cases of invasive ductal breast carcinoma, 1 case of renal-cell carcinoma, and 1 case of malignant melanoma. Rebif-treated patients with neoplasms included 1 case of mantle-cell lymphoma and 1 case of squamous-cell carcinoma in the chest.
    - Between the clinical cutoff dates of the 2 trials (April 2, 2015 [OPERA I] and May 12, 2015 [OPERA II]) and June 30, 2016, 5 additional cases of neoplasm (2 cases of breast cancer, 2 cases of basal-cell skin carcinoma, and 1 case of malignant melanoma) were observed during the OL extension phase in which all continuing patients received ocrelizumab.
- ORATORIO was an event-driven, Phase 3, double-blind, multicenter, placebo-controlled, RCT evaluating the efficacy and safety of ocrelizumab (600 mg administered by IV infusion every 6 months; given as 2-300 mg infusions 2 weeks apart for each dose) compared with placebo in 732 people with PPMS *(Montalban et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*. Double-blind treatment was administered for a minimum of 5 doses (120 weeks) until the occurrence of ~253 events of disability progression in the trial cohort that was confirmed for at least 12 weeks.
  - The majority of patients (~88%) reported no previous use of DMTs within 2 years of trial entry. The proportion of patients with Gd-enhancing lesions was similar (27.5% in the ocrelizumab group vs 24.7% in the placebo group); however, there was an imbalance in the mean number of Gd-enhancing lesions at baseline, with nearly 50% fewer lesions in the placebo group (1.21 vs 0.6) (*FDA Medical and Summary Reviews 2017*).
  - The percentages of patients with 12-week confirmed disability progression (primary endpoint) were 32.9% with ocrelizumab vs 39.3% with placebo (HR = 0.76, 95% CI: 0.59 to 0.98; relative risk reduction of 24%; $p = 0.03$).
  - The percentages of patients with 24-week CDP (secondary endpoint) were 29.6% with ocrelizumab vs 35.7% with placebo (HR=0.75, 95% CI: 0.58 to 0.98; relative risk reduction of 25%; $p = 0.04$).
  - Additional secondary endpoints included changes in the timed 25-foot walk, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.

- The proportion of patients with 20% worsening of the timed 25-foot walk confirmed at 12 weeks was 49% in ocrelizumab-treated patients compared to 59% in placebo-treated patients (25% risk reduction).
- From baseline to Week 120, the total volume of hyperintense brain lesions on T2-weighted MRI decreased by 3.37% in ocrelizumab-treated patients and increased by 7.43% in placebo-treated patients ($p < 0.001$).
- From Weeks 24 to 120, the percentage of brain volume loss was 0.90% with ocrelizumab vs 1.09% with placebo ($p = 0.02$).

- Infusion-related reactions, upper respiratory tract infections, and oral herpes infections occurred more frequently with ocrelizumab vs placebo.
- Neoplasms occurred in 2.3% (11/486) of patients treated with ocrelizumab vs 0.8% (2/239) of patients who received placebo. Among the ocrelizumab-treated patients that developed neoplasms, there were 4 cases of breast cancer, 3 cases of basal-cell carcinoma, and 1 case in each of the following: endometrial adenocarcinoma, anaplastic large-cell lymphoma (mainly T cells), malignant fibrous histiocytoma, and pancreatic carcinoma. In the placebo group, 1 patient developed cervical adenocarcinoma in situ and 1 patient developed basal-cell carcinoma.
  - Between the clinical cutoff date (July 24, 2015) and June 30, 2016, 2 additional cases of neoplasm (1 case of basal-cell skin carcinoma and 1 case of squamous-cell carcinoma) were detected during the open-label extension phase in which all patients received ocrelizumab.

Mayzent (siponimod)

- The Phase 3 trial, EXPAND was a double-blind, randomized, parallel-group, placebo-controlled, time-to-event study in patients with SPMS who had evidence of disability progression in the previous 2 years (*Bar-Or et al 2018, Fox et al 2015, Kappos et al 2018*).
  - A total of 1651 patients were randomized to treatment with either siponimod 2 mg (n = 1105) or placebo (n = 546).
  - A total of 82% of the siponimod-treated patients and 78% of placebo-treated patients completed the study.
    - The median age of patients was 49.0 years, 95% of patients were white, and 60% were female.
  - For the primary endpoint, 288 (26%) of 1096 patients receiving siponimod and 173 (32%) of 545 patients receiving placebo had a 3-month CDP (HR 0.79: 95% CI: 0.65 to 0.95: RR reduction, 21%; $p = 0.013$).
  - Key secondary endpoints included time to 3-month confirmed worsening of at least 20% from baseline in T25FW and change from baseline in T2 lesion volume on MRI. Siponimod did not show a significant difference in T25FW. Patients treated with siponimod had a 55% relative reduction in ARR (0.071 vs 0.16), compared to placebo (nominal $p < 0.01$). The absolute reduction in the ARR was 0.089 with siponimod.

Mavenclad (cladribine)

- The 96-week Phase 3 trial, CLARITY, was a double-blind, 3-arm, placebo-controlled, multicenter trial to evaluate the safety and efficacy of oral cladribine in 1326 patients with RRMS (*Giovannoni et al 2010*, *Giovannoni 2017*).
  - Patients were required to have at least 1 relapse in the previous 12 months. The median patient age was 39 years and the female-to-male ratio was 2:1. The mean duration of MS prior to study reenrollment was 8.7 years.
  - Patients were randomized to receive either placebo (n = 437), or a cumulative oral dose of cladribine 3.5 mg/kg (n = 433) or 5.25 mg/kg (n = 456) over the 96-week study period in 2 treatment courses.
  - The primary outcome was ARR.
  - ARRs at 96 weeks were reduced in both cladribine treatment groups vs placebo (0.14, 0.15, and 0.33 in the 3.5 mg/kg, 5.25 mg/kg and placebo groups, respectively; each $p < 0.001$).
  - A significantly higher percentage of patients remained relapse-free at 96 weeks both in the cladribine treatment groups vs placebo; a total of 79.7% and 78.9% of patients in the 3.5 mg/kg and 5.25 mg/kg groups, respectively, were relapse free vs 60.9% in the placebo group (each $p < 0.001$ vs placebo).
  - Cladribine 3.5 mg/kg significantly lowered the ARR vs the 5.25 mg/kg treatment group.

Symptomatic MS

- Despite the demonstrated efficacy of DMTs, for many patients there is little evidence of their effect on quality of life (QOL) in general or symptom management in particular. Impaired mobility contributes to direct and indirect costs *(Miravelle et al 2011)*.
  - Ampyra (dalfampridine) is the only FDA-approved agent for the symptomatic treatment of impaired mobility in patients with MS. Improvement of walking ability with dalfampridine was demonstrated in two 14-week, double-blind, Phase 3, RCTs of 540 patients of all MS types. Compared to placebo, dalfampridine significantly improved the

walking speed by about 25% in approximately one-third of MS patients as measured by the timed 25-foot walk (T25FW) *(Goodman et al 2009, Jensen et al 2014, Ruck et al 2014)*.
  - However, questions have been raised regarding the cost-effectiveness of dalfampridine, and whether treatment leads to a long-term clinically meaningful therapeutic benefit. To address the benefit of long-term therapy with dalfampridine, an open-label, observational study of 52 MS patients with impaired mobility was conducted. Results demonstrated that about 60% of patients were still on treatment after 9 to 12 months. Two weeks after treatment initiation, significant ameliorations could be found for T25FW, maximum walking distance, as well as motoric and cognitive fatigue, which persisted after 9 to 12 months *(Ruck et al 2014)*.

