Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, May 31, 2012 1:00-4:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to coverage, PDL composition, or utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff.

I. CALL TO ORDER 1:00 pm – 1:05 pm
- a. Roll Call & Introductions — B. Origer (Chair)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Approval of Agenda and Minutes — B. Origer (Chair)

II. DUR ACTIVITIES 1:05 pm – 1:50 pm
- a. DMAP Pharmacy Program Report — R. Magrish (DMAP)
- b. ProDUR Report — R. Holsapple (HP)
- c. RetroDUR Report — T. Williams (OSU)
- d. Quarterly Utilization Reports — R. Citron (OSU)
- e. ICS/LABA Policy Evaluation — K. Ketchum (OSU)
- f. Oregon State Drug Reviews — K. Sentena (OSU)
  1. Current Findings in the Off-Label Use of Atypical Antipsychotics

III. HOUSEKEEPING 1:50 pm – 1:55 pm
- a. Ondansetron Quantity Limit Removal* — R. Citron (OSU)

IV. OLD BUSINESS 1:55 pm – 2:10 pm
- a. Synagis Drug Use Evaluation* — K. Sentena (OSU)
  1. Proposed PA criteria
  2. Public Comment
  3. Discussion of clinical recommendations to OHA

BREAK 2:10 pm – 2:20 pm

V. NEW BUSINESS 2:20 pm – 3:15 pm
- a. Asthma Controller Class Update — K. Sentena (OSU)
  1 Updated PA Criteria
  2 Public Comment
  3 Discussion of clinical recommendations to OHA
- b. Seizure Medication Class Update and New Drug Reviews* — M. Herink (OSU)
  1. Onfi® (clobazam)
  2. Potiga® (ezogabine)
  3. Public comment
  4. Discussion of clinical recommendations to OHA

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

c. Topical Antiparasite Class Update and New Drug Reviews* K. Ketchum (OSU)
   1. Natroba® (spinosad topical)
   2. Ulesfia® (benzyl alcohol topical)
   3. Public comment
   4. Discussion of clinical recommendations to OHA

d. Other Lipid Lowering Agents Abbreviated Class Review* B. Liang (OSU)
   1. Lovaza® (omega-3-acid ethyl esters)
   2. Public Comment
   3. Discussion of clinical recommendations to OHA

VI. HERC COVERAGE GUIDANCE 3:15 pm – 3:45 pm

a. Low Back Pain* C. Livingston (HERC)
   1. Pharmacologic Interventions
   2. Non-Pharmacologic interventions
   3. Public Comment
   4. Discussion of clinical recommendations to OHA

VII. EXECUTIVE SESSION 3:45 pm

VIII. RECONVENE for PUBLIC RECOMMENDATIONS

IX. ADJOURN

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, April 26, 2012 1:00-4:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING MINUTES

Members Present: Zahia Esber, MD; Phillip Levine, PhD; Meena Mital, MD; William Origer, MD; David Pass, MD; James Slater, PharmD; Cathy Zehrung, RPh
Members Present by Phone: Joshua Bishop, PharmD; Stacy Ramirez, PharmD; Atif Zaman, MD (Ad-Hoc Member)
Staff Present: Roger Citron, RPh; Megan Herink, PharmD, BCPS; Kathy Ketchum, RPh, MPA:HA; Ann Hamer, PharmD, BCPP; Kathy Sentena, PharmD; Ted Williams, PharmD; Valerie Smith; Richard Holsapple, RPh; Ralph Magrish, MPA; Amy Burns, PharmD
Audience: Robert Jaramillo (Forest); Nate Miles; Kathy Kirk (OPMC); Alex Smith, Jim Graves (BMS); Anne Murray (BMS); Robert Chang (BMS); John Peterson (Gilead); Yoona Kim (Gilead); Deborah Wafer (Gilead); Mike Willet (Pfizer); Barry Benson (Merck); Lisa Valalka (Genzyme); Jeana Colabianchi (Sunovion); Michael Dutro (Pfizer); Julie Preston (Optimer) Daniko Webb (Actelion); Venus Holder (Lilly); Justin Druino (Lilly); Steve Wright (Boehringer Ingelheim); Mike Donabedan (Vertex); George Yauntzke (Actelion); Lorren Sandt (Caring Ambassadors); David Barba (Forest); Don Stetcher (Novartis); Paul Nielsen (MedImmune); Robert Kosesan; Molly Gelletz (Sunovion); Chris Bounoff (NAMI)

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I. CALL TO ORDER
- a. The meeting was called to order at approximately 1pm.
- b. Conflict of interest declarations were reviewed and no new conflicts were reported. Dr. Zaman's conflict of interest was presented to the members.
- c. The March 26, 2012 meeting minutes were reviewed.

ACTION: Approved as is.

II. ProDUR
- a. Dr. Burns presented on Kalydeco® (ivacaftor) recommending prior authorization criteria restricting use to genotype G551D.

***ACTION:** Approved as is.
- b. Mr. Citron presented the 15-day initial supply concept. Chris Bounoff with National Association for the Mentally Ill (NAMI) presented public comment on the issue.

***ACTION:** Committee was supportive of the idea but asked staff to present information on class adherence rates and experiences from other states after implementation. There was also concern regarding additional copays and how that would be addressed.
- c. Dr. Herink presented a new drug evaluation on Egrifta® (tesamorelin) recommending prior authorization criteria be implemented to ensure use for covered diagnoses and restrict use for lipodystrophy.

***ACTION:** Approved as is.

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

III. NEW BUSINESS

a. Dr. Sentena presented diabetes medications class update recommending updates to the Amylin Analogs, Incretin Enhancers and Incretin Mimetics prior authorization criteria, adding Tradjenta® (linagliptin) and Bydureon® (exenatide) and making linagliptin, linagliptin/metformin, saxagliptin, sitagliptin.simvastatin, sitagliptin/metformin ER non-preferred.

***ACTION**: Approved as is after Executive Session.

b. Dr. Herink presented a new drug evaluation for Dificid® (fidaxomicin) recommending that metronidazole 250mg and 500mg tablets and vancomicin 125mg & 250mg capsules and vancomycin IV vials be preferred and fidaxomicin be non-preferred and prior authorization criteria be implemented to ensure first line treatments were tried and failed.

***ACTION:** The Committee approved the recommendation but asked for an Infectious Disease consult to address lingering questions of disease severity identification, the resistance risk posed by preferring vancomycin and the appropriateness of metronidazole as a single first-line agent.

c. Dr. Hamer presented the Antidepressant new drug reviews recommending to make vilazodone non-preferred and include a dose limit for citalopram. Robert Jaramillo with Forest presented public comment on Viibryd.

***ACTION:** Approved after Executive Session. In addition selegiline patches were made non-preferred and generic escitalopram was recommended blocked with open access to the brand until the price decreases.

d. Dr. Burns presented the Smoking Cessation class update recommending that the Nicotine Replacement Therapy Class be added to the preferred drug list making Nicotrol and Nicotrol NS non-preferred and to include patches, gum, lozenges, buproprion sustained release as preferred with a 6 month quantity limit and varenicline as preferred with a 12 week quantity limits. Michael Dutro with Pfizer presented public comment.

***ACTION:** Approved after Executive Session with the recommendation of requiring prior authorization for second attempt of smoking cessation to require behavioral therapy.

e. Dr. Herink presented drug class scans.

1. Pulmonary Arterial Hypertension – Recommended that continue current prior authorization criteria to ensure appropriate patient selection. John Peterson from Gilead presented public comment on Letairis. George Yauhtzke from Actelion presented public comment on Tracleer.

***ACTION:** Approved after Executive Session.

2. Oral Hypoglycemics/TZDs – Recommended leaving the class as is.

*__ACTION__: Approved after Executive Session.

3. Insulins – Recommended leaving the class as is.

*__ACTION__: Approved after Executive Session.

IV. OLD BUSINESS

a. Dr. Herink presented on Hepatitis B recommending that prior authorization criteria be established for non-preferred products and making entacavir non-preferred. Ad-Hoc expert Dr. Atif Zaman agreed with the recommendations presented.

*__ACTION__: Approved after Executive Session.

V. The meeting was adjourned at approximately 4pm.

Agenda items with an asterisk will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)

ProDUR Alert Overview

DA Drug/Allergy Interaction: Triggers if there is an association between an ingredient and an allergy recorded in the recipient profile.

DC Inferred Disease Interaction: Triggers if there is a drug on the recipients profile that is indicated for a disease state that interacts with the drug being filled.

DD Drug to Drug Interaction: Triggers if there is an interaction between the drug being filled and another drug on the recipients profile.

ER Early Refill (Overutilization): Triggers if the drug being billed is too early based on previous billing and days supply. Allow filling when 75% of previous fill has been used.

HD High Dose: Triggers if the drug being billed, based on billed days supply, exceeds the maximum recommended daily quantity limit. **Currently only set for CNS Stimulants, Methadone, Asmanex, Lovenox, and the aspirin/APAP-narcotic combinations.**
****As of March 2012 all of the high dose quantity limits have been moved to a claims audit. The ProDUR alert is set to be informational now.**

ID Ingredient Duplication: Triggers if the drug being filled has a matching ingredient to another recently filled drug on the recipients profile.

LD Low Dose: Triggers if the drug being billed, based on billed days supply, is below the minimum recommended daily quantity limit. **Currently only set for Seroquel (quetiapine).**
****As of January 2012, Seroquel quantity minimum restriction moved to quantity limit audit and out of ProDUR. This alert is now only set as informational.**

LR Late Refill (Underutilization): Triggers if the drug being filled is late in being refilled for the recipient.

MC Drug to Disease Interaction: Triggers if there is a disease diagnosis on the recipients claim profile that interacts with the drug being filled.

MX Maximum Duration of Therapy: Triggers if the days supply on the claim is greater than the maximum days value.

PA Pediatric and Geriatric Age Limits: Triggers if the age of the recipient is less than the minimum (pediatric) or greater than the maximum (geriatric) age for the drug being billed.

PG Pregnancy/Drug Interaction: Triggers if the drug being filled is contraindicated for use in pregnancy and the patient profile indicates that the patient may be pregnant.

TD Therapeutic Duplication: Triggers if the class of drug being billed matches the drug class of another recently filled medication on the recipients profile.

ProDUR Report for February 2012-April 2012

High Level Summary by DUR Alert

DUR Alert	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
ER (Early Refill)	55,661	17,355	498	37,750	64.70%
HD (High Dose)	766	0	309	429	0.93%
PG (Pregnancy/Drug Interaction)	3,435	2,421	18	972	4.03%
LD (Low Dose)	1,028	336	0	678	1.17%
ID (Ingredient Duplication)	14,387	5,362	37	8,851	16.70%
TD (Therapeutic Duplication)	6,220	2,554	10	6,073	7.20%

ProDUR Report for February 2012-April 2012							
Top Drugs in Enforced DUR Alerts							
DUR Alert	**Drug Name**	**# Alerts**	**# Overrides**	**# Cancellations & Non-Response**	**# Claims Screened**	**% Alerts/Total Claims in Therapeutic Category**	**% Alerts Overridden**
ER	Oxycodone HCl	301	147	154	4,474	6.7%	48.8%
	Lithium Carbonate	765	310	452	5,964	12.8%	40.5%
	Zyprexa (Olanzapine)	966	357	604	8,226	11.7%	37.0%
	Clonazepam	746	270	473	6,786	11.0%	36.2%
	Geodon (Ziprasidone)	601	216	364	5,128	11.7%	35.9%
	Gabapentin	426	153	272	3,326	12.8%	35.9%
	Lorazepam	2,730	978	1,751	31,539	8.7%	35.8%
	Depakote (Divalproex Sodium)	1,201	411	790	10,993	10.9%	34.2%
	Seroquel (Quetiapine)	2,077	698	1,379	16,829	12.3%	33.6%
	Abilify (Aripiprazole)	1,606	526	1,080	13,753	11.7%	32.8%
	Remeron (Mirtazapine)	675	218	457	5,274	12.8%	32.3%
	Risperdal (Risperidone)	1,685	543	1,141	13,532	12.5%	32.2%
	Lamictal (Lamotrigine)	1,755	563	1,192	16,447	10.7%	32.1%
	Diazepam	1,032	328	703	13,562	7.6%	31.8%
	Hydrocodone Bit/APAP	532	163	362	10,241	5.2%	30.6%
	Prilosec (Omeprazole)	488	149	339	5,818	8.4%	30.5%
	Albuterol	502	152	350	7,986	6.3%	30.3%
	Buspar (Buspirone)	713	211	502	7,821	9.1%	29.6%
	Alprazolam	1,872	545	1,326	21,775	8.6%	29.1%
	Zoloft (Sertraline)	2,360	661	1,699	23,322	10.1%	28.0%
	Trazodone	2,991	804	2,186	28,516	10.5%	26.9%
	Celexa (Citalopram)	2,302	608	1,694	25,485	9.0%	26.4%
	Lexapro (Escitaloprim)	1,013	266	747	11,370	8.9%	26.3%
	Prozac (Fluoxetine)	1,945	507	1,438	21,272	9.1%	26.1%
	Effexor (Venlafaxine)	954	242	712	11,641	8.2%	25.4%
	Paxil (Paroxetine)	778	197	581	9,317	8.4%	25.3%
	Wellbutrin (Bupropion)	1,740	429	1,309	20,522	8.5%	24.7%
	Amitriptyline	1,240	303	936	14,050	8.8%	24.4%
	Cymbalta (Duloxetine)	1,507	346	1,161	15,982	9.4%	23.0%
	Straterra (Atomoxetine)	584	132	452	6,655	8.8%	22.6%
PG	Lorazepam	353	300	53	31,539	1.1%	85.0%
	Ibuprofen	564	465	99	4,312	13.1%	82.4%
	Alprazolam	317	249	68	21,775	1.5%	78.5%
	Norethindrone	237	178	59	832	28.5%	75.1%
	Lamictal	233	172	61	16,447	1.4%	73.8%
HD	Focalin XR (dexmethylphenidate)	30	0	29	220	13.6%	0.0%
	Ritalin (methylphenidate)	50	0	40	4,741	1.1%	0.0%
	Adderall XR	26	0	23	2,558	1.0%	0.0%
	Methadone	67	0	61	730	9.2%	0.0%
	Hydrocodone/APAP	443	0	440	10,241	4.3%	0.0%
	Oxycodone/APAP	98	0	97	2,128	4.6%	0.0%

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Retro-DUR Intervention History by Quarter - FFY 2011-2012 — Letters Sent

	Profile Review-Based Lettering	Polypharmacy	Duplicate PPIs	Duplicate Statins	Change Form Follow-Up (mult. str.)	Lock-In	Psychotropics in Children	Prescription Change Form Request	Antidepressants	Atypical antipsychotics
Quarter 1 Oct-Dec										
Unique Patients	0	0	0	0	80	0		285	47	
Unique Patients Sent Interventions	0	0	0	0	28	0		285	47	
% Sent	-	-	-	-	35%	-		100%	100%	
Quarter 2 Jan-Mar										
Unique Patients	0	0	0	0	255	0		278	23	
Unique Patients Sent Interventions	0	0	0	0	53	0		278	23	
% Sent	-	-	-	-	21%	-		100%	100%	
Quarter 3 Apr-Jun										
Unique Patients	0	0	0	0	102	169		78	22	
Unique Patients Sent Interventions	0	0	0	0	44	0		78	22	
% Sent	-	-	-	-	43%	0%		100%	100%	
Quarter 4 Jul-Sep										
Unique Patients	0	0	0	0	0	0		0	0	
Unique Patients Sent Interventions	0	0	0	0	0	0		0	0	
% Sent	-	-	-	-	-	-		-	-	
Year to date summary										
Unique Patients	0	0	0	0	437	169		641	92	
Unique Patients Sent Interventions	0	0	0	0	125	0		641	92	
% Sent	-	-	-	-	29%	0%		100%	100%	
ROI per intervention	$51	NA	NA	NA	NA	NA		$49	$220	
Estimated program savings	$0	NA	NA	NA	NA	NA		$31,409	$20,240	

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Retro-DUR Intervention History by Quarter - FFY 2011-2012 Letters Sent

	Criteria-based lettering	LABA Monotherapy	High Dose Methadone
Quarter 1 Oct-Dec			
All Patients on Drug of Interest	49	345
Patients Hitting Criteria in Qtr	29	156
Patients Hitting Criteria / 100 Users	59	45
Unique Patients	14	44
Unique Patients Sent Interventions	8	35
% Sent	57%	80%
Quarter 2 Jan-Mar			
All Patients on Drug of Interest	46	329
Patients Hitting Criteria in Qtr	23	143
Patients Hitting Criteria / 100 Users	50	43
Unique Patients	14	38
Unique Patients Sent Interventions	4	19
% Sent	29%	50%
Quarter 3 Apr-Jun			
All Patients on Drug of Interest	39	252
Patients Hitting Criteria in Qtr	20	98
Patients Hitting Criteria / 100 Users	51	39
Unique Patients	11	14
Unique Patients Sent Interventions	8	10
% Sent	73%	71%
Quarter 4 Jul-Sep			
All Patients on Drug of Interest	0	0
Patients Hitting Criteria in Qtr	0	0
Patients Hitting Criteria / 100 Users	-	-
Unique Patients	0	0
Unique Patients Sent Interventions	0	0
% Sent	-	-
Year to date summary			
Unique Patients	39	96
Unique Patients Sent Interventions	20	64
% Sent	51%	67%
ROI per intervention	NA	NA
Estimated program savings	NA	NA

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Retro-DUR Intervention History by Quarter - FFY 2011-2012 — Responses Received

	Profile Review-Based Lettering	Polypharmacy	Duplicate PPIs	Duplicate Statins	Change Form Follow-Up (mult. str.)	Lock-In	Psychotropics in Children	**Criteria-based lettering**	LABA Monotherapy	High Dose Methadone
Quarter 1 Oct-Dec										
Unique Prescribers Sent Interventions	0	0	0	0	27	0		8	36	
Responses Received	0	0	0	0	5	0		2	13	
Response Rate	-	-	-	-	18%	-		25%	37%	
% Agree with message	-	-	-	-	100%	-		50%	69%	
% Consider in future prescribing	-	-	-	-	-	-		100%	38%	
Quarter 2 Jan-Mar										
Unique Prescribers Sent Interventions	0	0	0	0	45	0		4	19	
Responses Received	0	0	0	0	7	0		1	7	
Response Rate	-	-	-	-	13%	-		25%	37%	
% Agree with message	-	-	-	-	71%	-		100%	71%	
% Consider in future prescribing	-	-	-	-	14%	-		-	43%	
Quarter 3 Apr-Jun										
Unique Prescribers Sent Interventions	0	0	0	0	8	0		8	11	
Responses Received	0	0	0	0	0	0		2	2	
Response Rate	-	-	-	-	-	-		25%	20%	
% Agree with message	-	-	-	-	-	-		50%	50%	
% Consider in future prescribing	-	-	-	-	-	-		-	-	
Quarter 4 Jul-Sep										
Unique Prescribers Sent Interventions	0	0	0	0	0	0		0	0	
Responses Received	0	0	0	0	0	0		0	0	
Response Rate	-	-	-	-	-	-		-	-	
% Agree with message	-	-	-	-	-	-		-	-	
% Consider in future prescribing	-	-	-	-	-	-		-	-	
Year to date summary										
Unique Prescribers Sent Interventions	0	0	0	0	80	0		20	66	
Responses Received	0	0	0	0	12	0		5	22	
Response Rate	-	-	-	-	10%	-		25%	34%	
% Agree with message	-	-	-	-	83%	-		60%	68%	
% Consider in future prescribing	-	-	-	-	8%	-		40%	36%	

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OHP FFS Average Cost PMPM Top 40 Drugs (brand name) - First Quarter 2012

previous year quarter is comparator (red = top 75th percentile of growth; yellow = top 50th percentile of growth)

			Cost PMPM			Rx Dispensed PMPM (x100)			Cost/Claim		
Rank	**Class Number**	**Brand Name**	**2012**	**2011**	**%**	**2012**	**2011**	**%**	**2012**	**2011**	**%**
1	7	ABILIFY	$3.63	$3.39	6.9%	0.57	0.59	-4.4%	$640	$573	11.8%
2	7	SEROQUEL	$2.50	$2.32	7.5%	0.51	0.58	-11.1%	$487	$403	20.8%
3	33	SYNAGIS	$1.72	$1.53	12.6%	0.07	0.09	-16.7%	$2,360	$1,747	35.1%
4	7	OLANZAPINE	$1.66			0.25			$653		
5	11	CYMBALTA	$1.59	$1.28	24.7%	0.72	0.63	13.9%	$222	$203	9.5%
6	10	METHYLPHENIDATE ER	$1.43			0.85			$168		
7	71	REMODULIN	$1.41	$1.10	28.8%	0.01	0.01	5.2%	$23,935	$19,537	22.5%
8	40	OXYCONTIN	$0.94	$1.29	-26.7%	0.19	0.31	-39.0%	$496	$412	20.2%
9	33	ATRIPLA	$0.88	$0.26	235.7%	0.05	0.02	201.1%	$1,696	$1,523	11.4%
10	33	INCIVEK	$0.85			0.01			$16,411		
11	33	TRUVADA	$0.83	$0.24	241.2%	0.08	0.03	152.5%	$1,067	$792	34.8%
12	15	SINGULAIR	$0.79	$0.65	21.6%	0.48	0.47	1.6%	$165.98	$138.62	19.7%
13	7	GEODON	$0.78	$0.86	-10.1%	0.16	0.20	-21.6%	$483.95	$421.82	14.7%
14	15	PROAIR HFA	$0.71	$0.54	30.9%	1.31	1.04	25.8%	$54.01	$52.00	3.9%
15	7	SEROQUEL XR	$0.64	$0.51	23.9%	0.15	0.14	8.9%	$426.38	$374.59	13.8%
16	58	LANTUS	$0.61	$0.60	3.2%	0.30	0.32	-4.7%	$205	$189	8.3%
17	11	STRATTERA	$0.61	$0.54	12.8%	0.28	0.28	-2.1%	$222	$192	15.3%
18	42	HUMIRA	$0.61	$0.47	29.9%	0.03	0.02	25.4%	$2,002.97	$1,932.65	3.6%
19	12	DEXTROAMPHETAMINE-AMPHETAMINE	$0.55	$0.40	38.2%	0.31	0.24	27.3%	$180.08	$165.94	8.5%
20	11	LEXAPRO	$0.50	$0.60	-16.1%	0.36	0.52	-30.5%	$139.13	$115.16	20.8%
21	99	PULMOZYME	$0.49	$0.33	49.8%	0.02	0.02	15.4%	$2,705.56	$2,084.57	29.8%
22	51	FLOVENT HFA	$0.47	$0.43	9.1%	0.30	0.28	6.2%	$157.54	$153.30	2.8%
23	23	TOBI	$0.47	$0.38	24.5%	0.01	0.01	7.5%	$5,027.37	$4,340.72	15.8%
24	15	ADVAIR DISKUS	$0.47	$0.86	-45.9%	0.19	0.36	-49.0%	$251.60	$237.60	5.9%
25	33	PEGASYS	$0.46	$0.13	254.5%	0.01	0.01	138.7%	$3,058.35	$2,051.07	49.1%
26	65	LIPITOR	$0.43	$0.41	4.9%	0.24	0.28	-12.8%	$175.75	$146.04	20.3%
27	40	HYDROCODONE-ACETAMINOPHEN	$0.42	$0.48	-13.6%	2.92	3.28	-10.9%	$14.20	$14.65	-3.0%
28	15	COMBIVENT	$0.41	$0.36	15.4%	0.18	0.20	-9.1%	$230.31	$181.24	27.1%
29	12	VYVANSE	$0.41	$0.30	36.7%	0.24	0.19	27.4%	$167.24	$155.79	7.4%
30	33	REYATAZ	$0.41	$0.17	146.3%	0.05	0.02	98.7%	$893.52	$723.44	23.5%
31	11	INTUNIV	$0.40	$0.18	123.9%	0.22	0.11	95.0%	$185.31	$161.34	14.9%
32	15	SPIRIVA	$0.40	$0.36	9.5%	0.16	0.16	-3.9%	$252.30	$221.52	13.9%
33	58	NOVOLOG	$0.39	$0.36	7.0%	0.17	0.17	-1.9%	$231.78	$212.16	9.2%
34	42	ENBREL	$0.38	$0.42	-9.3%	0.02	0.03	-18.3%	$1,837.65	$1,656.54	10.9%
35	11	PROVIGIL	$0.37	$0.28	31.2%	0.03	0.04	-13.3%	$1,194.03	$788.90	51.4%
36	77	LOVENOX	$0.37	$0.11	220.4%	0.04	0.02	62.8%	$1,042.81	$526.60	98.0%
37	40	FENTANYL	$0.36	$0.26	40.0%	0.17	0.11	57.4%	$206.36	$231.93	-11.0%
38	64	SUPPRELIN LA	$0.33	$0.15	111.8%	0.00	0.00	105.6%	$15,388.84	$14,937.64	3.0%
39	58	HUMALOG	$0.31	$0.28	11.4%	0.12	0.12	3.9%	$253.46	$236.86	7.0%
40	99	COPAXONE	$0.31	$0.40	-23.2%	0.01	0.01	-32.3%	$3,892.03	$3,426.26	13.6%
		Aggregate	$63.49	$57.59	10.2%	102.17	105.04	-2.7%	$80	$72	10.3%
		75th Percentile			29.7%			21.6%			13.9%
		50th Percentile (Median)			-4.4%			-3.1%			1.7%

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OHP FFS Average Cost PMPM Top 30 Drug Class – First Quarter 2012

previous year quarter is comparator (red = top 75th percentile of growth; yellow = top 50th percentile of growth)

			Cost PMPM			Rx Dispensed PMPM (x100)			Cost/Claim		
Rank	**Class Number**	**Class Description**	**2012**	**2011**	**%**	**2012**	**2011**	**%**	**2012**	**2011**	**%**
1	7	Ataractics, Tranquilizers	$11.56	$10.71	7.9%	6.3	6.4	-2.6%	$184	$166	10.6%
2	33	Antivirals	$7.12	$3.04	134.3%	0.8	0.5	54.5%	$904	$598	51.3%
3	11	Psychostimulants, Antidepressants	$5.19	$4.72	10.1%	9.5	9.2	4.1%	$53	$51	3.5%
4	15	Bronchial Dilators	$3.56	$3.70	-3.8%	3.5	3.9	-9.7%	$101	$95	6.4%
5	99	Miscellaneous	$2.96	$2.90	2.2%	1.5	1.5	3.9%	$191	$193	-1.3%
6	40	Narcotic Analgesics	$2.91	$3.53	-17.7%	7.3	8.4	-13.4%	$40	$42	-4.8%
7	48	Anticonvulsants	$2.62	$2.55	2.7%	5.4	5.5	-2.4%	$44	$42	5.9%
8	58	Diabetic Therapy	$2.43	$2.44	-0.2%	2.1	2.3	-9.7%	$116	$105	10.7%
9	10	CNS Stimulants	$2.42	$2.58	-6.1%	1.9	2.0	-4.4%	$126	$128	-1.7%
10	71	Other Hypotensives	$2.26	$1.90	19.3%	2.9	3.1	-6.7%	$76	$62	23.5%
11	42	Antiarthritics	$1.42	$1.36	4.5%	2.2	2.3	-6.9%	$65	$58	12.2%
12	12	Amphetamine Preps	$1.41	$1.11	26.5%	1.0	0.9	14.5%	$138	$124	11.6%
13	51	Gluco Corticoids	$1.28	$1.13	12.7%	2.0	2.1	-5.4%	$64	$54	18.2%
14	63	Oral Contraceptives	$1.23	$1.14	8.2%	2.6	2.5	5.8%	$47	$46	1.2%
15	30	Antineoplastic	$1.23	$0.78	57.1%	0.4	0.3	14.9%	$305	$241	26.5%
16	1	Antacids	$1.14	$1.49	-23.2%	3.6	3.9	-7.8%	$31	$38	-16.9%
17	64	Other Hormones	$1.08	$0.88	21.8%	0.1	0.1	-7.8%	$821	$727	12.8%
18	65	Lipotropics	$1.07	$1.13	-5.5%	2.0	2.2	-7.7%	$52	$51	2.4%
19	77	Anticoagulants	$0.86	$0.91	-4.9%	0.5	0.6	-11.4%	$172	$160	7.0%
20	41	Non-narcotic Analgesics	$0.84	$0.84	0.2%	5.1	4.9	4.2%	$16	$17	-4.6%
21	6	Laxatives	$0.66	$0.63	4.8%	5.3	5.3	1.1%	$12	$12	3.3%
22	87	Electrolytes and Misc Nutr	$0.62	$0.64	-2.6%	2.8	2.9	-3.6%	$22	$21	1.4%
23	23	Streptomycins	$0.56	$0.44	26.7%	0.0	0.0	-23.9%	$1,629	$928	75.4%
24	27	Other Antibiotics	$0.47	$0.53	-10.9%	0.7	0.9	-19.5%	$59	$57	3.5%
25	69	Enzymes	$0.38	$0.43	-11.1%	0.0	0.0	-5.0%	$859	$906	-5.2%
26	82	Multivitamins	$0.38	$0.36	6.3%	3.6	3.5	2.3%	$10	$10	3.1%
27	80	Fat Soluble Vitamins	$0.37	$0.35	4.4%	3.6	3.2	12.4%	$10	$11	-7.2%
28	94	Fungicides	$0.36	$0.12	199.4%	0.7	0.7	-5.6%	$45	$16	188.2%
29	14	Antihistamines	$0.30	$0.32	-6.5%	2.6	2.5	3.5%	$12	$13	-9.8%
30	76	Other Cardiovascular Preps	$0.29	$0.39	-25.1%	1.9	2.1	-11.5%	$16	$19	-15.5%
		Aggregate	$63.49	$57.59	10.2%	102.17	105.04	-2.7%	$80	$72	10.3%
		75th Percentile			22.8%			6.7%			11.0%
		50th Percentile (Median)			0.2%			-4.4%			1.2%

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Pharmacy Utilization Summary Report: April 2011 - March 2012

	2011									2012			
	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	JANUARY	FEBRUARY	MARCH	AVG/YTD
Eligibility													
Total Members	588,812	587,524	590,406	592,894	593,825	595,965	600,779	603,146	607,560	610,951	614,598	617,154	600,301
FFS Members	95,186	96,165	92,552	93,582	91,122	93,140	95,835	90,655	93,725	98,287	94,464	95,551	94,189
Standard	6,465	6,636	6,191	6,261	5,648	5,648	5,893	5,238	5,843	6,499	5,939	5,581	5,987
Plus	64,226	64,994	61,751	62,454	60,588	62,521	64,748	60,321	62,633	66,336	63,022	64,361	63,163
Medicare Wrap	24,495	24,535	24,610	24,867	24,886	24,971	25,194	25,096	25,249	25,452	25,503	25,609	25,039
Gross Figures													
Total Cost	$13,434,890	$13,927,185	$14,019,094	$13,441,500	$14,406,998	$13,874,141	$13,696,222	$13,730,339	$14,022,722	$14,773,307	$14,383,509	$15,044,931	$168,754,838
FFS Drugs	$4,120,989	$4,279,429	$4,297,788	$4,152,647	$4,269,073	$4,234,164	$4,063,544	$4,091,975	$4,132,762	$4,317,596	$4,225,959	$4,484,913	$50,670,839
Mental Health Carveout Drugs	$9,313,900	$9,647,756	$9,721,306	$9,288,853	$10,137,924	$9,639,977	$9,632,678	$9,638,364	$9,889,960	$10,455,711	$10,157,551	$10,560,018	$118,084,000
Total Rx	179,060	184,889	182,952	171,383	185,973	178,171	176,262	177,649	181,375	185,334	179,232	188,852	2,171,132
FFS Drugs	82,430	85,560	83,774	77,472	83,555	80,097	78,411	78,423	79,741	81,284	79,516	83,667	973,930
Mental Health Carveout Drugs	96,630	99,329	99,178	93,911	102,418	98,074	97,851	99,226	101,634	104,050	99,716	105,185	1,197,202
Cost/Rx	$75.03	$75.33	$76.63	$78.43	$77.47	$77.87	$77.70	$77.29	$77.31	$79.71	$80.25	$79.67	$77.72
FFS Drugs	$49.99	$50.02	$51.30	$53.60	$51.09	$52.86	$51.82	$52.18	$51.83	$53.12	$53.15	$53.60	$52.05
Mental Health Carveout Drugs	$96.39	$97.13	$98.02	$98.91	$98.99	$98.29	$98.44	$97.14	$97.31	$100.49	$101.86	$100.39	$98.61
Generic	$58.51	$58.79	$60.59	$63.14	$62.68	$63.25	$63.10	$63.36	$64.21	$33.61	$33.87	$32.44	$54.80
Brand	$5.15	$5.14	$5.17	$5.13	$5.03	$5.10	$5.06	$4.95	$4.81	$357.80	$360.92	$364.27	$94.05
PMPM Figures													
Cost PMPM	$59.11	$60.92	$62.90	$60.04	$63.92	$61.64	$58.44	$61.12	$60.37	$61.04	$61.26	$64.05	$61.23
Standard	$120.50	$137.87	$157.46	$153.77	$168.38	$159.60	$144.12	$160.64	$161.45	$151.46	$151.67	$175.17	$153.51
Plus	$62.70	$64.19	$65.25	$61.57	$66.91	$64.08	$60.73	$64.23	$63.00	$62.82	$63.94	$66.56	$63.83
Medicare Wrap	$16.57	$15.54	$16.17	$14.95	$17.25	$15.94	$15.17	$16.81	$15.15	$15.80	$17.33	$16.29	$16.08
FFS Drugs	$43.29	$44.50	$46.44	$44.37	$46.85	$45.46	$42.40	$45.14	$44.09	$43.93	$44.74	$46.94	$44.85
Mental Health Carveout Drugs	$15.82	$16.42	$16.47	$15.67	$17.07	$16.18	$16.03	$15.98	$16.28	$17.11	$16.53	$17.11	$16.39
Rx PMPM	1.03	1.06	1.07	0.99	1.09	1.02	0.98	1.03	1.02	1.00	1.00	1.05	1.03
Standard	2.01	2.11	2.20	1.98	2.31	2.16	2.00	2.21	2.07	1.95	2.04	2.23	2.11
Plus	0.91	0.93	0.94	0.86	0.95	0.91	0.84	0.90	0.88	0.86	0.87	0.91	0.90
Medicare Wrap	0.97	1.00	1.01	0.96	1.04	0.96	0.99	0.99	1.00	1.01	0.97	1.01	0.99
FFS Drugs	0.87	0.89	0.91	0.83	0.92	0.86	0.82	0.87	0.85	0.83	0.84	0.88	0.86
Mental Health Carveout Drugs	0.16	0.17	0.17	0.16	0.17	0.16	0.16	0.16	0.17	0.17	0.16	0.17	0.17
Utilization Percentages													
Generic %	83.6%	83.6%	83.5%	83.4%	83.5%	83.3%	83.3%	83.4%	83.4%	85.8%	85.8%	85.8%	84.0%
FFS Drugs	88.3%	88.2%	88.0%	88.1%	88.2%	88.0%	88.1%	88.4%	88.5%	88.9%	89.1%	89.1%	88.4%
Mental Health Carveout Drugs	79.6%	79.7%	79.6%	79.6%	79.6%	79.5%	79.5%	79.5%	79.4%	83.3%	83.2%	83.1%	80.5%
PDL %	80.2%	80.1%	79.9%	80.0%	79.9%	79.8%	79.7%	80.7%	80.8%	80.7%	80.8%	80.4%	80.3%

