Drug Utilization Review Board

Oklahoma Health Care Authority
4545 North Lincoln Boulevard, Suite 124
Oklahoma City, Oklahoma 73105
OHCA Board Room

Wednesday
December 9, 2009
6:00 p.m.

The University of Oklahoma

Health Sciences Center

COLLEGE OF PHARMACY

PHARMACY MANAGEMENT CONSULTANTS

MEMORANDUM

TO: Drug Utilization Review Board Members

FROM: Shellie Keast, Pharm.D., M.S.

SUBJECT: **Packet Contents for Board Meeting – December 9, 2009**

DATE: December 3, 2009

NOTE: THE DUR BOARD WILL MEET AT 6:00 P.M.

Enclosed are the following items related to the December meeting. Material is arranged in order of the Agenda.

Call to Order

Public Comment Forum

Action Item – Approval of DUR Board Meeting Minutes – See Appendix A.

Update on DUR / MCAU Program – See Appendix B.

Action Item – Vote on 2010 Meeting Dates – See Appendix C.

Action Item – Vote to Prior Authorize Intuniv™ – See Appendix D.

Action Item – Vote to Prior Authorize Valturna™ and Intermezzo®– See Appendix E.

Action Item – Vote to Prior Authorize Antiemetics – See Appendix F.

60 Day Notice to Prior Authorize Atypical Antipsychotics – See Appendix G.

FDA and DEA Updates – See Appendix H.

Future Business

Adjournment

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Drug Utilization Review Board

(DUR Board)

Meeting – December 9, 2009 @ 6:00 p.m.

Oklahoma Health Care Authority
4545 N. Lincoln Suite 124
Oklahoma City, Oklahoma 73105
Oklahoma Health Care Authority Board Room

AGENDA

Discussion and Action on the Following Items:

Items to be presented by Dr. Muchmore, Chairman:

1. Call To Order

A. Roll Call – Dr. Graham

Items to be presented by Dr. Muchmore, Chairman:

2. Public Comment Forum

A. Acknowledgment of Speakers and Agenda Items

Items to be presented by Dr. Muchmore, Chairman:

3. Action Item – Approval of DUR Board Meeting Minutes – See Appendix A.

A. November 12, 2009 DUR Minutes – Vote
B. November 13, 2009 DUR Recommendation Memorandum

Items to be presented by Dr. Keast, Dr. Muchmore, Chairman:

4. Update on DUR / Medication Coverage Authorization Unit – See Appendix B.

A. Retrospective Drug Utilization Review Response for August 2009
B. Medication Coverage Activity Audit for November 2009
C. Help Desk Activity Audit for November 2009

Items to be presented by Dr. Keast, Dr. Muchmore, Chairman

5. Action Item - Vote on 2010 Meeting Dates – See Appendix C.

Items to be presented by Dr. Moore, Dr. Muchmore, Chairman

6. Action Item – Vote to Prior Authorize Intuniv™ – See Appendix D.

A. COP Recommendations

Items to be presented by Dr. Le, Dr. Muchmore, Chairman

7. Action Item – Vote to Prior Authorize Valturna™ – See Appendix E.

A. Clinical Questions
B. COP Recommendations

Items to be presented by Dr. Le, Dr. Muchmore, Chairman

8. Action Item – Vote to Prior Authorize Antiemetics – See Appendix F.

A. COP Recommendations

Items to be presented by Dr. Le, Dr. Muchmore, Chairman

9. 60 Day Notice to Prior Authorize Atypical Antipsychotics – See Appendix G.

A. Product Summary
B. Utilization Review
B. COP Recommendations

Items to be presented by Dr. Graham, Dr. Muchmore, Chairman

10. FDA and DEA Updates – See Appendix H.

11. Future Business

A. Anxiolytic Criteria Review
B. Annual Review of Smoking Cessation Products
C. Annual Review of NSAIDs
D. New Product Reviews

12. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of NOVEMBER 12, 2009

BOARD MEMBERS:	PRESENT	ABSENT
Brent Bell, D.O., D.Ph.: Vice-Chairman	X	
Mark Feightner, Pharm.D.		X
Anetta Harrell, Pharm.D.	X	
Evelyn Knisely, Pharm.D.	X	
Thomas Kuhls, M.D.	X	
John Muchmore, M.D., Ph.D.: Chairman	X	
Paul Louis Preslar, D.O., MBA	X	
James Rhymer, D.Ph.		X
Bruna Varalli-Claypool, MHS, PA-C	X	
Eric Winegardener, D.Ph.	X	

COLLEGE of PHARMACY STAFF:	PRESENT	ABSENT
Metha Chonlahan, D.Ph.; Clinical Pharmacist		X
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison		X
Ronald Graham, D.Ph.; Pharmacy Director	X	
Shellie Keast, Pharm.D, M.S..; DUR Manager	X	
Chris Le, Pharm.D.; Clinical Pharmacist/Coordinator	X	
Carol Moore, Pharm.D.; Clinical Pharmacist	X	
Neeraj Patel, Pharm.D.; Clinical Pharmacist	X	
Lester A. Reinke, Ph.D.; Associate Dean for Graduate Studies & Research	X	
Jennifer Sipols, Pharm.D.; Clinical Pharmacist		X
Leslie Robinson, D.Ph.; PA Coordinator		X
Visiting Pharmacy Student(s): Michael MacGregor	X	

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Mike Fogarty, J.D., M.S.W.; Chief Executive Officer		X
Nico Gomez; Director of Gov't and Public Affairs		X
Lynn Mitchell, M.D., M.P.H,; Director of Medicaid/Medical Services	X	
Nancy Nesser, Pharm.D., J.D.; Pharmacy Director	X	
Howard Pallotta, J.D.; Director of Legal Services		X
Lynn Rambo-Jones, J.D.; Deputy General Counsel III	X	
Rodney Ramsey; Drug Reference Coordinator	X	
Jill Ratterman, D.Ph.; Pharmacy Specialist	X	
Kerri Wade, Senior Pharmacy Financial Analyst	X	

OTHERS PRESENT:

Richard Ponder, J&J	David Williams, Forest	Sam Smothers, MedImmune
Vanessa Papion, UCB Inc.	Lon Lowrey, Novartis	John Seidenberger, Boehringer-Ingelheim
Donna Erwin, BMS	Jennifer Whaley, Sanofi-Aventis	Pat Trahan, Taro
Janie Huff, Takeda	Tracy Copeland, Daiichi Sankyo	Rob Thomas, Sciele
Mark DeClerk, Lilly	Bruce Christian, Lilly	Holly Turner, Merck
Lisa Sherman, Strativa	Ron Schnare, Shire	Angela LeDay, Shire

PRESENT FOR PUBLIC COMMENT:

Agenda Item No. 6	Jenn Whaley, Pharm.D.; Sanofi-Aventis
Agenda Item No. 6	Becky Harmon, Pharm.D.; Lilly
Agenda Item No. 11	Angela LeDay, Pharm.D.; Shire

AGENDA ITEM NO. 1: **CALL TO ORDER**

1A: Roll Call

Dr. Muchmore called the meeting to order. Roll call by Dr. Graham established a quorum.