Clinically Isolated Syndrome (CIS)

- Avonex (IFNβ-1a IM) and Betaseron (IFNβ-1b) are FDA-approved for the treatment of the first clinical episode with MRI features consistent with MS. Copaxone (glatiramer acetate) and Aubagio (teriflunomide) have evidence supporting a significant delay in the time to development of a second exacerbation, compared to placebo, in patients with an isolated demyelinating event.
- In the PRECISE trial, glatiramer acetate significantly reduced the risk of converting to a CDMS diagnosis by 45% compared to placebo in patients with CIS (p = 0.005). In addition, the time for 25% of patients to convert to CDMS was significantly prolonged with glatiramer acetate compared to placebo (722 vs 336 days; p = 0.0041) *(Comi et al 2009)*. In the 2 year, open-label extension phase of PRECISE, early initiation of glatiramer acetate demonstrated a 41% reduced risk of CDMS compared to delayed glatiramer acetate (HR: 0.59; 95% CI: 0.44 to 0.8; p = 0.0005). Over the 2 year extension, the baseline-adjusted proportions of patients who developed CDMS were 29.4% and 46.5% for the early and late initiation treatment groups (odds ratio [OR]: 0.48; 95% CI: 0.33 to 0.7; p = 0.0002) *(Comi et al 2012)*.
- A meta-analysis of randomized, double-blind, placebo-controlled trials in patients with CIS found a significantly lower risk of CDMS with IFN therapy compared to placebo (p < 0.0001) *(Clerico et al 2008)*. A 10-year, multicenter, randomized clinical trial with IFNβ-1a IM demonstrated that immediate initiation of therapy in patients with CIS reduced the risk for relapses over 10 years, but it was not associated with improved disability outcomes compared to a control group that also initiated therapy relatively early in the disease *(Kinkel et al 2012)*. Over the 10-year study, the drop-out rate was significant. Similar results were observed with IFNβ-1b (BENEFIT study) over an 8-year observation period. Patients who received treatment early had a lower overall ARR compared to those patients who delayed treatment *(Kappos et al 2007, Edan et al 2014)*. In the first 3 years of BENEFIT, early treatment with IFNβ-1b reduced the risk for progression of disability by 40% compared to delayed treatment (16% vs 25%, respectively; HR = 0.6; 95% CI: 0.39 to 0.92; p = 0.022).
- A 2018 systematic review and network meta-analysis of RCTs was conducted to assess the potential short- and long-term benefits of treatment with IFN-β or glatiramer acetate in patients with CIS (*Armoiry et al 2018)*. The review identified 5 primary RCTs that assessed the time to clinically definite multiple sclerosis (CDMS) in patients with CIS treated with IFN-β or glatiramer acetate vs placebo. They found that all drugs reduced the time to CDMS when compared with placebo, with a pooled HR of 0.51 (95% CI: 0.44 to 0.61) and low heterogeneity, and there was no evidence that indicated that 1 active treatment was superior to another when compared indirectly. The authors noted that there was insufficient information to rate the risk of selection bias, 4 of the 5 studies were at high risk of performance bias, and 1 study was rated to have a high risk for attrition bias. Four of the trials had open-label extension studies performed over 5 to 10 years, all of which indicated that early DMT therapy (regardless of agent) led to an increase in time to CDMS when compared with placebo (HR = 0.64, 95% CI: 0.55 to 0.74; low heterogeneity). These results should be taken with caution; however, as all of the open-label extension arms were at a high risk for attrition bias and had large losses to follow-up noted.
- The TOPIC study enrolled 618 patients with CIS and found teriflunomide 7 and 14 mg doses reduced the risk of relapse defining CDMS compared to placebo *(Miller et al 2014)*. Teriflunomide 14 mg reduced the risk of conversion to CDMS by 42.6% compared to placebo (HR, 0.574; 95% CI: 0.379 to 0.869; p = 0.0087) whereas teriflunomide 7 mg reduced the conversion to CDMS by 37.2% compared to placebo (HR, 0.628; 95% CI: 0.416 to 0.949; p = 0.0271).

Progressive MS

- Limited treatment options are available for patients with non-active SPMS and PPMS. Mitoxantrone is FDA-approved for treating SPMS, while ocrelizumab has been specifically approved for the treatment of PPMS (and relapsing forms of MS).
- Mitoxantrone was shown to reduce the clinical relapse rate and disease progression in aggressive RRMS, SPMS, and progressive-relapsing MS *(Hartung et al 2002, Krapf et al 2005)*. For MRI outcome measures, mitoxantrone was not statistically significantly different than placebo at month 12 or 24 for the total number of MRI scans with positive Gd

enhancement or at month 12 for the number of lesions on T2 weighted MRI. However, the baseline MRI lesion number and characteristics were different among the groups *(Krapf et al 2005)*. In 2010, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluated all published data including cohort data for mitoxantrone. Evaluation of efficacy found that mitoxantrone is probably effective in modestly reducing clinical attack rate, MRI activity, and disease progression. A confirmatory trial is necessary before widespread adoption of mitoxantrone for DMT for MS can be made in light of the risks of cardiotoxicity and treatment-related leukemia *(Marriott et al 2010)*.

- The results of studies with the other agents for MS have failed to consistently demonstrate a benefit in progressive forms of MS, and due to being off-label, these uses are not included in Table 2. In the PROMISE trial, glatiramer acetate was no more effective than placebo in delaying the time to accumulated disability for patients with PPMS *(Wolinsky et al 2007)*. The ASCEND trial evaluated natalizumab in SPMS was found to have no significant difference in the rate of confirmed disability progression compared to placebo (*Kapoor et al 2018*).
- Several IFN trials in this population have yielded conflicting results *(Rizvi et al 2004)*. A systematic analysis evaluated 5 clinical trials (N = 3082) of IFNβ compared to placebo in the treatment of SPMS. In 4 trials with the primary outcome of sustained disability progression at 3 or 6 months, IFNβ demonstrated no benefit. The risk ratio for sustained progression with IFNβ was 0.98 (95% CI: 0.82 to 1.16; p = 0.79); however, between-study heterogeneity was high (I^2 = 57%) *(La Mantia et al 2013)*.

Timing of DMT initiation

- A 2017 systematic review by Merkel et al (2017) evaluated the effect of high-efficacy immunotherapies (ie, fingolimod, natalizumab, alemtuzumab) at different stages of MS. Twelve publications (9 RCTs + 3 observational studies) were identified as reporting information relevant to the outcomes of early vs delayed initiation of high-efficacy DMTs for RRMS. A number of these studies suggested that earlier commencement of high-efficacy DMTs resulted in more effective control of relapse activity than their later initiation. The evidence regarding the effect of the timing of high-efficacy therapies on disability outcomes was conflicting; additional data are required to answer this question.

Decisions to discontinue DMTs in MS

- Patient with RRMS eventually progress to SPMS. Patients experience worsening disability with or without relapses. Current therapies focus on relapsing forms of MS and are not indicated for non-active SPMS. The decision to discontinue DMTs has not been well studied. The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review evaluating the decision dilemmas surrounding discontinuation of MS therapies in the setting of progressive disease and pregnancy *(Butler et al 2015)*. No studies directly assess continued therapy vs discontinued therapy for MS in comparable populations. Based on low strength of evidence, long-term all-cause survival is higher for treatment-naïve MS patients who did not delay starting IFNβ-1b by 2 years and used DMT for a longer duration than those who delayed therapy. Very little evidence is available about the benefits and risks of discontinuation of therapy for MS in women who desire pregnancy (*Rae-Grant et al 2018[b]*).

Meta-Analyses

- A 2017 systematic review conducted by the Institute for Clinical and Economic Review (ICER) included ocrelizumab in a comparative efficacy analysis with other DMTs used in the treatment of MS.
  - Network meta-analyses demonstrated that for the treatment of RRMS, alemtuzumab, natalizumab, and ocrelizumab (in that order) were the most effective DMTs for reducing ARRs (~70% reduction vs placebo).
  - Ocrelizumab and alemtuzumab had the greatest reductions in disability progression (53% to 58% reduction vs placebo, respectively), closely followed by natalizumab (44%).
- A systematic review that identified 28 RCTs found that the magnitude of ARR reduction varied between 15 to 36% for all IFNβ products, glatiramer acetate, and teriflunomide; and from 50 to 69% for alemtuzumab, dimethyl fumarate, fingolimod, and natalizumab. The risk of 3-month disability progression was reduced by 19 to 28% with IFNβ products, glatiramer acetate, fingolimod, and teriflunomide; by 38 to 45% for peginterferon IFNβ, dimethyl fumarate, and natalizumab; and by 68% with alemtuzumab *(Fogarty et al 2016)*.
- RCTs (n = 39) evaluating 1 of 15 treatments for MS were analyzed for benefits and acceptability in 25,113 patients with RRMS *(Tramacere et al 2015)*. Drugs included were IFNβ-1b, IFNβ-1a (IM and SC), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, peginterferon IFNβ-1a, azathioprine, and immunoglobulins. Investigational agents, daclizumab and laquinimod, were also included. The studies had a median