PMPM calculated as sum of physical health and mental health carve-outs
Data from DSSURS and DMAP FCHP first of month reports
Dates are service dates
All eligibility groups included except for CAWEM, QS, QB
Drug Cost = Amt Paid +Copay + Other Insurance Paid

Last Updated: April 16, 2012

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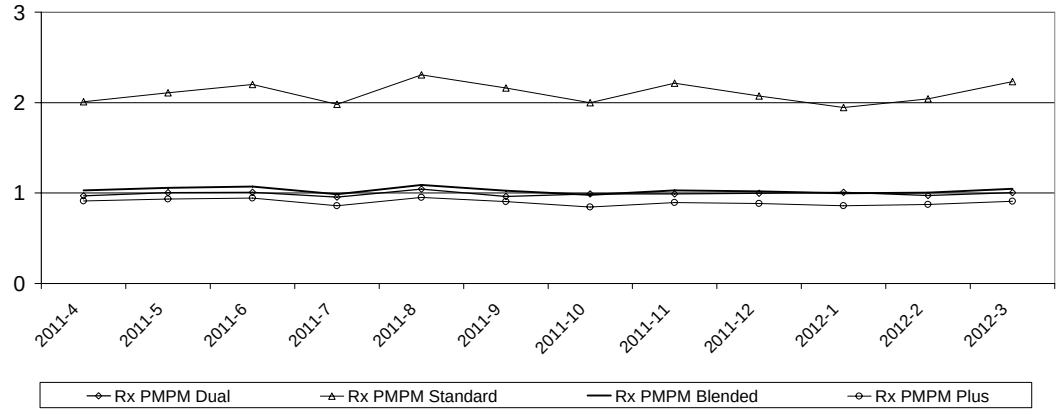
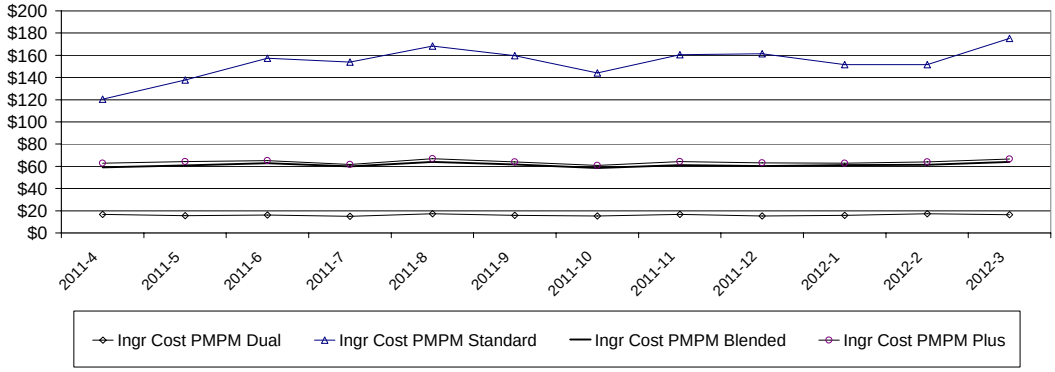
Pharmacy Utilization Summary Report: April 2011 - March 2012

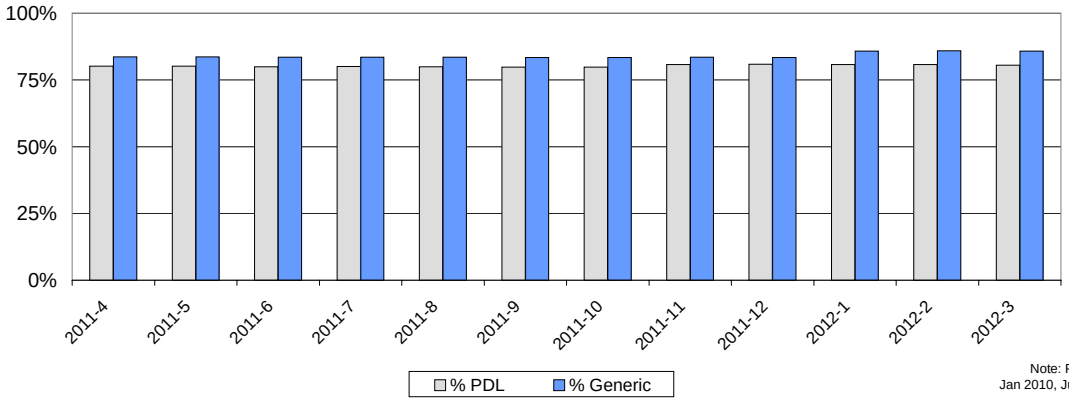
RX Dispensed PMPM



Ingredient Cost PMPM



Percent Generic and PDL



Note: PDL updated
Jan 2010, Jul 2010, Jan 2011

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Policy Evaluation:
Step Therapy Prior Authorization of Combination Inhaled Corticosteroid / Long-Acting Beta-Agonists

This review evaluates the effect of enforcing either the trial of an inhaled corticosteroid or evidence of severe disease for asthma or a trial of an anti-cholinergic and long-acting beta-agonist for Chronic Obstructive Pulmonary Disease (COPD) prior to approval of a combination inhaler.[1] This policy was initiated on January 1, 2011 and grandfathered all current patients. Automatic electronic approvals for COPD with prior use of an anti-cholinergic and long-acting beta-agonist were implemented on September 1, 2011.

Background

The Oregon Drug Use Review (DUR) Board reviewed combination inhaled corticosteroid / long-acting beta-agonist (ICS/LABA) use and literature at the March 2010 meeting.[2]

Major literature findings from the review include:

- Overall, systematic reviews and guidelines consistently demonstrate that adding LABA to ICS in adults and children with persistent asthma will improve airway function, asthma symptoms, quality of life and reduce short-acting rescue inhaler use compared to ICS dose escalation.
- The benefit of adding LABA to ICS for preventing severe exacerbations and mortality for asthma patients is not supported or is unclear.
- Combination ICS appears to reduce the risk of exacerbation, improve lung function, and health status in patients with COPD.
- The addition of ICS to LABA does not appear to have meaningful impact on mortality and increases the risk for pneumonia.
- Several systematic reviews have evaluated the association between LABA use and life threatening adverse events and the data is mixed for use of the combination of ICS/LABA. Based on FDA meta-analyses of over 60,000 patients the excess risk for asthma-related death, death or intubation, asthma hospitalization, or a composite safety measure were all significantly

elevated for patients using LABA. When trials were stratified by ICS at randomization, the risk appeared to be less and became non-significant, however due to lower sample sizes in these sub-analyses, the same risk excess cannot be ruled out.

- On February 18, 2010, the FDA issued a safety announcement based on these data and the past advisory group deliberations.[3] The FDA recommends the following to ensure the safe use of LABA for asthma (does not extend to the use of LABA for COPD):
    - The use of LABAs is contraindicated without the use of an asthma controller medication such as an inhaled corticosteroid. Single-ingredient LABAs should only be used in combination with an asthma controller medication; they should not be used alone.
    - LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications.
    - LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patients should then be maintained on an asthma controller medication.
    - Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure compliance with both medications.

Medicaid claims data analyses suggested that utilization patterns are not consistent with practice recommendations. This was consistent with a previous analysis in this population which found less than 10% of patients started on ICS/LABA had a history of ICS monotherapy use.[4] A Retrospective educational letter intervention was implemented in 2006 but was largely without effect on prescribing.

- Depending on the denominator, between 6% and 14% of patients were using ICS prior to starting ICS/LABA. Using a less conservative definition of controller increased the proportion of users to 22% to 50%.
- While asthma appears to represent the predominate condition treated, individuals with COPD may represent a significant proportion (13%) of individuals.
- Individuals with a history of higher severity of disease were more likely to have previous controller use prior to starting ICS/LABA treatment.
- General practitioners represent the largest prescribers of this drug class.

Previous DUR Board Recommendations included:

- Prior authorize new starts of ICS/LABA inhalers. Electronically exempt individuals with any evidence of increased asthma severity of disease such as HEDIS asthma definition, >1 oral steroid claim, specialist prescriber, any previous controller prescription or evidence of COPD. Current users would be grandfathered in.
  - Pros: Prospectively identifies patients for reduced exposure to LABA.
  - Cons: Risks delay of care for moderate-severe asthma patients in crisis. Risks are mitigated by electronically excluding clients with descriptors of more severe disease.
- Prior authorize LABA monotherapy. Electronically exempt individuals with evidence of COPD or evidence of concurrent asthma controller agent.
  - Pros: Prospectively identifies patients at highest risk for reduced exposure to unnecessary LABA.
  - Cons: Limited risk (currently very low utilization) of delay of care for moderate-severe COPD clients.

Methods:

The goals of the current analysis were to quantify any change in prescribing patterns of study groups temporal to the prior authorization policy implemented January 1, 2011. In addition, any change in use of the emergency department (ED) or hospitalizations for asthma or COPD were evaluated.

Patients were identified for inclusion in the analysis if they had a fee-for-service (FFS) drug claim for any drug in Appendix 1 from January 1, 2010 through December 31, 2011. Patients also eligible for Medicare Part D as identified by benefit package codes BMM or BMD were excluded. All FFS drug and medical claims from January 1, 2009 – March 31, 2010 for the identified patients were retained. These patients were further classified into four study groups; inhaled corticosteroid monotherapy (ICS), long-acting beta-agonist monotherapy (LABA), combination ICS/LABA inhaler (ICSLABA) and ICS + LABA if filled within 7 days of each other. The gross trend in utilization was reported as a count of unique patients on the study group drug each month divided by the number of patients enrolled in FFS each month (PMPM). The cost trend was reported using the amount reimbursed to pharmacies PMPM. The estimated pharmacy reimbursed costs avoided each month was the difference between the predicted costs PMPM based upon the trend for the 6 months prior to the policy and the actual costs incurred PMPM, multiplied by the FFS enrollment for the month.

The primary analysis focused on new users of the drugs of interest. Patients were included in the analysis if they had an index fills of a study drug in 2010 and 2011. An index fill is new fill for a drug in any of the study groups and no previous fills for any drug in

the study groups above for the same patient. Patients with valid demographic data between the ages of 5-64 on the index fill date were included. The age restriction was placed because the guidelines are most clear for those ages. Patients must have a minimum of 6 months FFS enrollment in the year prior to the index fill. This could be up to two discrete spans with no more than 31 days between spans.

Patients were identified as patients with an asthma diagnosis if they had any medical claim data with an asthma ICD-9 code during the year prior to the index fill (Appendix 2). Patients were identified as patients with a COPD diagnosis if they had any medical claim data with a COPD ICD-9 code during the years prior to the index fill (Appendix 2). Patients were then put into the following groups and can only be in 1 group:

1) Asthma (no COPD): Asthma flag and no COPD flag
2) Asthma + COPD: Asthma flag and COPD flag
3) COPD (no Asthma): COPD flag and no Asthma flag
4) No Asthma & no COPD: neither flag

Patients were further grouped as follows:
All Users = 1 + 2 + 3 + 4
Any Asthma = 1 + 2
COPD (no Asthma) = 3

Prescriber specialties were determined from the National Provider Identifier information used upon Oregon Medicaid provider enrollment. Hospital discharges were identified with claims where International Classification of Disease, 9th edition (ICD-9) codes had a diagnosis as defined in Appendix 2. The ICD-9 could reside as primary through sixth place on the claim. Discharge dates were used rather than service date for hospital encounters. ED visits and outpatient visits were identified with claims with ICD-9 codes associated with diagnoses in Appendix 2. These were used to establish patient disease severity at baseline using claims up to 1 year prior to the index fill. Hospital and ED visits were also measured for 90 days post index fill to detect differences in drug groups.

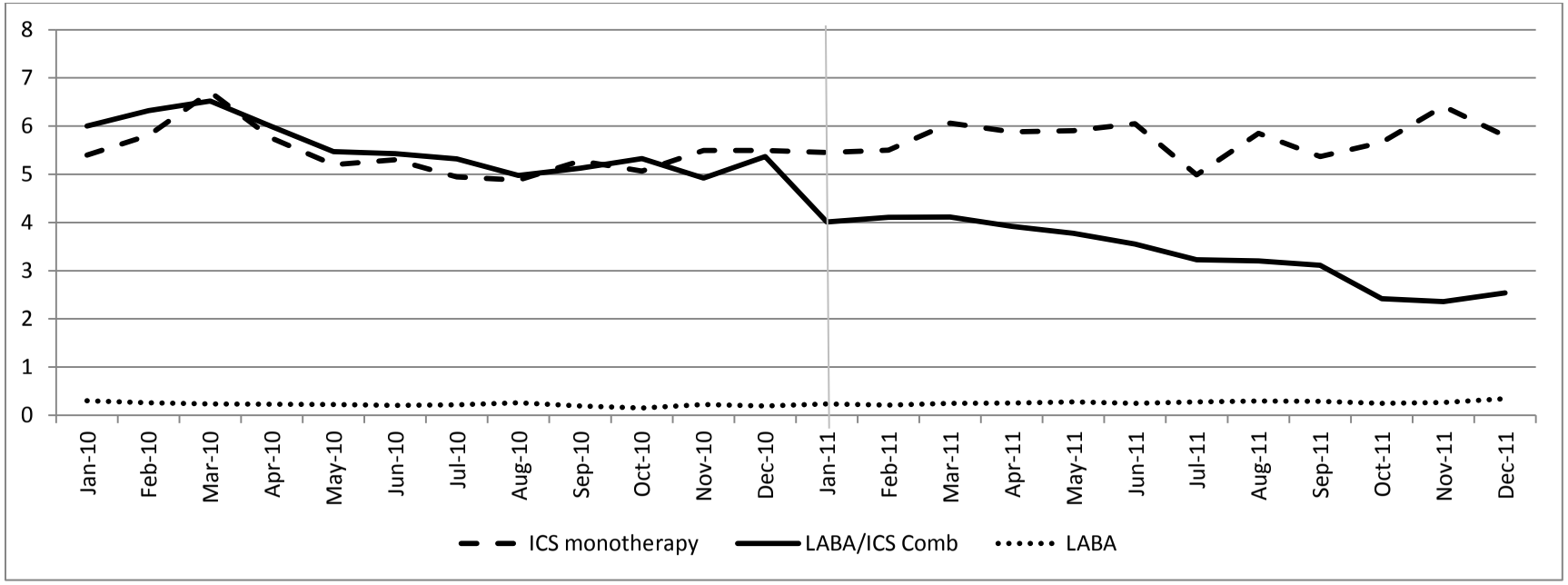
Disease severity was estimated using several measures. The number of ED, hospital encounters and fills for oral corticosteroids were constructed as possible metrics of asthma or COPD exacerbation. The Healthcare Effectiveness Data and Information Set (HEDIS) description of “persistent asthma” was used. A ratio of controller medication fills to total asthma medication fills was used

to identify individuals with ratios <50% for patients who had a minimum of 4 total asthma drug prescriptions in the previous year.[2] A combined disease severity variable was created to provide the greatest sensitivity for any history of possible asthma exacerbation. The asthma severity variable was defined by any of the following: a controller to total asthma drug ratio <50%, or >1 oral steroid prescription in the previous year, or ED visit or hospitalization related for asthma or COPD in the previous year or HEDIS persistent asthma.

Results

The gross number of patients using any ICS/LABA combination product decreased dramatically after the policy was implemented (Figure 1). While the use of ICS does trend upward, the slope is not as dramatic. There continues to be low use of LABA as monotherapy.

Figure 1 - Unique Patient Count Trend (all comers) PMPM x 1000



A summary of the drug group and diagnostic group proportions is represented in Table 1. A dramatic shift (~21%) from the ICS/LABA combination to ICS monotherapy can be observed across all groups. There is also an increase in the use of LABA monotherapy for COPD patients. General practice physicians remain the predominate prescribers of initial therapy, with pulmonologists identified as prescribers less than 7% of the time.

Table 1 – Study Group Proportions and Prescribers

	All users				Any Asthma				COPD (no Asthma)			
	2010		2011		2010		2011		2010		2011	
n=	1,019		658		513		298		72		58	
	count	%	count	%	count	%	count	%	count	%	count	%
Index Drug Characteristics												
ICS monotherapy	655	64.28%	562	85.41%	332	64.72%	262	87.92%	27	37.50%	36	62.07%
LABA/ICS Comb	354	34.74%	78	11.85%	176	34.31%	30	10.07%	43	59.72%	16	27.59%
LABA + ICS concurrently	4	0.39%	4	0.61%	2	0.39%	1	0.34%	2	2.78%	1	1.72%
LABA	6	0.59%	14	2.13%	3	0.58%	5	1.68%	0	0.00%	5	8.62%
Prescriber Specialty												
Pulmonary	31	3.04%	31	4.71%	22	4.29%	20	6.71%	4	5.56%	2	3.45%
Pediatrics	210	20.61%	139	21.12%	116	22.61%	66	22.15%	0	0.00%	1	1.72%
General Practice	625	61.33%	398	60.49%	304	59.26%	167	56.04%	55	76.39%	48	82.76%
Other	131	12.86%	66	10.03%	59	11.50%	35	11.74%	12	16.67%	6	10.34%

The comparative demographics for the study groups are presented in Table 2. Both the Asthma and COPD populations have more ED visits and oral steroid use than the All User populations which indicates poorer control or more disease severity or both. In addition the COPD population has more hospitalizations than the All User population. In general, there is a significant reduction in all drug use in this category from 2010 to 2011 (~45% overall). There was no asthma or COPD diagnosis on record for 43% of patients in 2010 and 46% of patients in 2011. Asthma is the predominant diagnosis of record (50% in 2010, 46% in 2011) with roughly 6-7% co-morbid with COPD. Patients with COPD and no asthma diagnosis comprise 7% of all users in 2010 and 9% in 2011. Disease severity indicators generally decreased from 2010 to 2011, notably ED and Hospital visits for asthma patients. However, COPD ED and hospital visits increased slightly

Table 2 – Baseline Demographics and Morbidity at Time of Index Fill.

	All users				Any Asthma				COPD (no Asthma)			
	2010		2011		2010		2011		2010		2011	
n=	1,019		658		513		298		72		58	
	mean	***SD***	***mean***	***SD***	***mean***	***SD***	***mean***	***SD***	***mean***	***SD***	***mean***	***SD***
Asthma/ COPD ED visits (mean visits per patient in year prior)	0.18	0.60	0.13	0.55	0.32	0.75	0.19	0.62	0.29	0.86	0.48	1.10
Asthma/ COPD Hospitalizations (mean hospitalization per patient in year prior)	0.03	0.19	0.02	0.13	0.04	0.20	0.02	0.13	0.14	0.45	0.10	0.31
Oral Steroid Rx in year prior	0.38	0.87	0.43	1.07	0.47	0.93	0.53	1.14	0.76	1.24	0.60	1.15
Age	27.00	18.77	28.13	18.67	22.11	16.68	23.18	16.53	53.60	9.22	53.43	8.31
	count	***%***	***count***	***%***	***count***	***%***	***count***	***%***	***count***	***%***	***count***	***%***
Sex (female)	613	60.16%	376	57.14%	294	57.31%	163	54.70%	43	59.72%	35	60.34%
Race (non-white)	212	20.80%	148	22.49%	121	23.59%	78	26.17%	8	11.11%	5	8.62%
Diagnostic Characteristics												
Asthma (no COPD)	479	47.01%	280	42.55%	479	93.37%	280	93.96%	0	0.00%	0	0.00%
Asthma + COPD	34	3.34%	18	2.74%	34	6.63%	18	6.04%	0	0.00%	0	0.00%
COPD (no Asthma)	72	7.07%	58	8.81%	0	0.00%	0	0.00%	72	100.00%	58	100.00%
No Asthma & no COPD	434	42.59%	302	45.90%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Disease Severity Indicators												
Persistent Asthma (HEDIS)	174	17.08%	77	11.70%	160	31.19%	62	20.81%	5	6.94%	5	8.62%
Controller Ratio < 50%	293	28.75%	191	29.03%	166	32.36%	85	28.52%	39	54.17%	31	53.45%
> 1 oral steroid	83	8.15%	51	7.75%	51	9.94%	24	8.05%	15	20.83%	9	15.52%
Patients with Asthma/COPD ED or Hospital Encounter	145	14.23%	59	8.97%	129	25.15%	43	14.43%	16	22.22%	16	27.59%
Any Severity Indicator	380	37.29%	232	35.26%	245	47.76%	115	38.59%	45	62.50%	38	65.52%

Table 3 counts patients in each study group that have any of the severity indicators. More patients using ICS monotherapy had severe disease as indicated by any of the indicators. There was an increase in the rate of ICS patients with severe disease in 2011 and is most dramatic for the COPD patients.

Table 3 - Any Severity Indicator by Index Drug

	All users				Any Asthma				COPD (no Asthma)			
	2010		2011		2010		2011		2010		2011	
n=	1,019		658		513		298		72		58	
	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
ICS monotherapy	219	21.49%	188	28.57%	147	28.65%	96	32.21%	18	25.00%	24	41.38%
LABA/ICS Comb	154	15.11%	32	4.86%	93	18.13%	15	5.03%	25	34.72%	10	17.24%
LABA + ICS concurrently	4	0.39%	3	0.46%	2	0.39%	1	0.34%	2	2.78%	1	1.72%
LABA	3	0.29%	9	1.37%	3	0.58%	3	1.01%	0	0.00%	3	5.17%

Table 4 presents the number of patients started on monotherapy who were switched to a combination inhaler within 90 days. This indicator was used as a proxy of inadequate control with the monotherapy. There is no appreciable difference before or after the step therapy was implemented.

Table 4 - Presence of ICSLABA Pharmacotherapy in 3 Months Following Initiation

	All users				Any Asthma				COPD (no Asthma)			
	2010		2011		2010		2011		2010		2011	
n=	1,019		658		513		298		72		58	
	count	%	count	%	count	%	count	%	count	%	count	%
ICS monotherapy	21	2.06%	12	1.82%	12	2.34%	6	2.01%	1	1.39%	1	1.72%
LABA + ICS concurrently	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
LABA	1	0.10%	1	0.15%	1	0.19%	1	0.34%	0	0.00%	0	0.00%

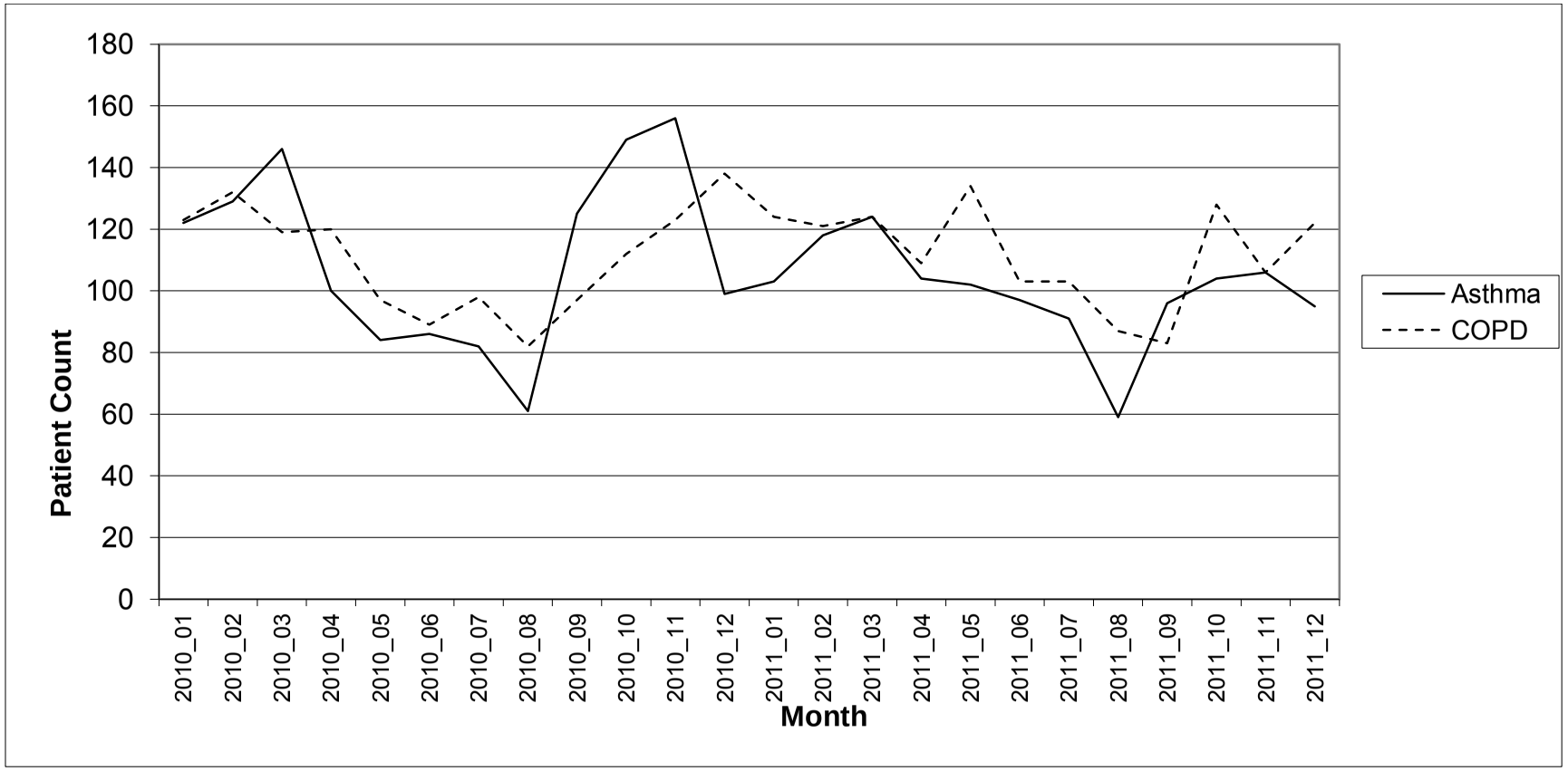
Table 5 represents the patients that were admitted to ED or hospital within 3 months of initiating therapy. The combination inhaler group having a diagnosis of asthma or COPD increased the number of ED or hospital visits in 2011. There was also an increase for those patients with COPD initiated on ICS or LABA monotherapy. All other groups remained similar or decreased.

Table 5 - Asthma/COPD ED/Hospital Admits Within 3 Months Following Therapy Initiation

	All users				**Any Asthma**				**COPD (no Asthma)**			
	2010		**2011**		**2010**		**2011**		**2010**		**2011**	
n=	1,019		658		513		298		72		58	
	mean	*SD*	*mean*	*SD*	*mean*	*SD*	*mean*	*SD*	*mean*	*SD*	*mean*	*SD*
Mean per Patient Asthma-related ED/Hospital Visits in the 3 months after initiating:												
ICS monotherapy	0.02	0.16	0.02	0.14	0.05	0.22	0.02	0.17	0.00	0.00	0.00	0.00
LABA/ICS Comb	0.03	0.18	0.04	0.25	**0.04**	**0.22**	**0.10**	**0.40**	0.00	0.00	0.00	0.00
LABA + ICS concurrently	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
LABA	0.17	0.41	0.07	0.27	0.33	0.58	0.20	0.45	0.00	0.00	0.00	0.00
Mean per Patient COPD-related ED/Hospital Visits in the 3 months after initiating:												
ICS monotherapy	0.00	0.06	0.01	0.10	0.01	0.08	0.00	0.00	**0.00**	**0.00**	**0.08**	**0.37**
LABA/ICS Comb	0.01	0.13	0.04	0.19	0.01	0.08	0.00	0.00	**0.02**	**0.15**	**0.19**	**0.40**
LABA + ICS concurrently	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
LABA	0.17	0.41	0.07	0.27	0.33	0.58	0.00	0.00	**0.00**	**0.00**	**0.20**	**0.45**

Figure 2 depicts a trend of all patients with a hospital and ED encounter with either an asthma or COPD diagnosis, regardless of drug therapy. It trends slightly downward overall in 2011 though the most prominent feature is a seasonal trend.

Figure 2 – Count of unique patients per month with hospital or ED encounter with asthma or COPD (no asthma) diagnosis on claim.



Discussion

There was a temporal and significant decrease (47%) in the use of ICS/LABA products and an increase (6%) of ICS monotherapy in 2011. There was an overall 45% decrease in use of all drugs in this class. This is concerning since this group of drugs is recommended treatment for both asthma and COPD control. However, most indicators of disease severity decreased in 2011 as well. There were no increases in the use of ED or hospitals within 90 days of index fill of ICS monotherapy for asthma and patients did not switch to the ICS/LABA within 90 days of the index fill. However, there was an increase in ED and hospital admits for ICS/LABA asthma patients, despite fewer indicators of severe disease in this group. ED and hospital admits for COPD patients increased. Overall, no increase in hospital or ED visits with asthma or COPD diagnoses was detected as a result of this policy.

This analysis is limited because it is retrospective and uses administrative data which is known to have the potential for missing data and miscoding. In particular, there is a known potential for loss of follow-up for patients with index fills in the latter part of 2011, where hospital and ED data may not be submitted yet by March 31, 2012. Limiting the follow-up period to 90-days was an attempt to limit this effect, but it may still account from some of the decrease in ED and hospital admits in 2011.

Recommendations:

1) Continue the policy to prior authorize ICS/LABA combinations for step therapy
2) Consider loosening the electronic criteria to require only a diagnosis of COPD OR prior anti-cholinergic inhaler use
3) Implement RetroDUR education lettering on LABA monotherapy in the absence of COPD indicators
4) Further study to evaluate patient outcomes after encountering a PA for ICS/LABA
5) Further study of patients without a diagnosis

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3. Postmarket Drug Safety Information for Patients and Providers > FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs). *United States Food and Drug Administration*. 2010. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm#_Ref252304498. Accessed April 19, 2012.

4. Oregon Drug Use Review Board. Drug Use Evaluation: LongActing Beta Agonist (LABA). *Oregon State University Drug Use Research and Management*. 2006. Available at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/evaluations/articles/laba.pdf. Accessed April 19, 2012.