ACTION: NONE REQUIRED

AGENDA ITEM NO. 2: **PUBLIC COMMENT FORUM**

Dr. Muchmore recognized the speakers for public comment.

Agenda Item No. 6 Jenn Whaley, Pharm.D.; Sanofi-Aventis
Agenda Item No. 6 Becky Harmon, Pharm.D.; Lilly
Agenda Item No. 11 Angela LeDay, Pharm.D.; Shire

ACTION: NONE REQUIRED

AGENDA ITEM NO. 3: **APPROVAL OF DUR BOARD MINUTES**

3A: October 14, 2009 DUR Minutes

Dr. Kuhls moved to approve as submitted; seconded by Dr. Harrell.

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: **UPDATE ON DUR/MCAU PROGRAM**

4A: Retrospective Drug Utilization Review: August 2009
4B: Retrospective Drug Utilization Review Response: July 2009
4C: Medication Coverage Activity Audit: October 2009
4D: Help Desk Activity Audit: October 2009

Reports included in agenda packet; presented by Dr. Keast.

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: **OHCA BUDGET REPORT**

Reports included in agenda packet; presented by Carrie Evans, OHCA CFO.

ACTION: NONE REQUIRED

AGENDA ITEM NO. 6: **VOTE TO PRIOR AUTHORIZE EFFIENT™**

For Public Comment, Jenn Whaley, Pharm.D.: I'm Jennifer Whaley. I'm just here for questions, if things come up where you need advice.

Dr. Muchmore: OK, so if anybody has any questions on that regard, we'll call on you.

For Public Comment, Becky Harmon, Pharm.D.: Hello, I'm Becky Harmon and I'm an Outcomes Liaison in the Medical Division at Lilly, and I'm here today to talk to you about Effient and I've been working on this product for about two and a half years. So my approach today is to briefly discuss the indication the results of our head-to-head study and to address two specific topics I was asked to talk about by the Board as follow-up items, one being the results of our study in terms of the perfect patient population specifically, the diabetes patients. And as well as to look at a couple of distinctive differences between clopidogrel and prasugrel, or Effient. And the final thing is that I'll ask you to consider potentially adding a couple of items to your proposed PA, but mainly I'm here to help answer any questions you may have as well. So as you all know, the current standard of care to prevent thrombotic events in acute coronary syndromes in percutaneous intervention is dual antiplatelet therapy with aspirin and a thienopyridine. Effient, or prasugrel, is a new thienopyridine with a more efficient metabolism than clopidogrel, or Plavix, which leads to number one, increased levels of platelet inhibition, number two, a quicker onset of action, and number three, a more consistent response. Specifically, Effient is indicated for the reduction of thrombotic cardiovascular events including stent thrombosis in patients with ACS therapy management with a PCI. And this does exclude patients with a prior TIA issue based on the contraindication in our label. And with limited use in patients who are greater than 75 years of age or patients who are less than 60 kg or 132 pounds. Efficacy of Effient was established in our large Phase 3 head-to-head study called the TRITON study which compared Effient plus aspirin to clopidogrel plus aspirin and customers have been asking us for years to please come to market with head-to-head data and so we've done just that. Effient in comparison to clopidogrel proved to have a statistically significant reduction of 19% in the primary composite endpoint of cardiovascular death, non-fatal MI and non-fatal stroke, and this composite endpoint was primarily driven by a reduction in MI. The primary safety endpoint was non coronary artery bypass graft or CABG, to mean major bleeding which was statistically significantly higher in the Effient arm of the clopidogrel arm with a rate of 2.2 versus 1.8%. So now I'll go ahead and like to address the two topics I was asked to discuss. Since diabetes, as you all know, is a very difficult disease state to manage and I'm sure a problem for you to manage in

your Medicaid patients. I've been asked just to briefly share the results from our TRITON study in the diabetes population that has acute coronary syndrome. So treatment with prasugrel, Effient, was associated with a 30% relative risk reduction when compared to clopidogrel and was associated with similar observed rates of non-CABG semi-major bleeding in diabetes patients. To the second topic I wanted to address is the distinctive differences between Effient and clopidogrel with regards to metabolism and some of the recent issues surrounding this. Recently clopidogrel's label was updated to reflect the possible drug-drug interaction with proton pump inhibitors and also data regarding CYP2C19 polymorphism which results in a variability of response to clopidogrel. This is of specific concern to your Medicaid population because upwards of 30% of patients may not be responders to clopidogrel. However, prasugrel can be given with drugs that elevate gastric pH which includes both the proton pump inhibitors and H2 blockers, and in addition, prasugrel does not have issue with CYP2C19 polymorphisms at all. So finally, I realized that this may not be a patient population that you necessarily deal with significantly with Medicare Part D and covers the medication for patients greater than or equal to 75, and you've done a very nice job with putting together the PA prior to the meeting. But a couple things I would maybe recommend considering adding is that patients that are greater than 75 or equal to 75 years of age, there is specific label language regarding, we did see statistically significant for patients that were greater than 75 years of age with diabetes, a significant reduction in our primary endpoint; as well as in patients with a prior MI and that were greater than 75 years of age. So therefore I would just ask you to consider adding those two exceptions for patients that are greater than or equal to 75 years of age being diabetes or prior MI. I'll be happy to answer any questions that you might have.
Board members held some discussion regarding contraindications and PA criteria.
Materials included in agenda packet; presented by Dr. Keast.
Dr. Kuhls moved to approve as amended *(Amended recommendations: 3.c. Effient will generally not be approved for members greater than 75 years of age.)*; seconded by Dr. Winegardener.
ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: **VOTE TO PRIOR AUTHORIZE ULESFIA™**
Materials included in agenda packet; presented by Dr. Patel.
Dr. Kuhls moved to approve as amended to "rebated to Tier 2 status only"; seconded by Dr. Harrell.
ACTION: MOTION CARRIED

AGENDA ITEM NO. 8: **VOTE TO PRIOR AUTHORIZE EDULAR™ AND INTERMEZZO®**
Materials included in agenda packet; presented by Dr. Le.
Dr. Winegardener moved to approve as amended to "rebated to Tier 2 status only"; seconded by Dr. Bell.
ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: **30-DAY NOTICE TO PRIOR AUTHORIZE ANTIEMETICS**
Materials included in agenda packet; presented by Dr. Le.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 10: **30-DAY NOTICE TO PRIOR AUTHORIZE VALTURNA™**
Materials included in agenda packet; presented by Dr. Le.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 11: **30-DAY NOTICE TO PRIOR AUTHORIZE INTUNIV™**
For Public Comment, Angela LeDay, Pharm.D.: Good afternoon. Thank you Mr. Chairman and committee. My name is Angela LeDay and I represent Shire Pharmaceuticals. I work with the medical liaison and our clinical department, and tonight I'm representing Intuniv. It's a selective alpha-2A agonist that's approved for the treatment of ADHD in both children and adolescents, so six to seventeen years old. It's an extended formulation of guanfacine hydrochloride that you may be aware of. However, this product is developed to be a long-acting product to reduce the peak and trough levels that are associated with multiple dosing of the guanfacine that's often used off-label in the treatment of ADHD. Its' PK profile in comparison to the immediate release is different; therefore the two products are not substitutable. As noted in the information here, the efficacy was established on the basis of two controlled trials that were eight and nine weeks in duration, but in addition to that, we do have long-term data up to 24 months or two years, that supports the safety of this medication. The most common adverse events again were somnolence, sedation and fatigue. These adverse events occurred very early on and they tended to decrease or dissipate over time with treatment. And I'm here to answer any questions that you may have. Thank you.