duration of 24 months with 60% of studies being placebo-controlled. The network meta-analysis evaluated the recurrence of relapses and disability progression.
  - Relapses: alemtuzumab, mitoxantrone, natalizumab, and fingolimod were reported to have greater treatment benefit compared to placebo. Over 12 months (29 studies; N = 17,897):
    - alemtuzumab: RR = 0.40, 95% CI: 0.31 to 0.51; moderate quality evidence
    - mitoxantrone: RR = 0.40, 95% CI: 0.20 to 0.76; low quality evidence
    - natalizumab: RR = 0.56, 95% CI: 0.43 to 0.73; high quality evidence
    - fingolimod: RR = 0.63, 95% CI: 0.53 to 0.74; low quality evidence
    - dimethyl fumarate: RR = 0.78, 95% CI: 0.65 to 0.93; moderate quality evidence
    - daclizumab (no longer on the market): RR = 0.79, 95% CI: 0.61 to 1.02; moderate quality evidence
    - glatiramer acetate: RR = 0.80, 95% CI: 0.68 to 0.93; moderate quality evidence
  - Relapses over 24 months vs placebo (26 studies; N = 16,800):
    - alemtuzumab: RR = 0.46, 95% CI: 0.38 to 0.55; moderate quality evidence
    - mitoxantrone: RR = 0.47, 95% CI: 0.27 to 0.81; very low quality evidence
    - natalizumab: RR = 0.56, 95% CI: 0.47 to 0.66; high quality evidence
    - fingolimod: RR = 0.72, 95% CI: 0.64 to 0.81; moderate quality evidence
  - Disability worsening over 24 months vs placebo (26 studies; N = 16,800):
    - mitoxantrone: RR = 0.20, 95% CI: 0.05 to 0.84; low quality evidence
    - alemtuzumab: RR = 0.35, 95% CI: 0.26 to 0.48; low quality evidence
    - natalizumab: RR = 0.64, 95% CI: 0.49 to 0.85; moderate quality evidence
  - Relapses and disability worsening over 36 months were only tested in 2 studies (CombiRx and CAMMS223). Both studies had a high risk of bias.
  - Acceptability: Higher rates of withdrawal due to adverse events compared to placebo over 12 months were reported for teriflunomide (RR = 2.24, 95% CI: 1.5 to 3.34); peginterferon beta-1a (RR = 2.8, 95% CI: 1.39 to 5.64); Avonex (RR = 4.36, 95% CI: 1.98 to 9.6); Rebif (RR = 4.83, 95% CI: 2.59 to 9); and fingolimod (RR = 8.26, 95% CI: 3.25 to 20.97).
  - Over 24 months, only fingolimod had a significantly higher proportion of participants who withdrew due to any adverse event (RR vs placebo = 1.69, 95% CI: 1.32 to 2.17).
    - mitoxantrone: RR = 9.82, 95% CI: 0.54 to 168.84
    - natalizumab: RR = 1.53, 95% CI: 0.93 to 2.53
    - alemtuzumab: RR = 0.72, 95% CI: 0.32 to 1.61
- Filippini et al (2013) conducted a Cochrane review of 44 RCTs on the relative effectiveness and acceptability of DMTs and immunosuppressants in patients with either RRMS or progressive MS (N = 17,401).
  - On the basis of high quality evidence, natalizumab and Rebif were superior to all other treatments for preventing clinical relapses in the short-term (24 months) in RRMS compared to placebo (OR = 0.32, 95% CI: 0.24 to 0.43; OR = 0.45, 95% CI: 0.28 to 0.71, respectively); they were also more effective than Avonex (OR = 0.28, 95% CI: 0.22 to 0.36; OR = 0.19, 95% CI: 0.06 to 0.6, respectively).
  - Based on moderate quality evidence, natalizumab and Rebif decreased the odds of patients with RRMS having disability progression in the short-term, with an absolute reduction of 14% and 10%, respectively, vs placebo.
  - Natalizumab and Betaseron were significantly more effective (OR = 0.62, 95% CI: 0.49 to 0.78; OR = 0.35, 95% CI: 0.17 to 0.7, respectively) than Avonex in reducing the number of patients with RRMS who had progression at 2 years of follow-up, and confidence in this result was graded as moderate.
  - The lack of convincing efficacy data showed that Avonex, IV immunoglobulins (IVIG), cyclophosphamide, and long-term corticosteroids have an unfavorable benefit-risk balance in RRMS.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a systematic review of 30 RCTs to assess the comparative clinical- and cost-effectiveness of drug therapies for the treatment of RRMS (N,= 16,998) (*CADTH, 2013).* Results suggested that all active treatments produce statistically significant reductions in ARR compared with no treatment, and that there were clear between-treatment differences.
  - Compared with no treatment, reductions in the ARR were approximately 70% for natalizumab and alemtuzumab, 50% for fingolimod or dimethyl fumarate, and 30% for SC IFNs, glatiramer acetate, or teriflunomide.
  - Among active comparisons, ARRs were lower for Betaseron (0.69, 95% CI: 0.54 to 0.87); Rebif (0.76, 95% CI: 0.59 to 0.98); and fingolimod (0.49, 95% CI: 0.38 to 0.63) compared with Avonex. In addition, ARRs were statistically lower for dimethyl fumarate (0.76, 95% CI: 0.62 to 0.93) compared with glatiramer acetate.

- Compared with placebo, all active treatments exhibited a lower risk of sustained disability progression, but results were only statistically significant for Avonex, Rebif, natalizumab, fingolimod, teriflunomide, and dimethyl fumarate; RR (95% CI) for these agents ranged from 0.59 (95% CI: 0.46 to 0.75) for natalizumab to 0.74 (95% CI: 0.57 to 0.96) for teriflunomide. Between-treatment differences were less apparent.
- Among active comparisons, the risk of sustained disability progression was statistically lower for alemtuzumab (0.59, 95% CI: 0.40 to 0.86) compared with Rebif, and for Betaseron (0.44, 95% CI: 0.2 to 0.80) compared with Avonex.
- Among active comparisons, MRI findings were more favorable for alemtuzumab compared with Rebif, and more favorable for all 3 of fingolimod, Betaseron, and Rebif compared with Avonex. Compared with glatiramer acetate, Tecfidera resulted in a lower mean number of T2 lesions, but the mean number of Gd-enhancing lesions was not statistically different between these 2 treatments.
- The incidence of serious adverse events and treatment discontinuations did not differ significantly between treatments in the majority of trials, except for a higher incidence of treatment discontinuation for Rebif compared to placebo and alemtuzumab.

- Hamidi et al (2018) conducted a systematic review and network meta-analysis of 37 studies including 26 RCTs from a health technology assessment (HTA) report and 11 supplemental RCTs published after the HTA. Eleven agents, including dimethyl fumarate, teriflunomide, IFNs, peginterferon, glatiramer acetate, natalizumab, fingolimod, and alemtuzumab were included and were compared to either placebo or any drug treatment in patients of varying treatment experience levels. Key findings from the network meta-analysis include:
  - Alemtuzumab 12 mg had the highest probability of preventing annual relapses (RR = 0.29, 95% CI: 0.23 to 0.35; high quality evidence).
  - Alemtuzumab 24 mg (RR = 0.36, 95% CI: 0.16 to 0.7; low quality evidence) and alemtuzumab 12 mg (RR = 0.40, 95% CI: 0.27 to 0.60; very low quality evidence) were the most effective against progression of disability.
  - Dimethyl fumarate 240 mg and fingolimod 0.5 mg and 1.25 mg were more effective treatments when considering annual relapse and disability progression:
    - Annual relapse:
      - Dimethyl fumarate 240 mg twice daily: RR = 0.5, 95% CI: 0.42 to 0.6; high quality evidence
      - Fingolimod 0.5 mg: RR = 0.46, 95% CI: 0.39 to 0.54; high quality evidence
      - Fingolimod 1.25 mg: RR = 0.45, 95% CI: 0.39 to 0.53; high quality evidence
    - Disability progression:
      - Dimethyl fumarate 240 mg twice daily: RR = 0.65, 95% CI: 0.49 to 0.85; high quality evidence
      - Fingolimod 0.5 mg: RR = 0.71, 95% CI: 0.55 to 0.90; high quality evidence
      - Fingolimod 1.25 mg: RR = 0.71, 95% CI: 0.56 to 0.90; high quality evidence
  - Withdrawal due to adverse events was difficult to assess due to the low quality of available evidence, however, the authors determined that:
    - Fingolimod 1.25 mg (RR = 2.21, 95% CI: 1.42 to 2.5; moderate quality evidence), and Rebif 44 mcg (RR = 2.21, 95% CI: 1.29 to 3.97; low quality evidence) were associated with higher withdrawals due to adverse events when compared with other treatment options.
  - Alemtuzumab 24 mg (mean difference = -0.91; 95% CI: -1.48 to -0.40), and 12 mg (mean difference = -0.6; 95% CI: -1.02 to -0.24) were more effective than other therapies in lowering the EDSS.
  - No treatments were found to significantly increase serious adverse events; peginterferon β-1a was associated with more adverse events overall when compared with other medications (RR = 1.66, 95% CI: 1.21 to 2.28).
  - None of the 11 agents studied were associated with a statistically significantly higher risk of mortality when compared to placebo.
- A Bayesian network meta-analysis evaluating DMTs for RRMS ranked the most effective therapies based on SUCRA analysis (*Lucchetta et al 2018*). A total of 33 studies were included in the analysis. For the ARR, alemtuzumab (96% probability), natalizumab (96%), and ocrelizumab (85%) were determined to be the most effective therapies (high-quality evidence).
- A meta-analysis of randomized controlled trials was conducted to evaluate the efficacy and safety of teriflunomide in reducing the frequency of relapses and progression of physical disability in patients with relapsing multiple sclerosis (*Xu et al 2016*). The results showed that teriflunomide (7 and 14 mg) reduced the ARR and teriflunomide 14 mg decreased the disability progression in comparison to placebo (RR = 0.69, 95% CI: 0.55 to 0.87).