Appendix 1 – Drugs of Interest and Study Group Classification

GSN	Generic Name	Route	Study Group
46698	BECLOMETHASONE DIPROPIONATE	IH	ICS
46699	BECLOMETHASONE DIPROPIONATE	IH	ICS
62240	BUDESONIDE	IH	ICS
46525	BUDESONIDE	IH	ICS
46526	BUDESONIDE	IH	ICS
62241	BUDESONIDE	IH	ICS
18165	BUDESONIDE	IH	ICS
58671	CICLESONIDE	IH	ICS
58672	CICLESONIDE	IH	ICS
213	FLUNISOLIDE	IH	ICS
17184	FLUNISOLIDE/MENTHOL	IH	ICS
21483	FLUTICASONE PROPIONATE	IH	ICS
21251	FLUTICASONE PROPIONATE	IH	ICS
19319	FLUTICASONE PROPIONATE	IH	ICS
19318	FLUTICASONE PROPIONATE	IH	ICS
21253	FLUTICASONE PROPIONATE	IH	ICS
19317	FLUTICASONE PROPIONATE	IH	ICS
51649	MOMETASONE FUROATE	IH	ICS
59326	MOMETASONE FUROATE	IH	ICS
59328	MOMETASONE FUROATE	IH	ICS
64012	MOMETASONE FUROATE	IH	ICS
64010	MOMETASONE FUROATE	IH	ICS
59327	MOMETASONE FUROATE	IH	ICS
212	TRIAMCINOLONE ACETONIDE	IH	ICS
62725	BUDESONIDE/FORMOTEROL FUMARATE	IH	ICSLABA
62726	BUDESONIDE/FORMOTEROL FUMARATE	IH	ICSLABA
43366	FLUTICASONE/SALMETEROL	IH	ICSLABA
43367	FLUTICASONE/SALMETEROL	IH	ICSLABA

43368	FLUTICASONE/SALMETEROL	IH	ICSLABA
61343	FLUTICASONE/SALMETEROL	IH	ICSLABA
61344	FLUTICASONE/SALMETEROL	IH	ICSLABA
61345	FLUTICASONE/SALMETEROL	IH	ICSLABA
66481	MOMETASONE/FORMOTEROL	IH	ICSLABA
66480	MOMETASONE/FORMOTEROL	IH	ICSLABA
61579	ARFORMOTEROL TARTRATE	IH	LABA
25621	FORMOTEROL FUMARATE	IH	LABA
63016	FORMOTEROL FUMARATE	IH	LABA
67600	INDACATEROL MALEATE	IH	LABA
17941	SALMETEROL XINAFOATE	IH	LABA
21604	SALMETEROL XINAFOATE	IH	LABA
31417	SALMETEROL XINAFOATE	IH	LABA

Appendix 2 – Diagnostic Criteria

Asthma	Any encounter with an ICD9 code for asthma in the year prior to index date
HEDIS Asthma	*one of the following* metrics using pharmacy, encounter, and hospitalization data from year prior to index date a. >=3 asthma med dispensing* **OR** b. >=1 hospital discharge with primary diagnosis of asthma **OR** c. >=1 ED visits with primary diagnosis of asthma **OR** d. >=2 outpatient visits for asthma (anywhere)
HEDIS Persistent Asthma	*one of the following* metrics using pharmacy, encounter, and hospitalization data from year prior to index date a.>=4 asthma med dispensing* **OR** b.>=1 hospital discharge with primary diagnosis of asthma **OR** c.>=1 ED visit with primary diagnosis of asthma **OR** d>=4 outpatient visits with asthma (anywhere) AND 2>= asthma dispensing*
COPD	Any ICD9 code for COPD in previous year
COPD (not asthma)	Any ICD9 code for COPD in previous year AND does meet HEDIS asthma criteria
Asthma ICD9 Codes	493 ASTHMA 4930 EXTRINSIC ASTHMA 49300 EXTRINSIC ASTHMA, UNSPECIFIED 49301 EXTRINSIC ASTHMA WITH STATUS ASTHMATICUS 49302 EXTRINSIC ASTHMA, WITH EXACERBATION 4931 INTRINSIC ASTHMA 49310 INTRINSIC ASTHMA, UNSPECIFIED 49311 INTRINSIC ASTHMA WITH STATUS ASTHMATICUS 49312 INTRINSIC ASTHMA, WITH EXACERBATION 4932 CHRONIC OBSTRUCTIVE ASTHMA 49320 CHRONIC OBSTRUCTIVE ASTHMA UNSPECIFIED 49321 CHRONIC OBSTRUCTIVE ASTHMA W/STATUS ASTHMATICUS 49322 CHRONIC OBSTRUCTIVE ASTHMA WITH EXACERBATION 4938 OTHER FORMS OF ASTHMA 49381 EXERCISE INDUCED BRONCHOSPASM 49382 COUGH VARIANT ASTHMA 4939 UNSPECIFIED ASTHMA 49390 ASTHMA, UNSPECIFIED, UNSPECIFIED STATUS 49391 ASTHMA UNSPECIFIED WITH STATUS ASTHMATICUS 49392 ASTHMA UNSPECIFIED WITH EXACERBATION
COPD ICD9 Codes	4912 OBSTRUCTIVE CHRONIC BRONCHITIS 49120 OBSTRUCTIVE CHRONIC BRONCHITIS WITHOUT EXACERBAT 49121 OBSTRUCTIVE CHRONIC BRONCHITIS WITH EXACERBATION 49122 OBST CHRONIC BRONCHITIS W/ACUTE BRONCHITIS 492 EMPHYSEMA 4920 EMPHYSEMATOUS BLEB 4928 OTHER EMPHYSEMA 496 CHRONIC AIRWAY OBSTRUCTION NEC 5064 CHRONIC RESPIRATORY CONDITIONS DUE FUMES&VAPORS 5181 INTERSTITIAL EMPHYSEMA 5182 COMPENSATORY EMPHYSEMA
*HEDIS asthma medication = ICS, theophylline, mast cell stabilizer, leukotriene active agent, LABA, anti-IgE	

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Current Findings in the Off-Label Use of Atypical Antipsychotics

By, Ann Hamer, Pharm D, BCPP, OptumHeatlh Behavioral Solutions and OSU College of Pharmacy

A class of medications once reserved for the most serious of mental illnesses, the atypical antipsychotic medications, has become routinely prescribed in primary care offices for the treatment of delirium, depression, autism, dementia, and other disorders. The treatment of many of these conditions with atypical antipsychotics is not approved by the FDA and the evidence base for their off-label use is often in question. In fact, 54% of all office visits associated with the prescription of an atypical antipsychotic involves off-label use.[1] Atypical antipsychotics are the fifth most expensive medication class in the U.S. In 2010, spending was $16.1 billion (aripiprazole $4.6 billion; quetiapine $4.4 billion; olanzapine $3.0 billion).[2] Because they have been associated with a lower incidence of extrapyramidal adverse effects, atypical antipsychotics have largely replaced traditional antipsychotics. As experience with the atypical agents accrues, however, serious and distinct adverse effects with atypicals have emerged.[1] Atypical antipsychotics can cause weight gain and lead to a higher risk of other metabolic abnormalities (e.g. diabetes) compared to the older, traditional antipsychotics.[3] Also, current comparative evidence (based on their indicated use for the treatment of schizophrenia) suggests no definitive differences in efficacy or net adverse effect profiles between the two drug classes.[4]

Patterns of Use

A recent study by Alexander, et al[1] evaluated the patterns of antipsychotic use in the outpatient setting and found that from 1995 to 2008 the use of atypical agents expanded for bipolar disorder (10 to 34%), remained stable for depression (12 to 14%), and declined for schizophrenia (56 to 23%). The authors concluded that atypical use has grown far beyond substitution for the infrequently used typical agents. Growth in use was seen in all age categories. They found that antipsychotic use for indications without FDA approval increased from 4.4 million visits in 1995 to 9.0 million in 2008 with an estimated cost associated with off-label use in 2008 of $6.0 billion. While the use of atypicals for the treatment of schizophrenia declined, their use in bipolar affective disorder, attention deficit hyperactivity disorder/conduct disorder, and anxiety all increased.

Agency for Healthcare Research and Quality Report

Not all off-label use is inappropriate. There is a growing body of evidence to support the use of certain atypical antipsychotics for off-label indications. A recent report from the Agency for Healthcare Research and Quality (AHRQ)[5] included a review of the following off-label uses for atypical antipsychotics: anxiety, attention deficit disorder (ADHD), dementia and severe geriatric agitation, major depressive disorder (MDD), eating disorders, insomnia, obsessive compulsive disorder (OCD), post traumatic stress disorder (PTSD), personality disorders, substance abuse, and Tourette's syndrome. The following are key findings from the report:

Current trends:

- Off-label use of atypical antipsychotics in various settings has increased rapidly since their introduction in the 1990s; risperidone, quetiapine, and olanzapine are the most common atypicals prescribed for off-label use.
- One recent study indicated that the 2005 regulatory warning from the FDA and Health Canada was associated with decreases in the overall use of atypical antipsychotics, especially among elderly dementia patients. Use of atypicals in the elderly is much higher in long-term care settings than in the community.
- Atypicals are frequently prescribed to treat PTSD in the U.S. Department of Veterans Affairs health system.
- At least 90% antipsychotics prescribed to children are atypical, rather than conventional antipsychotics. The majority of use is off-label.

Summary of the Evidence:

Table 1. Efficacy for the following off-label indications and atypical antipsychotics	
Moderate to High Evidence	
Off-label Indication	Atypical Antipsychotic
Generalized anxiety disorder	Quetiapine
Dementia (overall)	Aripiprazole, risperidone
Dementia (psychosis)	Risperidone
Dementia (agitation)	Olanzapine, risperidone
Depression (SSRI/SRNI augmentation)	Aripiprazole (labeled indication), quetiapine (labeled use for quetiapine XR), risperidone
Depression (monotherapy)	Quetiapine
Obsessive Compulsive Disorder (SSRI augmentation)	Risperidone
PTSD	Risperidone

Table 2. Inefficacy for the following off-label indications and atypical antipsychotics	
Moderate to High Evidence	
Off-label Indication	Atypical Antipsychotic
Eating Disorders	Olanzapine
Substance Abuse (alcohol)	Aripiprazole
MDD (monotherapy)	Olanzapine

- Strength of evidence is low for the following off-label indications:
  - ADHD
  - Insomnia
  - Substance abuse (cocaine, methamphetamine, methadone)
  - Personality disorders
  - Tourette's syndrome
- There is almost no evidence about how treatment efficacy may vary within populations, including variations due to gender, race, ethnicity, or medical comorbidities.
- In terms of adverse effects for the atypical antipsychotics, existing evidence varies by drug and by description of the adverse event (see Table 3)

Table 3. Adverse Events Associated with the Off-Label Use of Atypical Antipsychotics[5]	
Adverse Event	Placebo Comparison
Weight Gain--Elderly	More common in patients taking olanzapine and risperidone
Weight Gain—Adults	More common in patients taking aripiprazole, olanzapine, quetiapine and risperidone
Weight Gain--Children	More common with risperidone; No difference with ziprasidone
Mortality—Elderly	Difference in risk for death is small, but statistically significant for atypical antipsychotics. No differences between drugs in class (no studies for ziprasidone in this population)
Endocrine/ Diabetes—Adults	More common with quetiapine, risperidone, and ziprasidone in one PCT each. More common in olanzapine in two pooled PCTs. Diabetes more common in patients taking quetiapine in six pooled PCTs; however, the pooled odds ratio was elevated at 1.47 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large observational study
CVA—Elderly	More common in risperidone patients than placebo according to four PCTs pooled by the manufacturer. In the most recent meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine than placebo according to five PCTs pooled by the manufacturer.
EPS	More common in patients taking risperidone, according to our meta-analysis. Quetiapine and aripiprazole were not associated with an increase. More common in olanzapine in one PCT.
Sedation—Adults	More common in patients taking aripiprazole, olanzapine, quetiapine, ziprasidone and quetiapine than placebo
Abbreviations: PCT=placebo controlled trial; CVA=cerebrovascular accident; EPS=extrapyramidal symptoms	

- There are too few studies comparing doses of atypical antipsychotic medications to draw a conclusion about a minimum dose needed.
  - Most trials used flexible dosing, resulting in patients taking a wide range of doses.
  - According to the meta-analysis conducted by AHRQ, using the percentage of remitters and responders as identified by the MADRS as outcome, 150 mg quetiapine daily augmentation has equal efficacy as augmentation with 300 mg for patients with MDD who respond inadequately to SSRIs.
  - More trials examining different doses of other atypicals for MDD are needed as are dosage trials for treating conditions such as OCD, PTSD, and anxiety disorder.
- Though there is some trial data regarding duration of treatment in PTSD, eating disorders, and borderline personality disorder, the outcome of treatment appears to be the same regardless of reported follow-up time.

Summary

Recent evidence has demonstrated that the majority of atypical antipsychotic use is for off-label indications. The benefits and harms associated with atypical antipsychotics in off-label uses vary. For global behavioral symptom scores associated with dementia in elderly patients, small but statistically significant benefits have been observed for aripiprazole, olanzapine, and risperidone. Quetiapine has been associated with benefits in the treatment of generalized anxiety disorder, and risperidone is associated with benefits in the treatment of obsessive-compulsive disorder. Adverse effects, however, are common with each of these agents. The use of atypical antipsychotics, particularly for conditions that are considered off-label, requires a careful evaluation of their risks versus benefits. The benefits of using atypical antipsychotics should include clear and definable treatment goals especially if they are used in the place of other agents with demonstrated comparable or superior effectiveness

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[3] Smith M, Hopkins D, Peveler RC, et al. First v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. Br J Psychiatry 2008;192:406-411.

[4] Shekelle P, Maglione M, Bagley S, et al. Comparative effectiveness of off-label use of atypical antipsychotics: comparative effectiveness review no. 6 Prepared by the Southern California/RAND Evidence-based Practice Center. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed February 4, 2012.

[5] Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43. (Prepared by the Southern California/RAND Evidence-based Practice Center under Contract No. HHSA290-2007-10062-1.) AHRQ Publication No. 11-EHC087-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed February 4, 2012.

Antiemetics, New

Goal(s):

- Promote preferred drugs.
- Reserve costly antiemetics for appropriate indications.
- Restrict chronic use of non-preferred agents (> 3 days per week).
- If chemotherapy is more frequent than once weekly, approve a quantity sufficient for three days beyond the duration of chemotherapy.

Initiative:

- Initiative

Length of Authorization:

3 days to 6 months (criteria specific)

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Check the Reason for PA:

- Non-Preferred drugs will deny on initiation
- Preferred drugs will deny only when maximum dose exceeded (www.orpdl.org)

HICL	Generic	Brand	Quantity Limit
025058	Aprepitant	Emend	3 doses / 7 days
016576	Dolasetron	Anzemet	9 doses / 7 days
007611	Granisetron	Kytril Tablets Kytril Solution	6 doses / 7 days (30 ml liquid)
~~006055~~	~~Ondansetron~~	~~Zofran~~	~~9 doses / 7 days (300 ml liquid)~~
~~019058~~	~~Ondansetron~~	~~Zofran ODT~~	~~9 doses / 7 days~~

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
~~2. Is the drug requested preferred?~~	~~Yes: Go to #4.~~	~~No: Go to #3.~~

Formatted: No bullets or numbering

Approval Criteria		
~~3.~~2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA ~~for <4 days/week~~. • Preferred products have received evidence-based reviews for comparative effectiveness and safety by the Health Resources Commission (HRC).	Yes: Inform provider of covered alternatives in class and dose limits if aplicable. If dose > limits, continue to #34.	No: Go to #34.
~~4.~~3. Is client currently diagnosed with cancer AND receiving chemotherapy or radiation therapy more frequently than every 7 days?	Yes: Approve for 3 days past length of therapy. (Chemo regimen more frequently than weekly)	No: Go to #45.
~~5.~~4. Does client have refractory nausea that would require hospitalization or ER visits?	Yes: Go to #56.	No: Go to #78.
~~6.~~5. Has client tried and failed two conventional antiemetics, listed below? Generic Name / Brand Name Metoclopramide / Reglan Prochlorperazine / Compazine Promethazine / Phenergan	Yes: Approve up to 6 months.	No: Go to #67.
~~7.~~6. Does client have contraindications to conventional antiemetics, e.g. Allergy; or cannot tolerate?	Yes: Document reason and approve up to 6 months. (Contraindications to required alternative medications)	No: Pass to RPH; Go to #78.
~~8.~~7. RPH only All other indications need to be evaluated as to whether they are above the line or below the line. • Above: Deny, (Medical Appropriateness) • Below: Deny, (Not Covered by the OHP)		

P&T / DUR Action: *5/31/12(RC), 9/24/09(DO/KK), 2/23/06, 2/24/04, 11/18/03, 9/9/03, 5/13/03, 2/11/03*
Revision(s): *5/1/12, 1/1/10, 7/1/06, 3/20/06, 6/30/04 (added aprepitant), 3/1/04 (removed injectables), 6/19/03*
Initiated: *4/1/03*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
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Drug Use Evaluation: Synagis (palivizumab)

Summary of Findings:

- Palivizumab is effective in reducing RSV-associated hospitalizations in a selected population when used during the RSV season.
- New Guidelines from the American Academy of Pediatrics (AAP) recommends limiting doses for most patients to a total of 5.
- 13% of patient received more than 5 doses and this was associated with a cost of $167,600.
- 18% of claims in 2009-2010 occurred prior to the RSV season and 5% occurred after it. Cost associated with this practice was $42,400.
- Additionally there are 2 patients outside the age recommendations for use.

Background:

Palivizumab is FDA approved for prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in the pediatric population at high risk for severe disease[1] At present it is the sole pharmacological agent available for RSV prophylaxis. Safety and efficacy is well established for use in infants born at or prior to 35 weeks' gestation with or without chronic lung disease (CLD) of prematurity and for infants and children with hemodynamically significant heart disease. Palizumab use has been associated with reductions in hospitalization attributed to RSV in children ≤ 2 years old with CLD requiring continuing medical therapy and children with a history of ≤ 35 weeks' gestation who were ≤ 6 months old at the beginning of RSV season. These patients experienced a 55% overall reduction in hospitalization; 10.6% and 4.8% with placebo vs. palizumab, respectively [p<.001].[2] Additionally, a 45% reduction in hospitalization rate has been observed with use in infants and children with hemodynamically significant congenital heart disease (9.7% and 5.3% with placebo vs. palizumab, respectively [p=.003]). [3]

Dosing
Palivizumab, a humanized monoclonal antibody, is administered once a month via an intramuscular injection and is dosed by weight (15 mg/kg) during the RSV season. A maximum number of 5 doses per season are recommended based on results from clinical trials which have indicated that palivizumab trough concentrations beyond 30 days after the fifth dose provide a sufficient protective concentration for most infants.

Adverse Effects and Safety Issues
The adverse reactions most commonly observed were upper respiratory tract infection, otitis media, fever, rhinitis, rash, diarrhea, cough, vomiting, gastroenteritis, and wheezing. Upper respiratory tract infection, otitis media, fever, and rhinitis occurred at a rate of 1% or greater in the Synagis group compared to placebo. *Drug-Drug Interactions*
No formal drug-drug interaction studies have been conducted. In those receiving routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids no incremental increases in adverse reactions were observed. [4]

Duration of treatment
Guidelines for use of palizumab have been routinely updated by The American Academy of Pediatrics (AAP) with policy statements released, both in 1998 and 2003 along with a technical report in 2003. Recently in 2009, AAP updated recommendations on use of palizumab in an effort to ensure use in those who can benefit and promote cost-effectiveness.[5]

The AAP released a statement noting "[c]hildren who qualify for palivizumab prophylaxis for the entire RSV season (infants and children with chronic lung disease of prematurity or congenital heart disease or preterm infants born before 32 weeks' gestation) should receive palivizumab only during the 5 months following the onset of RSV season in their region (maximum of 5 doses), which should provide coverage during the peak of the season, when prophylaxis is most effective."

Monitoring of temporal and geographic patterns associated with the detection of RSV and other viruses are accomplished by a laboratory system from the Center for Disease Control and Prevention (CDC) National Respiratory and Enteric Virus Surveillance System (NREVSS). Annual summaries and alerts based on NREVSS data have been published periodically in the CDC's Morbidity and Mortality Weekly Report at www.cdc.gov/surveillance/nrevss/rsv/state.html. The onset of the RSV season in the region which includes Oregon typically has been observed to occur from November through April (See Figure1).[6]

Currently Oregon Health Plan (OHP) provides coverage of this medication without any restriction. Many other Medicaid programs including Washington, Utah, Iowa, California, Arkansas, and Mississippi do require a prior authorization for this niche drug in order to ensure appropriate use and prevent unnecessary waste.

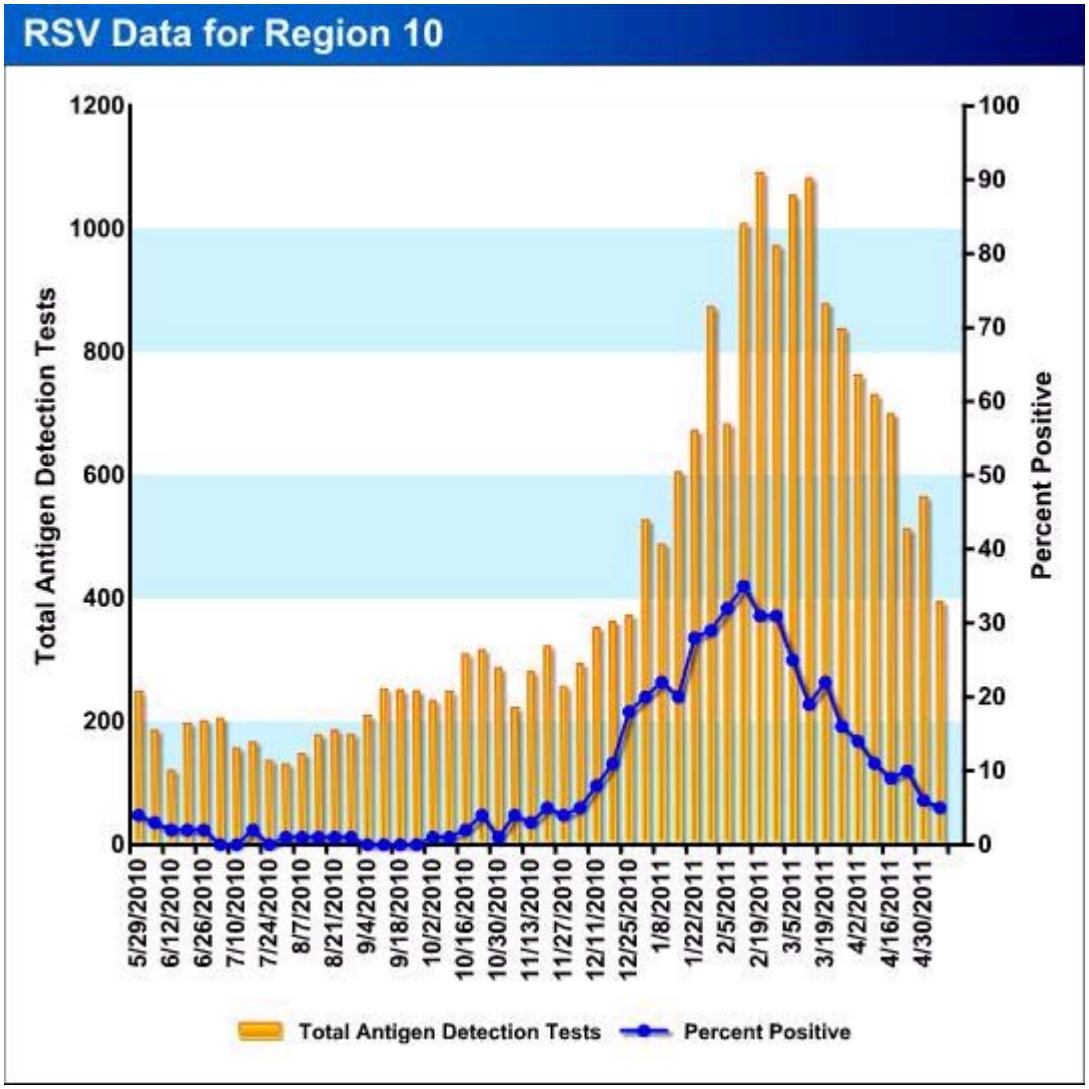


Figure 1. RSV detection data from NREVSS for region including Oregon.

Guideline Recommendations

The AAP recently updated the recommendations for use of palivizumab and sought to target children at the highest risk for severe disease.[5] In addition the definition of gestational age was changed from the previous definition of 32 weeks 1 day through 35 weeks 0 days **to** 32 weeks 0 days to 34 weeks 6 days.

1. Recommendations for initiation and termination of prophylaxis for the following groups remain unchanged: infants with congenital heart disease (CHD), CLD (formerly called bronchopulmonary dysplasia), and birth prior to 32 weeks' 0 days' gestation.
2. Regardless of the month when the first dose is administered or geographic location:
    a. **Maximum of 5 doses** for all for infants with CHD, CLD, or birth *prior t*o 32 weeks' 0 days' gestation.
    b. **Maximum of 3 doses** for infants with a gestational age 32 weeks 0 days to 34 weeks 6 days *without* hemodynamically significant CHD or CLD who qualify for prophylaxis.
3. Risk factors for infants born between 32 weeks' 0 days and 34 weeks' 6 days' gestation within 3 months prior to RSV season or any time throughout the RSV season with at least 1of the 2 risk factors below qualify for prophylaxis:
    a. Infants attending child care
    b. 1 or more siblings or other children younger than 5 years living permanently in child's household.
4. For infants born from 32 weeks' 0 days' through 34 weeks' 6 days' gestation who qualify for immunoprophylaxis a decrease in the length of prophylaxis from 5 months to 90 days **or maximum** of 3 doses (which ever comes first)

The Health Services Commission includes the following guideline in the prioritized list of health services that reflects this change:

OHP GUIDELINE NOTE 69, SYNAGIS
Line 3
CPT code 90378, Synagis (palivizumab), is covered for infants meeting one of the criteria given below (A-E), according to the treatment guidelines for each criterion:

A) Infants younger than 24 months who have congenital heart disease (CHD) or chronic lung disease of prematurity (CLD, formerly called bronchopulmonary dysplasia) AND require medical therapy
1) Therapy is initiated within 6 months before the start of the RSV season
2) Maximum 5 doses
B) Infants younger than 12 months with congenital abnormalities of the airway or neuromuscular disease
1) Maximum 5 doses
C) Had a gestation age of 28 weeks or less
1) Initiated during the RSV season before the infant reaches 12 months
2) Maximum 5 doses

D) Had a gestation age of 29 weeks and 0 days to 31 weeks and 6 days
1) Initiated during the RSV season before the infant reaches 6 months
2) Maximum 5 doses
E) Had a gestational age of 32 weeks 0 days to 34 weeks 6 days
1) Born within 3 months before the start of RSV season or at any time throughout the RSV season
2) Have at least 1 of these 2 risk factors
a) Infant attends child care; or
b) One or more siblings or other children younger than 5 years live permanently in the child's household.
3) Should receive prophylaxis only until they reach 90 days of age or ***a maximum of 3 doses*** *(whichever comes first).*

Methods:

Utilization Analysis
The goal of this analysis was to characterize the use and characteristics of clients using palivizumab in the Oregon Fee-For-Service Medicaid program during the 2009-2010 RSV season. Pharmacy and medical claims data ranging from 7/1/2009 through 6/30/2010 were utilized. Palivizumab users were identified using GSN of 59245 or 59246 in drug claims and procedure codes of C9003 or 90378 in medical claims.

Trends in palivizumab costs and utilization were quantified as a monthly per member per month (PMPM) value. Costs were defined as ingredient cost (paid amount + copay amount + other insurance paid – dispensing fee) and utilization was defined as the number of prescriptions dispensed. Dual Medicare/Medicaid enrollees were excluded from trend analyses.

The length of therapy was estimated for the pharmacy claims assuming each patient to have one treatment, and the length was simply the sum of all the day's supply for their palivizumab claims for that year (pharmacy claims only). Where a patient had two claims on the same day to accommodate dosing, the claims were counted as one and day's supply was also counted once.

Results:

The PMPM utilization of palivizumab is depicted in Figure 2 which shows that the majority of payments originate from pharmacy claims. Figure 3 illustrates the existence of claims both prior and after the RSV season along with the costs PMPM.

Figure 2 - Palivizumab Utilization July 2009 - June 2010

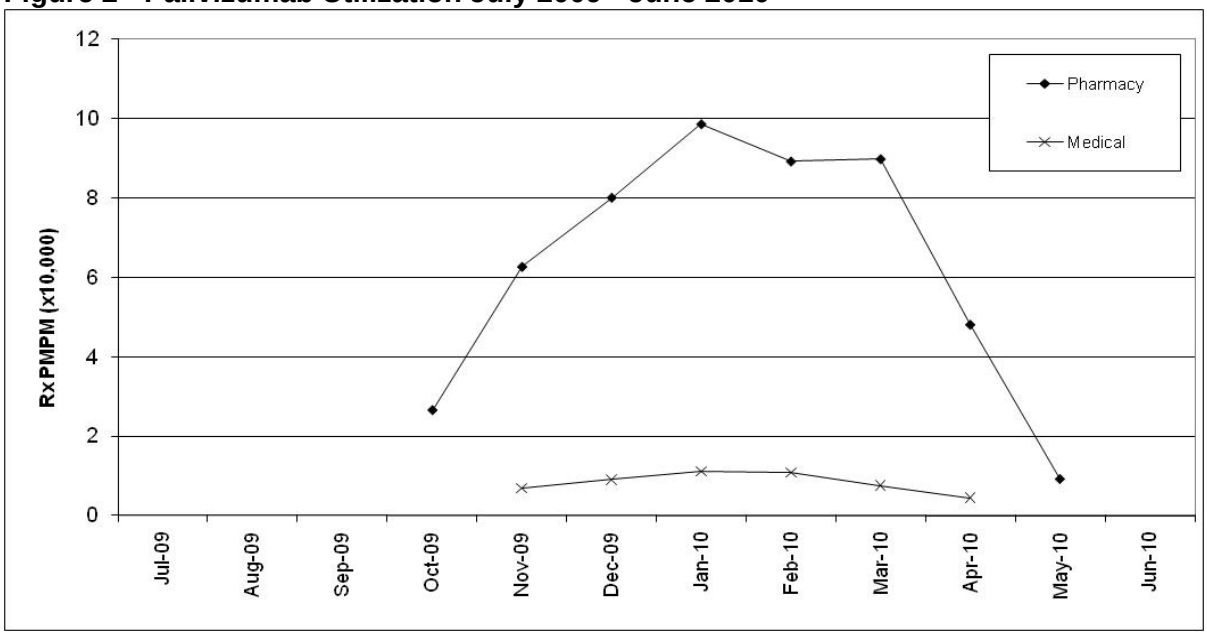
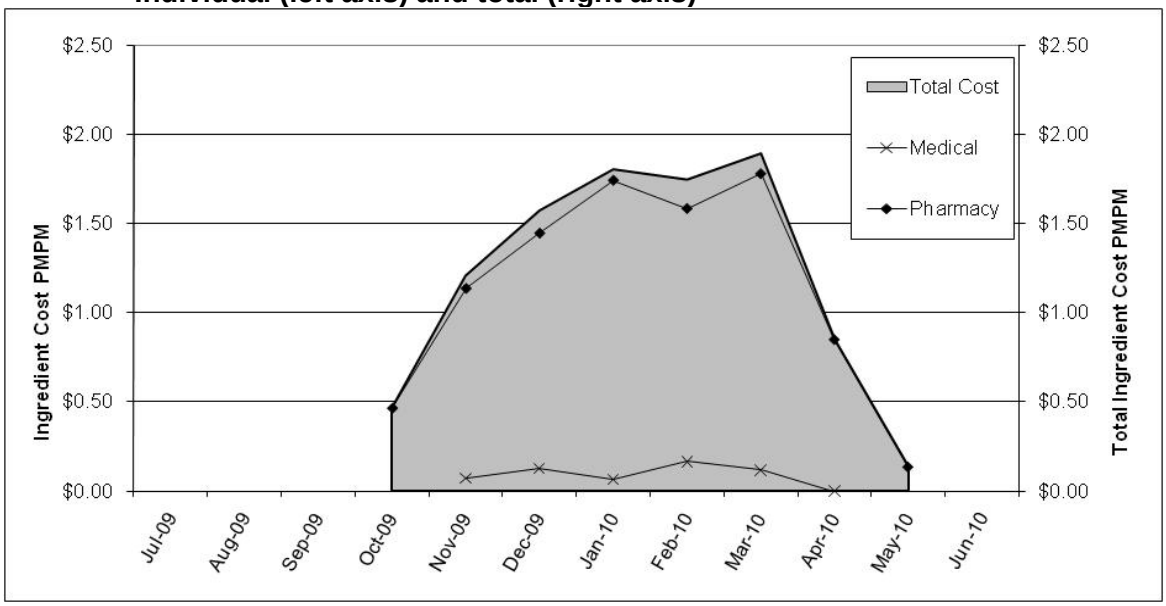


Figure 3: Palivizumab Costs (Ingredient cost PMPM)
Individual (left axis) and total (right axis)



There were 88 unique patients prescribed palivizumab during the study period (Table 1). Two patients were older than 24 months when palivizumab was initiated.

Table 1 – Palivizumab user demographics

Total	N=	88	(%)
Age in Months			
	Mean	9.8	Months
	Range	1-38	
	>24 mths	2	2.3%
	>12 and ≤ 24 mths	25	28.4%
	>6 and ≤ 12 mths	15	17.0%
	≤ 6 mths	46	52.3%
Female		41	46.6%
Race			
	White	62	70.5%
	Hispanic		0.0%
	American Indian	2	2.3%
	Black	2	2.3%
	Asian		0.0%
	Other	22	25.0%

Note: Age shown is age in months as of first Palivizumab claim

The pharmacy claims were evaluated for treatment length and depicted in Table 2. The average length of treatment was 86 days (range 28-196).

Table 2 – Treatment Length

Pharmacy Patients Only	N=79	%	Claim Count	Paid Amount
Unique Patient count for >=3 to <=5 months	24	30.4%	107	$286,634
Unique Patient count for > 5 months	10	12.7%	61	$167,644
Unique Patient count for < 3 months	45	57.0%	78	$165,520
Unique Patient count for claims before Nov 2009	14	17.7%	19	$33,420
Unique Patient count for claims after Apr 2010	4	5.1%	6	$8,997

Table 3 categorizes palivizumab users using the AAP guideline criteria where it is available from the claims data. Information is not available to categorize 46% of patients.

Table 3 – Patient counts for diagnostic categories

Age	ICD9 Description	ICD-9	N=88	%
	≤28 wks gestation	76521, 76522, 76523 or 76524	14	16%
	29 to ≤ 32 wks gestation	76525 or 76526	8	9%
	32 to 34 wks gestation	76527 or 76528	6	7%
<24 mths	CHD or CLD	746xx, 747xx or 748xx	19	22%
<12 mths	Neuromuscular Dx	358xx	0	0.0%

Conclusions:

Palivizumab is effective in reducing RSV-associated hospitalizations in a select population, yet is very costly. Timely use is important. Use beginning mid-season does not benefit high risk children and infants while continued use beyond the RSV season does not confer any benefit and is not cost-effective.[7]

The DUE documents use prior to and after the Oregon RSV season. There is also significant use of more than the recommended 5 doses. Additionally there are 2 patients outside the age recommendations for use.

Recommendations:

- **Require a prior authorization for use of palivizumab in compliance with AAP recommendations.**
- **Limit payment for palivizumab to pharmacy providers to eliminate the possibility of duplicate payment between pharmacy and medical providers.**

References:

1. FDA website http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm093366.htm.
2. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high risk infants. *Pediatrics.* 1998;102(3):531–537.
3. Feltes TF, Cabalka AK, Meissner HC, et al; Cardiac Synagis Study Group. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr.* 2003;143(4):532–540.
4. Synagis [package insert] Gaithersburg, MD: MedImmune, Inc.; 2009.
5. Modified Recommendations for Use of Palivizumab for Prevention of Respiratory Syncytial Virus Infections Committee on Infectious Diseases. Pediatrics 2009; 124; 1694-1701.
6. Centers for Disease Control and Prevention (CDC), National Center for Infectious Diseases, Respiratory and Enteric Viruses Branch. Respiratory Synctial Virus Regional Trends [website]. Atlanta, GA: CDC; http://www.cdc.gov/surveillance/nrevss/rsv/state.html. Accessed May 11, 2011.
7. Meissner HC, Anderson LJ, Pickering LK. Annual variation in respiratory syncytial virus season and d*ecisions re*garding immunoprophylaxis with palivizumab. *Pediatrics.*2004;114(4):1082–1084.