Dr. Kuhls: I have two quick questions. So did this all come around because of the common use of clonidine in the treatment of ADHD?
Dr. LeDay: Yes, actually both clonidine and guanfacine are sometimes used off-label to treat ADHD and so part of the problem with using clonidine and guanfacine is there are no adequately controlled trials to study them in ADHD, and so physicians are using them different times a day. Sometimes once a day, sometimes up to four times a day. In addition to that, they are often used in comorbid conditions, such as ADHD and tics. So therefore, Shire decided to actually study a long-acting formulation of this drug in the treatment of ADHD as monotherapy.
Dr. Kuhls: Just because you work for Shire, do you, how do you feel, or reading the literature and becoming an expert on this drug, how do you think efficacy-wise this drug compares to say, Vyvanse?
Dr. LeDay: I wouldn't make a direct comparison to a stimulant like Vyvanse, but I would say looking at the literature, not every ADHD patient will respond to a stimulant such as Vyvanse or even a methylphenidate as a stimulant. So for those 20 to 30% of the patients that will not respond to stimulant therapy, this is a non-stimulant option for those particular patients.
Dr. Kuhls: 'Cause I have Shire reps coming to my office all the time telling me how Vyvanse is better than this drug or that drug or this drug or that drug and you know that Shire does that, so that's why I was trying to get a feel for effectiveness of Vyvanse versus this drug for reference.
Dr. LeDay: Right. We have not done any head-to-head studies, so I wouldn't .....
Dr. Kuhls: But there's been no direct studies compared to any of the other stimulants and you keep on making comments in my office about that, so that's why I was asking that.
Dr. LeDay: I'm sorry. I'm not a sales representative. I'd be happy to relay that information. I mean what we have done is looked at just the overall efficacy .....
Dr. Kuhls: Well, I'm just trying to get a feel for ..... maybe I should put all my patients on this drug if you think it's better than Vyvanse, so that's .....
Dr. LeDay: No, I'm definitely not saying it's better than Vyvanse, but there are kids and adolescents that either cannot tolerate the stimulants, Vyvanse or even a methylphenidate. There are some for which there are contraindications, they may have cardiovascular problems, and then there are some parents or caregivers that choose not to give their children a stimulant and so this is an option for those patients.
Dr. Kuhls: So you're, so what you're telling me, what I'm listening to or which I think I'm hearing, is you believe this is kind of a second line drug for people that don't want to or can't take stimulants?
Dr. LeDay: I wouldn't say it's a second line. It may be a second line for some patients, but it may be a first line for those that have contraindications to a stimulant.
Dr. Kuhls: Well that's still to me a second line because you can't use the first line drug.
Dr. LeDay: Right. But again, according to the psychiatry guidelines, the child psychiatry guidelines, overall, stimulants are recommended as first line therapy and for those that either, again, as I mentioned, cannot tolerate stimulants, there are other, or have comorbid conditions for which stimulants are contraindicated, drugs such as guanfacine may be used in those patients.
Dr. Muchmore: Is this dosed once a day in the morning?
Dr. LeDay: All of our studies so far have looked at once a day dosing in the morning and we currently have on-going studies looking at p.m. dosing as well.
Dr. Kuhls: And then last, what's the, what's the actual incidence of hypotension?
Dr. LeDay: The incidence of hypotension in our studies was 6% for those on Intuniv versus 4% for the placebo, so it was relatively small.
Dr. Kuhls: Six versus four, huh?
Dr. LeDay: Right.
Dr. Muchmore: The key on all these ADDHD treatments is that a lot of the people taking them are school kids and you're much better off if they can take a once-a-day medication. There's several of those, but that really makes a case for extended release.
Dr. Kuhls: I'll talk about that in a minute.
Dr. Bell: The literature, the robustness of the response for stimulants is just far over anything. Nothing compares to stimulants with ADHD, you can't even compare the response rates. But the clonidine and guanfacine have uses also in violent patients and insomnia with ADHD, so there's other uses, tics, really good response rates with tics, so if you're thinking ADHD, you know stimulants are just the standard still.
Dr. LeDay: And I would also mention too that, you mentioned both guanfacine and clonidine, those immediate release formulations that have been used in the past, really just have not been studied in any robust trials for the treatment of ADHD, so this is the first time we're looking at guanfacine in extended release formulation of it.
Dr. Bell: You get less sedation with guanfacine.
Dr. LeDay: Right.
Materials included in agenda packet; presented by Dr. Moore.
Board members held some discussion regarding generics, brand name pricing, adverse effects of abruptly discontinuing medication.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 12: **FDA & DEA UPDATES**
Materials included in agenda packet; presented by Dr. Graham.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 13: **FUTURE BUSINESS**

Materials included in agenda packet; submitted by Dr. Graham.

13A: Anxiolytic Criteria Review
13B: Antipsychotic Review
13C: New Product Reviews
13D: Annual Reviews
ACTION: NONE REQUIRED

AGENDA ITEM NO. 14: **ADJOURNMENT**

The meeting was adjourned at 7:45 p.m.

The University of Oklahoma
Health Sciences Center
COLLEGE OF PHARMACY
PHARMACY MANAGEMENT CONSULTANTS

Memorandum

Date: November 13, 2009

To: Nancy Nesser, Pharm.D., J.D.
Pharmacy Director
Oklahoma Health Care Authority

From: Shellie Keast, Pharm.D., M.S.
Drug Utilization Review Manager
Pharmacy Management Consultants

Subject: DUR Board Recommendations from Meeting of November 12, 2009

Recommendation 1: Vote to Prior Authorize Effient™

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends placing a prior authorization on Effient™ after 90 days of therapy.

The approval criteria for Effient™ would be as follows:

1. Effient™ therapy will be approved for members who meet approved diagnostic criteria:
    a. The approved diagnoses are UA/NSTEMI and STEMI patients who are to be managed with percutaneous coronary intervention (PCI), primary or delayed.
2. Length of approval: 1 year.
3. Effient™ will not be approved for members with the following situations:
    a. CABG surgery
    b. Members with a history of TIA or stroke
    ~~c. Members greater than 75 years of age~~

4. Members greater than 75 years of age will generally not be approved without supporting information.

After the end of 15 months, prescribers should provide supporting information for the continuation of these products.