CLINICAL GUIDELINES

- The European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) published updated guidelines in 2018 (*Montalban et al 2018*).
- The main recommendations reported were the following:
  - The entire spectrum of disease-modifying drugs should be prescribed only in centers with adequate infrastructure to provide proper monitoring of patients, comprehensive assessment, detection of side effects, and capacity to address them properly. (Consensus statement)
  - Offer IFN or glatiramer acetate to patients with CIS and abnormal MRI findings with lesions suggesting MS who do not fulfill full criteria for MS. (Strong)
  - Offer early treatment with disease-modifying drugs in patients with active RRMS, as defined by clinical relapses and/or MRI activity (active lesions: contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually). (Strong)
  - For active RRMS, choosing among the wide range of available drugs from the modestly effective to the highly effective will depend on patient characteristics and comorbidity, disease severity/activity, drug safety profile, and accessibility of the drug. (Consensus statement)
  - Consider treatment with IFN in patients with active SPMS, taking into account, in discussion with the patient, the dubious efficacy, as well as safety and tolerability profile. (Weak)
  - Consider treatment with mitoxantrone in patients with active SPMS, taking into account the efficacy and specifically the safety and tolerability profile of this agent. (Weak)
  - Consider ocrelizumab for patients with active SPMS. (Weak)
  - Consider ocrelizumab for patients with PPMS. (Weak)
  - Always consult the summary of product characteristics for dosage, special warnings, and precautions of use, contraindications, and monitoring of side effects and potential harms. (Consensus statement)
  - Consider combining MRI with clinical measures when evaluating disease evolution in treated patients. (Weak)
  - When monitoring treatment response in patients treated with disease-modifying drugs, perform standardized reference brain MRI within 6 months of treatment onset and compare the results with those of further brain MRI, typically performed 12 months after starting treatment. Adjust the timing of both MRIs, taking into account the drug's mechanism and speed of action and disease activity, including clinical and MRI measures. (Consensus statement)
  - When monitoring treatment response in patients treated with disease-modifying drugs, the measurement of new or unequivocally enlarging T2 lesions is the preferred MRI method, supplemented by Gd-enhancing lesions for monitoring treatment response. Evaluation of these parameters requires high-quality standardized MRI scans and interpretation by highly qualified readers with experience in MS. (Consensus statement)
  - When monitoring treatment safety in patients treated with disease-modifying drugs, perform standard reference MRI every year in patients at low risk for PML, and more frequently (3 to 6 months) in patients at high risk for PML (JC virus positivity, natalizumab treatment duration over 18 months) and in patients at high risk for PML who switch drugs at the time the current treatment is discontinued and the new treatment is started. (Consensus statement)
  - Offer a more efficacious drug to patients treated with IFN or glatiramer acetate who show evidence of disease activity, assessed as recommended above. (Strong)
  - When deciding on which drug to switch to, in consultation with the patient, consider patient characteristics and comorbidities, drug safety profile, and disease severity/activity. (Consensus statement)
  - When treatment with a highly efficacious drug is stopped, whether due to inefficacy or safety, consider starting another highly efficacious drug. When starting the new drug, take into account disease activity (clinical and MRI; the greater the disease activity, the greater the urgency to start new treatment), the half-life and biological activity of the previous drug, and the potential for resumed disease activity or even rebound (particularly with natalizumab). (Consensus statement)
  - In treatment decisions, consider the possibility of resumed disease activity or even rebound when stopping treatment, particularly with natalizumab. (Weak)
  - Consider continuing a disease-modifying drug if the patient is stable (clinically and on MRI) and shows no safety or tolerability issues. (Weak)
  - Advise all women of childbearing potential that disease-modifying drugs are not licensed during pregnancy, except glatiramer acetate 20 mg/mL. (Consensus statement)

- For women planning a pregnancy, if there is a high risk for disease reactivation, consider using IFN or glatiramer acetate until pregnancy is confirmed. In some very specific (active) cases, continuing this treatment during pregnancy could also be considered. (Weak)
- For women with persistent high disease activity, it would generally be advised to delay pregnancy. For those who still decide to become pregnant or have an unplanned pregnancy, treatment with natalizumab throughout pregnancy may be considered after full discussion of potential implications; or treatment with alemtuzumab could be an alternative for planned pregnancy in very active cases provided that a 4-month interval is strictly observed from the latest infusion until conception. (Weak)

- The American Academy of Neurology (AAN) performed a systematic review that included 20 Cochrane reviews and 73 additional articles in order to assess the available evidence on initiation, switching, and stopping DMTs in patients with MS (*Rae Grant et al 2018[a]*). The results of the systematic review were used to assist in formulating updated AAN treatment guidelines (*Rae Grant et al 2018[b]*). The main recommendations were as follows:
  - Starting DMT
    - Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with 2 or more brain lesions that have imaging characteristics consistent with MS (Level B). After discussing the risks and benefits, clinicians should prescribe DMTs to people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS who decide they want this therapy. (Level B)
    - Clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity. (Level B)
    - Clinicians should monitor the reproductive plans of women with MS and counsel regarding reproductive risks and use of birth control during DMT use in women of childbearing potential who have MS. (Level B)
    - Clinicians should counsel men with MS on their reproductive plans regarding treatment implications before initiating treatment with teriflunomide. (Level B)
    - Because of the high frequency of severe adverse events, clinicians should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks. (Level B)
    - Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS. (Level B)
    - Clinicians may initiate natalizumab treatment in people with MS with positive anti-JCV antibody indices above 0.9 only when there is a reasonable chance of benefit compared with the low but serious risk of PML. (Level C)
    - Clinicians should offer ocrelizumab to people with PPMS who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits. (Level B)
  - Switching DMTs
    - Clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT. (Level B)
    - Clinicians should evaluate the degree of disease activity, adherence, adverse event profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use. (Level B)
    - Clinicians should discuss a change to non-injectable or less frequently injected DMTs in people with MS who report intolerable discomfort with the injections or in those who report injection fatigue on injectable DMTs. (Level B)
    - Clinicians should inquire about medication adverse events with people with MS who are taking a DMT and attempt to manage these adverse events, as appropriate (Level B). Clinicians should discuss a medication switch with people with MS for whom these adverse events negatively influence adherence. (Level B)
    - Clinicians should monitor laboratory abnormalities found on requisite laboratory surveillance (as outlined in the medication's package insert) in people with MS who are using a DMT (Level B). Clinicians should discuss switching DMTs or reducing dosage or frequency (where there are data on different doses [eg, interferons, teriflunomide]) when there are persistent laboratory abnormalities. (Level B)
    - Clinicians should counsel people with MS considering natalizumab, fingolimod, ocrelizumab, and dimethyl fumarate about the PML risk associated with these agents (Level B). Clinicians should discuss switching to a DMT with a lower PML risk with people with MS taking natalizumab who are or who become JCV antibody–positive, especially with an index of above 0.9 while on therapy. (Level B)
    - Clinicians should counsel that new DMTs without long-term safety data have an undefined risk of malignancy and infection for people with MS starting or using new DMTs (Level B). If a patient with MS develops a malignancy while using a DMT, clinicians should promptly discuss switching to an alternate DMT, especially for people with MS

using fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate (Level B). People with MS with serious infections potentially linked to their DMTs should switch DMTs (does not pertain to PML management in people with MS using DMT). (Level B)
    - Clinicians should check for natalizumab antibodies in people with MS who have infusion reactions before subsequent infusions, or in people with MS who experience breakthrough disease activity with natalizumab use (Level B). Clinicians should switch DMTs in people with MS who have persistent natalizumab antibodies. (Level B)
    - Physicians must counsel people with MS considering natalizumab discontinuation that there is an increased risk of MS relapse or MRI-detected disease activity within 6 months of discontinuation (Level A). Physicians and people with MS choosing to switch from natalizumab to fingolimod should initiate treatment within 8 to 12 weeks after natalizumab discontinuation (for reasons other than pregnancy or pregnancy planning) to diminish the return of disease activity. (Level B)
    - Clinicians should counsel women to stop their DMT before conception for planned pregnancies unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should discontinue DMTs during pregnancy if accidental exposure occurs, unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should not initiate DMTs during pregnancy unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy. (Level B)
  - Stopping DMTs
    - In people with RRMS who are stable on DMT and want to discontinue therapy, clinicians should counsel people regarding the need for ongoing follow-up and periodic reevaluation of the decision to discontinue DMT (Level B). Clinicians should advocate that people with MS who are stable (that is, those with no relapses, no disability progression, and stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial off therapy is warranted. (Level B)
    - Clinicians should assess the likelihood of future relapse in individuals with SPMS by assessing patient age, disease duration, relapse history, and MRI-detected activity (eg, frequency, severity, time since most recent relapse or gadolinium-enhanced lesion) (Level B). Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or gadolinium enhanced lesions on MRI activity) and have not been ambulatory (EDSS 7 or greater) for at least 2 years. (Level C)
    - Clinicians should review the associated risks of continuing DMTs vs those of stopping DMTs in people with CIS using DMTs who have not been diagnosed with MS. (Level B)
- According to the 2013 Canadian recommendations for treatment of MS, treatment decisions should be based on the level of concern for the rate and severity of relapses, degree of functional impairment due to relapses and disability progression. First-line treatment recommendations for RRMS include IFNβ products and glatiramer acetate. Second-line therapies for RRMS include fingolimod and natalizumab *(Freedman et al 2013)*.
- With an increasing number of options for the treatment of RRMS, the place in therapy for an individual agent is not straightforward. Treatment decisions will likely be based on a consideration of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences. The 2015 AAN position statement supports access to all DMT for patients with MS. In addition, step therapy should be driven by evidence-based clinical and safety information and not just based on costs. Highly individualized treatment decisions are necessary for patients with MS according to the AAN *(Corboy et al 2015)*.
- The 2015 Association of British Neurologists state that all available DMTs are effective in reducing relapse rate and MRI lesion accumulation *(Scolding et al 2015)*. Evidence is less clear on the impact of DMT on long-term disability. Drugs are separated into 2 categories based on relative efficacy. Category 1 – moderate efficacy includes IFNs (including pegIFN), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. Category 2 – high efficacy includes alemtuzumab and natalizumab – these drugs should be reserved for patients with very active MS.
- In September 2018, the MS Coalition published an update to its consensus paper on the principles and current evidence concerning the use of DMTs in MS. Major recommendations included the following:
  - Initiation of treatment with an FDA-approved DMT is recommended as soon as possible following a diagnosis of relapsing or primary progressive MS, regardless of the person's age; for individuals with a first clinical event and MRI features consistent with MS in whom other possible causes have been excluded; and for individuals with progressive MS who continue to demonstrate clinical relapses and/or demonstrate inflammatory activity.
  - Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, fingolimod, ocrelizumab or natalizumab for newly-diagnosed individuals with highly active MS.

- Treatment with a given DMT should be continued indefinitely unless any of the following occur (in which case an alternative DMT should be considered):
  - Suboptimal treatment response as determined by the individual and his or her treating clinician
  - Intolerable side effects
  - Inadequate adherence to the treatment regimen
  - Availability of a more appropriate treatment option
  - The healthcare provider and patient determine that the benefits no longer outweigh the risks.
- Movement from one DMT to another should occur only for medically appropriate reasons as determined by the treating clinician and patient.
- When evidence of additional clinical or MRI activity while on treatment suggests a sub-optimal response, an alternative regimen (eg, different mechanism of action) should be considered to optimize therapeutic benefit.
- Due to significant variability in the MS population, people with MS and their treating clinicians require access to the full range of treatment options for several reasons:
  - Different mechanisms of action allow for treatment change in the event of a sub-optimal response.
  - Potential contraindications limit options for some individuals.
  - Risk tolerance varies among people with MS and their treating clinicians.
  - Route of delivery, frequency of dosing, and side effects may affect adherence and quality of life.
  - Individual differences related to tolerability and adherence may necessitate access to different medications within the same class.
  - Pregnancy and breastfeeding limit the available options.
- Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, sex, or ethnicity.
- Absence of relapses while on treatment is a characteristic of treatment effectiveness and should not be considered a justification for discontinuation of treatment.

SAFETY SUMMARY

- Warnings for IFNβ include decreased peripheral blood cell counts including leukopenia, higher rates of depression, suicide and psychotic disorders, injection site reactions, and risk of severe hepatic injury. IFNβ (Avonex, Rebif, Betaseron, Extavia, and Plegridy) is associated with influenza-like symptoms including injection site reactions, musculoskeletal pain, fatigue, and headache. All IFNβ products carry a warning for thrombotic microangiopathy including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Adverse events related to IFNβ therapy appear to be dose-related and transient.
- Glatiramer acetate is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol. Patients treated with glatiramer acetate may experience a transient, self-limited, post-injection reaction of flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, and urticaria immediately following injection. Injection site reactions including lipodystrophy and skin necrosis have been reported. Because glatiramer acetate can modify immune response, it may interfere with immune functions. In controlled studies of glatiramer acetate 20 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions, vasodilatation, rash, dyspnea, and chest pain. In a controlled study of glatiramer acetate 40 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions.
- Fingolimod was originally approved with a risk evaluation and mitigation strategies program (REMS) to inform healthcare providers about the serious risks including bradyarrhythmia, atrioventricular block, infections, macular edema, respiratory effects, hepatic effects, fetal risk, increased blood pressure, basal cell carcinoma, immune system effects following discontinuation, and hypersensitivity reactions; however, the FDA lifted the REMS requirements in November 2016. Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with fingolimod. Patients with pre-existing cardiac disease may poorly tolerate fingolimod and may require additional monitoring. In clinical trials, the most common adverse reactions (incidence ≥ 10% and > placebo) were headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. If a serious infection develops, consider suspending fingolimod and reassess risks and benefits prior to re-initiation. Elimination may take up to 2 months thus, monitoring for infections should continue during this time. Do not start fingolimod in patients with active acute or chronic infection until the infection is resolved. Life-threatening and fatal infections have been reported in patients taking fingolimod. Establish immunity to varicella zoster virus prior to therapy initiation. Recent safety labeling changes warn of an increased risk of cutaneous malignancies, including melanoma, in patients treated with fingolimod. Cases of PML

have occurred in the postmarketing setting in patients who were treated with fingolimod for at least 2 years. A warning for PML has been added to the fingolimod labeling; at the first sign or symptom suggestive of PML, fingolimod should be withheld and an appropriate diagnostic evaluation performed. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Additionally, severe increases in disability after discontinuation of fingolimod have been described in post marketing reports.