SYNAGIS (PALIVIZUMAB)

Goals:

- ***To promote and ensure use of palivizumab that is supported by the medical literature.***
- ***To eliminate any duplicate billing between pharmacy and medical providers***

OHP GUIDELINE NOTE 69, SYNAGIS
Line 3
CPT code 90378, Synagis (palivizumab), is covered for infants meeting one of the criteria given below (A-E), according to the treatment guidelines for each criterion:

A) Infants younger than 24 months who have congenital heart disease (CHD) or chronic lung disease of prematurity (CLD, formerly called bronchopulmonary dysplasia) AND require medical therapy
1) Therapy is initiated within 6 months before the start of the RSV season
2) Maximum 5 doses
B) Infants younger than 12 months with congenital abnormalities of the airway or neuromuscular disease
1) Maximum 5 doses
C) Had a gestation age of 28 weeks or less
1) Initiated during the RSV season before the infant reaches 12 months
2) Maximum 5 doses
D) Had a gestation age of 29 weeks and 0 days to 31 weeks and 6 days
1) Initiated during the RSV season before the infant reaches 6 months
2) Maximum 5 doses
E) Had a gestational age of 32 weeks 0 days to 34 weeks 6 days
1) Born within 3 months before the start of RSV season or at any time throughout the RSV season
2) Have at least 1 of these 2 risk factors
a) Infant attends child care; or
b) One or more siblings or other children younger than 5 years live permanently in the child's household.
3) Should receive prophylaxis only until they reach 90 days of age or ***a maximum of 3 doses*** *(whichever comes first).*

Synagis (palivizumab)

Length of Authorization: Based on individual factors; may extend up to 5 months (5 doses).

Approval Criteria

1. What is the diagnosis being treated?	**Record ICD9 code and reject/internal error code**	
2. Is the patient currently RSV negative?	**YES**: Go to 3	**NO:** Pass to RPH:**DENY** (Medical Appropriateness). Synagis is only FDA approved for prevention, not treatment for RSV.

3. Is the current age of the patient < 24 months?	**YES: Go to 4.**	**No: Pass to RPh, DENY.** (Medical Appropriateness). Synagis not recommended for patients ≥24 months old.
4. Does the patient have with CLD (chronic lung disease) ICD-9 7485x or 7486x **and** in the past 6 months has required medical treatment with at least one of the following; a. bronchodilators, b. chronic corticosteroid therapy, c. home oxygen therapy, d. diuretics?	**YES: Go to 11,** (Group a)**.**	**NO: Go to 5.**
5. Does the patient have hemodynamically significant congenital heart disease (CHD)ICD-9 746xx or 747xx **and** at least one of the following: **a.** Are receiving treatment for congestive heart failure, **or** **b.** Have moderate to severe pulmonary hypertension, **or** **c.** Have cyanotic heart disease	**YES: Go to 11,** (Group b)**.**	**NO: Go to 6.**
6. Is the current age ≤ 12 months?	**YES: Go to 7.**	**NO: Pass to RPh, Deny.** (Medical Appropriateness).
7. Is the gestational age ≤ 28 weeks.	**YES: Go to 11,** (Group c).	**NN: Go to 8.**
8. Is gestational age ≤ 34 weeks and 6 days with congenital abnormalities of the airway or neuromuscular disease compromising handling of secretions?	**YES: Go to 11,** (Group d).	**NO: Go to 9.**
9. Current age < 6 months and gestational age ≤ 29-31 weeks and 6 days.	**YES: Go to 11,** (Group e)**.**	**NO: Go to 10.**
10. Current age < 90 days AND gestational age ≤ 32-34 weeks and 6 days AND with at least one of the following risk factors: **a.** Daycare attendance **b.** Siblings less than 5 years of age	**YES: Go to 11,** (Group f)**.**	**NO**: **Pass to RPh, Deny** (Medical Appropriateness). ***May approve for the following on a case by case basis:*** · ***>5 doses or additional doses after March 31st.*** · ***Prophylaxis for a second/ subsequent RSV season***
11. What is the weight of the patient? _____ How many doses did the patient receive in the hospital? _____	Approve 15mg/kg and the number of doses according to Table 1	

Table 1. Maximum number of doses to approve for RSV prophylaxis based on diagnosis. For Preterm Infants, based on birth date, gestational age, and presence of risk factors

	Maximum number of doses for Season Beginning November		
Criteria Group (from above)	Group a-d	Group e	Group f
November 1 – March 31 of previous RSV season	**5**	Zero doses; infant will be older than 6 months at start of RSV season	Zero doses; infant will be older than 90 days at start of RSV season
April	**5**	Zero doses, infant will be older than 6 months at start of RSV season	
May	**5**	**5**	
June	**5**	**5**	
July	**5**	**5**	
August	**5**	**5**	**1***
September	**5**	**5**	2*
October	**5**	**5**	**3***
November	**5**	**5**	**3***
December	**4**	**4**	**3***
January	**3**	**3**	**3***
February	**2**	**2**	2*
March	**1**	**1**	**1***

*infant may require less doses than listed based on age at the time of discharge from the hospital

Notes:

- Dose: 15 mg/kg via intramuscular injection once monthly throughout the RSV season.
- The start date for Synagis is November 1 each year (or sooner if RSV is detected in the community) for a total of up to **five doses**.
- Approval for more than five doses or additional doses after March 31 is considered on a case-by-case basis. Results from clinical trials indicate that Synagis trough concentrations greater than 30 days after the 5th dose will be well above the protective concentration so 5 doses will provide more than 20 weeks of protection.

DUR Board Action: 05/17/11(DO/KK)
Revision(s):
Initiated:

Synagis (palivizumab)

Goal(s):

- Promote safe and effective use of Synagis.

Length of Authorization: Based on individual factors; may extend up to 5 months (5 doses).

<table>
<tr><th>Approval Criteria</th><th></th><th></th></tr>
<tr><td>1. What is the diagnosis being treated?</td><td colspan="2">Record ICD9 code and reject/internal error code</td></tr>
<tr><td>2. Is the request for immunoprophylaxis between the months of November and March?</td><td>Yes: Go to #4</td><td>No: Go to #3</td></tr>
<tr><td>3. Is the request for immunoprophylaxis starting in October due to an early onset* of the RSV season in the region from which the patient resides (see below)?

* Onset is defined as 2 consecutive weeks where % positive is ≥10% (data is provided by the Oregon's Weekly Respiratory Syncytial Virus Surveillance Report from the Oregon Public Health Division based on regions. Weekly updates are found at: https://public.health.oregon.gov/DiseasesConditions/DiseasesAZ/Pages/disease.aspx?did=40)

<table>
<tr><th>Region</th><th>Counties</th></tr>
<tr><td>NW Oregon- SW Washington</td><td>Benton, Clackamas, Clatsop, Columbia, Lane, Lincoln, Linn, Marion, Multnomah, Polk, Tillamook, Washington, Yamhill</td></tr>
<tr><td>Central Oregon</td><td>Crook, Deschutes, Grant, Harney, Jefferson, Wheeler</td></tr>
<tr><td>Columbia Gorge – NE Oregon</td><td>Baker,, Gilliam, Hood River, Morrow, Sherman, Umatilla, Union, Wasco, Wallowa</td></tr>
<tr><td>Southern Oregon</td><td>Coos, Curry, Douglas, Jackson, Josephine, Klamath, Lake, Malheur</td></tr>
</table>
</td><td>Yes: Go to #4</td><td>No: Pass to RPH: DENY (Medical Appropriateness). Prophylaxis is indicated only during high viral activity.</td></tr>
<tr><td>4. Is the current age of the patient < 24 months at start of RSV season?</td><td>Yes: Go to #5</td><td>No: Pass to RPH: DENY (Medical Appropriateness). Synagis not recommended for patients ≥24 months old.</td></tr>
<tr><td>5. <u>GROUP A</u>
Does the patient have the CLD (chronic lung disease) ICD9 7485x or 7486x <u>and</u> in the past 6 months has required medical treatment with at least one of the following:
a. bronchodilators
b. chronic corticosteroid therapy
c. home oxygen therapy
d. diuretics</td><td>Yes: Go to #12</td><td>No: Go to #6</td></tr>
<tr><td>6. <u>GROUP B</u>
Does the patient have hemodynamically significant congenital heart disease (CHD) ICD9 746xx or 747xx <u>and</u> at least one of the following:
a. Receiving treatment for congestive heart failure <u>or</u>
b. Have moderate to severe pulmonary hypertension <u>or</u>
c. Cyanotic heart disease</td><td>Yes: Go to #12</td><td>No: Go to #7</td></tr>
<tr><td>7. Will the patient be < 12 months at start of RSV season?</td><td>Yes: Go to #8</td><td>No: Pass to RPH:</td></tr>
</table>

		DENY (Medical Appropriateness).
8. GROUP C Is the gestational age ≤ 28 weeks?	**Yes:** Go to #12	**No:** Go to #9
9. GROUP D Infants with congenital abnormalities of the airway or neuromuscular disease compromising handling of secretions?	**Yes:** Go to #12	**No:** Go to #10
10. GROUP E Will the patient be < 6 months at the start of the RSV season and the gestational age ≤ 29-31 weeks and 6 days?	**Yes:** Go to #12	**No**: Go to #11
11. GROUP F Will the patient be < 90 days at the start of the RSV season AND have a gestational age of ≤ 32-34 weeks and 6 days AND have at least one of the following risk factors: a. Daycare attendance b. Siblings less than 5 years of age	**Yes:** Go to #12	**No:** Pass to RPH: DENY (Medical Appropriateness).
12. Is the request for more than 5 doses within the same RSV season or for dosing <28 days apart?	**Yes:** Pass to RPH: DENY (Medical Appropriateness). Prophylaxis is indicated for 5 months maximum and doses should be administered ≥28 days apart. **May approve for the following on a case by case basis:** **a. > 5 doses or additional doses after March 31st.** **b. Prophylaxis for a second/subsequent RSV season.**	**No:** Go to #13
13. Has the patient had a weight taken within the last 30 days?	**Yes:** Document weight and date and go to #14 Weight:_____ Date: _____	**No:** Pass to RPH: obtain recent weight so accurate dose can be calculated.

14. Approve palivizumab for a dose of 15mg/kg. Document number of doses received in hospital and total number approved according to **BIRTH DATE** and **GROUP** based on start of RSV season:

- Immunoprophylaxis between November - March refer to **Table 1**
- Immunoprophylaxis starting in October based on above (#3) refer to **Table 2**

Total number of doses approved for RSV season:_____

Number of doses received in the hospital:_____

Table 1. Maximum number of doses to approve for RSV prophylaxis (Based on Criteria Group from Above) – Beginning **NOVEMBER 1st**

MONTH OF BIRTH	GROUP A-D (Child is <24 or <12 mo. old at start of season)	GROUP E (Child is <6 mo. old at start of season)	GROUP F (Child is <3 mo. old at start of season)
November 1 – March 31 of previous RSV season	5	Zero doses; infant will be older than 6 months at start of RSV season	Zero doses; infant will be older than 90 days at start of RSV season
April	5	Zero doses; infant will be older than 6 months at start of RSV season	
May	5	5	
June	5	5	
July	5	5	
August	5	5	1*
September	5	5	2*
October	5	5	3*
November	5	5	3*
December	4	4	3*
January	3	3	3*
February	2	2	2*
March	1	1	1*

* Infant may require less doses than listed based on age at the time of discharge from the hospital. Subtract number of doses given in hospital from total number of approved doses.

Table 2. Maximum number of doses to approve for RSV prophylaxis (Based on Criteria Group from Above) – Beginning **OCTOBER 1-31**

MONTH OF BIRTH	GROUP A-D (Child is <24 or <12 mo. old at start of season)	GROUP E (Child is <6 mo. old at start of season)	GROUP F (Child is <3 mo. old at start of season)
November 1 – March 31 of previous RSV season	5	Zero doses; infant will be older than 6 months at start of RSV season	Zero doses; infant will be older than 90 days at start of RSV season
April	5	5	
May	5	5	
June	5	5	
July	5	5	1*
August	5	5	2*
September	5	5	3*
October	5	5	3*
November	5	5	3*
December	4	4	3*
January	3	3	3*
February	2	2	2*
March	1	1	1*

* Infant may require less doses than listed based on age at the time of discharge from the hospital. Subtract number of doses given in hospital from total number of approved doses.

Notes:

- Dose: 15 mg/kg via intramuscular injection once monthly throughout RSV season.
- The start date for Synagis is November 1 each year (or sooner when the Oregon Public Health Division has determined that RSV season onset has occurred) for a total of up to five doses.
- Approval for more than five doses or additional doses after March 31 is considered on a case-by-case basis. Results from clinical trials indicate that Synagis trough concentrations greater than 30 days after the 5th dose will be well above the protective concentration therefore five doses will provide more than 20 weeks of protection.

DUR Board Action: 05/17/11 (DO/KK), 5/24/12 (KS)
Revision(s): 3/30/12 (KS)
Initiated:

Asthma Controller Update

Month/Year of Review: May 2012 **End date of literature search:** April 2012
PDL Class: Asthma Controllers
Preferred Agents: Beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate (diskus and HFA), formoterol fumarate, mometasone furoate, montelukast sodium, salmeterol xinafoate, zafirlukast
Non-preferred Agents: Ciclesonide, triamcinolone acetonide, zileuton, arformoterol, formoterol fumarate/eformoterol, omalizumab, indacterol, mometasone/formoterol

Purpose of Review:
To update the evidence on efficacy and safety of available asthma controller medications since original evaluation presented March, 2010.

Previous Recommendations[1]:

1. Inhaled corticosteroids (ICS) are recommended for adults and children with persistent asthma. ICS are considered the most potent and effective long-term control treatment. ICS have been shown to reduce the symptoms of asthma severity, improve quality of life, improve lung function, prevent exacerbations, reduce healthcare utilization, and reduce the risk of death due to asthma.
2. Long-acting beta-agonists (LABA) are the preferred adjunctive therapy, when combined with an ICS, in adults and children with persistent asthma not controlled with an ICS alone. Systematic reviews and guidelines suggest the addition of LABA improve airway function, quality of life and reduce asthma symptoms and short-acting rescue inhaler use. New safety data recommends that equal consideration should be given to increasing the dose of ICS or adding a LABA in patients with uncontrolled persistent asthma. FDA labeling states that ICS/LABA combination products are indicated for patients not adequately controlled on other asthma controller medications.
3. Asthma controller medications that are alternatives, but not preferred options, for patients requiring step 2 care (persistent asthma) include: cromolyn sodium, nedocromil, montelukast, zafirlukast, zileuton and theophylline.
4. Anti-IgE therapy, i.e., omalizumab, is recommended for patients whom have a specific sensitivity to a relative allergen and require step 5 or 6 care (persistent asthma on high-dose ICS, LABA or montelukast +/- oral steroids).

Issues:

- Is there new evidence to suggest that there is a meaningful difference between asthma controller products (outcomes or safety) that would justify a change in current PDL management?

Summary of New Evidence:
In 2011 the Drug Effectiveness Review Project (DERP) released a new report on asthma controller medications comparative efficacy and safety.[2] ICS were found to be more effective or as effective as other asthma controller therapy and safer than LABA. LABA was found to be more effective when added to ICS compared to maintaining the same ICS dose or when adding a LTRA. The findings in the DERP are consistent with the FDA, suggesting that ICS might mitigate some of the safety risks associated with LABA treatment, however, ICS alone is still recommended as first line. There was insufficient evidence to suggest a difference between the LMs, except that zileuton is associated with changes in liver function tests. Efficacy data offers that there may be a modest benefit to adding a LM to ICS compared to maintaining the same dose of ICS.

Several Cochrane Reviews evaluated the efficacy and safety of asthma controllers.[3-11] Studies involving LABA found an increase risk of serious adverse events with imprecise date regarding asthma-related mortality. There is insufficient data to determine the role of ICS in mitigating the risk of LABA adverse events and the effects in children. Studies using ICS/LABA combinations found adverse events to be too infrequent to draw conclusions. In efficacy studies the addition of a LABA to ICS was more effective than maintaining or increasing the dose of ICS. However, in children the addition of a LABA didn't significantly reduce the need for systemic corticosteroids and there were no significant differences in exacerbations. Adding LABA was superior to ICS on improvements in lung function. LABA was also found to be superior to LTRAs in patients inadequately controlled on ICS.

Additional studies are being required by the Food and Drug Administration (FDA) to further define the risks of severe exacerbations and death with LABA. The studies will be analyzing the effect of adding LABA/ICS combination compared to ICS alone.[12]

Conclusions:
Available evidence suggests that ICS should be offered as first line agents for patients with persistent asthma. The addition of a LABA needs to be weighed against the possible risks and should be used for patients with uncontrolled symptoms despite ICS therapy. Other asthma controllers have a role in the treatment of persistent asthma but data on improved lung function and exacerbations is not as robust as for other therapies. Additional data on the safety of LABA, especially in children, is needed to help delineate the risks and benefits of treatment.

Recommendations
1. No significant new evidence is available to suggest changes in the PDL or currently available PA criteria for asthma controller medications.

Background
Long-term control medications are recommended by the National Heart Lung and Blood Institute (NHLBI) Guidelines for the Diagnosis and Management of Asthma Expert Panel Report 3 (EPR3) for the control of persistent asthma.[1] Inhaled corticosteroids are considered the most potent and effective long-term control treatment and have been documented to reduce asthma severity, improve quality of life, improve lung function, prevent exacerbations, reduce emergent health services utilization, and reduce the risk of death due to asthma. They have been shown to more effectively improve asthma control compared to any other single controller agent. Long-acting beta-agonists are recommended to be used in combination with ICS and as the preferred adjunctive therapy in those 12 years and older. However, safety issues concerning an increased risk of

severe asthma exacerbations and asthma-related death with LABA therapy has prompted the FDA to advise that equal consideration should be given to increasing the dose of ICS or adding a LABA for patients not adequately controlled on ICS alone. Other asthma controllers that are not preferred but are alternatives for patients with persistent asthma (step 2 care) include: cromolyn sodium, nedocromil, luekotriene modifiers [LM (montelukast, zafirlukast, and zileuton)] and methylxanthines (i.e., theophylline). Anti-IgE therapy, i.e., omalizumab, is recommended for patients whom have a specific sensitivity to a relative allergen and require step 5 or 6 care (persistent asthma on high-dose ICS, LABA or montelukast +/- oral steroids).

DERP Update[2]:

DERP looked the comparative efficacy and safety of inhaled corticosteroids (ICS), long-acting beta-2 agonists (LABAs), leukotriene modifiers (LM), anti-IgE therapy, combination products and tiotropium in individuals with persistent asthma.

ICS:

- The report found no notable differences between the different ICS products at equipotent doses on outcomes of controlling asthma symptoms, exacerbation prevention, reduction in the need for additional rescue medication and adverse events (moderate strength of evidence).
- There was high strength of evidence that ICS monotherapy offered a greater benefit than LM monotherapy.
- Evidence suggests that ICS and leukotriene receptor antagonists are safer than LABAs for use as monotherapy (high strength of evidence).
- Increasing the dose of ICS compared to adding a leukotriene receptor antagonists offered the same outcomes of efficacy and safety (moderate strength of evidence).

LABA:

- There was moderate strength of evidence (in children 12 and older, insufficient for <12) that there was no difference found between formoterol and salmeterol in symptom control, exacerbations, quality of life, or harms in patients not controlled on an ICS alone. There was also no difference found between budesonide/formoterol and fluticasone/salmeterol for efficacy or harms when administered as a combination in a single inhaler (moderate strength of evidence for 12 and over, insufficient for <12).
- Indirect evidence suggests that increased risk of asthma-related death may be isolated to patients not taking an ICS.
- No evidence was available to suggest using combination ICS/LABA treatment first-line compared to ICS alone.
- Study data suggests that the addition on a LABA offers greater efficacy than a higher dose of ICS (high strength of evidence for over 12, insufficient for <12) for poorly controlled persistent asthma.
- There was high strength of evidence that greater efficacy was noted when a LABA was added compared to maintaining the same dose of ICS in patients with poorly controlled persistent asthma.
- There was high strength of evidence (over 12 years old) to support the addition of a LABA to ICS compared to adding a LTRA to ICS with similar adverse events (low strength of evidence for <12).

LM:

- There was low strength of evidence that there is no difference between montelukast and zafirlukast in decreasing rescue medication use and quality of life (insufficient evidence in <12).
- There was low strength of evidence that adding LM to an ICS improved rescue medication use compared to maintaining the same dose of ICS.
- Zilueton was found to be more harmful than the other LM, requiring liver function monitoring.

Anti-IgE Therapy:

- Omalizumab was found to be more effective than placebo for most outcomes, however, it was associated with an increased number of injection site reactions and anaphylaxis.

Conclusion:

- No medication within each class was found to be more effective or harmful compared to medication within that same class.
- ICS was recommended as the initial agent for those with persistent asthma.
- The addition of a LABA is recommended for patients with poorly controlled persistent asthma already on an ICS.

<u>Cochrane Reviews:</u>

A 2011 Cochrane review looked at serious adverse events associated with salmeterol treatment[3]. Thirty-four trials were included comparing salmeterol to placebo and salbutamol. An increased risk of serious adverse events was found in studies comparing salmeterol to placebo. An increase in risk of asthma-related mortality in patients not on an ICS was found in data from two large surveillance studies. Data on asthma-related mortality in patients taking an ICS was imprecise, so no conclusion could be drawn on the ability of ICS to eliminate the increased risk associated with salmeterol. There was insufficient evidence to determine the safety effects of salmeterol in children. A similar review analyzed twenty two studies on serious adverse events in persons treated with formoterol with or without ICS. Serious adverse events were more common in formoterol groups compared to placebo but not when formoterol was compared to salbutamol or terbutaline. Data used in the analysis from the FDA suggests that serious adverse events were not mitigated fully by ICS.[4]

Another Cochrane Review found adverse events to be too infrequent to draw safety conclusions on salmeterol and formoterol treatment (on background ICS therapy) based on four open-label studies.[5] A Cochrane Review of the combination products, salmeterol/fluticasone and formoterol/budesonide, reported asthma-related adverse events occurred infrequently and there were no asthma-related deaths. Adverse event rates were similar between the treatments.[6]

Four Cochrane Reviews examined the effect of adding a LABA to ICS in various scenarios in adults and children with asthma. The addition of LABA to ICS as a first line treatment in patients whom had persistent asthma and were steroid-naïve compared to ICS alone, resulted in no significant difference in the need for oral steroid treatment for exacerbations between the two therapies. However, the LABA and ICS combination resulted in improvements in FEV1, symptoms and reduced rescue beta2-agoinst use compared to ICS with similar rates of adverse events. In a second comparison the LABA/ICS combination was associated with a greater risk for needing oral steroids compared to ICS alone.[7] An other review looked at adding a LABA to ICS compared to continuing the same dose of ICS in adults and children. The addition of LABA to ICS was found to reduce the

need for oral steroid therapy, improve FEV1, and slightly decrease the need for rescue beta2-agonists. The differences in serious adverse events were similar between groups.[8] An updated review from 2008 analyzed the addition of a LABA to ICS compared to a higher dose of ICS in adults and children with moderate persistent asthma. Unlike the previous review, this review found that the addition of a LABA to ICS was more effective in reducing the risk of exacerbations in adolescents and adults as well as improving lung function, symptoms, beta2-agonist rescue use and less withdrawals due to poor asthma control. In children the addition of a LABA to ICS was associated with a greater risk of exacerbations requiring oral steroids compared to an increased dose of ICS.[9] An additional review looked just at children and the effect of adding LABA to ICS compared with the same or increased dose of ICS. Adding a LABA to ICS did not significantly reduce the need for systemic corticosteroids but was superior to maintaining the ICS dose on improving lung function. When a higher ICS dose was used there was no significant difference found in exacerbations compared to adding a LABA to ICS.[10]

A Cochrane review of 17 randomized, controlled trials in patients with chronic asthma compared the addition of a LABA versus anti-leukotrienes (LTRA) to ICS therapy. The addition of LABA to ICS resulted in a lower number of patients requiring oral steroids compared to the addition of a LTRA with a number needed to treat (NNT) of 38 (95% CI 22 to 244) to prevent one exacerbation over 48 weeks by adding a LABA compared to a LTRA. The addition of a LABA was found to be associated with more severe adverse events compared to LTRAs (RR 1.35, 95% CI 1.00 to 1.82). Overall, the addition of a LABA was superior to LTRAs in patients inadequately controlled on ICS, however, there was insufficient evidence in children to make a recommendation.[11]

<u>FDA Warnings[12]:</u>

LABA:

- 4/2011: The FDA is requiring the manufacturers of LABAs to conduct five randomized, double-blind, controlled clinical trials comparing the addition of LABAs to ICS versus ICS alone. The recommendation is to further evaluate the safety of LABAs. Four trial will be conducted in persons with asthma 12 and older and one trial in pediatric patients 4-11 years old. Results are expected in 2017.
- 6/2010: The FDA requires updated recommendations for using LABA to be added to drug labels. Labels must warn patients of increased risk of severe exacerbations of asthma symptoms and possibly death.
- New recommendations state:
    - Use of LABA alone or without use of long-term asthma control medication, such as an ICS, is <u>contraindicated</u> (absolutely advised against) in the treatment of asthma.
    - LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose ICS.
    - LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as inhaled corticosteroid.
    - Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with long-term asthma control medication, such as an inhaled corticosteroid.
    - Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an ICS and a LABA, to ensure adherence with both medications.

Other Literature:

- Salpeter provided an updated analysis on the safety of long-acting beta-agonists in patients using ICS. A previous meta-analysis by Salpeter found LABA was associated with an increased risk of exacerbations requiring hospitalizations and an increase in life-threatening exacerbations. In this recent analysis of pooled trial data , catastrophic asthma events (asthma-related intubation or death) were increased four times the amount with LABA and ICS compared to ICS alone (OR 3.7, 95% CI 1.4 to 9.6).[12]

Appendix 1
CURRENT PA CRITERIA

Asthma Controller Drugs

Goal(s):

- *The purpose of this prior authorization policy is to ensure that non-preferred asthma controller drugs are used for an above the line indication.*

Iniative: Asthma Controller PDL

Length of Authorization: up to 12 months

Requires PA :

- Non-preferred drugs

Covered alternatives:
See PDL list at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Is the requested drug montelukast (Singulair®)?	Yes: Go to Leukotriene Inhibitor Criteria	No: Go to #2
2. What is the diagnosis being treated?	Record ICD-9 Code	
3. Is this an OHP covered diagnosis?	Yes: Go to #4	NO: PASS TO RPH DENY (not covered by OHP)
4.Is this a continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims.	Yes: Document prior therapy in PA record. Approve for 1 year.	No: Go to #5
5. Will the provider consider a change to a preferred product? Message: - Preferred products do not require a PA - Preferred products are evidence-based reviewed for comparative	Yes: Inform provider of covered alternatives	No: Approve for 1 year or length of prescription, whichever is less.

effectiveness and safety by the Health Resources Commission (HRC).		

LABA/ICS Inhalers

Goal(s):

- *Approve LABA/ICS only for covered diagnosis (e.g. COPD or Asthma and on concurrent controller medication)*
- *LABA are only indicated for use in clients with Asthma already receiving treatment with an asthma controller medication (e.g. Inhaled corticosteroids or leukotriene receptor antagonists).*
- *Promote use that is consistent with Oregon Asthma Guidelines and medical evidence. http://www.oregon.gov/DHS/ph/asthma/pubs.shtml#oregon*

Iniative: LABA/ICS Step Therapy

Length of Authorization: 6 months - 1 year

Covered alternatives that DO NOT require a PA:
See PDL list at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Step Therapy Required prior to coverage:

Asthma: oral corticosteroid inhalers (see preferred drug list options at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml),

COPD: short and long-acting beta-agonist inhalers, anticholinergics (Atrovent, Combivent), inhaled corticosteroids (see preferred drug list options at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml), and theophylline DO NOT require prior authorization.

Requires PA: Advair diskus and Advair HFA (fluticasone/salmeterol) HICL= 19963, Symbicort (budesonide/formoterol) HICL= 21993, Dulera (mometasone/formoterol) HICL = 37050

Approval Criteria		
3. Does patient have asthma or reactive airway disease (ICD-9: 493, 493.0-493.93)?	**Yes:** Go to **2**	**No:** Go to **3**
4. Has patient: • failed an inhaled corticosteroid or other controller medication OR • Is there documentation of step 3 or 4 asthma OR • Is there a hospital admission or ER visit related to asthma or reactive airway	**Yes**: Document the following: Date of trial, drug, reason(s) for failure or contraindications OR chart notes of asthma severity in the PA record	**No**: **PASS TO RPH DENY (Medical Appropriateness).** *Oregon Asthma guidelines*

disease within last 60 days?	Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy and patient is well controlled on current dose.	*recommend combination inhaled corticosteroids plus LABA after failure of low or medium dose ICS.* *http://www.oregon.gov/DHS/ph/asthma/pubs.shtml#Oregon_Guiding_Documents_for_Asthma*
3. Does patient have COPD (ICD-9 496) or Chronic bronchitis (491.1-2.)?	**Yes:** Go to **4**	**NO: PASS TO RPH DENY (Medical Appropriateness).** *Need a supporting diagnosis. If prescriber believes diagnosis appropriate inform them of the provider reconsideration process for Medical Director Review.*
4. Has patient failed a combination of **short acting** (ipratroprium or ipratroprium/albuterol) **and long-acting** (salmeterol, formoterol and/or tioptropium) inhaled bronchodilators?	**Yes:** Document the following: Date of trial, drug, reason(s) for failure or contraindications in the PA record**.** Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy and patient is well controlled on current dose.	(**No:** Pass to RPH; Deny, (Medical Appropriateness). *Gold guidelines recommend addition of inhaled corticosteroid if disease severity persistent despite use of combination of short acting and long-acting bronchodilators.* *http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf*

Leukotriene Inhibitors

Goals:

- Approve motelukast only for covered diagnosis.
- Allergic rhinitis treatment is covered by the OHP only when complicated by other diagnoses (e.g. asthma, sleep apnea).
- Promote use that is consistent with Oregon Asthma Guidelines and medical evidence**.**

Length of Authorization: 6 months or 2 years (diagnosis specific)

Covered Alternatives:

- Preferred alternatives listed at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml
- Allergic Rhinitis: cetirizine, chlorpheniramine, diphenhydramine, loratidine, and hydroxyzine DO NOT require prior authorization.

- Asthma: Oral corticosteroid inhalers and zafirlukast (Accolate®) DO NOT require a prior authorization.

Requires PA:

- Non-preferred drugs
- Montelukast (Singulair ®)

Approval Criteria		
1. What is the diagnosis being treated?	Record ICD-9	
2. Does the client have asthma or reactive airway disease (ICD-9:493.xx)?	Yes: Approve for 2 years	No: Go to #3
3. Does the client have a diagnosis of allergic rhinitis, allergic conjunctivitis, or chronic rhinitis/pharyngitis/nasopharngitis? (ICD-9: 472.xx, 372.01-05, 372.14, 372.54, 372.56, 477.xx, 995.3, Vo7.1)	Yes: Go to #4	No: Go to #6
4. Does the client have other co-morbid conditions or complications that are above the line? - Acute or chronic inflammation of the orbit (376.0-376.12) - Chronic sinusitis (473.xx) - Acute sinusitis (461.xx) - Sleep apnea (327.20, 327.21, 327.23-327.29, 780.51, 780.53, 780.57) - Wegener's Granulomatosis (ICD-9: 446.4)	Yes: Go to #5	No:Pass to RPH; Deny (Not covered by the OHP)
5. Does the client have contraindications (e.g.pregnant) or had insufficient response to at least 2 alternatives? Document	Yes: Approve for 6 months	No: Pass to RHP; Deny (Cost-Effectiveness)
6. Is the diagnosis COPD (496) or Obstructive Chronic Bronchitis? (491.1-491.2)	Yes: Pass to RPH; Deny (Medical appropriateness, leukotrienes not indicated)	No: Pass to RPH; Go to #7
7. Is the diagnosis Chronic Bronchitis? (491.0, 491.8, 491.9)	Yes: Pass to RPH; Deny (Not covered by OHP) Message: "The treatment for you condition is not a covered service on the Oregon Health Plan"	No: Pass to RPH, Go to #8
8. RPH only: Is the diagnosis above the line or below the line?	Above: Deny with yesterday's date (medically appropriateness) Use clinical judgment to approve for 1 month starting today to allow for time to appeal.	Below: Deny, (Not covered by the OHP) Message: "The treatment for you condition is not a covered service on the Oregon Health Plan" (e.g. URI-465.9 or uticaria -708.0, 708.1, 708.5, 708.8, 995.7 should be denied)

	Message: “Although the request has been denied for long term use because it is considered medically inappropriate, it has also been approved for one month to allow time to appeal.”	

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Month/Year of Review: May 2012
Generic Name: clobazam
PDL Class: Oral Anticonvulsants

End date of literature search: April 2012
Brand Name (Manufacturer): Onfi™
Dossier Received: Yes

FDA Approved Indications: Clobazam is a benzodiazepine indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older.[1]

Background: LGS is an epilepsy syndrome characterized by multiple seizure types, cognitive impairment, and specific electroencephalogram (EEG) features.[2,3] Age of onset is most commonly between 3 and 10 years, with commonly a history of infantile spasms. Long-term prognosis for both neurocognitive outcomes and seizure control is poor. It is a rare syndrome and requires input from specialists with expertise in the area. Recent updated guidelines from the National Institute for Clinical Excellence (NICE) identify seizure freedom, at least 50% reduction in seizure frequency, and withdrawals due to adverse events to be the most important outcomes in evaluating LGS.[2] The NICE guidance recommends sodium valproate as first-line treatment to children with LGS. This recommendation however is based on extrapolated evidence from idiopathic generalized epilepsy and consensus guidelines. There is limited comparative evidence evaluating treatment in LGS. Lamotrigine is recommended as adjunctive treatment if sodium valproate is ineffective or not tolerated (based on two low quality placebo controlled trials demonstrating lamotrigine to be more effective in reducing at least 50% the seizure frequency). If adjunctive treatment is ineffective, the NICE guidance recommends that rufinamide and topiramate may be considered by a specialist if adjunctive treatment is ineffective (based on low quality evidence).[2] Felbamate is recommended as last line therapy after all other therapy has shown to be ineffective or not tolerated. Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, and vigabatrin should not be offered for LGS because clinical practice suggests seizures can be aggravated by these medications.[2,3]

Clobazam was FDA approved in the United States in 2011 based on data from two multicenter studies.[4,5] As clobazam is indicated to treat a disease or condition that affects fewer than 200,000 people in the United States, it was granted orphan drug designation by the FDA. This is the sixth medication approved for LGS in the United States. It is a 1,5 benzodiazepine (the only representative of that class in clinical use today) and is a federally controlled schedule four substance (C-IV).[6] Clobazam has also been studied off-label in patients with partial epilepsy and as monotherapy for childhood epilepsy.[6]

Conclusions:
Head to head comparative evidence is lacking for the treatment of LGS and optimal medical therapy is uncertain. Valproate may be first-line treatment based on NICE guidance and consensus guidelines. Antiepileptic drugs (AEDs) approved as adjunctive therapy for LGS include lamotrigine, topiramate, rufinamide, felbamate, and now clobazam. There is low to moderate quality evidence that adjunctive therapy with clobazam may reduce drop seizures in patients with LGS.