Recommendation 2: Vote to Prior Authorize Ulesfia™

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends placement of Ulesfia™ in Tier 3 of the Topical Antiparasitic Product Based Prior Authorization Category.

Tier 1	Tier 2	Tier 3*
Covered OTC Lice Products Generics with SMAC Pricing	Supplemental Rebated Tier 3	Lindane Lotion & Shampoo Malathion (Ovide) Crotamiton (Eurax®) Lotion Benzyl Alcohol (Ulesfia™) Lotion

*May be rebated to Tier 2 status only

The following restrictions also apply:

- Member must be at least 6 months old
- Due to mechanism of action, requires retreatment after 7 days
- Hair length would be required in order to approve the appropriate number of bottles if requesting more than 2 bottles per treatment (4 bottles for both treatments)

Recommendation 3: Vote to Prior Authorize Edluar™ and Intermezzo®

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends placement of Edluar™ and Intermezzo® in Tier 3 of the Hypnotics Category with a manual prior authorization. The existing prior authorization criteria for this category will apply. In addition, the petition should also include information regarding why member must have the sublingual formulation of zolpidem. A Quantity Limit similar to all other hypnotic medications will apply.

Tier 1*	Tier 2	Tier 3‡
Estazolam (ProSom®) Temazepam (Restoril®) 15 and 30mg Flurazepam (Dalmane®) Triazolam (Halcion® zolpidem (Ambien®) Zaleplon (Sonata®)	Supplemental Rebated Tier 3	Eszopiclone (Lunesta®) Temazepam (Restoril®) 7.5 and 22.5 mg Ramelteon (Rozerem®) Zolpidem (Ambien CR®) Zolpidem† Oral Spray (Zolpimist™) Zolpidem† SL Tabs (Edluar™) Zolpidem† SL Tabs (Intermezzo®)

*Mandatory Generic Plan Applies.
†Requires special reason for use.
‡May be rebated to Tier 2 status only

Appendix B

Retrospective Drug Utilization Review Report

Claims Reviewed for August 2009

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Limits which were applied	Established, Major, Males and Females, Age 19-35	Narcotics, Males and Females, Age 28-29	Contraindicated, Epilepsy, Males and Females, Age 51-150	High Dose, Modified Cyclics (Trazodone), Males and Females, Age 0-150

Response Summary (Prescriber)
Letters Sent: 146
Response Forms Returned: 88

The response forms returned yielded the following results:

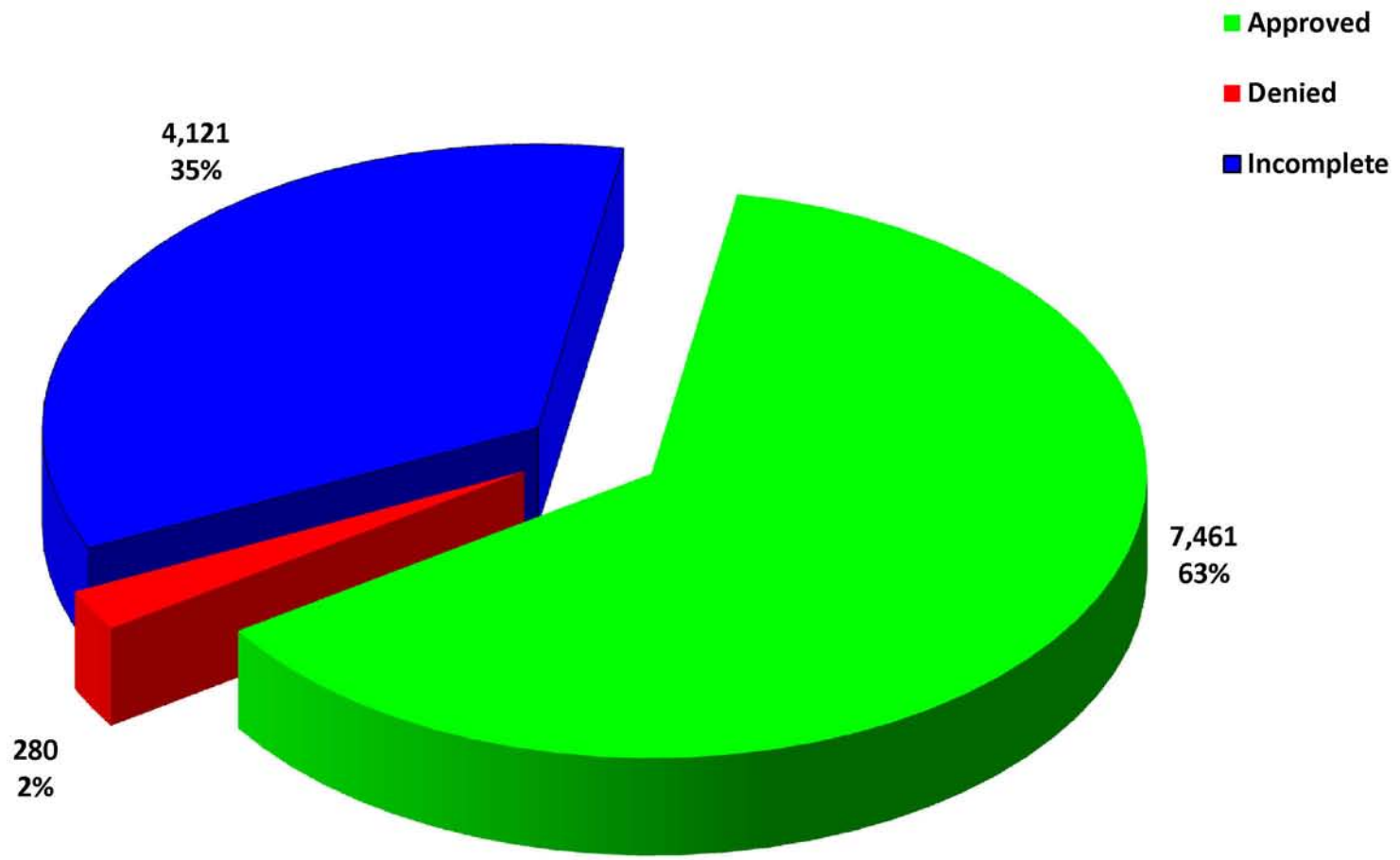
3 (3%)	*Record Error—Not my patient.*
6 (7%)	*No longer my patient.*
8 (9%)	*Medication has been changed prior to date of review letter.*
26 (30%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
23 (26%)	*I am aware of this situation and will plan to continue monitoring therapy.*
22 (25%)	*Other*

Response Summary (Pharmacy)
Letters Sent: 25
Response Forms Returned: 9

The response forms returned yielded the following results:

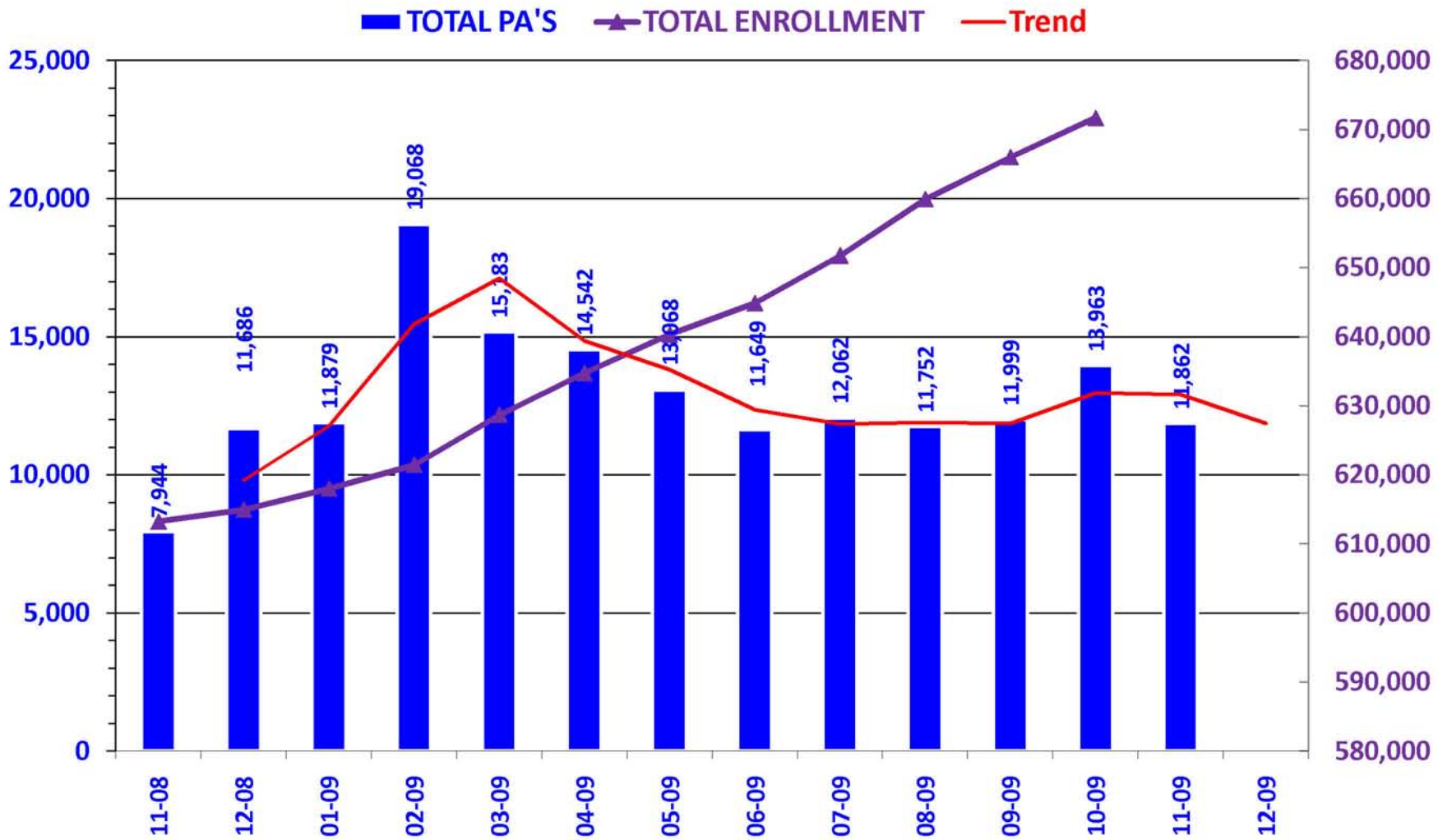
0 (0%)	*Record Error—Not my patient.*
0 (0%)	*No longer my patient.*
1 (11%)	*Medication has been changed prior to date of review letter.*
2 (22%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
3 (33%)	*I am aware of this situation and will plan to continue monitoring therapy.*
3 (33%)	*Other*

PRIOR AUTHORIZATION ACTIVITY REPORT: November 2009



PA totals include overrides

PRIOR AUTHORIZATION REPORT: November 2008 – November 2009



PA totals include overrides

Prior Authorization Activity

November 2009

	Average Length of Approvals in Days	Approved	Denied	Incomplete	Total
Advair/Symbicort	356	313	2	323	638
Amitiza	109	12	0	13	25
Antidepressant	344	160	10	378	548
Antihistamine	302	187	4	211	402
Antihypertensives	344	60	3	110	173
Benzodiazepines	94	3,608	17	716	4,341
Bladder Control	362	5	0	10	15
Byetta	207	3	0	2	5
Elidel/Protopic	90	22	0	24	46
ESA	61	139	1	19	159
Fibric Acid Derivatives	0	0	0	5	5
Fortamet/Glumetza	359	1	0	2	3
Forteo	361	1	0	1	2
Glaucoma	257	5	1	10	16
Growth Hormones	168	52	3	5	60
HFA Rescue Inhalers	197	49	0	49	98
Insomnia	114	43	5	115	163
Misc Analgesics	100	8	21	39	68
Muscle Relaxant	68	57	56	78	191
Nasal Allergy	363	3	35	94	132
NSAIDS	286	31	4	71	106
Nucynta	0	0	2	0	2
Ocular Allergy	91	1	0	14	15
Ocular Antibiotics	56	4	0	10	14
Opioid Analgesic	167	82	3	111	196
Other	170	144	17	271	432
Pediculicides	9	18	3	26	47
Plavix	357	88	0	44	132
Proton Pump Inhibitors	145	101	6	234	341
Qualaquin (Quinine)	0	0	1	0	1
Singulair	267	384	2	364	750
Smoking Cessation	63	25	2	53	80
Statins	349	21	0	35	56
Stimulant	230	608	6	295	909
Synagis	133	134	42	75	251
Topical Antibiotics	87	5	0	24	29
Topical Antifungals	48	5	0	33	38
Ultram ER and ODT	360	2	0	10	12
Xolair	0	0	0	1	1
Xopenex Nebs	250	24	0	33	57
Zetia (Ezetimibe)	360	14	0	8	22
Emergency PAs		1	0	0	1
Total		**6,420**	**246**	**3,916**	**10,582**

Overrides					
Brand	148	63	2	17	82
Dosage Change	14	388	10	25	423
High Dose	180	5	0	0	5
IHS - Brand	36	52	0	3	55
Ingredient Duplication	14	7	1	2	10
Lost/Broken Rx	13	103	0	0	103
Nursing Home Issue	10	44	0	7	51
Other	37	35	0	3	38
Quantity vs. Days Supply	233	332	21	148	501
Stolen	5	12	0	0	12
Overrides Total		**1,041**	**34**	**205**	**1,280**
Total Regular PAs + Overrides		**7,461**	**280**	**4,121**	**11,862**