- Teriflunomide is contraindicated in patients with severe hepatic impairment; patients who are pregnant, of childbearing potential, or that are not using reliable contraception; and with concurrent use of leflunomide. Labeling includes boxed warnings regarding hepatotoxicity and teratogenicity/embryolethality that occurred in animal reproduction studies in multiple animal species at plasma teriflunomide exposures similar to or lower than in humans. Other warnings include risk of leukopenia, peripheral neuropathy, severe skin reactions, and elevated blood pressure. Teriflunomide has a half-life of 4 to 5 months; therefore, use of activated charcoal or cholestyramine in an 11-day regimen upon discontinuation of teriflunomide is recommended to reduce serum levels over 2 weeks. The most common adverse reactions (≥ 10% and ≥ 2% greater than placebo) are headache, diarrhea, nausea, alopecia, and an increase in alanine aminotransferase (ALT).
- Dimethyl fumarate has no contraindications, except in patients with hypersensitivity to dimethyl fumarate or any excipients. Warnings include anaphylaxis and angioedema, PML, lymphopenia, and clinically significant cases of liver injury reported in the post-marketing setting. Consider therapy interruption if severe lymphopenia for more than 6 months occurs. Cases of PML have been reported following dimethyl fumarate therapy. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Common adverse events (incidence ≥ 10% and ≥ 2% more than placebo) were flushing, abdominal pain, diarrhea, and nausea. Administration of non-enteric aspirin up to 325 mg given 30 minutes prior to each dose or temporary dose reduction to 120 mg twice daily may reduce flushing.
- Natalizumab has a boxed warning regarding the risk of PML. PML is an opportunistic viral infection of the brain that usually leads to death or severe disability. Due to the risk of PML, natalizumab is only available through the TOUCH® Prescribing Program which is a restricted distribution program. Natalizumab is contraindicated in patients who have or have had PML and in patients who have had a hypersensitivity reaction. The most common adverse reactions (incidence ≥ 10%) were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort hypersensitivity reaction to natalizumab. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Other warnings with natalizumab include hypersensitivity reactions, increased risk of Herpes encephalitis and meningitis, acute retinal necrosis, increased risk of infections (including opportunistic infections), and hepatotoxicity, diarrhea (not otherwise specified), and rash.
- Mitoxantrone has boxed warnings for the risk of cardiotoxicity, risk of bone marrow suppression, and secondary leukemia. Congestive heart failure (CHF), potentially fatal, may occur either during therapy with mitoxantrone or months to years after termination of therapy. The maximum cumulative lifetime dose of mitoxantrone for MS patients should not exceed 140 mg/kg/m^2. Monitoring of cardiac function is required prior to all mitoxantrone doses.
- Alemtuzumab is contraindicated in patients with human immunodeficiency virus (HIV). The boxed warning for alemtuzumab includes autoimmunity conditions (immune thrombocytopenia and anti-glomerular basement membrane disease), serious and life-threatening infusion reactions, serious and life-threatening stroke within 3 days of administration, and the possibility of an increased risk of malignancies. Alemtuzumab is only available through a restricted distribution and REMS program which requires the member, provider, pharmacy and infusion facility to be certified by the REMS program. Approximately one-third of patients who receive alemtuzumab develop thyroid disorders. The most commonly reported adverse events reported in at least 10% of alemtuzumab-treated patients and more frequently than with IFNβ-1a were rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. Nearly all patients (99.9%) in clinical trials had lymphopenia following a treatment course of alemtuzumab. Alemtuzumab may also increase the risk of acute acalculous cholecystitis; in controlled clinical studies, 0.2% of alemtuzumab-treated MS patients developed acute acalculous cholecystitis, compared to 0% of patients treated with IFNβ-1a. During postmarketing use, additional cases of acute acalculous cholecystitis have been reported in alemtuzumab-treated patients. Recent updates to the safety labeling include a warning that patients taking alemtuzumab are at risk for serious infections caused by *Listeria monocytogenes*. Patients that are prescribed alemtuzumab should be counseled about this risk, and to avoid or appropriately heat any foods that may be a source of *Listeria*, such as deli meats and unpasteurized cheeses. Patients should undergo tuberculosis screening according to local guidelines.

- The labeling of ocrelizumab does not contain any boxed warnings; however, ocrelizumab is contraindicated in patients with active hepatitis B virus (HBV) infection and in those with a history of life-threatening infusion reactions to ocrelizumab. Additional warnings for ocrelizumab concern infusion reactions, infections, and an increased risk of malignancies.
  - As of June 30, 2016, the overall incidence rate of first neoplasm among ocrelizumab-treated patients across all 3 pivotal studies and a Phase 2, dose-finding study *(Kappos et al [2011])* was 0.40 per 100 patient-years of exposure to ocrelizumab (6467 patient-years of exposure) vs 0.20 per 100 patient-years of exposure in the pooled comparator groups (2053 patient-years of exposure in groups receiving Rebif or placebo) *(Hauser et al 2017, Ocrevus Formulary Submission Dossier 2017)*.
    - Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with Rebif or placebo), the labeling of ocrelizumab additionally recommends that patients follow standard breast cancer screening guidelines.
    - In related postmarketing requirements, the FDA has asked the manufacturer to conduct a prospective, longitudinal, observational study in adult patients with RMS and PPMS exposed to ocrelizumab to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study need to be followed for a minimum of 5 years or until death following their first exposure to ocrelizumab and the protocol must specify 2 appropriate populations to which the observed incidence and mortality rates will be compared *(FDA approval letter 2017)*.
  - No cases of PML have been reported to date in any studies of ocrelizumab (*Hauser et al 2017, McGinley et al 2017, Montalban et al 2017, Ocrevus Formulary Submission Dossier 2017*).
  - In patients with RMS, the most common adverse reactions with ocrelizumab (incidence ≥ 10% and greater than Rebif) were upper respiratory tract infections and infusion reactions. In patients with PPMS, the most common adverse reactions (incidence ≥ 10% and greater than placebo) were upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.
- Dalfampridine is contraindicated in patients with a history of seizure, moderate or severe renal impairment (CrCl ≤ 50 mL/min), and a history of hypersensitivity to dalfampridine or 4-aminopyridine. Dalfampridine can cause anaphylaxis; signs and symptoms of anaphylaxis have included respiratory compromise, urticaria, and angioedema of the throat and or tongue. Urinary tract infections (UTIs) were reported more frequently as adverse reactions in controlled studies in patients receiving dalfampridine 10 mg twice daily (12%) as compared to placebo (8%). The most common adverse events (incidence ≥ 2% and at a rate greater than the placebo rate) for dalfampridine were UTI, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, MS relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain.
- Siponimod is contraindicated in patients with a cytochrome P4502C9*3/*3 genotype, presence of Mobitz type II second-degree, third degree atrioventricular (AV) block or sinus syndrome. It is also contraindicated in patients that have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack or decompensated heart failure requiring hospitalization in the past 6 months. Warnings and precautions of siponimod include macular edema, increased blood pressure, bradyarrhythmia and AV conduction delays, decline in pulmonary function, and liver injury. Women of childbearing potential should use effective contraception during and for 10 days after stopping siponimod due to fetal risk. The most adverse events are headache, hypertension, and transaminase increases.
- Cladribine is contraindicated in patients with current malignancy, HIV infection, active chronic infection such as hepatitis or tuberculosis, hypersensitivity to cladribine, and in pregnant women. There is a boxed warning for potential malignancy and risk of teratogenicity. The warnings and precautions are lymphopenia, active infection, hematologic toxicity, liver injury, and graft vs host disease with blood transfusion. The most common adverse events are upper respiratory tract infection, headache, and lymphopenia.

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ampyra (dalfampridine)	Tablets	Oral	Twice daily	May be taken with or without food. Tablets should only be taken whole; do not divide, crush, chew, or dissolve.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				In patients with mild renal impairment (CrCl 51 to 80 mL/min), dalfampridine may reach plasma levels associated with a greater risk of seizures, and the potential benefits of dalfampridine should be carefully considered against the risk of seizures in these patients. Dalfampridine is contraindicated in patients with moderate or severe renal impairment (CrCl ≤ 50 mL/min). Based on animal data, dalfampridine may cause fetal harm.
Aubagio (teriflunomide)	Tablets	Oral	Once daily	May be taken with or without food. No dosage adjustment is necessary for patients with mild and moderate hepatic impairment; contraindicated in patients with severe hepatic impairment. Teriflunomide is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Exclude pregnancy before the start of treatment with teriflunomide in females of reproductive potential and advise females of reproductive potential to use effective contraception during teriflunomide treatment and during an accelerated drug elimination procedure after teriflunomide treatment. Teriflunomide should be stopped and an accelerated drug elimination procedure used if the patient becomes pregnant. Teriflunomide is detected in human semen; to minimize any

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				possible risk, men not wishing to father a child and their female partners should use effective contraception. Men wishing to father a child should discontinue use of teriflunomide and either undergo an accelerated elimination procedure or wait until verification that the plasma teriflunomide concentration is less than 0.02 mg/L.
Avonex (interferon β-1a)	Injection	IM	Once weekly Titration: To reduce the incidence and severity of flu-like symptoms that may occur during initiation, Avonex may be started at a dose of 7.5 mcg and the dose may be increased by 7.5 mcg each week for the next 3 weeks until the recommended dose of 30 mcg is achieved.	Following initial administration by a trained healthcare provider, Avonex may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with Avonex use. Use caution in patients with hepatic dysfunction.
Betaseron (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Copaxone (glatiramer acetate) [and Glatopa]	Injection	SC	20 mg once daily **OR** 40 mg 3 times per week at least 48 hours apart Note: The 2 strengths are not interchangeable.	Following initial administration by a trained healthcare provider, Glatiramer acetate may be self-administered. Areas for SC self-injection include arms, abdomen, hips, and thighs.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Extavia (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Gilenya (fingolimod)	Capsules	Oral	Once daily Note: Patients who initiate fingolimod and those who re-initiate treatment after discontinuation for longer than 14 days require first dose monitoring (see right).	May be taken with or without food. Approved for adults and pediatric patients 10 years of age or older. For pediatric patients ≤40 kg, a lower dose is recommended. First dose monitoring: Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of the observation period are required. Monitor until resolution if heart rate < 45 bpm, atrioventricular (AV) block, or if lowest post-dose heart rate is at the end of the observation period. Monitor symptomatic bradycardia with ECG until resolved. Continue overnight if intervention is required; repeat first dose monitoring for second dose. Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with known risk of torsades de pointes. Fingolimod exposure is doubled in patients with severe hepatic impairment; patients with severe