Recommendations:
LGS is one of the intractable epilepsies and seizures tend not to respond to most AEDs. Recommend adding clobazam to the oral anticonvulsant PDL class with no restrictions for use.

Clinical Efficacy:
Clobazam was evaluated in one phase II dose ranging study and one fair quality fair phase III efficacy study.[4, 5] Details of these are included in the evidence table below. The pivotal phase III trial (COMTAN)[5] was a fair quality study evaluating the efficacy and safety of three doses of clobazam (0.25-, 0.5-, and 1.0-mg/kg/day) compared to placebo as adjunctive therapy for LGS. Approximately 50% of all patients were receiving concomitant valproate. All of treatment arms, 0.25-, 0.5-, and 1.0-mg/kg/day, had a significantly greater decrease in average weekly rate of drop seizures from baseline compared to placebo. Mean differences from the placebo group were 29.1%, 37.3%, and 56.1% for the low-, medium-, and high-dosage groups with a linear trend ($p<0.0001$) of increasing efficacy with increasing dosage. The effect on nondrop seizures was not significant. Responder rates increased with increasing clobazam dosages and there was a statistically significant increase over placebo in the 0.5- ($p=0.0159$, OR 2.8; 95% CI 1.2 to 6.5) and 1.0mg/kg/day ($p<0.0001$, OR 7.5; 95% CI 3.0 to 18.5). An overall attrition rate of 25.6% occurred in the trial (30.5% in placebo group vs. 13.8%, 27.4%, and 30.5% in the 0.25-, 0.5-, and 1.0 mg/kg/day groups, respectively). 21 participants were excluded from the intention to treat population for primary efficacy analysis who did not have ≥ 1 daily seizure measurement during the maintenance period. There was also a potentially relevant difference in baseline mean average weekly drop seizure rate between the groups, potentially causing a less severe group of patients in the 0.5 mg/kg/day group compared to the others.

A second phase II, dose-ranging study compared a total of 68 patients on either high dose clobazam (target dose of 1mg/kg/day) or low dose clobazam (target dose 0.25 mg/kg/day). At baseline, patients were on stable doses of 1-3 AEDs and had at least 2 drop seizures per week. From baseline to maintenance, the percentage change in drop seizures was significant in both the low-dosage (12 ± 122%, $p = 0.0162$) and high-dosage groups (85 ± 16.8%, $p < 0.0001$). The reduction was also significantly greater in the high dosage group when compared with the low-dosage group. Responder rate was significantly greater in the high dosage group versus the low dosage group (83% vs. 38%, $p=0.0001$; 0.46; 95% CI (0.3 to 0.7). However, this trial included some potentially fatal flaws in design and results should be interpreted with caution. It was unclear if appropriate methods for generation of randomization sequence and allocation concealment were used, an unblinded physician adjusted the dose during the taper period, and there was a lack of specific information to compare baseline characteristics of participants.

Adverse events occurred with >10% difference between placebo and clobazam were somnolence, pyrexia, lethargy, drooling, and constipation Somnolence and drooling increased in frequency with increasing dosage. There was also a dosage-related trend observed for the overall incidence of adverse events (AEs) leading to discontinuation with a statistically significant difference between the high dose clobazam group compared to placebo (20.3% vs. 3.4%, p=0.005; RR 6.0, 95% CI 1.4 to 38.4). Nine patients had pneumonia reported as a serious adverse event during the trial The authors further detailed that 4 of these patients had either a history of gastroesophageal reflux disease or G-tube placements. Currently an open label extension is underway to further assess the long-term safety of clobazam in patients with LGS.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:
1) Seizure Freedom
2) Proportion of participants experiencing at least a 50% reduction in seizure frequency (responders)
4) Withdrawals due to adverse effects

Primary Study Endpoint:
1) Percent decrease in average weekly rate of drop seizures from the 4-week baseline period to the maintenance period vs. placebo (CONTAIN)
2) Percent reduction in drop seizures rate within each treatment group (phase II study).

Ref./ Study Design	Drug Regimens	Patient Population	N	Duration	Efficacy Results	ARR / NNT[ch]	Safety Results (CI, p-values)	ARI / NNH	Quality Rating; Comments
CONTAIN									Quality Rating: Fair;
Ng, et al., [5]DB, PC	T: clobazam 0.25 mg/kg/day T2: clobazam 0.5 mg/kg/day T3: clobazam 1.0 mg/kg/day C: Placebo	Mean Age: 12.4 yrs Range (2-54) Male: 60.5% White: 61.8% currently on ≥ 1 AED's Exclusion criteria: receiving felbamate, unstable hepatic, renal, CV, pulmonary or GI disease, h/o of poor compliance	N=305 Randomized =238 mITT =217 T: 58 T2: 62 T3: 59 C: 59	Outcome assessed @ 15 weeks Trial consisted Of 4 wk baseline phase + 3 wk dose titration phase + 12 weeks maintenance phase	<u>% decrease in mean weekly drop seizure rates:</u> T: -41.2% T2: -49.4% T3: -68.3% C: -12.1% P=0.0120, T v C P=0.0015, T2 v C P<0.0001, T3 v C <u>Responder rates:</u> T: 23 (43.4%) T2: 34 (58.6%) T3: 38 (77.6%) C: 18 (31.6%) P=0.735, T v C OR 0.68; 95% CI (0.3-1.3) P=0.0159, T2 v C OR 0.36; 95% CI (0.16-0.8) P<0.0001, T3 v C OR 0.24; 95% CI (0.1-0.56) <u>Patients who were seizure free</u> T: 5 (7.5%) T2: 7 (12.1%) T3: 12 (24.5%) C: 2 (3.5%) P=0.24, T v C OR 0.37; 95% CI (0.048-2.3) P=0.1, T2 v C OR 0.0.28; 95% CI (0.038-1.5) P=0.005, T3 v C OR 0.14; 95% CI (0.02-0.7)	NA T v C ; NS T2 v C ARR: 27% NNT: 4 T3 v C ARR: 46% NNT: 3 NS	<u>Withdrawals due to Adverse events:</u> T: 4 (6.9%) T2: 8 (12.9%) T3: 13 (20.3%) C: 2 (3.4%) P = NS; T v C and T2 v C P=0.005; T3 v C RR: 6.0; 95% CI (1.3 -38.4)	T v C; NS T1 v C; NS T2 v C: ARI 16.9% NNH: 6	**Internal Validity:** <u>Selection- Central</u> randomization throu interactive voice response system. Stu protocol revised after 81 patients enro due to many premature discontinuatio and entry into the open label extensio <u>Performance</u>- matching placebo tablet used to account for blinding <u>Detection</u> – unclear blinding of evaluat <u>Attrition</u> - Overall attrition rate of 25.6 21 participants (8.8%) initially randomi not included in mITT population and analysis and almost half of them (n=10 were excluded from the high dose clobazam group **External Validity:** Recruitment – not reported Patient Characteristics –Baseline mean average weekly drop seizure rate overa was 86.6, but differed between groups (only 58.8 in clobazam 0.5mg/kg/, and in 0.25mg/kg/day group
Phase II, Dose Ranging									

Conry, et al.[4] Phase II, dose rating study	T1: clobazam 0.25 mg/kg/day T2: clobazam 1.0 mg/kg/day	Median Age: 7.4 yrs LGS on 1-3 AEDs at least 2 drop seizures per week Exclusion criteria: status epilepticus within 12 weeks, progressive neurologic disease	N=68 mITT =61 T: 32 T2: 36	Outcomes assessed @ 7 weeks Trial consiste Of 4 wk baseline phase + 3 wk dose titration phase + 4 weeks maintenance phase	<u>% decrease in average weekly drop seizure rates:</u> *Low-dose* T1: 12%±122% P=0.0162 *High -dose* T2: 85 ± 16.8% P<0.0001 *High-dose vs. Low-dose* T2>T1; p=0.0001 <u>Responder rates:</u> T1: 12 (38%) T2: 30 (83%) High dose vs. low dose, P=0.0001 RR 0.46; 95% CI (0.3 to 0.7) <u>Patients who were seizure free</u> T1: 2(6%) T2: 8 (22%) P=0.0629 RR 0.28; 95% CI (0.042 to 1.3)	NA ARR 45% NNT 2.2 NS	<u>Withdrawals due to Adverse events:</u> T1: 3 (10%) T2: 6(19%) P=NS RR 1.8; 95% CI (0.4 to 8.6	NS	Quality Rating: Poor **Internal Validity:** <u>Selection-</u> Unclear on randomization generation sequence. Unclear if appropriate meth for allocation concealment <u>Performance</u>- An unblinded physician adjusted the patient's dose during the taper period <u>Detection</u> – unclear blinding of evaluat <u>Attrition</u> - Efficacy analysis used a mod intent-to-treat population, which exclu 7 patients from efficacy analysis (10%) Total attrition rates: 15% ○ T1: 4 (12.5%) ○ T2: 6 (16.7%) **External Validity:** Recruitment – not reported Patient Characteristics – Baseline characteristic data not provided, media age of 7.4 years appropriate

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

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2. National Institute for Health and Clinical Excellence (NICE). National Clinical Guideline Centre. Pharmacological Update of Clinical Guideline 20. The diagnosis and management of the epilespsies in adults and children in primary and secondary care. 2012.

3. Lennox-Gastaut syndrome. In DynaMed [database online]. EBSCO publishing. 2012. Available at: http://search.ebscohost.com.liboff.ohsu.edu/login.aspx?direct=true&site=DynaMed&id=113862.

4. Conry JA, Ng Y-T, Paolicchi JM, et al. Clobazam in the treatment of Lennox-Gastaut syndrome. *Epilepsia*. 2009;50(5):1158–1166.

5. Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. *Neurology*. 2011;77(15):1473–1481.

6. Onfi Dossier. Evidentiary Submission for Formulary Consideration of Onfi (clobazam) Tablets. Lundbeck Inc.

Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY[1]

Clobazam is a long-acting 1,5-benzodiazepine, the only representative of that class in clinical use today. The exact mechanism of action for clobazam, a 1,5-benzodiazepine, is not fully understood but is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the GABAA receptor.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	100%
Protein Binding	80-90%
Elimination	11% in feces and 82% urine
Half-Life	36-42 hours
Metabolism	Liver; primarily CYP3A4

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Clobazam 5mg, 10mg, or 20mg	Oral	Twice daily (the 5 mg dose can be administered as a single daily dose)	≤30kg: initiate at 5 mg daily and titrate as tolerated up to 20 mg daily >30kg: initiate at 10 mg daily and titrate as tolerated up to 40 mg daily	No dose adjustment is required for patients with mild and moderate renal impairment.	There are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of clobazam. Dosing titration should proceed slowly.	Approved for ≥2 y/o	Starting dose 5 mg/day. Titrated to half the normal dose, as tolerated.	• Reduce dose, or discontinue drug, gradually. • Tablets can be administered whole, crushed and mixed in applesauce. • Dose escalation should not proceed more rapidly than weekly, because serum concentrations of clobazam a its active metabolite require 5 and 9 days, respectively, to reach steady-state.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications): None

Warnings and Precautions:

Somnolence or Sedation: Clobazam causes somnolence and sedation. In clinical trials, somnolence or sedation were reported at all effective doses and were dose-related. In general, somnolence and sedation begin within the first month of treatment and may diminish with continued treatment. Prescribers should monitor patients for somnolence and sedation, particularly with concomitant use of other central nervous system depressants. Prescribers should caution patients against engaging in hazardous activities requiring mental alertness, such as operating dangerous machinery or motor vehicles.

Withdrawal: Abrupt discontinuation of clobazam should be avoided. Clobazam should be tapered by decreasing the dose every week by 5-10 mg/day until discontinuation. The risk of withdrawal symptoms is greater with higher doses. Withdrawal symptoms (e.g., convulsions, psychosis, hallucinations, behavioral disorder, tremor, and anxiety) have been reported following abrupt discontinuance of benzodiazepines.

Physical and Psychological Dependence: Patients with a history of substance abuse should be under careful surveillance.

Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs), including clobazam, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Look-alike / Sound-alike (LA/SA) Error Risk Potential: Clobazam may be confused with clonazePAM.

Abbreviated Update: Oral Anticonvulsants
New Drug: ezogabine (Potiga)

Month/Year of Review: May 2012
Current PDL Class: Oral Anticonvulsants
New drugs: ezogabine (Potiga™) **Manufacturer:** GlaxoSmithKline

Current Preferred Agents:			Current Non-Preferred Agents:
Carbamazepine	Lamotrigine	Rufinamide (Banzel)	Felbamate (Felbatol)
Carbamazepine ER (Tegretol XR)	Levetiracetam	Tiagabine (Gabitril)	Pregabalin (Lyrica)
Clonazepam	Methobarbital (Mebaral)	Topiramate	Vigabatrin (Sabril)
Diastat (Brand only)	Methosuximide (Cleontin)	Valproic Acid	
Divalproex	Oxcarbazepine	Zonisamide	
Ethosuximide	Phenobarbital	Gabapentin	
Ethotoin (Peganone)	Phenytoin	Lacosamide (Vimpat)	
Primidone			

Previous HRC Conclusions (April 2010):

- Evidence does not support a difference in efficacy/effectiveness (Grade B).
- Evidence does not support a difference in harms/adverse events (Grade B).
- Felbamate is not indicated as first line antiepileptic
- Vigabatrin is the only agent indicated for treatment of infantile spasm
- Consideration of "Grandfather" the chemical entity for epilepsy diagnoses.
- Consider inclusion of all agents for epilepsy diagnoses
- Consider PA criteria/quantity limit for diazepam rectal gel
- Consider PA vigabatrin for appropriate populations.

Reason for Review:
In September 2010, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the oral anticonvulsants. A December 2009 Provider Synergies Review[1] was used as the evidence source. Since this review, a new drug has been approved by the FDA as adjunctive treatment of partial-onset seizures in patients aged 18 years and older (ezogabine).[2] Ezogabine is the first potassium channel opener antiepileptic drug (AED) approved by the FDA. In addition, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review evaluating the effectiveness and safety of antiepileptic medications in patients with epilepsy.[3] The National Institute for Health and Clinical Excellence (NICE) published a pharmacological update of clinical guideline 20 regarding the management of epilepsies in adults and children in primary and secondary care.[4, 5] Therefore, this review will focus on the use of oral anticonvulsants in the treatment of epilepsy.

Research Questions:
- Is there any new relative evidence from high quality systematic reviews or evidence based guidelines suggesting recommended changes to our current management of the PDL class?
- Is ezogabine more effective than currently available agents?
- Is ezogabine safer than currently available agents?
- Are there unique patients or situations where ezogabine may be more effective or safer than currently available agents?

Conclusions:
- There is moderate quality evidence that ezogabine improves response rate in patients with epilepsy when used as adjunct treatment after previous treatment with 1-3 AEDs has not provided adequate response.
- There is insufficient evidence to evaluate efficacy of ezogabine in the outcome of freedom from seizures.
- There is insufficient evidence to make comparative conclusions with other adjunctive treatments for epilepsy.
- Updated NICE guidelines recommend carbamazepine or lamotrigine as first line agents for focal seizures (moderate to very low quality evidence) and sodium valproate as first line treatment for tonic-clonic seizures (low to very low quality evidence).
- Based on a recent AHRQ review, there in insufficient to low strength of evidence suggesting that switching from an innovator to a generic, generic to generic, or generic to innovator version of the same medication increases the short-term risk of hospitalization and hospital stay duration and increases the short-term risk of a composite of having an emergency department and hospitalization visit with or without ambulance service utilization.

Recommendations:
- Make ezogabine a second line non-preferred oral anticonvulsant to ensure appropriate use; in patients 18 years and older as adjunct treatment when previous treatment with other AEDs has not provided adequate response or has not been tolerated.
- Continue to prefer generic alternatives where appropriate.

Background:
Epilepsy is a common neurological disorder characterized by recurring epileptic seizures. Antiepileptic drugs (AEDs) to prevent recurrence of seizures are the mainstay of treatment.[5] There are between 16 and 51 cases of new-onset epilepsy per 100,000 people every year and over a lifetime, approximately 10 percent of people in the United States will suffer a seizure.[6,3] The three main types of seizures in patients include partial, generalized, and unclassified. The overall goals of antiepileptic therapy are to prevent seizures and avoid unnecessary side effects with a drug regimen that is relatively convenient.[3] People usually begin treatment with one medication, but many will become refractory to this medication. It is estimated that up to 22.5% of patients have drug-resistant epilepsy.[6] Selecting an effective drug with the least potential for side effects is a critical decision for clinicians. Since 1993, the FDA has approved several newer AEDs and it has been a continued interest to compare the effectiveness and safety of the newer AEDs to the older AEDs. Another concern in the management of epilepsy is the continued controversy surrounding the practice of generic substitution of innovator AEDs.[3] Seizure freedom is commonly the most important outcome and goal of treatment, although reduction in seizure frequency of 50% or more is generally accepted as demonstrating efficacy for FDA approval.[4,6] When initial drugs have failed and adjunctive treatment is used seizure reduction is likely to be the primary aim.

Methods:
A Medline literature search ending April 2012 for new systematic reviews and randomized controlled trials (RCT's) comparing medications head-to-head in the treatment of epilepsy was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Guidelines:
NICE updated the 2004 guideline on the management of the epilepsies in adults and children with regard to drug management (January 2012).[4] A literature search was performed and updated at 6 weeks before the end of guideline development. The evidence for outcomes were assessed for quality and presented using an adaption of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) toolbox. The majority of the new recommendations are based on moderate to very low quality evidence from randomized controlled trials and the opinion of the guideline development group. General and new 2012 recommendations were:

- It is recommended that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom. If trials of combination therapy do not bring about worthwhile benefits, treatment should revert to the regimen (monotherapy or combination therapy) that has proved most acceptable to the child, young person or adult, in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects.

- If an AED has failed because of adverse effects or continued seizures, a second drug should be started (which may be an alternative first-line or second-line drug) and built up to an adequate or maximum tolerated dose and then the first drug should be tapered off slowly.
- If using carbamazepine, offer controlled-release preparations (new 2012) due to similar efficacy and a better adverse effect profile (based on consensus opinion).

Focal seizures

- Offer carbamazepine or lamotrigine as first line treatment (based on moderate to very low quality evidence).
- If these are unsuitable or not tolerated, offer an alternative from carbamazepine, lamotrigine, oxcarbazepine, levitiracetam, or sodium valproate (moderate to very low quality evidence).
- If first line treatments are ineffective, offer adjunctive treatment with carbamazepine, clobazam, gabapentin, lamogtrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate (moderate to very low quality evidence).

Generalized tonic-clinic seizures

- Offer sodium valproate as first line treatment and if it is unsuitable, offer lamotrigine (low to very low quality evidence). .
- Consider carbamazepine and oxcarbazepine, but be aware of the risk of exacerbating myoclonic or absence seizures.
- If first line treatments are ineffective or not tolerated, offer lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment (high to very low quality evidence).

Prolonged or repeated seizures

- Only prescribe buccal midazolam or rectal diazepam for use in the community for those who have had a previous episode of prolonged or serial convulsive seizures (based on consensus opinion).
- Administer buccal midazolam as first line treatment in the community. Administer rectal diazepam if preferred or if buccal midazolam is not available (high to very low quality evidence).

NICE has also issued guidance and a final appraisal determination recommending retigabine (ezogabine) as an option for the adjunctive treatment of partial (the term focal has been used in this guideline) onset seizures with or without secondary generalization in adults aged 18 years and older with epilepsy, when previous treatment with other AEDs (carbamazepine, oxcarbamazepine, sodium valproate, gabapentin, lamotrigine, levitiracetam, and topiramate) has not provided adequate response or has not been tolerated.[7] The Committee also reported that research investigating the health-related quality of life of people with epilepsy would be of value for defining the appropriate use of this medication.

Systematic Review:

A recent AHRQ comparative effectiveness review was prepared to examine the comparative efficacy, safety, and tolerability of the newer versus older and innovator versus generic AEDs.[3] A literature search was conducted through March 23, 2011 and each study was assessed for validity and rated as good, fair, or poor. Newer versus older comparisons were largely limited to studies using carbamazepine or valproic acid and to a lesser extent phenytoin and sustained/controlled-release carbamazepine. Comparisons versus clonazepam, phenobarbital, ethosuximide, or primidone were very limited or not conducted at all. Newer versus older comparisons were also largely limited to gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate and vigabatrin.[3] Comparisons versus felbamate, lacosamide, pregabalin, tiagabine, and zonisamide were very limited or

not conducted at all. Innovator versus generic antiepileptic medication comparisons are limited predominantly to studies of carbamazepine and to a lesser extent phenytoin and valproic acid. The use of an "A" rated generic could only be verified in one controlled clinical trial and a minority of controlled observational studies. General conclusions were:

- Patients given newer antiepileptic medications were less likely to be seizure free for 6–12 months or 24 months and had a greater risk of withdrawing due to a lack of efficacy than those receiving carbamazepine.
- There was low strength of evidence that there is no difference in mortality between newer AED's compared to carbamazepine, phenytoin, or valproic acid (RR 0.75; 95% CI 0.51 to 1.12, RR 0.30; 95% CI 0.05 to 195, RR 0.94; 95% CI 0.31 to 2.80 respectively)
- Patients receiving newer antiepileptic medications were more likely to withdraw due to a lack of efficacy than those receiving carbamazepine sustained or controlled release products but are more likely to withdraw due to adverse events and skin rash (low to insufficient strength of evidence).
- There was low to moderate strength of evidence that there was no significant difference in the risk of being seizure free for the study duration when newer antiepileptic medications were compared against phenytoin or valproic acid, or the risk of being seizure free at 6–12 or 24 months for valproic acid.
- No significant differences were seen for newer antiepileptic medications versus either phenytoin or valproic acid for withdrawals for any reason, withdrawals due to lack of efficacy, or withdrawals due to adverse events.
- There was high strength of evidence that the risk of gum hyperplasia was reduced with newer AEDs compared to phenytoin (RR 0.10; 95% CI 0.04 to 0.27, NNT 6).
- For the comparison of innovator antiepileptic medications to their respective generic versions, we found that seizure occurrence (low strength evidence), seizure frequency, total withdrawals, withdrawals due to lack of efficacy, or withdrawals due to adverse events were not significantly different in controlled clinical trials.
- There was insufficient to low strength of evidence (using data from observational studies), that switching from an innovator to a generic, generic to generic, or generic to innovator version of the same antiepileptic medication may increase the short-term risk of hospitalization, hospital stay duration, and the short-term risk of a composite of medical service utilization but may not increase outpatient service utilization.

New Drug Evaluation: Ezogabine (Potiga®)

FDA Indication:
Ezogabine is a potassium channel opener indicated as adjunctive treatment of partial-onset seizures in patients aged 18 years and older. Ezogabine is administered in 3 divided daily doses. Initial dosage should be 100 mg 3 times daily for 1 week, titrating to maintenance dose at weekly intervals by no more than 150 mg per day. The optimal effective dosage is between 600 mg/day and 1200 mg/day. In the clinical trials however, 1200 mg /day showed limited improvement compared to 900 mg/day with an increase in adverse reactions and discontinuations.

Potential Off-label Use:
Although not FDA-approved, ezogabine has been studied in post-herpetic neuralgia and bipolar disorder. The limited evidence demonstrated no significant improvement in efficacy in either off-label use.[8]

Clinical Efficacy:
Ezogabine was approved based on three double-blind studies (two 16-week[9,10] and one 18-week[11]) involving 1,239 patients with inadequately controlled partial-onset seizures already receiving 1-3 AEDs. The studies evaluated doses from 600mg – 1200mg. In one poor quality study, ezogabine 900mg/day and 1200mg/day demonstrated a statistically significant reduction in the total partial seizure rate compared to placebo (-29.3% in 900mg/day arm, -35.2% in 1200mg/day arm, and -13.1% in placebo; p=0.0387 and 0.0024, respectively).[10] These treatment groups also showed a significantly higher responder rate, defined as ≥50% reduction in 28-day rate of seizures (900mg/day: 31.6%, 1200mg/day: 33%, placebo: 15.6%; p=0.0214 and 0.016, respectively).[10] Ezogabine 600mg/day did not reach statistical significance for either endpoint. However, this study was rated poor because there was no information reported regarding the generation of randomization sequence or allocation concealment method. Also, dropout rates were not included with a breakdown of reasons other than discontinuations. Therefore, results need to be interpreted with some caution.

Two fair quality trials were also evaluated for drug approval.[9,11] In the first 16 week study, ezogabine 600mg/day and 900mg/day were shown to significantly improve the change in partial seizure frequency compared to placebo (-27.9% vs. -39.9% vs. -15.9%, for 600mg/day, 900mg, and placebo; p<0.007 and <0.001 respectively). Both doses also demonstrated a significant increase in responder rate compared to placebo (600mg/day 32% vs. placebo 17%, RR 1.9; 95% CI 1.2-2.9, p=0.002 and 900mg/day 39% vs. placebo 17%, RR 2.4; 95% CI 1.7 to 3.6, p<0.001). In the second fair quality, 18-week study, participants taking ezogabine 1200mg/day showed significant improvement in reduction in seizure frequency compared to placebo (-44.3% vs. -17.5%, p<0.001) and a greater responder rate (44.4% vs. 17.8%, RR 2.5; 95% CI 1.7 to 3.8, p<0.001). There was no significant difference in the proportion of patients who were seizure free. The other two studies did not report the proportion of patients who were seizure free. In this study, baseline AED medications were no provided and there was an unequal distribution in the two groups regarding percentage of patients on 1, 2, or 3 concurrent AEDs.

All studies showed a statistically significant increase in withdrawal due to adverse events with ezogabine compared to placebo with rates of discontinuation due to adverse events ranging from 14.4% to 29.2% and appeared to be dose-related (25% across all three studies for ezogabine vs. 11% for placebo). The two studies that reported total attrition rates also demonstrated higher total dropout rates with treatment compared to placebo. The most common adverse reactions leading to withdrawal were dizziness (6%), confusional state (4%), fatigue and somnolence (3%). In the clinical trials, dizziness was reported in 23% of patients treated with ezogabine compared to 9% of patients on placebo. Confusional state, psychotic symptoms and hallucinations were reported more frequently in patients treated with ezogabine than in those treated with placebo in the clinical trials (9% of ezogabine participants experienced a confusional state versus 3% in the placebo group). Ezogabine also caused urinary

retention in clinical trials. In trials, "urinary retention, urinary hesitation and dysuria were reported in 0.9%, 2.2%, and 2.3% of patients on ezogabine, respectively, and in 0.5%, 0.9%, and 0.7% of patients on placebo, respectively.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Proportion of seizure free patients
2) Proportion of participants experiencing at least a 50% reduction in seizure frequency (responders)
3) Quality of Life
4) Withdrawals

Primary Study Endpoint:

1) Percent change in 28-day total partial seizure frequency

Ref./ Study Design[a]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[b]	ARR / NNT[c]	Safety Results (CI, p-values)	ARI / NNH	Quality Rating[d]; Comments
RESTORE 1									Fair; • Study did not list out baseline AED medications in each group. • Placebo group had a higher % of pts on 3 AEDs 40.5% vs 27.5% in EZG group, while EZG group had more patients on 1 or 2 AED's in the than placebo (71.6% vs. 59.9%) • Total attrition rates: o T: 56 (36.6%) o C: 26 (17.1%) • Appropriate randomization, allocatio concealment, and blinding of patient and caregiver • Intention to treat (ITT) included all patients who received at least 1 dose of study drug • LOCF used for missing data
French et. al. Phase III, RCT, DB, PC	T: Ezogabine 1,200mg/day w/background therapy of 1-3 AEDs and/or vagus nerve stimulation C: Placebo + Background therapy of 1-3 AEDs and/or vagus nerve stimulation	Mean Age: 37 yrs Male: 46% White: 54% Drug resistant partial epilepsy patients w/ or without 2° generalizations currently on 1-3 AED's and/or vagus nerve stimulation	T: 153 C: 152	Outcomes assessed @ 18 weeks Trial consisted Of 8 wk baseline phase + 6 wk dose titratio phase + 12 weeks maintenance phase	<u>% Δ in 28-day seizure frequency at week 18:</u> T: -44.3% C: -17.5% P=<0.001 <u>% patients w/ ≥50% in seizure frequency over 28 days:</u> T: 68 (44.4%) C: 27 (17.8%) RR 0.4 95% CI 0.26 to 0.59 P=<0.001 <u>Patients who were seizure free</u> T: 3 (2%) C: 0 (0%) P=0.083 RR 0; 95% CI 0 to 2.25	NA ARR: 26.6% NNT: 4 NS	<u>Withdrawals due to Adverse events:</u> T: 41 (26.8%) C: 13 (8.6%) P<0.001 RR:3.12 95% CI (1.7-5.9)	ARI: 18.2% NNH:	
Restore2									

Brodie et. al. Phase III, RCT, DB, PC	T1: Ezogabine 600mg/day T2: Ezogabine 900mg/day C: Placebo	Mean Age: 37 yrs Male: 48% White: 52% Drug resistant epilepsy currently on 1-3 AED's and/or vagus nerve stimulation, >=4 seizures/ 28 days, and without a seizure-free period of more than 21 days Exclusion = CrC <50 ml/min,	T1: 181 T2: 178 C: 179	Outcomes assessed @ 16 weeks Trial consisted Of 8 wk baseline phase + 4 wk dose titratio phase + 12 weeks maintenance phase	<u>% Δ in 28-day seizure frequency:</u> T1: -27.9% T2: -39.9% C: -15.9% P=<0.007, T1 vs. C P=<0.001, T2 vs. C <u>% patients w/ ≥50% in seizure frequency during the maintenance phase:</u> T1: 57 (32%) T2: 70 (39%) C: 31 (17%) P=0.002, T1 vs. C RR 1.9; 95% CI (1.2-2.9) P<0.001, T2 vs. C RR 2.4; 95% CI (1.7 to 3.6)	NA T1 v C ARR: 15% NNT: 7 T2 v C ARR: 22% NNT: 5	<u>Withdrawals due to Adverse events:</u> T1: 26 (14.4%) P=0.049 T2: 46 (25.8%) P=0.049 C: 14 (7.8%) T1 RR:1.8 T2 RR:3.3	T1 AR 6.6% T1 NNH: 6 T2 AR 18 T2 NNH:	Fair; • Randomization stratified by baseline partial seizure frequency per 4 weeks and geographic region • Allocation concealment using interactive voice response system • Blinding of care giver and patient • Unlike RESTORE 1, this study listed ou background AEDs by class. The most common individual AEDs were also reported. • Total attrition rates: o T1: 46 (25%) o T2: 56 (31%) o C: 27 (15.0%) • Intention to treat (ITT) included all patients who received at least 1 dose of study drug

Porter et. al. Phase III, RCT, DB, PC	T1: Ezogabine 600mg/day T2: Ezogabine 900mg/day T3: Ezogabine 1200mg/day C: Placebo	Mean Age: 36 yrs Male: 52% White: 48% Drug resistant partial epilepsy on stable doses of 1-2 AEDs , no 30-day seizure free period	T1: 99 T2: 95 T3: 106 C: 96	Outcomes assessed @ 16 weeks Trial consisted Of 8 wk baseline phase + 8 wk dose titratio phase + 8 week maintenance phase	<u>Median change in monthly seizure frequency from baseline:</u> T1: -23.4% T2: -29.3% T3: -35.2% C: -13.1% P=NS; T1 v C P=0.0387; T2 v C P=0.0024; T3 v C <u>% patients w/ ≥50% in seizure frequency (responder rate):</u> T1: 23 (23.2%) T2: 30 (31.6%) T3: 35 (33.0%) C: 15 (15.6%) <u>T1 v C</u> RR 1.5; 95% CI (0.8-2.8) P=NS <u>T2 v C</u> RR 2.0; 95% CI (1.1 to 3.7) p=0.0214 <u>T3 v C</u> RR2.1; 95% CI (1.2 to 3.8) P=0.016	N/A T1 : NS T2 ARR: 16% NNT: 7 T3 ARR: 17.4% NNT:6	<u>Withdrawals due to Adverse events:</u> T1: 17 (17%) P=0.361 T2: 19 (20%) P=0.161 T3: 31 (29.2%) C: 12 (12.5%) P=0.004	T1 AR NS T2 AR NS T3 ARI:18 5% T3 NNH:	Poor; • Unclear how the generation sequence for randomization was done • Unclear if any method for allocation concealment • Blinded to patient and care provider, no information on outcome assessor • No information on attrition rates or a breakdown of reason for dropouts other than the discontinuations due t AE • Intention to treat (ITT) included all patients who received at least 1 dose of study drug, had a baseline seizure evaluation, and at least one evaluatio during the double-blind treatment phase (only excluded 3 patients) • Missing data imputed based on the assumption that seizures are uniformly distributed over time • During titration phase, the target dos was only reached in 50% of the patients in the 1200mg/day arm

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

References:
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Preferred Drug List (PDL) – Non-Preferred Drugs in Select PDL Classes

Goal(s):

- The purpose of this prior authorization policy is to ensure that non-preferred drugs are used for an above-the-line condition.