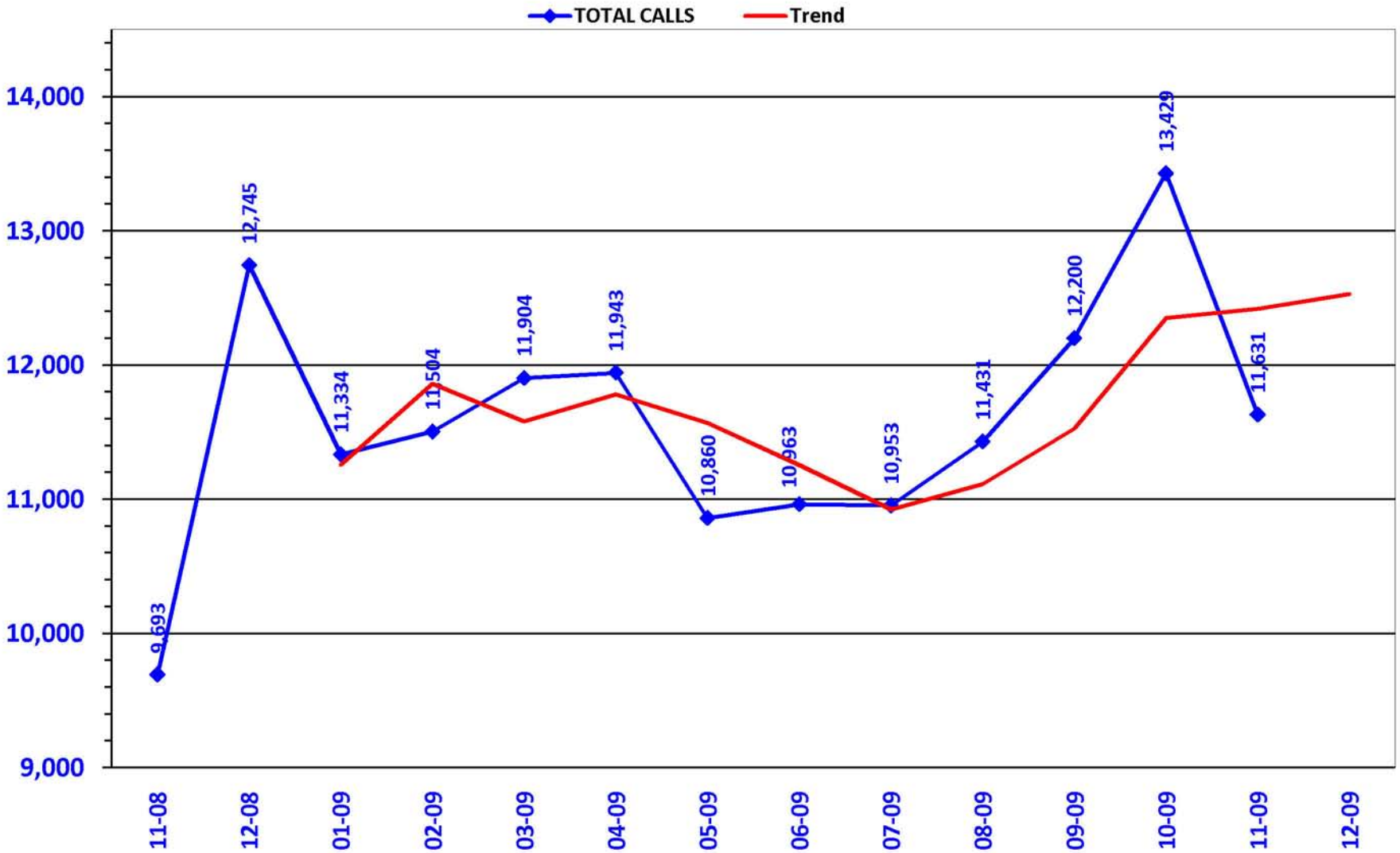
Denial Reasons

Lack required information to process request.	1,996
Unable to verify required trials.	1,677
Does not meet established criteria.	163
Member has active PA for requested medication.	148
Considered duplicate therapy. Member has a prior authorization for similar medication.	138
Not an FDA approved indication/diagnosis.	134
Requested dose exceeds maximum recommended FDA dose.	89
Medication not covered as pharmacy benefit.	17
Drug Not Deemed Medically Necessary	4

Duplicate Requests: 823

Changes to existing PAs: 925

CALL VOLUME MONTHLY REPORT:
November 2008 – November 2009



Appendix C

Vote on 2010 DUR Meeting Dates

Oklahoma Health Care Authority
December 2009

Meetings are held the second Wednesday of each month.

JANUARY 13, 2010

FEBRUARY 10, 2010

MARCH 10, 2010

APRIL 14, 2010

MAY 12, 2010

JUNE 9, 2010

JULY 14, 2010

AUGUST 11, 2010

SEPTEMBER 8, 2010

OCTOBER 13, 2010

NOVEMBER 10, 2010

DECEMBER 8, 2010

Appendix D

Vote to Prior Authorize Intuniv™ (guanfacine)

Oklahoma Health Care Authority
December 2009

Manufacturer	Shire US Inc.
Classification	Selective Alpha$_{2A}$ Receptor Agonist
Status	Prescription Only

Recommendations

The College of Pharmacy recommends placement of Intuniv™ in Tier 2 of the ADHD Product Based Prior Authorization Category. The existing criteria for this category will apply.

Tier-1*	Tier-2	Tier 3
amphetamine salt combo **(Adderall®)**	atomoxetine **(Strattera®)**	armodafinil **(Nuvigil®)**
dexmethylphenidate **(Focalin®)**	methylphenidate ER **(Metadate® CD)**	methamphetamine **(Desoxyn®)**
methylphenidate IR **(Ritalin®, Methylin®)**	methylphenidate ER **(Metadate® ER)**	methylphenidate patch **(Daytrana™)**
methylphenidate SR **(Ritalin SR®)**	methylphenidate ER **(Ritalin® LA)**	modafinil **(Provigil®)**
methylphenidate ER **(Concerta®)**	amphetamine salt combo **(Adderall XR®)**	dextroamphetamine **(Dexedrine®, Dexedrine Spansules®)**
dexmethylphenidate **(Focalin XR®)**	guanfacine **(Intuniv™)**	
lisdexamfetamine **(Vyvanse®)**		

Mandatory Generic Plan applies.
*** Immediate release products do not count as adequate tier-1 trials**
Blue Color indicates Supplemental Rebate Participation

Appendix E

Vote to Prior Authorize Valturna™ (aliskiren and valsartan)

Oklahoma Health Care Authority
December 2009

Manufacturer	Novartis Pharmaceuticals, Inc.
Classification	Direct Renin Inhibitor (DRI) and Angiotensin II Receptor Blocker (ARB)
Status	Prescription Only

Clinical Questions

Indications for Valturna as listed on the package insert as of September 2009[1]: Treatment of HTN

- in patients not adequately controlled with monotherapy
- may be substituted for titrated components
- as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals

Combination Therapy in the Treatment of Hypertension

- More than 2/3 of individuals with hypertension will require 2 or more medications to maintain their blood pressure at goal[2]
- In many instances increasing the dose of a medication to its highest indicated dosage strength may increase the adverse effects without a significant increase in blood pressure control. Using multiple medications in combination at lower strengths can result in a decrease in blood pressure with fewer side effects. [3,4]
- If the systolic blood pressure is >20mmHg above goal or the diastolic pressure is >10mmHg above goal, the use of two agents (or a second agent) should be considered[5]
- The European Society of Cardiology states that combination therapy should be as first line treatment particularly in patients with hypertension ≥160/100 mmHg and in patients with grade 1 hypertension with compelling indications such as diabetes, cardiovascular disease, renal disease, etc.[6]
- According to JNC 7 recommendations, if the blood pressure goal cannot be met with lifestyle modifications, then thiazide-type diuretics should be used as monotherapy or in combination with one of the following classes of medication:
  - ACEI
  - ARBs
  - BBs
  - CCBs

Recommended drug classes for indications that may exist in association with hypertension

Compelling Indication	Diuretic	BB	ACEI	ARB	CCB	Aldo. Antag.
Heart Failure	√	√	√	√		√
Postmyocardial Infarction		√	√			√
High Coronary Disease Risk	√	√	√		√	
Diabetes	√	√	√	√	√	
Chronic Kidney Disease			√	√		
Recurrent Stroke Prevention	√		√			

Adapted from Table 12 of the JNC 7

Emergent Data in the Treatment of Hypertension

- No data regarding JNC 8 can be accessed at this time.
- JNC 8 guidelines are expected to be made available for public review and comment in March of 2010.[7]
- Expected release date of JNC 8 guidelines is during the summer of 2010.[8]
- In May of 2009, a follow-up analyses of the ALLHAT, including subsequent trials and meta-analytic data, was published in the Archives of Internal Medicine[9], which confirmed the initial ALLHAT findings that **thiazide diuretics are still the preferred first line option in treatment of hypertension**:
    - Chlorthalidone was superior to
        (1) doxazosin mesylate in preventing combined CVD (CCVD), especially HF and stroke;
        (2) lisinopril in preventing CCVD, including stroke (in black persons only) and HF;
        (3) amlodipine besylate in preventing HF.
    - Results were consistent by age, sex, race (except for stroke and CCVD), DM status, metabolic syndrome status, and renal function level.
    - Neither amlodipine nor lisinopril was superior to chlorthalidone in preventing end-stage renal disease overall, by DM status, or by renal function level.
    - New-onset diabetes associated with thiazides does not increase cardiovascular disease risk.
    - Despite having more favorable effects on glucose and lipid levels and other surrogate variables, neither the [alpha]-blocker, ACE inhibitor, nor the CCB surpasses the thiazide-type diuretic as initial therapy for control of BP or reduction of cardiovascular or renal clinical outcomes (when compared at appropriate dosage).

Recommendations

The College of Pharmacy recommends placement of Valturna™ in Tier 3 of the Direct Renin Inhibitors Product Based Prior Authorization Category. The existing criteria for this category will apply.

Approval Criteria

- FDA approved indication
- Recent trial, within the previous 6 months and at least 4 weeks in duration, of an ACE Inhibitor (or an ARB if previous trial of an ACEI) and a diuretic, used concomitantly at recommended doses, that did not yield adequate blood pressure control.
- Clinical exceptions will be granted for members already currently on aliskiren and valsartan at the available doses of Valturna™.

Direct Renin inhibitors (Tekturna® and Tekturna HCT®)		
Tier-1	**Tier-2**	**Tier-3**
Tier-1 ACE Inhibitor + Diuretic	ARB + Diuretic	Aliskiren **(Tekturna™)** Aliskiren/HCTZ **(Tekturna HCT™)** Aliskiren/Valsartan **(Valturna™)**

REFERENCES

[1] **Valturna™ (aliskiren and valsartan tablets) Product Information.** Novartis Pharmaceuticals Corporation. September 2009.

[2] Cushman WC, Ford CE, Cutler JA, Margolis KL, Davis BR, Grimm RH, et al. **Success and predictors of blood pressure control in diverse North American settings: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).** J Clin Hypertens (Greenwich) 2002; 4:393-404.

[3] Sica DA. **Rationale for fixed-dose combinations in the treatment of hypertension: The cycle repeats.** Drugs 2002; 62: 443-62.

[4] Law MR, Wald NJ, Morris JK, Jordan RE. **Value of low dose combination treatment with blood pressure lowering drugs: Analysis of 354 randomized trials.** BMJ 2003; 326: 1427-34.

[5] Sica DA. **Rationale for fixed-dose combinations in the treatment of hypertension: The cycle repeats.** Drugs 2002; 62: 443-62.

[6] Mancia G, De Backer G, Dominiczak A, et al. **Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). European Heart Journal.** 28(12):1462-536, 2007 Jun.

[7] National Heart Lung and Blood Institute. **The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8).** Accessed at: http://www.nhlbi.nih.gov/guidelines/hypertension/jnc8/index.htm.

[8] National Heart Lung and Blood Institute. **The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8).** Accessed at: http://www.nhlbi.nih.gov/guidelines/hypertension/jnc8/index.htm.

[9] Wright, Jackson T Jr. Probstfield, Jeffrey L. Cushman, William C. Pressel, Sara L. Cutler, Jeffrey A. Davis, Barry R. Einhorn, Paula T. Rahman, Mahboob. Whelton, Paul K. Ford, Charles E. Haywood, L Julian. Margolis, Karen L. Oparil, Suzanne. Black, Henry R. Alderman, Michael H. ALLHAT Collaborative Research Group. **ALLHAT findings revisited in the context of subsequent analyses, other trials, and meta-analyses.** Archives of Internal Medicine. 169(9):832-42, 2009 May 11.

Appendix F

Vote to Prior Authorize Anti-Emetics
Oklahoma Healthcare Authority
December 2009

Recommendations

The College recommends prior authorization of granisetron, dolasetron, aprepitant, and cannabinoids. The following are the proposed approval criteria.

Approval Criteria for granisetron (Kytril® and Sancuso®), dolasetron (Anzemet®), and aprepitant (Emend®):

- Approved Diagnosis
- A recent (within the past 6 months) trial of ondansetron used for at least 3 days or during one cycle/post-op event that resulted in inadequate response.
- Approval length based on duration of need.
- Existing quantity limits apply.

Approval Criteria for cannabinoids (Marinol® and Cesamet®):

- For the diagnosis of HIV related loss of appetite: approve for 6 months
- For chemotherapy induced nausea and vomiting: A recent (within the past 6 months) trial of ondansetron used for at least 3 days or one cycle that resulted in inadequate response.
- Approval length based on duration of need.
- A quantity limit of 60 per 30 days also applies.

Appendix G

60 DAY NOTICE TO PRIOR AUTHORIZE

ATYPICAL ANTIPSYCHOTICS

OKLAHOMA HEALTH CARE AUTHORITY
DECEMBER 2009

INTRODUCTION

This category was introduced as future business in November 2009. This notice and statement of potential economic impact are presented to meet the statutory requirements of 63 O.S. Sec. 5030.5.