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				hepatic impairment should be closely monitored. No dose adjustment is necessary in mild-to-moderate hepatic impairment. The blood level of some fingolimod metabolites is increased (up to 13-fold) in patients with severe renal impairment; blood levels were not assessed in patients with mild or moderate renal impairment.
Lemtrada (alemtuzumab)†	Injection	IV	**2 treatment courses** First course: 12 mg/day on 5 consecutive days Second course: 12 mg/day on 3 consecutive days 12 months after the first treatment course Subsequent course: 12 mg/day for 3 consecutive days may be administered, as needed, at least 12 months after the last dose of any prior treatments courses. Important monitoring: Complete blood count with differential (prior to treatment initiation and at monthly intervals thereafter); serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter); urinalysis with urine cell counts (prior to treatment initiation and at monthly intervals thereafter); and a test of thyroid function, such as thyroid stimulating hormone level (prior to treatment initiation and every 3 months thereafter). Conduct baseline and yearly skin exams to monitor for melanoma.	Infused over 4 hours for both treatment courses; patients should be observed for infusion reactions during and for at least 2 hours after each Lemtrada infusion. Vital signs should be monitored before the infusion and periodically during the infusion. Pre-medicate with corticosteroids prior to Lemtrada infusion for the first 3 days of each treatment course. Administer antiviral agents for herpetic prophylaxis starting on the first day of alemtuzumab dosing and continuing for a minimum of 2 months after completion of Lemtrada dosing or until CD4+ lymphocyte count is more than 200 cells/microliter, whichever occurs later. Patients should complete any necessary immunizations at least 6 weeks prior to treatment with alemtuzumab.
Mavenclad (cladribine)	Tablet	Oral	Cumulative dosage of 3.5 mg/kg divided into 2 yearly treatment courses of 1.75	The use of Mavenclad in patients weighing less than 40 kg has not been investigated.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			mg/kg per treatment course. Each treatment course is divided into 2 treatment cycles: • First course/first cycle: start anytime • First cycle/second cycle: administer 23 to 27 days after the last dose of first course/first cycle. • Second course/first cycle: administer at least 43 weeks after the last dose of first course/second cycle. • Second course/second cycle: administer 23 to 27 days after the last dose of second course/first cycle.	Mavenclad is contraindicated in pregnant women and in female/males of reproductive potential that do not plan to use effective contraception. The safety and effectiveness in pediatric patients have not been established.
Mayzent (siponimod)	Tablets: starte pack of tablets	Oral	Once daily	Mayzent can cause fetal harm when administered to pregnant women. Dosage should be titrated based on patient's CYP2C9 genotype. Patients with sinus bradycardia (HR < 55 bpm), first- or second-degree AV block or a history of myocardial infarction or heart failure should undergo first dose monitoring for bradycardia.
mitoxantrone	Injection	IV	Every 3 months Note: Left ventricular ejection fraction (LVEF) should be evaluated prior to administration of the initial dose of mitoxantrone injection (concentrate) and all subsequent doses. In addition, LVEF evaluations are recommended if signs or symptoms of congestive heart failure develop at any time during treatment with mitoxantrone. Complete blood counts, including platelets, should be monitored prior to each course of mitoxantrone and in	For MS-related indications: 12 mg/m^2 given as a short IV infusion over 5 to 15 minutes Mitoxantrone injection (concentrate) should not be administered to MS patients with an LVEF < 50%, with a clinically significant reduction in LVEF, or to those who have received a cumulative lifetime dose of > 140 mg/m^2. Mitoxantrone generally should not be administered to MS patients with neutrophil counts less than 1500 cells/mm^3. Mitoxantrone therapy in MS patients with abnormal liver

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			the event that signs or symptoms of infection develop. Liver function tests should be monitored prior to each course of therapy.	function tests is not recommended because mitoxantrone clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments. Mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant.
Ocrevus (ocrelizumab)	Injection	IV	Every 6 months (24 weeks) Titration: Initial dose: 300 mg IV, followed 2 weeks later by a second 300 mg IV infusion. Subsequent doses: 600 mg IV infusion every 6 months Hepatitis B virus screening is required before the first dose.	Observe patients for at least 1 hour after the completion of the infusion. Dose modifications in response to infusion reactions depend on the severity. See package insert for more details. Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (eg, diphenhydramine) prior to each infusion. An antipyretic (eg, acetaminophen) may also be considered. Administer all necessary immunizations according to immunization guidelines at least 6 weeks prior to initiation of ocrelizumab. Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab.
Plegridy (peginterferon β-1a)	Injection	SC	Every 14 days Titration: Start with 63 mcg on day 1, 94 mcg on day 15, and 125 mcg (full dose) on day 29	Following initial administration by a trained healthcare provider, Plegridy may be self-administered. Patients should be advised to rotate injection sites; the usual sites are the abdomen, back of the upper arm, and thigh.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms. Monitor for adverse reactions due to increased drug exposure in patients with severe renal impairment.
Rebif (interferon β-1a)	Injection	SC	Three times per week at least 48 hours apart Titration: Generally, the starting dose should be 20% of the prescribed dose 3 times per week, and increased over a 4-week period to the targeted recommended dose of either 22 mcg or 44 mcg injected SC 3 times per week	Following initial administration by a trained healthcare provider, Rebif may be self-administered. Patients should be advised to rotate the site of injection with each dose to minimize the likelihood of severe injection site reactions or necrosis. Decreased peripheral blood counts or elevated liver function tests may necessitate dose reduction or discontinuation of Rebif administration until toxicity is resolved. Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms associated with Rebif use on treatment days.
Tecfidera (dimethyl fumarate)	Capsules	Oral	Twice daily Titration: 120 mg twice daily for 7 days (initiation), then 240 mg twice daily (maintenance) Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. The incidence of flushing may be reduced by administration of dimethyl fumarate with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to dimethyl fumarate dosing may reduce the incidence or severity of flushing. Obtain a complete blood cell count including lymphocyte count before initiation of therapy. Obtain serum aminotransferase, alkaline phosphatase, and total

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				bilirubin levels prior to treatment with dimethyl fumarate.
Tysabri (natalizumab)†	Injection	IV	Once a month (every 4 weeks)	Both MS and Crohn's disease indications are dosed the same: 300 mg infused over 1 hour and given every 4 weeks. Tysabri should not be administered as an IV push or bolus injection. Patients should be observed during the infusion and for 1 hour after the infusion is complete.

*See the current prescribing information for full details
†Currently available through a restricted distribution program as part of a REMS requirement.

CONCLUSION

- DMTs for MS have shown benefits in patients with RRMS such as a decreased relapse rate and a slower accumulation of brain lesions on MRI. Therefore, it is recommended that all patients with a diagnosis of definite RRMS begin DMTs *(MS Coalition 2017)*.
- IFNβ products have been shown to decrease MRI lesion activity, prevent relapses, and delay disease progression. In general, patients treated with IFNβ or glatiramer acetate can expect a 30% reduction in ARR during a 2-year period *(MS Coalition 2017)*. Head-to-head clinical trials have found IFNβ and glatiramer acetate to be comparable in terms of efficacy on relapse rate. Several studies have demonstrated an improved tolerability at the cost of a decreased therapeutic response with the low dose IM IFNβ-1a compared to the higher dose SC IFNβ-1a *(Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*. Influenza-type symptoms, injection site reactions, headache, nausea, and musculoskeletal pain are the most frequently reported adverse events with IFNβ products including Plegridy. With IFNβ, use caution in patients with depression or other mood disorders. Peginterferon β-1a every 2 weeks has demonstrated efficacy in reducing the ARR in relapsing forms of MS compared to placebo. Potential advantages of Plegridy are less frequent administration every 2 weeks and possibly the reduced risk of NAb development. Adverse effect profile is similar among the IFNs.
- The most frequently reported adverse events with glatiramer acetate include a transient, self-limiting, post-injection systemic reaction immediately following drug administration consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria. Glatiramer acetate does not have any known drug interactions and is not associated with an increased risk of hepatotoxicity or depression. Glatiramer acetate is generically available.
- Despite advancements in treatment, many patients fail initial DMTs with glatiramer acetate or IFNβ, primarily due to intolerable adverse effects or perceived inadequate efficacy *(Coyle 2008, Portaccio et al 2008)*. Clinical trials have shown that patients switching from IFNβ to glatiramer acetate therapy and vice versa, due to poor response, may achieve a significant reduction in relapse rates and a delay in disease and disability progression *(Coyle 2008, Caon et al 2006, Zwibel 2006)*. The guidelines suggest that all first-line MS DMTs should be made accessible, and the choice of initial treatment should be based on patient-specific factors *(Corboy et al 2015, MS Coalition 2017, Scolding et al 2015, Montalban et al 2018)*. Premature discontinuation rate is high among patients with MS; therefore, factors that will maximize adherence should be considered when initiating therapy. Failure with 1 agent does not necessarily predict failure to another. Therefore, patients experiencing an inadequate response or drug-induced adverse event should be switched to a different DMT *(Coyle 2008, Portaccio et al 2008)*.
- There are now 5 available oral agents: Gilenya (fingolimod), which was approved in 2010, Aubagio (teriflunomide), which was approved 2012, and Tecfidera (dimethyl fumarate), which was approved in 2013. The 2 new agents are Mavenclad (cladribine) and Mayzent (siponimod). Among other potential benefits, it is expected that the availability of oral agents may increase convenience and improve patient adherence to their drug regimen *(Sanvito et al 2011)*. The available oral drugs each have different mechanisms of action and tolerability profiles. The oral products have not been compared to

one another in any head-to-head trials. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.