Select classes include:
Alzheimers Drugs
Analgesics, Topical
Analgesics/Anesthetics, Topical
Angiotensin Converting Enzyme Inhibitors
Angiotensin Converting Enzyme Inhibitors + Hydrochlorothiazide
Angiotensin II Receptor Blockers
Angiotensin II Receptor Blockers + Hydrochlorothiazide
Antibiotics, Ophthalmic
Antibiotics, Oral
Antibiotics, Otic
Antibiotics-Steroid Combination, Ophthalmic
Antibiotics, Topical
Anticholinergic, Inhaled bronchodilators
Anticonvulsants
Antihyperuricemics
Anti-Inflammatories, Ophthalmic
Antiparasitics, Topical
Antiparkinsons Agents
Beta-Agonists, Inhaled Short-Acting
Beta-Blockers, Oral
Calcium Channel Blockers, Oral Dihydropyridine
Calcium Channel Blockers, Oral Non-Dihydropyridine
Colony Stimulating Factors
Diabetes, Oral Hypoglycemics
Diabetes, Oral Thiazolidinediones
Glaucoma, Ophthalmic
Histamine H2 Receptor Antagonists
Hormone Replacement Therapy, Oral
Hormone Replacement Therapy, Topical
Hormone Replacement Therapy, Vaginal
Multiple Sclerosis Drugs
Overactive Bladder Drugs
Pancreatic Enzymes
Phosphate Binders
Platelet Inhibitors
Statins & Combinations
Steroid, Topical
Targeted Immune Modulators
Ulcerative Colitis

Initiative:

- PDL: Preferred Drug List

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an OHP-covered diagnosis?	Yes: Go to #3.	No: Go to #4.
3. Will the prescriber consider a change to a preferred product? Message: Preferred products do not require a PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC).	Yes: Inform provider of covered alternatives in class.	No: Approve for 1 year or length of prescription, whichever is less.
4. RPH only; All other indications need to be evaluated as to whether they are above the line or below the line diagnosis. • If above the line and clinic provides supporting literature: Approve for length of treatment. • If below the line: Deny, (Not Covered by the OHP).		

P&T / DUR Action: *9/16/10 (KS/DO), 9/24/09(DO), 5/21/09*
Revision(s): *1/1/11, 9/16/10 (KS/DO)*
Initiated:

Abbreviated Update
Drugs for Lice and Scabies

Month/Year of Review: May 2012
Current PDL Class: Topical Antiparasitics

New drugs:	spinosad 0.9% topical suspension (Natroba™)	**Manufacturer:** ParaPRO LLC
	ivermectin 0.5% topical lotion (Sklice™)	DPT Laboratories LTD
New indication:	ivermectin 3mg & 6mg oral tablets (Stomectol™)	Merck & Co., Inc.

Current Status of PDL Class:

- Preferred Agents: PERMETHRIN CREAM, PERMETHRIN LIQUID, PIP BUTOX/PYRETHRINS/PERMETH KIT, PIPERONYL BUTOXIDE/PYRETHRINS GEL, PIPERONYL BUTOXIDE/PYRETHRINS KIT, PIPERONYL BUTOXIDE/PYRETHRINS LIQUID, PIPERONYL BUTOXIDE/PYRETHRINS SHAMPOO
- Non Preferred: BENZYL ALCOHOL 5 % LOTION, CROTAMITON 10 % CREAM, CROTAMITON 10 % LOTION, LINDANE 1 % LOTION, LINDANE 1 % SHAMPOO, MALATHION 0.5 % LOTION, POTASS HYD/GLYCO/PQ10/HE-CELL GEL, SPINOSAD 0.9 % SUSPENSION (pending review), IVERMECTIN 0.5% LOTION (pending review).

Previous HRC Conclusions (April 2010):

- No evidence was found to support a difference in efficacy/effectiveness between members of this class.
- No evidence was found to support a difference in harms between members of this class other than lindane (CNS toxicity, rare/severe pediatric seizures, low ovicidal activity, resistance).
- Recommend inclusion of permethrin to assure adequate coverage for scabies, and consider including OTC and prescription medications.
- Consider excluding lindane.

Reason for Review:
In April 2010, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the topical antiparasitics. A December 2009 Provider Synergies Review[1] was used as the evidence source. Since this review, two new drugs have been approved by the FDA for the treatment of peduculosis capitis (spinosad 0.9% topical suspension[2] and ivermectin 0.5% lotion[3]). In addition, oral ivermectin[4] has been studied for treatment of peduculosis capitis off-label. Clinical Evidence[5] (June 2010) and The Canadian Agency for Drugs and Technologies in

Health[6] (May 2010) published comparative reviews. Additionally, the American Academy of Pediatrics[7] published updated treatment guidelines in August 2010.

Research Questions:

- Are the new agents more effective for treating peduculosis capitis than currently available agents?
- Are the new agents safer than currently available agents?
- Are there unique patients or situations where the new agents may be more effective or safer than currently available agents?

Conclusions:

- There is insufficient evidence of superiority of either spinosad 0.9% topical suspension or ivermectin 0.5% lotion over permethrin.
- There is insufficient evidence that either spinosad 0.9% topical suspension or ivermectin 0.5% lotion are safer than permethrin.
- No unique patient groups or situations were identified where either spinosad 0.9% topical suspension or ivermectin 0.5% lotion are safer or more effective than permethrin.
- For patients that have failed permethrin or malathion, there is moderate evidence from one good quality RCT that oral ivermectin is more effective than malathion 0.5% lotion. However, oral ivermectin is not FDA approved for this indication and the malathion lotion studied is not available in the same vehicle in the United States.

Recommendations:

- Make both spinosad 0.9% topical suspension or ivermectin 0.5% lotion due to insuffient evidence of effectiveness or safety relative to permethrin.
- No action recommended for oral ivermectin. It is currently available without restriction.

Background:

There are three varieties of parasitic lice affecting humans: Pediculus humanus capitis (head lice), Pediculus humanus humanus (body lice) and Phthirus pubis (pubic lice or "crabs").[8] The new drugs are indicated only for head lice so it will be the focus of this update and background. Head lice are found worldwide, among all socioeconomic backgrounds, affecting children and females predominantly.[8] Black children are less commonly affected, possibly due to hair type.[8] Disease is spread through direct contact via playmates, clothing, combs, headphones, towels and beds.[8] The life span of a female louse is about one month and she is expected to lay about 7-10 eggs (aka nits) daily.[8] The nits are cemented to the base of host hair and hatch in eight days releasing nymphs that mature in another eight days.[8] Both adult sexes feed on the scalp and adjacent face and neck.[8] Most patients are asymptomatic and prognosis is almost harmless.[5] Itching and erythema may be due to an allergic reaction to the lice saliva.[8] Secondary streptococcal and staphylococcal pyoderma may occur.[5] Resistance to topical insecticides is a growing concern and varies geographically. [8]

Methods:

A Medline literature search ending March Week 1 2012 for new systematic reviews and randomized controlled trials (RCT's) comparing medications head-to-head in the treatment of peduculosis was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane

Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. After review of the citations from Medline, 2 new relevant head-to-head trials[9 10] and 2 new systematic reviews[5 6] were evaluated.

Systematic Reviews:

CADTH[6] published a review June 11, 2010 that focused on both head lice and scabies. Search dates for the head lice portion ran from January 1, 2005 to May 10, 2010. The largest body of evidence was for the comparison of permethrin to lindane. The evidence for the majority of comparisons was ranked as low or very low due to the limited number of studies. The authors noted there was no standard criteria for judging success of treatment. Relevant key findings were:

- Permethrin was more effective for eradicating lice than lindane. Although lindane has been associated with central nervous system toxicity, there were no reports of serious adverse effects in the identified trials.
- Malathion lotion may be more effective for lice eradication than phenothrin or permethrin.
- Results from RCTs comparing malathion or permethrin to wet combing were conflicting. This may have been the result of varying resistance patterns based on geographic location.
- There was insufficient evidence to judge whether combinations of insecticides increased effectiveness when compared with single insecticides or other treatments.

Clinical Evidence[5] posted a review of the literature through June 2010. Relevant key findings were:

Likely to be beneficial

- Malathion lotion may increase lice eradication compared with placebo, phenothrin, or permethrin. Current best practice is to treat with two applications 7 days apart, and to check for cure at 14 days.
- Permethrin may be more effective at eradicating lice compared with placebo or lindane. CAUTION: Lindane has been associated with central nervous system toxicity.
- Spinosad may be more effective at eliminating lice than permethrin.

Trade off between benefits and harms

- Oral ivermectin may be more effective at eradicating head lice than malathion in people with previous failed treatment with insecticides.

Unknown effectiveness

- We don't know whether pyrethrum is beneficial compared with other insecticides.
- Benzyl alcohol may be more effective at eradicating lice than placebo. However, we don't know whether benzyl alcohol is more effective than insecticides or other treatments used in routine clinical practice.
- Studies comparing malathion or permethrin with wet combing have given conflicting results, possibly because of varying insecticide resistance.

- We don't know whether combinations of insecticides are beneficial compared with single agents or other treatments.

New Guidelines:
The American Academy of Pediatrics[7] recommendations regarding drug selection are:

- Unless resistance has been proven in the community, 1% permethrin or pyrethrins can be used for treatment of active infestations.
- Instructions on the proper use of products should be carefully communicated. Because current products are not completely ovicidal, applying the product at least twice, at proper intervals, is recommended if permethrin or pyrethrin products are used or if live lice are seen after malathion therapy.
- If resistance to available OTC products has been proven in the community, if the patient is too young, or if parents do not wish to use a pediculicide, consider recommending "wet-combing" or an occlusive method (such as petroleum jelly or Cetaphil), with emphasis on careful technique, and repeating for at least 2 weekly cycles,
- Benzyl alcohol 5% can be used for children older than 6 months, or malathion 0.5% can be used for children 2 years old or older, in areas where resistance to permethrin or pyrethrins has been demonstrated or for a patient with a documented infestation that has failed to respond to appropriately administered therapy with permethrin or pyrethrins.
- New products should be evaluated for safety and effectiveness.

Randomized Controlled Trials (RCTs):
No head to head studies comparing ivermectin 0.5% lotion to currently available therapies were identified. It was approved based upon two phase III placebo controlled trials.

Stough et al[10] is an investigator blinded, RCT including two identical phase III studies comparing spinosad 0.9% topical suspension without nit-combing to permethrin 1% with nit-combing. A third arm with spinosad 0.9% topical suspension with nit-combing was performed but results were only reported in combination with the first spinosad arm for adverse events. There were 87.4% of the spinosad patients lice free at 14 days compared to 48.3% of permethrin treated patients (RR 1.93 95% CI: 1.73 – 2.16). However, this study was rated poor because it was not blinded to patient or care-giver and it was unclear if the evaluators were blinded. The allocation concealment method was not reported. Thus the results need to be interpreted with some suspicion. Withdrawals were not reported and reported adverse events (limited to dermatologic) were not appreciably different.

Chosidow et al[9] is a good quality, double-blind RCT that compares oral ivermectin 400 mcg/kg to a single application of malathion 0.5% lotion. The exact malathion preparation is not available in the United States, though it is available in the same strength as a topical lotion. This study admitted only patients that had previously failed either permethrin or malathion within the 2-6 weeks prior. It was pre-established as a non-inferiority study at ARR 5% for the primary outcome of proportion of patients lice free at Day 15. It met non-inferiority but did not establish superiority (ARR 10.2% 95% CI: 4.6–15.7, NNT 10). There was a response of 378 (95.2%) in the ivermectin group compared to 352 (85.0%) in the malathion group (RR: 1.12 95% CI: 1.07 -1.17). Withdrawals due to adverse events were not appreciably different.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Lice free at 14 days
2) Withdrawals due to adverse effects

Study Endpoints:

1) Lice free at 14 or 15 days
2) Withdrawals due to adverse effects

Reference / Study Design[a]	Patient Population Demographics/ Inclusion/ Exclusion	Intervention Description / Length of Tx	n= ITT / m-ITT / safety analysis /Attrition (rate)	Results[2]: Primary Endpoint / Relevant Secondary Endpoint (s)	ARR / NNT[b]	Safety: Withdrawals d/t ADE / ADEs	ARI / NNH[b]	Quality Rating / Interval Validity Risks of Bias / External Validity Concerns
Stough 2009[10] 2-identical phase III, MC, RCT, PG, SB (investigator),	12 US research centers Sep 2007 – Apr 2008 Mean age (14-19 yrs) Age Range (0.5–84 yrs) Female % (76.2-86.4) **Includes:** ≥ 6 months old with active head lice as diagnosed by "trained evaluator" or house-hold member **Excludes:** - Hx of sensitivity to pediculicides or hair care products, - a skin condition that could interfere with the scalp evaluation - previous tx with a pediculicide within 48 hrs, - household with >6 members with head lice or where 1 infected member would not enroll in the study or use the rescue lice treatment - use of an excluded medication or systemic antibiotic - pregnant or breastfeeding - drug abuse within 12 months - Participation in a clinical trial within 30 days	4:4:1 ratio to 1 of 3 treatment groups: **S** -Spinosad 0.9% no nit-combing x7 days; if live lice present x additional 7 days. **PC** – Permethrin 1% with nit combing x7 days; if live lice present x additional 7 days. **SC** – Spinosad 0.9% with nit combing x7 days; if live lice present x additional 7 days. All individuals in a single household were treated with a single agent. **Txs not allowed:** -topical salicylic acid, -topical corticosteroids, -anthralin, -vitamin D analogs, -retinoids, -immunosuppressants -topical hair growth formulations, -topical dandruff treatments	**ITT:** *Individual (household)* 1038 (391) **S:** 446 (174) **PC:** 470 (173) **SC:** 122 (44) **Safety (≥ 1 treatment):** **S+SC:** 552 **PC:** 457 **Attrition: n (%)** S: 32 (7.2%) PC: 47 (10.0%) SC: 10 (8.2%)	**Primary:** proportion of participants lice free @ 14 days **S:** 376 (87.4%) **PC:** 205(48.3%) **SC:** NR (NR %) **RR:** 1.93 **95% CI:** 1.73 – 2.16 **P** <0.001 **Secondary:** proportion of patients lice free @ 7 days **S:** 309 (73.4%) **PC:** 115(24.8%) **SC:** NR (NR %) **RR:** 2.83 **95% CI:** (2.39 -3.37)	**ARR:** 40% **NNT:** 2 **ARR:** 44.8% **NNT:** 2	**Withdrawals d/t ADE:** NR **Ocular hyperemia:** **S+SC:** 12 (2.2%) **PC:** 15 (3.3%) **RR:** 0.66 **95% CI:** 0.31 – 1.40 **P**= 0.329 **Application site erythema:** **S+SC:** 17 (3.1%) **PC:** 31 (6.8%) **RR:** 0.45 **95% CI:** 0.25 – 0.81 **P**= 0.007 **Application site irritation:** **S+SC:** 5 (0.9%) **PC:** 7 (1.5%) **RR:** 0.59 **95% CI:** 0.19 – 1.85 P=0.395	**ARI:** -1.1% **NNT:** NS **ARI:** -3.7% **NNH:** 27 **ARI:** -0.6% **NNT:** NS	**Quality Rating: POOR** **Internal Validity RoB:** Selection- Centralized randomization but unclear allocation concealment Performance-no blinding of patients or care-givers Detection-unclear blinding of evaluators Attrition-low attrition; data provided for ITT calculation **External Validity:** Recruitment-Not reported Patient characteristics-older than likely to use. Setting-Not reported Outcomes – - Efficacy: Evaluator training and criteria not well described but outcome itself is clinically relevant. - Safety: FDA agreed to reduced safety evaluations based upon Phase II trial results. First 25 qualifying pediatric participants in each study had clinical laboratory assessments on days 0 (screening) and 14 only. Results not reported; authors state in text there were no serious ADEs in spinosad group and 3 serious ADEs in permethrin group.

Reference / Study Design[a]	Patient Population Demographics/ Inclusion/ Exclusion	Intervention Description / Length of Tx	n= ITT / m-ITT / safety analysis / Attrition (rate)	Results[2]: Primary Endpoint / Relevant Secondary Endpoint (s)	ARR / NNT[b]	Safety: Withdrawals d/t ADE / ADEs	ARI / NNH[b]	Quality Rating / Interval Validity Risks of Bias / External Validity Concerns
Chosidow[9] 2010 MC, cluster-randomized, DB, DD, XO	7 centers (4 in UK, 1 in Ireland, 1 France, 1 Israel) Mar 9 – Sep 14, 2004. Median Age: 10 Female 87% **Inclusion criteria:** - ≥2 years, ≥15 kg, - head-lice infestation (defined as the presence of live lice) confirmed by study staff by combing the dry hair with a dedicated fine-toothed comb,24 Live lice seen during this examination were counted, to provide baseline data. - previously failed a pyrethroid-based or malathion insecticide **Exclusion criteria:** -PG/breastfeeding -active scalp disease -use of pediculicidal treatment within 2 weeks prior. -hair style precluding comb use, dyes, bleach, perm or hair relaxing in previous 2 weeks -prior residence of Africa known to be endemic for oncocerciasis, lymphatic flariasis, loa loa -known or suspected intestinal helminth infection -known hypersensitivity to either study drug.	2 stage; 1-first 15 days 2-those not lice free XO **I:** Ivermectin 3 mg tablets (400mcg/kg) + placebo 100% isopopanol lotion. **M:** placebo tablets + 0.5% malathion lotion.	Clusters = Households **ITT (LOCF):** Indivs (households) **I:** 397 (184) **M:** 414 (191) **PP:** Indivs (households) **I:** 349 (166) **M:** 364 (171) **Attrition:** **I:** 12.3% **M**: 12.1%	**Primary:** Lice free on Day 15 **I:** 378 (95.2%) **M** 352 (85.0%) **RR:** 1.12 **95% CI:** 1.07 -1.17 P <0.001 **Secondary**: Lice free on Day 29 **I:** 382 (96.2%) **M** 362 (87.4%) **RR:** 1.10 **95% CI:** 1.06 -1.15 P <0.001	**ARR:** 10.2% **NNT:** 10 **ARR:** 8.8% **NNT:** 11	**Withdrawal d/t ADE:** **I:** 7 (1.76%) **M:** 5 (1.21%) **RR:** 1.46 **95% CI:** 0.47 – 4.56 The following specific adverse events led to discontinuation: in the ivermectin group, impetigo (in two patients), nausea or vomiting (in one), gastroenteritis (in three), and convulsions (in one), and in the malathion group, rash or urticaria (in three patients) and gastroenteritis (in two).	**ARR:** 0.06% **NNT:** NS	**Quality Rating: Good** **Internal Validity RoB:** Selection- Centralized randomization/Allocation concealment not reported Performance-low risk; good blinding Detection- low risk; good blinding Attrition- Low risk due to low attrition and even distribution between groups. ITT analysis used with LOCF which biases towards the null. **External Validity:** Recruitment- Patients were recruited from the community by advertising or nurse outreach. Patient characteristics- similar to patients likely to use. Setting- Patients were recruited from the community by advertising or nurse outreach. Outcomes- Appropriate and relevant. **Analysis:** -99% power for noninferiority (noninferiority margin 5%) - >96% power for the superiority step.

[a]Study Design: RCT= randomized trial, MC= Multicenter, PC=placebo-controlled, DB= double blind, PG=Parallel Group, XO=cross-over

[b]Results abbreviations: RR = Risk Ratio, ARR = absolute risk reduction, ARI = absolute risk increase, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis, LOCF = last observation carried forward

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Non-Statin Lipid Lowering Agents: Abbreviated Class Review

Month/Year of Review: March 2012
Classes Included: Bile Acid Sequestrants, Nicotinic Acid, Fibrates, Ezetimibe and Omega-3 fatty acid.

Executive Summary

Reason for Review:
There are several classes of lipid lowing medications available with various mechanisms of action and pharmacokinetic properties. Although the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, known as statins remained to be the most widely prescribed lipid lowering medications, it could be difficult to obtain the low- density lipoprotein (LDL) treatment goal with a single statin for subset of patients with high baseline LDL or those who have developed adverse events from statin therapy. Recent new safety alerts including new restrictions, contraindications and dose limitations for high potency statins, such as simvastatin and rosuvastatin, were released by the FDA to reduce the risk of muscle injury. This may pose additional challenges in the management of lipid lowering. The other classes of lipid lowering agents have not been reviewed for the Preferred Drug List (PDL). This update will examine their place in therapy for these agents, and identify relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Conclusion:
Among other lipid lowering classes, agents from bile Acid Sequestrants (BAS), nicotinic acid, and fibrates have showed reduced major coronary events and/or total mortality or cardiovascular disease related deaths based on clinical trial results. Drugs from these classes can be treatment options for patients who cannot tolerate a statin or require additional lipid lowering in addition to a statin therapy to reach treatment goal. Evidence is lacking directly comparing drugs within each class.

Bile Acid Sequestrants (BAS): There is limited evidence comparing one agent to another. Cholestyramine has been shown to reduce major coronary events and coronary heart disease deaths, while all BAS (cholestyramine, colestipol, and colesevelam) have been shown to be effective in reducing LDL-C. Colesevelam has been studied in pediatrics ages 10 to 17 years of age. There is low quality evidence demonstrating no difference in mortality, vascular death, or severe adverse events when comparing the combination of a BAS and statin to statin monotherapy.

Fibrates: Gemfibrozil has demonstrated reductions in CV events and CHD mortality. As a class, the evidence is insufficient to show a reduction in all-cause mortality. Data from the ACCORD trial resulted in the FDA informing the public that fenofibric acid (Trilipix) may not lower a patient's risk of having a heart

attack or stroke in patients with diabetes. Fibrates are recommended in the management of patients with dyslipidemia and especially elevated triglycerides, which is consistent with ATP III recommendations. There is very low quality evidence that there is no difference in all cause mortality between the combination of a statin plus fenofibrate and statin monotherapy.

Nicotinic Acid: There is low quality evidence that no significant difference exists in all cause mortality, vascular death, or severe adverse events between the combination of niacin plus a statin versus statin monotherapy. Nicotonic Acid has been shown to reduce major coronary events and possibly mortality. Niaspan is an extended release form of niacin formulated to reduce the side effects.

Ezetimibe: To date, ezetimibe only has intermediate data on LDL lowering and no clinical data to support its value in reduced cardiovascular (CV) and stroke related outcomes.

Omega-3-fatty acids: Omega-3-fatty acid reduces triglycerides in patients with very high triglycerides (>500mg/dl) and although it appears to have a role in cardiovascular risk reduction, evidence remains inconclusive. In general, omega-3 fatty acid is an alternative to fibric acid derivatives and niacin for the treatment of high triglycerides. There is low quality evidence demonstrating no difference in all cause mortality or serious adverse events between the combination of a statin plus omega-3 and statin monotherapy.

Recommendations:

- Add Bile Acid Sequestrants (BAS) to the PDL and include cholestyramine, which has shown improved CV related or stroke outcomes as a preferred drug.
- Add fibrates to the PDL and include gemfibrozil, which has shown improved CV related or stroke outcomes as preferred drugs. Due to the interaction with statin medications, consider including other drugs in the class dependent on price comparisons for management of dyslipidemia, especially elevated triglycerides.
- Nicotonic Acid has been shown to reduce cardiovascular outcomes in a meta-analysis including both niacin and niacin extended release formulation. Add nicotinic acid drugs to PDL and consider price comparisons for drugs.
- Make ezetimibe a non-preferred lipotropic agent and implement prior authorization criteria requiring failure or intolerance to all of the following: a statin, BAS, fibrate and niacin therapy (Appendix D).
- Add omega -3 fatty acids to PDL and evaluate price comparisons of individual agents due to a lack of clinical distinction.
- Include prior authorization criteria for Lovaza requiring documented triglycerides > 500mg/dl and a trial of fenofibrate or gemfibrozil and niacin and OTC fish oil at maximum tolerable doses. (Appendix E)

Background:

Lipids (fats), together with proteins and carbohydrates, are the main components of living cells. Cholesterol and triglycerides are lipids that are stored in the body and served as a source of energy in addition to their role in cell structure. When cholesterol levels are high, fatty deposits can build up in the arteries, causing atherosclerosis. This can lead to heart disease and stroke. In the U. S, approximately one in every six adults has high cholesterol defined as total cholesterol of 240mg/dL or above.[1] It affects over 65 million Americans.[2] People with high cholesterol have double the risk for heart disease as people with

lower levels. Evidence indicates levels of LDL correlate with the development of coronary heart disease (CHD), while the levels of high-density lipoprotein cholesterol (HDL) are associated with a lower risk of disease. The lowering LDL reduces CHD and stroke, which makes LDL a primary treatment target. In 2001, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommendations provide guidance on the targeted LDL goal based on patient's CHD risk.[3]

After the publication of ATP III guideline, 5 major clinical trials of statin therapy with clinical end points confirmed the benefit of cholesterol lowing therapy in high-risk patients with targeted LDL goal of less than 100mg/dL; moreover the findings from these trials suggested subset of patients with very high risk, additional benefit maybe obtained by reducing LDL levels to substantially below 100mg/dL.[4, 5] In light of this clinical trial evidence, in 2004, the National Cholesterol Education Program (NCEP) published ATP III updated recommendations to include an LDL goal of < 70mg/dL as a therapeutic option for patients at very high risk category.[6]

Issues:

- Is there reliable evidence showing lipid lowering agents besides statins reduce the risk of nonfatal myocardial infarcation (MI), CHD, mortality, stroke, or hospitalization?
- Is there evidence showing other classes of lipid lowering agents differ in benefits and harms within subgroups of patients?
- Is there any difference in effectiveness or harms among agents within the same lipid lowing class?

Methods:

A MEDLINE Ovid search was conducted using all lipid lower agents including: hyperlipidemia, hypercholesterolemia, cardiovascular disease, hydroxyl-3-methyglutaryl coenzyme A (HMG COA) reductase inhibitors, statin, ezetimibe, fibrates, nicotinic acid, niacin, bile acid sequestrant (BAS) and omega-3 fatty acids. The search was limited to randomized controlled trials and meta-analysis, English language, and to studies conducted in humans from September 2009 to present. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Previous conclusions from guidelines and systematic reviews are listed in Appendix A, including an AHRQ systematic review from 2009 comparing the clinical outcomes of high-dose statin monotherapy with those of statin combination therapy in adults at high risk for coronary disease

Drugs Included in This Review

Drug	Dosage Form	Generic Availability
Bile Acid Sequestrants		
Cholestyramine (Questran®, Questran Light®)	9gm or 4gm (packet or scoop)	Yes
Colestipol (Cholestid®)	5gm/scoop granules or 1gm tablets	Yes

Colesevelam (Welchol®)		625mg tablets	No
Fibrates			
Gemfibrozol (Lopid®)		600mg tablets	Yes
Fenofibrate	Tricor®	48mg and 145mg tablets	Yes
	Lofibra®	54mg and 160mg tablts	Yes
	Lipofen®	50mg and 150mg capsules	No
	Triglide®	50mg and 160mg tablets	No
	Fenoglide®	40mg and 120mg tablets	No
Micronized fenofibrate	Lofibra® capsules	67mg, 134mg and 200mg capsules	Yes
	Antara®	43mg and 130mg capsules	Yes
Fenofibric Acid	Fibricor®	35mg and 105mg tablets	No
	Trilipix®	45mg and 135mg capsules	No
Nicotinic Acid			
Niacin IR (Niacor®)		500mg tablets	Yes
Niacin ER (Niaspan®)		500mg, 750mg and 1000mg tablets	No
Nicotinic acid (Slo-Niacin®) over-the-counter		50mg, 100mg, 250mg, 500mg, 750mg and 1000mg ER tablets	Yes
Omega-3 Fatty Acid			
Omega-3 fatty acid (fish oil) over-the-counter			Yes
Omega-fatty acid (Lovaza®)		1gm capsules	No
Ezetimibe			
Ezetimibe (Zetia®)		10mg tablets	No

New Systematic Reviews:
There were no new systematic reviews published within this review timeframe. In December 2010, the Cochrane Collaboration published a review protocol to assess the effectiveness of and safety of statins, exetimibe, fibrates, or fish oil for treating dyslipidemia in HIV-infected patients receiving highly active antiretroviral therapy. Clinical effectiveness was measured in terms of prevention (primary and secondary) of cardiovascular events (Fatal or nonfatal myocardia infarction, stroke and angina).[8]

New Guidelines:
In June 2011, the National Lipid Association Expert Panel on Familial Hypercholesterolemia published updated clinical guidance on screening, diagnosis and management of familial hypercholesterolemia (FH) in pediatric and adult patients. The guideline made the following drug treatment recommendations:

Drug Treatment Recommendations for adults:

- Both children and adults with LDL cholesterol ≥190 mg/dL [or non-high-density lipoprotein (HDL) cholesterol ≥220 mg/dL] after lifestyle changes will require drug therapy.
- For adult FH patients (≥20 years of age), drug treatment to achieve an LDL cholesterol reduction ≥50% should be initiated.
- Statins should be the initial treatment for all adults with FH.
- Higher risk patients may need intensification of drug treatment to achieve more aggressive treatment goals (LDL cholesterol < 100 mg/dL and non-HDL cholesterol < 130 mg/dL).
- Ezetimibe, niacin, and bile acid sequestrants are reasonable treatment options for intensification of therapy, or for those intolerant of statins.
- The potential benefit of multidrug regimens for an individual patient should be weighed against the increased cost and potential for adverse effects and decreased adherence.

Drug Treatment Recommendations in children:

- Statins are preferred for initial pharmacologic treatment in children after initiation of diet and physical activity management.
- Clinical trials with medium term follow up suggest safety and efficacy of statins in children.
- More aggressive LDL cholesterol targets should be considered for those with additional CHD risk factors.

Bile Acid Sequestrants (BAS):
BAS bind bile acids in the bowel. The bound bile acids are excreted in the feces, in turn it prevents re-absorption and depletion the intrahepatic pool of bile acids. BAS have been available for over 30 years. BAS are not absorbed in the intestine, hence do not have systemic side effects. However, these agents have significant gastrointestinal side effects such as constipation, frequent dosing and potential to interfere with absorption of other drugs and essential nutrition nutrients, which limit the use of these agents in practice. The BAS currently on the market include: cholestyramine (Qustran®, Qustran® light), colestipol (Colestid®) and colesevelam (Welchol®). Among all three agents, colesevelam is the latest BAS approved by FDA in May 2000. Both cholestyramine and colestipo have shown clinical benefits in reducing CHD death, nonfatal myocardial infarction or stroke[9-11], whereas colesevelam has only demonstrated benefit on intermediate outcomes such as LDL reductions.

AHRQ Review BAS Conclusions (September 2009[7]):

- A total of four parallel group randomized trials compared statin plus BAS combinations and statin monotherapy that reported one or more clinical outcomes.

- Based on a single study in participants requiring intensive lipid lowering therapy, the grade of evidence is "very low" for an increase of participants reaching ATP III LDL-c goals for the combination of any dose statin plus BAS and high dose statin monotherapy (OR 4.51; 95% CI 1.34 to 15.14).
- Based on a single study in participants followed up for more than 24 weeks, the grade of evidence is "very low" for no difference in all cause mortality (OR 1.07; 95% CI 0.11 to 10.51) between the combination of any dose statin plus BAS and any dose statin monotherapy.
- Based on studies in participants regardless of baseline risk the grade of evidence is "very low" for no a difference in all cause mortality (3 trials; OR 1.07; 95% CI 0.11 to 10.51), no difference in serious adverse events (2 trials; OR 0.39; 95% CI 0.06 to 2.36) and an increase of participants reaching ATP III LDL-c goals (1 trial; OR 4.51; 95% CI 1.34 to 15.14).

New Systematic Reviews:
In March 2011, the National Lipid Association Expert Panel on Familial Hypercholesterolemia conducted a systematic review of BAS therapy in children with familial hypercholesterolemia[13]. In total, five clinical studies were identified that evaluated BAS monotherapy, whereas two studies were identified that evaluated combination therapy with a BAS and low-dose statin. The five BAS monotherapy studies showed a significant improvement in total cholesterol (percent change from baseline ranged from -7% to -14%) and LDL (percent change from baseline from -7% to -20%), but no significant change in HDL or TG. Only one studied evaluated colesevelam. Two combination therapy of BAS plus a statin studies (one study used cholestipol, one study used colesevelam as choice of BAS) showed significant improvement in total cholesterol (percent change from baseline ranged from -7% to -13%) and LDL (percent change from baseline from 5% to -17%). Change in HDL or TG are not significant. The main limitation of this review is that none of the studies were reviewed for quality or risk of bias. (Appendix B)

Conclusions:
The most recent AHRQ review indicated "very low" grade evidence for increasing the number of patients reaching LDL goals, no difference all cause mortality, and no difference in serious adverse events between BAS plus statin and statin monotherapy. However, when comparing BAS plus a statin with any dose statin with the older agents such as cholestyramine and colestipol, BAS plus a statin did demonstrate reduced major coronary events and CAD death. Colesevelam does not have cardiovascular clinical outcomes data. In addition, the recent treatment guideline from the National Lipid Association Expert Panel on Familial Hypercholesterolemia recommended BAS as treatment option for high-risk patients requiring intensive therapy or for those intolerant to statin therapy. ATP III guidelines also recommended combination of statin and BAS for patients with very high LDL.