- Mayzent (siponimod) is a sphingosine 1-phosphate receptor modulator, similar to fingolimod, indicated for the treatment of relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease. In a trial comparing Mayzent to placebo, Mayzent significantly reduced the risk of 3-month CDP, delayed the risk of 6-month CDP, and reduced the ARR (*Kappos et al 2018*). First dose cardiac monitoring is recommended for patients with a heart rate < 55 bpm or a history of cardiac disease. Siponimod shares many of the same warnings as fingolimod.
- Mavenclad (cladribine) is a purine antimetabolite indicated for the treatment of relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease. In a trial comparing Mavenclad to placebo, both Mavenclad 3.5 mg/kg and 5.25 mg/kg treatment groups had reduced ARRs and disability progression vs placebo (*Giovannoni et al 2010*). Lymphopenia is the most common adverse effect.
- Gilenya (fingolimod) is a sphingosine 1-phosphate receptor modulator. In a trial comparing fingolimod to placebo, fingolimod-treated patients had a decreased ARR, improved MRI outcomes, and a lower likelihood of disability progression *(Kappos et al 2010)*. In a trial comparing fingolimod to IFNβ-1a IM (Avonex), fingolimod-treated patients had a decreased ARR and improved MRI outcomes, but disability progression was similar in the 2 groups *(Cohen et al, 2010)*. The adverse event profile for fingolimod includes cardiovascular risks including bradycardia. First dose administration of fingolimod requires at least 6 hours of observation with hourly monitoring of heart rate and blood pressure, and patients should have an ECG before dosing and at the end of the observation period.
  - Fingolimod is also FDA-approved for MS in the pediatric population. In a trial evaluating patients between 10 and 17 years of age, fingolimod significantly reduced ARR and the rate or new or newly enlarged lesions compared to IFNβ-1a (*Chitnis et al 2018*).
- Tecfidera (dimethyl fumarate) has efficacy similar to that of fingolimod; its benefit-risk profile makes it a reasonable initial or later stage DMT option for most patients with RRMS *(CADTH 2013, Wingerchuk et al 2014)*. Gastrointestinal intolerance and flushing are common side effects that may wane with time; slow titration to maintenance doses, taking the medication with food, and premedication with aspirin may reduce their severity.
- Aubagio (teriflunomide) inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. Although its exact mechanism of action is unknown, it may involve a reduction in the number of activated lymphocytes in the CNS. Patients treated with teriflunomide in a clinical trial experienced a reduction in the ARR and improved MRI outcomes compared to placebo. Patients in the higher dose group (14 mg) also had a lower likelihood of disability progression, but this difference was not statistically significant in the lower dose group (7 mg) *(O'Connor et al, 2011)*. Teriflunomide has boxed warnings for the possibility of severe liver injury and teratogenicity. The most common adverse reactions include increases in ALT, alopecia, diarrhea, influenza, nausea, and paresthesia.
- Tysabri (natalizumab) has demonstrated very high efficacy vs placebo and although PML is a major safety concern, the overall incidence of PML has remained low (0.4%). Natalizumab can only be obtained through a restricted distribution program.
- Lemtrada (alemtuzumab) is a highly efficacious DMT that has demonstrated superiority in reducing relapses when compared to Rebif in both treatment-naïve and treatment-experienced patients. The dosing schedule of 2 annual treatment courses is counterbalanced by the need for regular monitoring of the increased risk for autoimmunity. Lemtrada is best reserved for patients who have failed at least 2 other DMTs and are not candidates for natalizumab (*Garnock-Jones 2014*).
- Ocrevus (ocrelizumab) is a recombinant monoclonal antibody designed to selectively target CD20-positive B cells. As a humanized form of Rituxan (rituximab), ocrelizumab is expected to be less immunogenic with repeated infusions and may have a more favorable benefit-to-risk profile than Rituxan *(Sorensen et al 2016)*.
  - The approval of Ocrevus provides another DMT option to the growing armamentarium of highly effective agents indicated for the treatment of RMS. Ocrelizumab is also indicated for the treatment of PPMS, making it the first DMT with substantial evidence supporting its use in this form of MS. Although the pivotal studies of ocrelizumab were of sufficient length to assess efficacy, more long-term safety data are needed to evaluate the effects of ocrelizumab on emergent neoplasms and the risk of PML.
- Mitoxantrone is a synthetic intercalating chemotherapeutic agent. While it is approved for the treatment of RRMS, SPMS, and PRMS, cumulative dose-related cardiac toxicity and the risk for secondary leukemia markedly limit its use. Mitoxantrone is, therefore, reserved for use in patients with aggressive disease.
- While DMTs do not sufficiently address QOL in RRMS, symptomatic agents such as Ampyra (dalfampridine) can be used to complement treatment with DMTs. Although a 25% improvement in T25FW may appear marginal, it has been

established that improvements in T25FW speed of ≥ 20% are meaningful to people with MS. Dalfampridine can complement DMTs, which do not address the specific symptom of walking speed. Improved walking could potentially contain some of the direct and indirect costs (eg, reduced productivity, disability, unemployment, costs of assistive devices and caregivers) associated with MS.

- With an increasing number of DMTs currently on the market and no specific MS algorithm in place to guide treatment decisions, the selection of an agent is generally based on considerations of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences.

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Please note: All information below is required to process this request.
Fax to 1-800-527-0531
Mon-Sat: 7am to 7pm Central

Multiple Sclerosis Prior Authorization Request Form (Page 1 of 2)

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

Medication Information (required)

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

Clinical Information (required)

Select the medication being requested:

❑ Ampyra	❑ Betaseron	❑ Glatopa	❑ Mitoxantrone	❑ Tecfidera
❑ Aubagio	❑ Extavia	❑ Gilenya	❑ Plegridy	❑ Tysabri
❑ Avonex	❑ Copaxone	❑ Lemtrada	❑ Rebif	❑ Zinbryta

Select the diagnosis below:

❑ Moderate-to-severe Crohn's disease (Tysabri only)
❑ Multiple sclerosis
❑ Other diagnosis: _____ ICD-10 Code(s): _____

Prescriber's specialty:

Select if the requested medication is prescribed by or in consultation with one of the following specialists:
❑ Gastroenterologist (Tysabri only)
❑ Neurologist
❑ Physiatrist (Ampyra only)

For Ampyra, answer the following:

Does the patient have a history of seizures? ❑ **Yes** ❑ **No**

For Aubagio, Avonex, Betaseron, Extavia, Copaxone, Glatopa, Gilenya, Lemtrada, Plegridy, Rebif, Tecfidera, Tysabri, or Zinbryta answer the following:

Does the patient have a relapsing form of multiple sclerosis? ❑ **Yes** ❑ **No**

For mitoxantrone, answer the following:

Select the form of multiple sclerosis that applies to the patient:
❑ Progressive relapsing multiple sclerosis
❑ Secondary progressive multiple sclerosis
❑ Worsening relapsing-remitting multiple sclerosis

Quantity limit requests:

What is the quantity requested per MONTH? _____
What is the reason for exceeding the plan limitations?
❑ Titration or loading dose purposes
❑ Patient is on a dose-alternating schedule (e.g., one tablet in the morning and two tablets at night, one to two tablets at bedtime)
❑ Requested strength/dose is not commercially available
❑ Patient requires a greater quantity for the treatment of a larger surface area **[Topical applications only]**
❑ Other: _____

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Multiple Sclerosis Prior Authorization Request Form (Page 2 of 2)

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

_____

_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-800-527-0531.