Fibrates:
Unlike statins, fibrates do not work on lipid synthesis pathway. They reduce the levels of fatty acids by facilitating oxidation of these molecules. Two fibrates, gemfibrozil and fenofibrate or fibric acid derivative, are available in the U. S. Fibric acid derivatives inhibit triglyceride synthesis and stimulate catabolism of triglyceride-rich lipoproteins; whereas gemfibrozil inhibits peripheral lipolysis, decreases hepatic free fatty acid extraction, inhibits synthesis and increases clearance of VLDL carrier apolipoprotein B. Fibrates reduce triglyceride levels by 30-50% and may have beneficial effects on HDL and LDL levels depending on the baseline phenotype.[14] As statins do not have significant impact on triglyceride levels, use of these agents has been an option in populations with hypertriglyceridemia or mixed dyslipidemia, in place of or in addition to statins.[15] For individuals with diabetes or metabolic syndrome carry high CHD risk, fibrate therapy may be considered.[15]

Previous studies have demonstrated gemfibrozil to reduce the risk of CHD in patients with high TG and low HDL and more significantly in patients with diabetes. The combination of simvastatin and fenofibrate was not shown to reduce the rate of fatal CV events, nonfatal Mi, or nonfatal stroke, compared with simvastatin monotherapy in high-risk patients. In November 2011, the FDA informed the public that fenofibric acid (Trilipix) may not lower a patient's risk of having an MI o stroke, based on data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial.[1]

AHRQ Review Concluded (September 2009[7]):

- Based on a single study in participants requiring intensive lipid lowering therapy, the grade is "very low" grade for no difference in all cause mortality (O 0.46, 95% CI 0.03 to 7.57), and the number of participants reaching ATP III LDL-c goals (OR not pooled) between the combination of lower dose statin plus fenofibrate and higher dose statin monotherapy.
- Based on studies in participants requiring intensive lipid lowering therapy, the evidence grade is "very low" quality evidence demonstrating no difference in all cause mortality (1 trial; OR 0.46, 95% CI 0.03 to 7.57), no difference in serious adverse events (1 trial, OR not reported) and no difference in the number of participants reaching ATP III LDL-c goals (2 trials, OR not pooled) between the combination of any dose statin plus fibrate and any dose statin monotherapy.
- Based on studies in participants with diabetes mellitus, the evidence grade is "very low" for no difference in all cause mortality (1 trial; OR 0.46, 95% CI 0.03 to 7.57) and the number of participants reaching ATP III LDL-c goals (2 trials; OR not pooled) between the combination of any dose statin plus fibrate and any dose statin monotherapy.
- Based on a one study in participants followed up for more than 24 weeks, the evidence grade is "very low" grade for difference in all cause mortality (1 trial; OR not reported), serious adverse events (1 trial, OR not reported) and the participants reaching ATP III LDL-c goals (1 trial, OR 9.75, 95% CI 1.16 to 82.11) between the combination of any dose statin plus fibrate and any dose statin monotherapy.
- Based on studies in participants regardless of baseline risk, the evidence grade is "very low" for no difference in all cause mortality (3 trials; OR 0.28, 95% CI 0.03 to 2.97), serious adverse events (2 trials; OR 1.2, 95% CI 0.42 to 3.46) and the number of participants attaining ATP III LDL-c goals (2 trials; OR not pooled) between the combination of any dose statin plus fibrate and any dose statin monotherapy.

New Systematic Reviews (Appendix B):

- Meng et al. published a meta-analysis in 2011 to examine the efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia.[16] Among the six trials that met selection criteria for inclusion, the authors found that compared to placebo, the greatest benefit with fibrate treatment was seen in 7,389 subjects with high triglycerides. Fibrate therapy reduced the risk of vascular events (RR 0.75, 95% CI 0.65 to 0.86, P < 0.001). In 5,068 subjects with both high triglycerides and low HDL-C fibrate therapy reduced the risk of vascular events (RR 0.71, 95% CI 0.62 to 0.82, P < 0.001). Less effect on vascular events was noted in 15,303 subjects selected for low HDL-C (RR 0.84, 95% CI 0.77 to 0.91, P < 0.001). Among 9,872 subjects with neither high triglycerides nor low HDL-C, fibrate therapy did not reduce subsequent vascular events (RR 0.96, 95% CI 0.85 to 1.09, P = 0.53) The fibrates that were used in the trials include gemfibrozil, fenofibrate and bezafibrate (not available in the U. S).

- Similar findings were also reported in another systematic review and meta-analysis by Bruckert E, et al in a Feb. 2011 publication.[17] The authors performed a computerized Pub Med literature search that focused on major randomized controlled trials evaluating fibrates in the prevention of cardiovascular disease, published between January 1966 and March 2010. In addition, authors also searched the reference lists of retrieved articles and of previously conducted systematic review and meta-analysis on lipid-lowering treatment for additional studies. The literature search identified 1239 citations. After reviewing the titles and abstracts, 21 articles were read in full and 8 eligible major randomized controlled trials were identified, and 5 trials were identified for analysis. The authors performed a meta-analysis of the 5 large trials assessing the impact of fibrates on cardiovascular end points and providing information on low HDL-C and high triglyceride levels. Subgroups were determined according to values closest to predetermined cut-offs for both HDL-C and triglycerides (<35 and >200 mg/dL, respectively). Overall, 4,671 patients (2,401 in fibrate group and 2,270 in placebo group) were classified as having an atherogenic dyslipidemia featuring low HDL-c combined with high triglyceride levels. Across trials, the proportion of patients classified in this subgroup ranged from 11% to 33%. A significant greater fibrate effect was found in high triglyceride levels subgroup (pooled RR, 0.72; 95% CI, 0.61to 0.85) in comparison with the counterpart subgroups (pooled RR, 0.94; 95% CI, 0.87 to 1.02, P for between-group heterogeneity = 0.002). A greater effect size was found in patients with high triglyceride levels or atherogenic dyslipidemia phenotype where fibrates were estimated to reduce the cardiovascular risk by 28% [95% confidence interval (CI), 15% to 39%; P < 0.001] or 30% (95% CI, 19% to 40%, P < 0.0001), respectively, but only by 6% (95% CI, 22% to 13%, P = 0.13) in nonatherogenic dyslipidemia patients. The authors concluded that targeting patients with high triglyceride levels or atherogenic dyslipidemia with fibrates may help reduce residual vascular risk. Fibrates that were evaluated included gemfibrozil (2 trials), fenofibrate (1 trial), fenofibrate + simvastatin (1 trial), and bezafibrate (1 trial).

Conclusions:
Although the AHRQ 2009 review indicated "very low" evidence level on various clinical outcomes comparing statin combination with fibrates vs. statin therapy, one significant limit of this review is that the trials included have heterogeneous characteristics of participants and most trials excluded participants with triglycerides above 300-600 mg/dL. The most recent systematic reviews focused on the clinical outcomes of patients with high triglycerides. Statins do not have significant role in reduction of triglycerides and gemfibrozil and fenofibrate have shown reduced vascular events in this situation. The most appropriate place in therapy for fibrates in the management of patients with dyslipidemia, are in those patients with especially elevated triglycerides, which is consistent with ATP III recommendation.

Nicotinic Acid
The exact mechanism of how niacin (nicotinic acid) reduces LDL and increases HDL is unknown. It is suspected to be involved in the metabolism of apolipoproteins, stimulating production of Apo A-I and Apo A-II, and possibly decreasing their turnover. It is also thought to decrease synthesis of LDL and VLDL without affecting fecal excretion of fats and bile acids.[18] Niacin was first introduced in 1954 and is available in immediate release, slow release and extended release forms. Flushing and rashes are common side effects associated with the use of niacin, which may occur in up to 60% of individuals.[19] However, this can be minimized by giving aspirin prior to niacin and slow titration of niacin dose.

The FDA announced in May 2011 a review of results from the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) clinical trial.[2] This trial compared simvastatin monotherapy to simvastatin + niacin extended release in patients with

established CVD. The trial was halted early due to lack of incremental benefit on cardiovascular risk reduction in the niacin extended release group. Also, a small, unexplained, increase in the rate of ischemic stroke was noted in the combination group. At this time, FDA has made no new conclusions or recommendations regarding the use of extended-release niacin alone or in combination with simvastatin or other statins.[2]

Prospective observational cohort studies have confirmed the status of low high-density lipoprotein cholesterol (HDL-C) concentration as an independent risk factor for cardiovascular disease, which may partly account for the residual risk. The Inter Heart Study[20], a case–control study involving almost 30,000 participants in 52 countries, defined the proportion of the risk of adverse cardiovascular outcomes attributable to individual risk factors. In this analysis, an elevated ratio of apolipoprotein B to apolipoprotein A1, the principal apolipoproteins of LDL-C and HDL-C, respectively, accounted for more than half of the overall population-attributable risk for a first myocardial infarction. In addition HDL-C remains a strong predictor of the risk of having cardiovascular events in statin-treated patients who have reached their target LDL-C concentrations.[21] Niacin is the most potent lipid lowering agent that increases the HDL level. The analysis of the phase 3 trials of niacin-laropiprant 2 g shows reductions in triglycerides by 23%, 18% in LDL-C and a 20% increase in HDL-C.[22] Similar results were previously obtained with the Niaspan formulation of modified release niacin and with crystalline immediate-release niacin.[23] In the Coronary Drug Project (CDP), patients treated with nicotinic acid had significant reductions in coronary events compared with placebo-treated patients.[24, 25] A subsequent analysis on the relationship between on-treatment lipid values and outcomes in the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial study showed that for every 0.13 mmol/L (5 mg/dL) increase in HDL-C, there was an 11% relative risk reduction in coronary heart disease.[26] Niacin might be an attractive alternative for statin-intolerant patients and or in combination with statin.

AHRQ Review Concluded (September 2009[7]):

- Based on a single study in participants requiring intensive lipid lowering therapy, the evidence grade is “very low” demonstrating no difference in all cause mortality (OR 1.84; 95% CI 0.16 to 20.76) and no difference in participants reaching ATP III LDL-c goals (OR 1.51, 95% CI 0.56 to 4.08) between the combination of any dose statin plus niacin and to any dose statin monotherapy.
- Based on a single study in participants with established vascular disease, the evidence grade is “very low” demonstrating no significant difference in all cause mortality (OR 1.84, 95% CI 0.16 to 20.76), no difference in vascular death (OR not reported) and no difference in number of participants reaching ATP III LDLc goals (OR 1.51, 95% CI 0.56 to 4.08) between the combination of any dose statin plus niacin and any dose statin monotherapy.
- Based on studies in participants followed up for more than 24 weeks in mixed populations, the evidence grade is “very low” showing no significant difference in all cause mortality (4 trials; OR 1.08, 95% CI 0.17 to 6.72), no difference in vascular death (1 trial; OR 0.53, 95% CI 0.03 to 8.64) and no significant difference in serious adverse events (3 trials; OR 1.00, 95% CI 0.26 to 3.86) between the combination of any dose statin plus niacin and any dose statin monotherapy.
- Based on studies in participants regardless of baseline risk and comparing the combination of any dose statin plus niacin to any dose statin, “very low” grade for no difference in all cause mortality (6 trials; OR 1.08, 95% CI 0.17 to 6.72), no difference in vascular death (2 trials; OR 0.53, 95% CI 0.03 to 8.64), no difference in serious adverse events (5 trials; OR 1.29, 95% CI 0.44 to 3.80) and no difference in participants reaching ATP III LDL-c goals (1 trial, OR not pooled).
- The only significant difference was observed in change in HDL-C in participants requiring intensive lipid lowering therapy, favoring combination therapy (mean difference 13.00; 95% CI 6.01 to 20)

New Systematic Reviews (Appendix B):

- In 2010 Bruckert E et al. conducted a meta-analysis to examine the effect of niacin alone or in combination on CV events and atherosclerosis.[27] Among 587 citations, 29 full articles were read and 14 were eligible for inclusion. The authors identified ten randomized controlled trials that enrolled 2647 patients in the active group and 3898 patients in the control group. The largest trial accounted for 60% of the pooled sample.
  . In the primary analysis, a significant response to treatment with niacin (alone or combined) was observed whatever the clinical outcome was. The relative odds reduction was 25% (95% CI = 14, 35) for major coronary events, 26% (95% CI = 8, 41) for stroke, and 27% (95% CI = 15, 37) for any cardiovascular event. A significant heterogeneity across studies was observed for any cardiovascular event. However, using a random-effect model, the effect size remained significant with a relative odds reduction of 48% (95% CI = 21, 65). Except for stroke, the pooled between-group difference remained significant in the sensitivity analysis excluding the largest trial. The authors concluded although the studies were conducted before statin therapy become standard care, and mostly in patients in secondary prevention, with various dosages of nicotinic acid 1–3 g/day, this meta-analysis found positive effects of niacin alone or in combination on all cardiovascular events and on atherosclerosis evolution. In addition to some inherent limitations of meta-analyses, the authors acknowledged that some of the clinical trials might have not been included in the review as the literature search was limited to Pub Med database only. However, for studies that were included in the analysis, the heterogeneity, sensitivity tests and the review of study quality and potential bias were conducted, although details on methods for quality assessment were not provided.
- Dugall JK et al. published a systematic review on March 5, 2010 on the effects of niacin on CV outcomes in patients with CAD, including randomized placebo-controlled trials.[28] There were 7 randomized control trials with total of 5,137 patients met the study inclusion criteria. Quality assessment was limited in this meta-analysis, including only concealment of the randomized treatment sequence and a follow-up of at least 90%.The analysis showed niacin therapy significantly reduced CAD revascularization compared to placebo (RR: 0.307 with 95% CI: 0.150 – 0.628; p = 0.001), nonfatal MI; (RR: 0.719; 95% CI: 0.603 – 0.856; p = 0.000), stroke and transient ischemic attack (TIA) (RR: 0.759; 95% CI: 0.613 – 0.940; p = 0.12), as well as possible but non-significant decrease in cardiac mortality (RR: 0.883; 95% CI 0.773 – 1.008; p = 0.066). The authors concluded that in this meta-analysis of 7 trials of secondary prevention, niacin was associated with a significant reduction in CV events and possible small but non-significant cardiovascular mortality.

Conclusions:

The main limitations of AHRQ review and the most recent reviews are 1) most trials included in the review were small and done prior to statin being used as first line; 2) the small numbers of end points in these older trials. Despite these limitations, niacin did show a positive effect on cardiovascular events. It remains to be the most potent agent to increase the HDL, which is a strong predictor of the risk of having cardiovascular events in statin-treated patients who have reached their target LDL-C concentrations. There is role of niacin especially in patients who cannot tolerate statin therapy. Niaspan® is extended released form of niacin formulated to reduce the side effects, especially flushing and rashes from the immediate release or slow release formulation of niacin.

Ezetimibe

Ezetimibe is an agent that inhibits intestinal absorption of cholesterol at the small intestine brush border by acting on the sterol transporter NPC1L1.[29] In clinical trials when used as monotherapy, it has shown to reduce LDL-c by 18% approximately.[30] It has minimal effects on TG and increases HDL modestly. Because it has

different mechanism of action and works on absorption of cholesterol, the combination therapy using statin plus ezetimibe has the potential to influence both biosynthetic pathway and absorption, resulting a greater reduction in LDL-c levels with either agent alone. However, up to date, the greater degree of LDL-c leve reduction when ezetimibe used in combination with statin has not demonstrated better clinical outcomes such as reduction in CV events, stroke or mortality. In addition, three recent clinical trials, ENHANCE[31], SEAS[32], and ARBITER 6-HALTS[33] have raised questions about the efficacy and safety of ezetimibe and have led to a re-examination of its clinical use as a drug for managing lipid risk factors (Appendix C). Both ENHANCE and ARBITER 6-HALTS trials showed no change in carotid intima-media thickness, a surrogate marker for arthrosclerosis. SEAS trial raised the potential of cancer risk from ezetimibe. See Appendix C for abstract of these studies.

AHRQ Review Concluded (September 2009[7]):

- Based on studies in participants requiring intensive lipid lowering therapy, there was very low quality of evidence demonstrating no difference in all cause mortality (14 trials; OR 0.61, 95% CI 0.22 to 1.71), no difference in vascular death (1 trial; OR 1.98, 95% CI 0.21 to 19.14) and a significant increase the number of participants reaching ATP III LDL-c goals in the combination group (18 trials; OR not pooled) between the combination of any dose statin plus ezetimibe and any dose statin monotherapy.
- Based on six studies in participants with established vascular disease, the evidence grade is "very low" showing no significant difference in all cause mortality (OR 0.66, 95% CI 0.19 to 2.31) and a significant increase in the number of participants reaching ATP III LDL-c goals favoring combination therapy (OR not pooled) between the combination of any dose statin plus ezetimibe and any dose statin monotherapy.
- Based on studies in participants regardless of baseline risk, the evidence grade is "very low" for no difference in all cause mortality (24 trials; OR 0.95, 95% CI 0.37 to 2.41), no difference in vascular death (2 trials; OR 2.70, 95% CI 0.38 to 19.2), no significant difference in serious adverse events (27 trials; OR 1.08, 95% CI 0.88 to 1.33) and a significant increase in the number of participants reaching ATP III LDL-c goals (23 trials; not pooled) between the combination of any dose statin plus ezetimibe and any dose statin monotherapy.

New Systematic Reviews:
There are no new systematic reviews evaluating the comparative effectiveness in long term cardiovascular outcomes. The only new systematic review published recently assessed the LDL lowering with the addition of ezetimibe to statin vs. statin titration in patients with hypercholesterolaemia.[34]

Conclusions:
Although ezetimibe acts on different pathway and has been shown to lower the LDL-C alone and in combination with a statin, it has not been shown to reduce long term cardiovascular clinical outcomes. Also, its safety has been questioned in a recent RCT.

Omega-3 Fatty Acids
Omega-3 fatty acids have been postulated to have a number of beneficial effects in patients at risk for vascular disease, including antithrombotic and blood pressure lowering effects. They are considered to be lipid lowering agents due to a reduction in triglycerides, particularly postprandially.[35-39] There are two forms of omega-3 fatty acids, eicosapentaenoic (EPA), dicisapentaenoic (DPA) and docosahexaenoic (DHA), and the plant oil derived alpha linolenic acid (ALA). Omega-3-acid reduces TG in patients with very high TG (>500mg/dl). American Heart Association (AHA) nutrition committee has recommended an intake of one

gram of EPA + DHA per day for individuals with documented CHD and 2-4 grams per day for those needing to lower triglyverides.[40] Its efficacy in the secondary prevention of CVD remains inconclusive.

One large randomized open-label, blinded endpoint analysis, long term study was done in Japan by Yokoyama M.[41] The study enrolled total of 18,645 patients with a total cholesterol of 6.5 mmol/L (251mg/dL) or greater were recruited from local physicians throughout Japan between 1996 and 1999. Patients were randomly assigned to receive either 1800 mg of EPA daily with a statin (EPA group; n=9326) or a statin only (controls; n=9319) with a 5-year follow-up. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. At mean follow-up of 4.6 years, study results showed the primary endpoint in 262 (2.8%) patients in the EPA group and 324 (3.5%) in controls, demonstrating a 0.7% absolute risk reduction in major coronary events (p=0.011). Unstable angina and non-fatal coronary events were also significantly reduced in the EPA group. Sudden cardiac death and coronary death did not differ between groups. In patients with a history of coronary artery disease who were given EPA treatment, major coronary events were reduced by 19% (secondary prevention subgroup: 158 [8.7%] in the EPA group vs. 197 [10.7%] in the control group; p=0.048). In patients with no history of coronary artery disease, EPA treatment reduced major coronary events by 18%, but this finding was not significant (104 [1.4%] in the EPA group vs. 127 [1.7%] in the control group; p=0.132). These results should be interpreted with caution due to its open label, poor study design.

AHRQ Review Concluded (September 2009[7]):

- Based on studies in participants regardless of baseline risk, the evidence grade is "very low" grade showing no significant difference in all cause mortality (3 trials; OR 1.08, 95% CI 0.91 to 1.28), and no significant difference serious adverse events (1 trial; OR 4.44, 95% CI 0.49 to 40.29) between the combination of any dose statin plus omega-3 and any dose statin monotherapy.
- No evidence was available to make conclusion regarding participants attainting the ATP III LDL goals or vascular death.
- Based on a single study in participants followed up for more than 24 weeks, the evidence grade is "very low" for no difference in all cause mortality (OR 1.08, 95% CI 0.91 to 1.28) between the combination of any dose statin plus omega-3 compared and any dose statin monotherapy.

New Systematic Reviews (Appendix B):

G.D. Eslick et al. published an updated the meta-analysis that included all placebo-controlled randomized trials of parallel design that evaluated any of the main blood lipid outcomes: total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol or triglycerides (TG).[42] Unfortunately this analysis did not examine the cardiovascular or stroke outcomes.

A recent meta-analysis investigated the efficacy of EPA and DPA in the secondary prevention of CVD including randomized, placebo-controlled trials.[3] The Jadad scale was used to assess the quality of each trial and of the fourteen RCTs included in the analysis, the mean Jadad score was 4.4 points for 7 trials using inappropriate randomization methods and 1 trial not describing the loss to follow-up. Results showed that omega-3 fatty acid supplementation did not reduce the risk of overall cardiovascular events (RR 0.99; 95% CI 0.89 to 1.09) and there were no significant differences in all cause mortality, sudden cardiac death,

myocardial infarction, or stroke between the two groups. However, ometa-2 fatty acid supplementation did significantly reduce cardiovascular death (RR 0.91; 95% CI 0.84 – 0.99).[3] A significant reduction was not seen when one trial was excluded that had a significant difference in the proportions with a history of angina between the two groups.[3]

New Guideline:

There are no new guidelines published during this review period. However, American Heart Association AHA) published a scientific statement on Triglyceride and Cardiovascular disease in May 2011.[43] The statement stated "As monotherapy, fibrates offer the most TG reduction, followed by immediate-release niacin, omega-3 methyl esters, extended-release niacin, statins, and ezetimibe". It recommends 2 to 4 grams of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) per day for patients who need to lower their TG level.

Conclusions:

Omega fatty acids appear to have a role in cardiovascular risk factor management but the evidence base for therapeutic applications is still poorly defined. Although it is recommended by AHA for treatment of hypertriglyceridemia, several conflicting meta-analyses have failed to agree on the efficacy of taking fish oils for preventing cardiovascular disease or reducing cardiovascular mortality.[44 - 51] Omega fatty acid can be a treatment option for patients who have very high TG (>500 mg/dl) and failed or have contraindication to other triglyceride lowing agents.

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APPENDIX A: Previous Guidelines and Systematic Reviews:

Previous Guidelines

ATP III Update 2004[6]

- Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering.
- In high-risk persons, the recommended LDL-C goal is < 100 mg/dL.
  - An LDL-C goal of < 70 mg/dL is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk.
  - If LDL-C is ≥ 100 mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes.
  - If baseline LDL-C is < 100 mg/dL, institution of an LDL-lowering drug to achieve an LDL-C level < 70 mg/dL is a therapeutic option on the basis of available clinical trial evidence.
  - If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When triglycerides are ≥ 200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal.
- For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is < 130 mg/dL; an LDL-C goal _100 mg/dL is a therapeutic option on the basis of available clinical trial evidence. When LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level < 100 mg/dL is a therapeutic option on the basis of available clinical trial evidence.
- Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.
- When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.
- For people in lower-risk categories, recent clinical trials do not modify the goals and cutpoints of therapy.

ATP III Guidelines on Drug Therapy May 2001[3]

- Progression of drug therapy in primary prevention
  - Start statin or bile acid sequestrant or nicotinic acid
  - Consider higher dose of statin or add bile acid sequestrant or nicotinic acid
- Management of Specific Dyslipidemias
  - Very high LDL cholesterol (≥ 190mg/dL): often require combination drug therapy such as statin + bile acid sequestrant to achieve the LDL goal.
  - Elevated serum triglycerides:
    - Very high triglycerides (≥ 500mg/dL): TG lowering agent such as fibrate or nicotinic acid.
    - When lowered to < 500mg/dL: Intensify therapy with an LDL-lowering drug or add nicotinic acid or fibrate to achieve non-HDL cholesterol gaol.

Previous Systematic Review Conclusions (September 2009)[7]

❖ **Key Question 1. Long-Term Benefits and Serious Adverse Events**

- **All-cause mortality:** The quality of evidence was very low for all available comparisons of combinations and monotherapy reported. For individuals requiring intensive therapy, limited evidence was available for statin combinations with ezetimibe and fibrates compared to higher doses of statins.
- **Vascular death:** Treatments aimed at modifying lipids might be expected to lower the rates of death due to vascular diseases such as heart disease and stroke. However, no trials examined this outcome in a high-risk population and compared the combination to a higher statin dose.
- **Other clinical outcomes:** For the outcomes of reduction of MI or stroke or avoidance of revascularization procedures on the carotid or coronary vessels, no evidence comparing combination therapy with a higher dose of statin was available.
- **Serious adverse events:** The quality of evidence was very low for all available combination and monotherapy comparisons.
- **Cancer.** Evidence pertained to all available trial populations and not only those in need of intensive treatment. Some data were available for individuals at any risk level and statin dose.

❖ **Key Question 2. LDL-c Targets, Short-Term Side Effects, Tolerability, and Adherence**

- **Participants attaining ATP III LDL-c goals:** The available evidence is of very low quality for all comparisons of combination with monotherapy.
- **LDL-c:** When comparing a specific statin in combination with a higher dose statin in populations requiring intensive treatment, evidence was either insufficient or absent for statin-fibrate, statin-niacin, statin-BAS, and statin-omega-3 combinations.
- **HDL-c:** There is lack of evidence permitting meaningful conclusions from trials comparing a combination with higher dose of statin monotherapy in populations requiring intensive treatment.
- **Total cholesterol:HDL-c ratio:** When comparing a specific statin in combination with a higher dose statin in populations requiring intensive treatment, evidence was either absent or based on single-trial data, precluding robust conclusions across any combination therapy.
- **Measures of atherosclerosis:** Carotid intimal media thickness (IMT) can be measured by ultrasound and correlates with the presence of atherosclerotic plaque and vascular risk factors. Previous research has shown that statin treatment reduces the progression of this marker. Two trials were available that compared mean change from baseline in the IMT with combination therapy compared to statin monotherapy. Both trials yielded indeterminate results.
- **Adherence and harm:** For the comparison of a specific statin in combination with a higher dose of its monotherapy across all trial populations, insufficient evidence was available for all combinations except statin-ezetimibe, which showed no significant differences between treatments for the outcomes of withdrawal due to adverse events and liver toxicity (defined as AST/ALT above three times the upper limit of normal). Most trials had a short duration of treatment and follow up.

❖ **Key Question 3. Benefits and Harms Within Subgroups of Patients**

- **Participants with diabetes mellitus:** Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with a higher dose of statin monotherapy for any relevant outcomes.
- **Participants with established vascular disease:** Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with higher dose statin monotherapy for any relevant outcomes in individuals with pre-existing vascular disease.
- **Participants with baseline LDL-c of 190 mg/dL or above:** Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with higher dose statin monotherapy for any relevant outcomes.
- **Participants with cerebrovascular disease, females, participants of 80 years of age or older, participants of African descent, participants of Asian descent, and Hispanics:** No evidence was available for participants with cerebrovascular disease and those age 80 years and over. Sparse evidence of very low quality, precluding meaningful conclusions, was available in subgroups of participants of different ethnic origins and females.

APPENDIX B: Abstract of Systematic Reviews

1. A systematic review of bile acid sequestrant therapy in children with familial hypercholesterolemia Michael H. Davidson, MD, FACC, FACP, FNLA The University of Chicago Pritzker School of Medicine, 515 North State Street, Suite 2700, Chicago, IL 60654, USA.
   Journal of Clinical Lipidology 5, no. 2 (April 2011): 76–81.

   Abstract: Familial hypercholesterolemia, which arises as a result of a mutation in the low-density lipoprotein (LDL) receptor gene, is characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C), regardless of dietary and lifestyle modifications. Pharmacological therapy is often required to adequately control the elevated LDL-C levels associated with familial hypercholesterolemia. However, children with this genetic condition present many challenges for physicians, who must weigh the benefits of lipid-lowering therapy against the risks associated with the various treatment options. Furthermore, because familial hypercholesterolemia is a chronic condition, children will likely require long-term lipid-lowering therapy. As such, the potential effect of pharmacological treatment on development is of paramount importance in this population. Bile acid sequestrants represent a unique treatment option for children with familial hypercholesterolemia in that these agents are not systemically absorbed but rather exert their lipid-lowering effects via binding to bile acids within the gastrointestinal tract. A literature search was performed to identify clinical data related to the use of bile acid sequestrant therapy in children (,18 years of age) with familial hypercholesterolemia. Studies published in English between 1990 and December 2010 that were retrieved from MEDLINE and EMBASE were included in this systematic review. In total, five clinical studies were identified that evaluated bile acid sequestrant monotherapy, whereas two studies were identified that evaluated combination therapy with a bile acid sequestrant and low-dose statin. This review summarizes the clinical data regarding the efficacy and safety of bile acid sequestrants in this specialized population.

2. Efficacy offibratesforcardiovascularriskreductioninpersonswithatherogenic dyslipidemia: Ameta-analysis by Meng Lee a,b, JeffreyL.Savera,b, AmytisTowfighic, JessicaChowd, BruceOvbiagelee. Atherosclerosis (2011), doi:10.1016/j.atherosclerosis.2011.04.020

   Background: Recent datasuggestthatnon-targetedtreatmentwithfibratesmodestlyreducestheriskof incident cardiovascular events. However, the effect of fibrate treatment maybe particularly beneficial in patients with guideline-endorsed indications for therapy due to evidence of atherogenic dyslipidemia. We conducted a systematic review and meta-analysis to investigate the influence of fibrates on vascular risk reduction in persons with atherogenic dyslipidemia.

   Methods: Systematic search of Pub med, CENTRAL and recent reviews was conducted to identify atherogenic dyslipidemia (serum high density lipoprotein cholesterol [HDL-C]<40mg/dl or triglycerides >200mg/dl) cohorts from randomized controlled trials. RR with 95%CI was used as a measure of the association between fibrate therapy and risk of cardiovascular diseases, after pooling data across trials in a random-effects model.

   Results: Six trials met selection criteria. Compared to placebo, the greatest benefit with fibrate treatment was seen in 7,389 subjects with high triglycerides, fibrate therapy reduced risk of vascular events (RR 0.75, 95%CI0.65to0.86, P < 0.001); and in 5,068 subjects with both high triglycerides anc

low HDL-C (RR 0.71, 95%CI 0.62to0.82, P < 0.001). Less benefit was noted in 15,303 subjects selected for low HDL-C (RR 0.84, 95%CI 0.77to0.91, P < 0.001). Among 9872 subjects with neither high triglycerides nor low HDL-C, fibrate therapy did not reduce subsequent vascular events (RR0.96, 95%CI 0.85to1.09, P = 0.53).

Conclusions: Fibrate treatment directed at markers of atherogenic dyslipidemia substantially reduce subsequent vascular event risk.

3. Fibrates Effect on Cardiovascular Risk Is Greater in Patients With High Triglyceride Levels or Atherogenic Dyslipidemia Profile: A Systematic Review and Meta-analysis by Eric Bruckert, MD, PhD, Julien Labreuche, BS, Dominique Deplanque, MD, PhD, Pierre-Jean Touboul, MD, and Pierre Amarenco, MD. *Journal of Cardiovascular Pharmacology* 57, no. 2 (February 2011): 267–272.

Abstract: According to recently published data, fibrates may reduce the risk of major cardiovascular events. Whether patients with low high-density lipoprotein cholesterol (HDL-C), high triglyceride levels, or both may have additional benefits remains under debate. We performed a meta-analysis of the 5 large trials assessing the impact of fibrates on cardiovascular end points and providing information on low HDL-C and high triglyceride levels. Subgroups were determined according to values closest to predetermined cut-offs for both HDL-C and triglycerides (35 and 200 mg/dL, respectively). Overall, 4,671 patients (2,401 in fibrate group and 2,270 in placebo group) were classified as having an atherogenic dyslipidemia featuring low HDLC combined with high triglyceride levels. Across trials, the proportion of patients classified in this subgroup ranged from 11% to 33%. We found a significant difference in the magnitude of fibrate effect across dyslipidemia subgroups (P for between-group heterogeneity = 0.0002). A greater effect size was found in patients with high triglyceride levels or atherogenic dyslipidemia phenotype where fibrates were estimated to reduce the cardiovascular risk by 28% [95% confidence interval (CI), 15% to 39%; P , 0.001] or 30% (95% CI, 19% to 40%, P , 0.0001), respectively, but only by 6% (95% CI, 22% to 13%, P = 0.13) in nonatherogenic dyslipidemia patients. Targeting patients with high triglyceride levels or atherogenic dyslipidemia with fibrates may help reduce residual vascular risk.

4. Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis by Eric Bruckerta, Julien Labreucheb,c, Pierre Amarenco. *Atherosclerosis* 210, no. 2 (June 2010): 353–361.

Objective: High-density lipoprotein cholesterol (HDL-C) concentration is a strong predictor of cardiovascular events in both naïve and statin-treated patients. Nicotinic acid is an attractive option for decreasing residual risk in statin-treated or statin-intolerant patients since it increases HDL-C by up to 20% and decreases low-density lipoprotein cholesterol and lipoprotein(a) plasma concentrations.

Methods: We performed a computerized Pub Med literature search that focused on clinical trials evaluating niacin, alone or in combination with other lipid-lowering drugs, published between January 1966 and August 2008.

Results: Among 587 citations, 29 full articles were read and 14 were eligible for inclusion. Overall 11 randomized controlled trials enrolled 2682 patients in the active group and 3934 in the control group. In primary analysis, niacin significantly reduced major coronary events (relative odds reduction = 25%,

95% CI 13, 35), stroke (26%, 95% CI = 8, 41) and any cardiovascular events (27%, 95% CI = 15, 37). Except for stroke, the pooled between-group difference remained significant in sensitivity analysis excluding the largest trial. In comparison with the non-niacin group, more patients in the niacin group had regression of coronary atherosclerosis (relative increase = 92%, 95% CI = 39, 67) whereas the rate of patients with progression decreased by 41%, 95% CI = 25, 53. Similar effects of niacin were found on carotid intima thickness with a weighted mean difference in annual change of −17μm/year (95% CI =−22, −12).

Conclusions: Although the studies were conducted before statin therapy become standard care, and mostly in patients in secondary prevention, with various dosages of nicotinic acid 1–3 g/day, this meta-analysis found positive effects of niacin alone or in combination on all cardiovascular events and on atherosclerosis evolution.

5. Effect of Niacin Therapy on Cardiovascular Outcomes in Patients With Coronary Artery Disease by Jasleen K. Duggal, Mukesh Singh, Navneet Attri, Param P. Singh, Neyaz Ahmed, Suneet Pahwa, Janos Molnar, Sarabjeet Singh, Sandeep Khosla and Rohit Arora. *Journal of Cardiovascular Pharmacology and Therapeutics* 15(2) 158-166.

Background: Niacin or nicotinic acid (vitamin B3) raises the levels of high-density lipoprotein cholesterol (HDL) by about 30% to 35%. In patients with prior coronary disease, 7 trials have been published on clinical cardiovascular disease outcomes and the results, not surprisingly, are inconsistent. Hence we performed this meta-analysis of randomized placebo-controlled trials (RCTs) to evaluate the effect of niacin on cardiovascular outcomes in patients with coronary artery disease.

Methods: A systematic search using PubMed, EMBASE, and Cochrane library databases was performed. Seven studies with a total of 5137 patients met our inclusion criteria. Heterogeneity of the studies was analyzed by the Cochran Q statistics. The significance of common treatment effect was assessed by computing the combined relative risks using the Mantel-Haenszel fixed-effect model. A 2-sided alpha error of less than .05 was considered statistically significant ($P < .05$).

Results: Compared to placebo group, niacin therapy significantly reduced coronary artery revascularization (RR [relative risk]: 0.307 with 95% CI: 0.150-0.628; $p = 0.001$), nonfatal myocardial infarction ([MI]; RR: 0.719; 95% CI: 0.603-0.856; $p = 0$ .000), stroke, and TIA ([transient ischemic attack] RR: 0.759; 95%CI: 0.613-0.940; $p = 0$ .012), as well as a possible but nonsignificant decrease in cardiac mortality (RR: 0.883: 95% CI: 0.773-1.008; $p = 0.066$).

6. Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis by Guy D. Eslick a,b, Peter R.C. Howe c, Caroline Smith a, Ros Priest a, Alan Bensoussan a. *International Journal of Cardiology* 136 (2009) 4–16.

Background: Fish oils have been widely reported as a useful supplement to reduce fasting blood triglyceride levels in individuals with hyperlipidemia. We performed an updated meta-analysis to quantitatively evaluate all the randomized trials of fish oils in hyperlipidemic subjects.

Methods: We conducted a systematic literature search using several electronic databases supplemented by manual searches of published reference lists, review articles and conference abstracts. We included all placebo-controlled randomized trials of parallel design that evaluated any of the main blood lipid outcomes: total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol or triglycerides (TG). Data were pooled using DerSimonian–Laird's random effects model.

Results: The final analysis comprised of 47 studies in otherwise untreated subjects showed that taking fish oils (weighted average daily intake of 3.25 g of EPA and/or DHA) produced a clinically significant reduction of TG (−0.34 mmol/L, 95% CI: −0.41 to −0.27), no change in total cholesterol (−0.01 mmol/L, 95% CI: −0.03 to 0.01) and very slight increases in HDL (0.01 mmol/L, 95% CI: 0.00 to 0.02) and LDL
cholesterol (0.06 mmol/L, 95% CI: 0.03 to 0.09). The reduction of TG correlated with both EPA+DHA intake and initial TG level.

Conclusion: Fish oil supplementation produces a clinically significant dose-dependent reduction of fasting blood TG but not total, HDL or LDL cholesterol in hyperlipidemic subjects.

7. Kwak SM, Myung SK, Lee YJ, Seo HG; for the Korean Meta-analysis Study Group. Efficacy of Omega-3 Fatty Acid Supplements (Eicosapentaenoic Acid and Docosahexaenoic Acid) in the Secondary Prevention of Cardiovascular Disease: A Meta-analysis of Randomized, Double-blind, Placebo-Controlled Trials. Arch Intern Med. 2012 Apr 9. [Epub ahead of print]

   Background: Although previous randomized, double-blind, placebo-controlled trials reported the efficacy of omega-3 fatty acid supplements in the secondary prevention of cardiovascular disease (CVD), the evidence remains inconclusive. Using a meta-analysis, we investigated the efficacy of eicosapentaenoic acid and docosahexaenoic acid in the secondary prevention of CVD.

   Methods:We searched PubMed, EMBASE, and the Cochrane Library in April 2011. Two of us independently reviewed and selected eligible randomized controlled trials.

   Results: Of 1007 articles retrieved, 14 randomized, double-blind, placebo-controlled trials (involving 20 485 patients with a history of CVD) were included in the final analyses. Supplementation with omega-3 fatty acids did not reduce the risk of overall cardiovascular events (relative risk, 0.99; 95% CI, 0.89-1.09), all-cause mortality, sudden cardiac death, myocardial infarction, congestive heart failure, or transient ischemic attack and stroke. There was a small reduction in cardiovascular death (relative risk, 0.91; 95% CI, 0.84-0.99), which disappeared when we excluded a study with major methodological problems. Furthermore, no significant preventive effect was observed in subgroup analyses by the following: country location, inland or coastal geographic area, history of CVD, concomitant medication use, type of placebo material in the trial, methodological quality of the trial, duration o treatment, dosage of eicosapentaenoic acid or docosahexaenoic acid, or use of fish oil supplementation only as treatment.

Conclusion: Our meta-analysis showed insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease.

APPENDIX C: Selected Abstract of RTCs

1. **Simvastatin with or without ezetimibe in familial hypercholesterolemia.**

Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, Visseren FL, Sijbrands EJ, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, de Groot E; ENHANCE Investigators. Collaborators (13)
Source: Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands. j.j.kastelein@amc.uva.nl

Erratum in N Engl J Med. 2008 May 1;358(18):1977.

Abstract

BACKGROUND: Ezetimibe, a cholesterol-absorption inhibitor, reduces levels of low-density lipoprotein (LDL) cholesterol when added to statin treatment. However, the effect of ezetimibe on the progression of atherosclerosis remains unknown.

METHODS: We conducted a double-blind, randomized, 24-month trial comparing the effects of daily therapy with 80 mg of simvastatin either with placebo or with 10 mg of ezetimibe in 720 patients with familial hypercholesterolemia. Patients underwent B-mode ultrasonography to assess the intima-media thickness of the walls of the carotid and femoral arteries. The primary outcome measure was the change in the mean carotid-artery intima-media thickness, which was defined as the average o the means of the far-wall intima-media thickness of the right and left common carotid arteries, carotid bulbs, and internal carotid arteries.

RESULTS: The primary outcome, the mean (+/-SE) change in the carotid-artery intima-media thickness, was 0.0058+/-0.0037 mm in the simvastatin-only group and 0.0111+/-0.0038 mm in the simvastatin-plus-ezetimibe (combined-therapy) group (P=0.29). Secondary outcomes (consisting of other variables regarding the intima-media thickness of the carotid and femoral arteries) did not differ significantly between the two groups. At the end of the study, the mean (+/-SD) LDL cholesterol level was 192.7+/-60.3 mg per deciliter (4.98+/-1.56 mmol per liter) in the simvastatin group and 141.3+/-52.6 mg per deciliter (3.65+/-1.36 mmol per liter) in the combined-therapy group (a between-group difference of 16.5%, P<0.01). The differences between the two groups in reductions in levels of triglycerides and C-reactive protein were 6.6% and 25.7%, respectively, with greater reductions in the combined-therapy group (P<0.01 for both comparisons). Side-effect and safety profiles were similar in the two groups.

CONCLUSIONS: In patients with familial hypercholesterolemia, combined therapy with ezetimibe and simvastatin did not result in a significant difference in changes in intima-media thickness, as compared with simvastatin alone, despite decreases in levels of LDL cholesterol and C-reactive protein.

(ClinicalTrials.gov number, NCT00552097 [ClinicalTrials.gov].).

2. **The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis): final results and the impact of medication adherence, dose, and treatment duration.**

Villines TC, Stanek EJ, Devine PJ, Turco M, Miller M, Weissman NJ, Griffen L, Taylor AJ.

Source: Cardiology Service, Walter Reed Army Medical Center, Washington, DC 20307, USA. todd.villines@amedd.army.mil

Abstract

OBJECTIVES: This report describes the final results of the ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis) trial.

BACKGROUND: The ARBITER 6-HALTS trial was terminated early on the basis of a pre-specified interim analysis showing superiority of niacin over ezetimibe on change in carotid intima-media thickness (CIMT). After termination, an additional 107 subjects completed a close-out assessment.

METHODS: Patients with coronary heart disease (CHD) or CHD equivalent with low-density lipoprotein cholesterol <100 mg/dl and high-density lipoprotein cholesterol <50 mg/dl for men or 55 mg/dl for women while receiving stable statin treatment were randomly assigned to ezetimibe (10 mg/day) or extended-release niacin (target dose, 2,000 mg/day). The primary end point was change in mean CIMT, analyzed according to a last observation carried forward method. The relationships of study medication adherence, dosage, and cumulative exposure (product of adherence, dose, and time) with change in CIMT were explored.

RESULTS: Results in 315 patients included 208 with 14-month follow-up and 107 after mean treatment of 7 +/- 3 months. Niacin (n = 154) resulted in significant reduction (regression) in mean CIMT (-0.0102 +/- 0.0026 mm; p < 0.001) and maximal CIMT (-0.0124 +/- 0.0036 mm; p = 0.001), whereas ezetimibe (n = 161) did not reduce mean CIMT (-0.0016 +/- 0.0024 mm; p = 0.88) or maximal CIMT (-0.0005 +/- 0.0029 mm; p = 0.88) compared with baseline. There was a significant difference between ezetimibe and niacin treatment groups on mean changes in CIMT, favoring niacin, for both mean CIMT (p = 0.016) and maximal CIMT (p = 0.01). Increased cumulative drug exposure was related to regression of CIMT with niacin, and progression of CIMT with ezetimibe.

CONCLUSIONS: Niacin induces regression of CIMT and is superior to ezetimibe for patients taking statins. (Comparative Study of the Effect of Ezetimibe Versus Extended-Release Niacin on Atherosclerosis; NCT00397657).

3. **Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis.**

Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, Gerdts E, Gohlke-Bärwolf C, Holme I, Kesäniemi YA, Malbecq W, Nienaber CA, Ray S, Skjaerpe T, Wachtell K, Willenheimer R; SEAS Investigators. Collaborators (445) Source:Division of Cardiology, Aker University Hospital, Trondheimsveien 235, N-0514 Oslo, Norway anne@rossebo.net

Abstract

BACKGROUND: Hyperlipidemia has been suggested as a risk factor for stenosis of the aortic valve, but lipid-lowering studies have had conflicting results.

METHODS: We conducted a randomized, double-blind trial involving 1873 patients with mild-to-moderate, asymptomatic aortic stenosis. The patients received either 40 mg of simvastatin plus 10 mg of ezetimibe or placebo daily. The primary outcome was a composite of major cardiovascular events, including death from cardiovascular causes, aortic-valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke. Secondary outcomes were events related to aortic-valve stenosis and ischemic cardiovascular events.

RESULTS: During a median follow-up of 52.2 months, the primary outcome occurred in 333 patients (35.3%) in the simvastatin-ezetimibe group and in 355 patients (38.2%) in the placebo group (hazard ratio in the simvastatin-ezetimibe group, 0.96; 95% confidence interval [CI], 0.83 to 1.12; P=0.59). Aortic-valve replacement was performed in 267 patients (28.3%) in the simvastatin-ezetimibe group and in 278 patients (29.9%) in the placebo group (hazard ratio, 1.00; 95% CI, 0.84 to 1.18; P=0.97) Fewer patients had ischemic cardiovascular events in the simvastatin-ezetimibe group (148 patients) than in the placebo group (187 patients) (hazard ratio, 0.78; 95% CI, 0.63 to 0.97; P=0.02), mainly because of the smaller number of patients who underwent coronary-artery bypass grafting. Cancer occurred more frequently in the simvastatin-ezetimibe group (105 vs. 70, P=0.01).

CONCLUSIONS: Simvastatin and ezetimibe did not reduce the composite outcome of combined aortic-valve events and ischemic events in patients with aortic stenosis. Such therapy reduced the incidence of ischemic cardiovascular events but not events related to aortic-valve stenosis. (ClinicalTrials.gov number, NCT00092677.)

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

DRAFT COVERAGE GUIDANCE: LOW BACK PAIN: PHARMACOLOGIC INTERVENTIONS*
DATE: XX/XX/XXXX

HERC COVERAGE GUIDANCE

Pharmacologic interventions for low back pain:

- Initial pharmacologic therapy should be acetaminophen or non-steroidal anti-inflammatory medications and/or skeletal muscle relaxants
- Second line agents include benzodiazepines and opioids, due to associated risks
- Systemic steroids should not be covered
- For chronic low back pain, tricyclic antidepressants should be covered
- For acute exacerbations of chronic low back pain, the herbal therapies of devil's claw, willow bark, and capsicum are beneficial

*Coverage guidance for imaging, percutaneous interventions and surgery for low back pain will be addressed in subsequent documents.

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on five principles. Selected topics must represent:

- a significant burden of disease,
- important uncertainty with regard to efficacy or harms,
- important variation or controversy in clinical care,
- high costs, significant economic impact, and/or
- high public interest.

Coverage guidance development follows to translate the evidence review to a policy decision. In addition to an evidence-based guideline developed by the Evidence-based Guideline Subcommittee and a health technology assessment developed by the Heath Technology Assessment Subcommittee, coverage guidance may utilize an existing evidence report produced in the last 5 years by the Agency for Healthcare Research and Quality, the Medicaid Evidence-based Decisions Project or the Washington Health Technology Assessment Program.

EVIDENCE SOURCES

Livingston, C., King, V., Little, A., Pettinari, C., Thielke, A., & Gordon, C. (2011). *State of Oregon Evidence-based Clinical Guidelines Project. Evaluation and management of low back pain: A clinical practice guideline based on the joint practice guideline of the American College of Physicians and the American Pain Society (Diagnosis and treatment of low back pain).* Salem: Office for Oregon Health Policy and Research. Available at: http://www.oregon.gov/OHA/OHPR/HERC/Evidence-Based-Guidelines.shtml

Chou, R., Huffman, L. *Medications for Acute and Chronic Low Back Pain:A Review of the Evidence for an American Pain Society/American College of Physicians Clinical Practice Guideline.* Ann Intern Med. 2007; 147; 505-514. Available at: http://www.annals.org/content/147/7/505.full.pdf+html

Chou R., Qaseem, A., Snow, V., Casey, D., Cross, J.T., Jr., Shekelle, P., Owens, D.K.; Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society Low Back Pain Guidelines Panel. *Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society.* Annals of Internal Med. 2007; 147(7); 478-491. Available at: http://www.annals.org/content/147/7/478.long

The summary of evidence in this document is derived directly from this evidence source, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Low back pain is the fifth most common reason for all physician visits in the United States. Approximately one quarter of U.S. adults reported having low back pain lasting at least 1 whole day in the past 3 months, and 7.6% reported at least 1 episode of severe acute low back pain within a 1-year period. Low back pain is also very costly: Total incremental direct health care costs attributable to low back pain in the U.S. were estimated at $26.3 billion in 1998. In addition, indirect costs related to days lost from work are substantial, with approximately 2% of the U.S. work force compensated for back injuries each year.

Many patients have self-limited episodes of acute low back pain and do not seek medical care. Among those who do seek medical care, pain, disability, and return to work typically improve rapidly in the first month. However, up to one third of patients report persistent back pain of at least moderate intensity 1 year after an acute episode, and 1 in 5 report substantial limitations in activity. Approximately 5% of the people with back pain disability account for 75% of the costs associated with low back pain.

Many options are available for evaluation and management of low back pain. However, there has been little consensus, either within or between specialties, on appropriate clinical evaluation and management of low back pain. Numerous studies show unexplained, large variations in use of diagnostic tests and treatments. Despite wide variations in practice, patients seem to experience broadly similar outcomes, although costs of care can differ substantially among and within specialties.

Evidence Review

Recommendation 1: *For patients with low back pain, clinicians should consider the use of medications with proven benefits in conjunction with back care information and self-care. Clinicians should assess severity of baseline pain and functional deficits, potential benefits, risks, and relative lack of long-term efficacy and safety data before initiating therapy (strong recommendation, moderate-quality evidence). For most patients, first-line medication options are acetaminophen or nonsteroidal anti-inflammatory drugs.*

Medications in several classes have been shown to have moderate, primarily short-term benefits for patients with low back pain. Each class of medication is associated with unique trade-offs involving benefits, risks, and costs. For example, acetaminophen is a slightly weaker analgesic than NSAIDs but is a reasonable first-line option for treatment of acute or chronic low back pain because of a more favorable safety profile and low cost. Nonselective NSAIDs are associated with well-known gastrointestinal and renovascular risks, and there is an association between exposure to cyclooxygenase-2–selective or most nonselective NSAIDs and increased risk for myocardial infarction. Opioid analgesics or tramadol are an option when used judiciously in patients with acute or chronic low back pain who have severe, disabling pain that is not controlled (or is unlikely to be controlled) with acetaminophen and NSAIDs. Because of substantial risks, including aberrant drug-related behaviors with long-term use in patients vulnerable or potentially vulnerable to abuse or addiction, potential benefits and harms of opioid analgesics should be carefully weighed before starting therapy.

For skeletal muscle relaxants, although the antispasticity drug tizanidine has been well studied for low back pain, there is little evidence for the efficacy of baclofen or dantrolene, the other FDA-approved drugs for the treatment of spasticity. Other medications in the skeletal muscle relaxant class are an option for short-term relief of acute low back pain, but all are associated with central nervous system adverse effects (primarily sedation). Tricyclic antidepressants are an option for pain relief in patients with chronic low back pain and no contraindications to this class of medications. Antidepressants in the selective serotonin reuptake inhibitor class and trazodone have not been shown to be effective for low back pain, and serotonin–norepineprhine reuptake inhibitors (duloxetine and venlafaxine) have not yet been evaluated for low back pain.

Gabapentin is associated with small, short-term benefits in patients with radiculopathy and has not been directly compared with other medications or treatments. There is

insufficient evidence to recommend for or against other antiepileptic drugs for back pain with or without radiculopathy. For acute or chronic low back pain, benzodiazepines seem similarly effective to skeletal muscle relaxants for short-term pain relief but are also associated with risks for abuse, addiction, and tolerance. Herbal therapies, such as devil's claw, willow bark, and capsicum, seem to be safe options for acute exacerbations of chronic low back pain, but benefits range from small to moderate. Systemic corticosteroids are not recommended for treatment of low back pain with or without sciatica, because they have not been shown to be more effective than placebo.

[Evidence source]

Overall Summary

Medications in several classes, including NSAIDs, opioids, tramadol, skeletal muscle relaxants, antidepressants and antiepileptics, have been shown to have moderate, primarily short-term benefits for patients with low back pain. Each class of medication is associated with unique trade-offs involving benefits, risks, and costs. For most patients, first-line medications are acetaminophen or NSAIDs.

PROCEDURES

Pharmacologic therapy

DIAGNOSES

Low back pain

APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
720.1	Spinal enthesopathy
720.2	Sacroiliitis, not elsewhere classified
721.3	Lumbosacral spondylosis without myelopathy
721.42	Spondylosis with myelopathy, lumbar region
721.5	Kissing spine
721.6	Ankylosing vertebral hyperostosis
721.7	Traumatic spondylopathy
721.8	Other allied disorders of spine
721.9	Spondylosis of unspecified site

CODES	DESCRIPTION
722.1	Displacement of thoracic or lumbar intervertebral disc without myelopathy
722.2	Displacement of intervertebral disc, site unspecified, without myelopathy
722.32	Schmorl's nodes, lumbar region
722.39	Schmorl's nodes, other region
722.5	Degeneration of thoracic or lumbar intervertebral disc
722.6	Degeneration of intervertebral disc, site unspecified
722.70	Intervertebral disc disorder with myelopathy, unspecified region
722.72	Intervertebral disc disorder with myelopathy, thoracic region
722.73	Intervertebral disc disorder with myelopathy, lumbar region
722.80	Postlaminectomy syndrome, unspecified region
722.82	Postlaminectomy syndrome, thoracic region
722.83	Postlaminectomy syndrome, lumbar region
722.90	Other and unspecified disc disorder, unspecified region
722.92	Other and unspecified disc disorder, thoracic region
722.93	Other and unspecified disc disorder, lumbar region
724	**Other and unspecified disorders of back** 724.0 Spinal stenosis other than cervical 724.00 Spinal stenosis, unspecified region 724.01 Spinal stenosis, thoracic region 724.02 Spinal stenosis, lumbar region, without neurogenic claudication 724.03 Spinal stenosis, lumbar region, with neurogenic claudication 724.09 Spinal stenosis, other region 724.1 Pain in thoracic spine 724.2 Lumbago 724.3 Sciatica 724.4 Thoracic or lumbosacral neuritis or radiculitis, unspecified 724.5 Backache, unspecified 724.6 Disorders of sacrum 724.7 Disorders of coccyx 724.70 Unspecified disorder of coccyx 724.71 Hypermobility of coccyx 724.79 Other disorders of coccyx 724.8 Other symptoms referable to back 724.9 Other unspecified back disorders
732.0	Juvenile osteochondrosis of spine
733.0	Osteoporosis
737.2	Lordosis (acquired)
737.30	Scoliosis [and kyphoscoliosis], idiopathic
737.39	Other kyphoscoliosis and scoliosis
737.4	Curvature of spine associated with other conditions
737.8	Other curvatures of spine
737.9	Unspecified curvature of spine
738.4	Acquired spondylolisthesis

CODES	DESCRIPTION
738.5	Other acquired deformity of back or spine
739.2	Nonallopathic lesions, thoracic region
739.3	Nonallopathic lesions, lumbar region
739.4	Nonallopathic lesions, sacral region
754.2	Congenital musculoskeletal deformities of spine
756.1	Congenital anomalies of spine
846	Sprains and strains of sacroiliac region
847.1-9	847.1 Sprain of thoracic 847.2 Sprain of lumbar 847.3 Sprain of sacrum 847.4 Sprain of coccyx 847.9 Sprain of unspecified site of back
ICD-9 Volume 3 (procedure codes)	
None	
CPT Codes	
None	
HCPCS Level II Codes	
J7506	Prednisone, oral, per 5 mg
J7509	Methylprednisolone, oral, per 4 mg
J7510	Prednisolone, oral, per 5 mg

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

DRAFT COVERAGE GUIDANCE: LOW BACK PAIN: NON-PHARMACOLOGIC/NON-INVASIVE INTERVENTIONS*

DATE: XX/XX/XXXX

HERC COVERAGE GUIDANCE

For pain ≤ 4 weeks, self-care is recommended, and for those who do not improve with self-care, spinal manipulation should be covered.

For pain > 4 weeks duration, the following treatments may be covered:

- Acupuncture
- Cognitive-behavioral therapy
- Exercise therapy
- Intensive interdisciplinary rehabilitation
- Massage therapy
- Progressive relaxation
- Spinal manipulation
- Yoga (viniyoga)

The following should NOT be covered for low back pain:

- Continuous or intermittent traction
- Transcutaneous electrical nerve stimulation

*Coverage guidance for imaging, percutaneous interventions and surgery for low back pain will be addressed in subsequent documents.

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. In addition to an evidence-based guideline developed by the Evidence-based Guideline Subcommittee and a health technology assessment developed by the Heath Technology Assessment Subcommittee, coverage guidance may utilize an existing evidence report produced in the last 5 years by the Agency for Healthcare Research and Quality, the Medicaid Evidence-based Decisions Project or the Washington Health Technology Assessment Program.

EVIDENCE SOURCES

Livingston, C., King, V., Little, A., Pettinari, C., Thielke, A., & Gordon, C. (2011). *State of Oregon Evidence-based Clinical Guidelines Project. Evaluation and management of low back pain: A clinical practice guideline based on the joint practice guideline of the American College of Physicians and the American Pain Society (Diagnosis and treatment of low back pain).* Salem: Office for Oregon Health Policy and Research. Available at: http://www.oregon.gov/OHA/OHPR/HERC/Evidence-Based-Guidelines.shtml

Chou, R., Huffman, L. *Nonpharmacologic Therapies for Acute and Chronic Low Back Pain:A Review of the Evidence for an American Pain Society/American College of Physicians Clinical Practice Guideline.* Ann Intern Med. 2007; 147; 492-504. Available at: http://www.annals.org/content/147/7/492.full.pdf+html

Chou R., Qaseem, A., Snow, V., Casey, D., Cross, J.T., Jr., Shekelle, P., Owens, D.K.; Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society Low Back Pain Guidelines Panel. *Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society.* Annals of Internal Med. 2007; 147(7); 478-491. Available at: http://www.annals.org/content/147/7/478.long

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Low back pain is the fifth most common reason for all physician visits in the United States. Approximately one quarter of U.S. adults reported having low back pain lasting at least 1 whole day in the past 3 months, and 7.6% reported at least 1 episode of severe acute low back pain within a 1-year period. Low back pain is also very costly: Total incremental direct health care costs attributable to low back pain in the U.S. were estimated at $26.3 billion in 1998. In addition, indirect costs related to days lost from work are substantial, with approximately 2% of the U.S. work force compensated for back injuries each year.

Many patients have self-limited episodes of acute low back pain and do not seek medical care. Among those who do seek medical care, pain, disability, and return to work typically improve rapidly in the first month. However, up to one third of patients report persistent back pain of at least moderate intensity 1 year after an acute episode, and 1 in 5 report substantial limitations in activity. Approximately 5% of the people with back pain disability account for 75% of the costs associated with low back pain.

Many options are available for evaluation and management of low back pain. However, there has been little consensus, either within or between specialties, on appropriate clinical evaluation and management of low back pain. Numerous studies show unexplained, large variations in use of diagnostic tests and treatments. Despite wide variations in practice, patients seem to experience broadly similar outcomes, although costs of care can differ substantially among and within specialties.

Evidence Review

Recommendation 1: *Clinicians should provide patients with evidence-based information on low back pain with regard to their expected course, advise patients to remain active, and provide information about effective self-care options (strong recommendation, moderate-quality evidence).*

Clinicians should inform all patients of the generally favorable prognosis of acute low back pain with or without sciatica, including a high likelihood for substantial improvement in the first month. General advice on self-management for nonspecific low back pain should include recommendations to remain active, which is more effective than resting in bed for patients with acute or subacute low back pain. Self-care education books based on evidence-based guidelines, such as *The Back Book* are recommended because they are an inexpensive and efficient method for supplementing clinician-provided back information and advice and are similar or only slightly inferior in effectiveness to such costlier interventions as supervised exercise therapy, acupuncture, massage, and spinal manipulation.

[Evidence source]

Recommendation 2: *For patients who do not improve with self-care options, clinicians should consider the addition of nonpharmacologic therapy with proven benefits—for acute low back pain, spinal manipulation; for chronic or subacute low back pain, intensive interdisciplinary rehabilitation, exercise therapy, acupuncture, massage therapy, spinal manipulation, yoga, cognitive-behavioral therapy, or progressive relaxation (weak recommendation, moderate-quality evidence).*

For acute low back pain (duration <4 weeks), spinal manipulation administered by providers with appropriate training is associated with small to moderate short-term benefits. Supervised exercise therapy and home exercise regimens are not effective for acute low back pain, and the optimal time to start exercise therapy after the onset of symptoms is unclear. For subacute (duration >4 to 8 weeks) low back pain, intensive interdisciplinary rehabilitation (defined as an intervention that includes a physician consultation coordinated with a psychological, physical therapy, social, or vocational intervention) is moderately effective, and functional restoration with a cognitive-behavioral component reduces work absenteeism due to low back pain in occupational settings. For chronic low back pain, moderately effective nonpharmacologic therapies include acupuncture, exercise therapy, massage therapy, Viniyoga-style yoga, cognitive-behavioral therapy or progressive relaxation, spinal manipulation, and intensive interdisciplinary rehabilitation. Transcutaneous electrical nerve stimulation has conflicting and insufficient evidence to support efficacy. Intermittent and continuous traction (in patients with or without sciatica) are ineffective for low back pain.

[Evidence source]

Overall Summary

Non-pharmacologic treatments that have been shown to be effective for LBP include spinal manipulation, intensive interdisciplinary rehabilitation, exercise therapy, acupuncture, massage therapy, yoga, cognitive-behavioral therapy and progressive relaxation. Transcutaneous electrical nerve stimulation has not been proven effective, and intermittent or continuous traction have been proven ineffective in the treatment of LBP.

PROCEDURES

Acupuncture

Cognitive-behavioral therapy

Continuous or intermittent traction

Exercise therapy

Intensive interdisciplinary rehabilitation

Massage therapy

Progressive relaxation

Spinal manipulation

Transcutaneous electrical nerve stimulation

Viniyoga-style yoga

DIAGNOSES

Low back pain

APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
720.1	Spinal enthesopathy
720.2	Sacroiliitis, not elsewhere classified
721.3	Lumbosacral spondylosis without myelopathy
721.42	Spondylosis with myelopathy, lumbar region
721.5	Kissing spine
721.6	Ankylosing vertebral hyperostosis
721.7	Traumatic spondylopathy
721.8	Other allied disorders of spine
721.9	Spondylosis of unspecified site
722.1	Displacement of thoracic or lumbar intervertebral disc without myelopathy
722.2	Displacement of intervertebral disc, site unspecified, without myelopathy
722.32	Schmorl's nodes, lumbar region
722.39	Schmorl's nodes, other region
722.5	Degeneration of thoracic or lumbar intervertebral disc
722.6	Degeneration of intervertebral disc, site unspecified
722.70	Intervertebral disc disorder with myelopathy, unspecified region
722.72	Intervertebral disc disorder with myelopathy, thoracic region
722.73	Intervertebral disc disorder with myelopathy, lumbar region
722.80	Postlaminectomy syndrome, unspecified region
722.82	Postlaminectomy syndrome, thoracic region
722.83	Postlaminectomy syndrome, lumbar region
722.90	Other and unspecified disc disorder, unspecified region
722.92	Other and unspecified disc disorder, thoracic region
722.93	Other and unspecified disc disorder, lumbar region
724	**Other and unspecified disorders of back** 724.0 Spinal stenosis other than cervical 724.00 Spinal stenosis, unspecified region 724.01 Spinal stenosis, thoracic region 724.02 Spinal stenosis, lumbar region, without neurogenic claudication 724.03 Spinal stenosis, lumbar region, with neurogenic claudication 724.09 Spinal stenosis, other region 724.1 Pain in thoracic spine 724.2 Lumbago 724.3 Sciatica 724.4 Thoracic or lumbosacral neuritis or radiculitis, unspecified 724.5 Backache, unspecified 724.6 Disorders of sacrum 724.7 Disorders of coccyx 724.70 Unspecified disorder of coccyx

	724.71 Hypermobility of coccyx 724.79 Other disorders of coccyx 724.8 Other symptoms referable to back 724.9 Other unspecified back disorders
732.0	Juvenile osteochondrosis of spine
733.0	Osteoporosis
737.2	Lordosis (acquired)
737.30	Scoliosis [and kyphoscoliosis], idiopathic
737.39	Other kyphoscoliosis and scoliosis
737.4	Curvature of spine associated with other conditions
737.8	Other curvatures of spine
737.9	Unspecified curvature of spine
738.4	Acquired spondylolisthesis
738.5	Other acquired deformity of back or spine
739.2	Nonallopathic lesions, thoracic region
739.3	Nonallopathic lesions, lumbar region
739.4	Nonallopathic lesions, sacral region
754.2	Congenital musculoskeletal deformities of spine
756.1	Congenital anomalies of spine
846	Sprains and strains of sacroiliac region
847.1-9	847.1 Sprain of thoracic 847.2 Sprain of lumbar 847.3 Sprain of sacrum 847.4 Sprain of coccyx 847.9 Sprain of unspecified site of back
ICD-9 Volume 3 (procedure codes)	
None	
CPT	
Spinal Manipulation	
98925	Osteopathic manipulative treatment (OMT); 1-2 body regions involved
98926	3-4 body regions involved
98927	5-6 body regions involved
98928	7-8 body regions involved
98929	9-10 body regions involved
98940	Chiropractic manipulative treatment (CMT); spinal, 1-2 regions
98941	spinal, 3-4 regions
98942	spinal, 5 regions
98943	extraspinal, 1 or more regions
Acupuncture	
97810	Acupuncture, 1 or more needles; without electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient
+97811	without electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s)
97813	with electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient
+97814	with electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s)
Cognitive Behavioral Therapy	

90804	Individual psychotherapy, insight oriented, behavior modifying and/or supportive, in an office or outpatient facility, approximately 20 to 30 minutes face-to-face with the patient
90805	with medical evaluation and management services
90806	Individual psychotherapy, insight oriented, behavior modifying and/or supportive, in an office or outpatient facility, approximately 45 to 50 minutes face-to-face with the patient
90807	with medical evaluation and management services
90808	Individual psychotherapy, insight oriented, behavior modifying and/or supportive, in an office or outpatient facility, approximately 75 to 80 minutes face-to-face with the patient
90809	with medical evaluation and management services
90810	Individual psychotherapy, interactive, using play equipment, physical devices, language interpreter, or other mechanisms of non-verbal communication, in an office or outpatient facility, approximately 20 to 30 minutes face-to-face with the patient
90811	with medical evaluation and management services
90812	Individual psychotherapy, interactive, using play equipment, physical devices, language interpreter, or other mechanisms of non-verbal communication, in an office or outpatient facility, approximately 45 to 50 minutes face-to-face with the patient
90813	with medical evaluation and management services
90814	Individual psychotherapy, interactive, using play equipment, physical devices, language interpreter, or other mechanisms of non-verbal communication, in an office or outpatient facility, approximately 75 to 80 minutes face-to-face with the patient
90815	with medical evaluation and management services
90875	Individual psychophysiological therapy incorporating biofeedback training by any modality (face-to-face with the patient), with psychotherapy (eg, insight oriented, behavior modifying or supportive psychotherapy)
97001	Physical therapy evaluation
97002	Physical therapy re-evaluation
97012	Traction, mechanical
97014	Electrical stimulation (unattended)
97110	Therapeutic procedure, 1 or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility
97112	neuromuscular reeducation of movement, balance, coordination, kinesthetic sense, posture, and/or proprioception for sitting and/or standing activities
97116	gait training (includes stair climbing)
97124	massage, including effleurage, petrissage and/or tapotement (stroking, compression, percussion)
97140	Manual therapy techniques (eg, mobilization/manipulation, manual lymphatic drainage, manual traction), 1 or more regions, each 15 minutes
97150	Therapeutic procedures(s), group (2 or more individuals) (Group therapy procedures involve constant attendance of the physician or therapist, but by definition do not require one-on-one patient contact by the physician or therapist)
97530	Therapeutic activities, direct (one-on-one) patient contact by the provider (use of dynamic activities to improve functional performance), each 15 minutes
HCPCS Level II Codes	
E0830	Ambulatory traction device, all types, each
E0941	Gravity assisted traction device, any type
H0002	Behavioral health screening to determine eligibility for admission to treatment

	program
H0004	Behavioral health counseling and therapy, per 15 minutes
H0031	Mental health assessment, by nonphysician
H0032	Mental health service plan development by nonphysician
H2000	Comprehensive multidisciplinary evaluation
H2001	Rehabilitation program, per ½ day
S9451	Exercise classes, nonphysician provider, per session

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

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