Background

In the early 1950s, chlorpromazine entered the market and changed the treatment of mental disorders. Chlorpromazine was the prototypic antipsychotic that was shown incontestably to be more effective than nonpharmacologic treatment in alleviating the acute symptoms of schizophrenia and preventing their recurrence.[1,2] Subsequent first generation antipsychotics offered different adverse-effect profiles and dosage forms. The second generation antipsychotics, also referred to as the atypical antipsychotics, were later developed in response to concerns with older typical agents which had troublesome adverse effects, especially extrapyramidal symptoms (EPS) and tardive dyskinesia (TD). In 1990 Clozapine, the first of the atypical antipsychotics was introduced in the United States. The class has grown to include:

- risperidone (Risperdal®) in 1994
- olanzapine (Zyprexa®) in 1996
- quetiapine (Seroquel®) in 1998
- ziprasidone (Geodon®) in 2001
- aripiprazole (Abilify®) in 2002
- paliperidone (Invega®) in 2006
- quetiapine extended release (Seroquel XR®) in 2007
- asenapine (Saphris®) in 2009

Iloperidone (Fanapt®) is anticipated to enter the market in 2010. The atypical antipsychotics were originally reserved for the treatment of schizophrenia and acute manic or mixed episodes associated with Bipolar I disorders. However, their use has increased due to non-FDA approved or off-label uses. In 2008, according to IMS Health, a provider of pharmaceutical and healthcare market intelligence, the class of antipsychotics rose to become the top therapeutic class in the United States by sales, topping at $14.6 billion dollars.[3] Recently, the FDA approved a new indication for aripiprazole (Abilify®) for adjunctive use in the treatment of depression, and another atypical antipsychotic is currently applying for this new indication. This has the potential to further increase the use of atypical antipsychotics when considering the prevalence of depression in the adult population (6.7%) is almost double that of schizophrenia (1.1%) and bipolar disorders (2.6%) combined.[4]

The following are the anticipated patent expirations:

- olanzapine (Zyprexa®) in 2011
- quetiapine (Seroquel®) in 2011 or 2012
- ziprasidone (Geodon®) in 2012
- aripiprazole (Abilify®) in 2014
- paliperidone (Invega®) in 2012
- quetiapine extended release (Seroquel XR®) in 2012
- asenapine (Saphris®) in 2015

CURRENTLY AVAILABLE ATYPICAL ANTIPSYCHOTICS

Generic Name	Trade Name	FDA Indications	Dosage Forms Available	Youngest Age Indicated	Frequency of Dosing
Clozapine†	Clozaril® Fazaclo®	- Schizophrenia: treatment-resistant or suicidal behavior, recurrent-initial and maintenance - Schizoaffective DO: suicidal behavior, recurrent-initial and maintenance	Tabs, ODT	No Pediatric Indications	QD, 12.5mg – 900mg
†Risperidone	Risperdal®	- Schizophrenia: initial and maintenance - Bipolar I DO: initial and maintenance as monotherapy or combo with Lithium or Valproate - Autistic DO: irritability in children-initial and maintenance	Tabs, ODT, Oral Solution, Powder for reconstitution (IM Inj)	5 years of age	1mg – 6mg QD-BID Q 2 wks (IM)
Olanzapine	Zyprexa®	- Schizophrenia - Bipolar I DO: maintenance or acute mixed or manic episodes - Agitation: Schizophrenia or Bipolar I DO	Tabs, ODT, Powder for reconstitution (IM Inj)	No Pediatric Indications	5mg – 20mg QD Q 2-4 hrs (IM)
Quetiapine	Seroquel® Seroquel XR®	- Schizophrenia: initial, maintenance, re-initiation - Bipolar DO: depressed phase or maintenance - Manic Bipolar I DO: initial, maintenance, or re-initiation	Tabs, Extended Release Tablets	No Pediatric Indications	25mg – 800mg QD-TID
Ziprasidone	Geodon®	- Schizophrenia: initial and maintenace - Bipolar I DO: acute manic or mixed episodes -Agitation, acute: Schizophrenia	Caps, Powder for reconstitution (IM Inj)	No Pediatric Indications	20mg – 160mg BID Q 2-4 hrs (IM)
Aripiprazole	Abilify®	- Schizophrenia: initial and maintenance - Bipolar I DO: adjunct to Lithium or Valproate; monotherapy, manic or mixed episodes - Major Depressive DO: adjunct to antidepressants - Psychomotor agitation: Schizophrenia and Bipolar DO -Irritability assoc with Autistic DO	Tabs, ODT, Oral Solution, Solution for IM injection	6 years of age	10mg – 30mg QD Q 2 hrs (IM)
Paliperidone	Invega®	- Schizophrenia - Schizoaffective DO	Extended Release Tablets	No Pediatric Indications	6mg – 12mg QD
Asenapine	Saphris®	- Schizophrenia - Acute treatment - Bipolar I DO - Acute manic or mixed episodes	Sublingual Tablets (5mg and 10mg)	No Pediatric Indications	5mg-10mg SL BID

† available as generic.

DIAGNOSIS AND TREATMENT OF SCHIZOPHRENIA AND BIPOLAR DISORDERS

Diagnosis of Schizophrenia[5]

Schizophrenia is a group of complex disorders characterized by hallucinations, delusions, and behavioral disturbances, disrupted social functioning, and associated symptoms. The etiology of schizophrenia has not been determined, but may be due to genetic factors, structural or neurochemical changes in the brain, neurophysiological changes, viral or immunological factors, and/or endocrine originated factors. The lifetime incidence for schizophrenia is approximately 1% and is consistent across racial and cultural sectors. The diagnosis of schizophrenia requires at least a six month period of continuous signs and symptoms, which may include:

- **Delusions**, which are false beliefs that (1) persist despite what most people would accept as evidence to the contrary and (2) are not shared by others in the same culture or subculture.
- **Hallucinations**, which are perceptions that appear to be real when no such stimulus is actually present. Hallucinations may involve any of the five normal senses, but in schizophrenia they are usually auditory.
- **Disorganized speech**.
- **Grossly disorganized or catatonic behavior**. Catatonia, a syndrome characterized by stupor with rigidity or flexibility of the musculature, may alternate with periods of over activity.
- **Negative symptoms**, such as (1) affective flattening or decreased emotional reactivity; (2) alogia or poverty of speech; (3) avolition or lack of purposeful action. Usually, work performance, social relations, and self-care decrease below the highest previous levels.

Another common subtype of schizophrenia is schizoaffective disorder. According to DSM IV, the diagnosis of schizoaffective disorder requires a continuous period of illness during which time there is either a major depressive, manic, or mixed (manic and depressive) episode that is concurrent with the active symptoms of schizophrenia. Also, during this time there must be delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms. The mood symptoms should be present for a substantial portion of the active and residual phases of the illness.

Treatment of Schizophrenia[6]

Pharmacologic treatment with antipsychotic medications has become the mainstay of treatment for schizophrenia. Inpatient treatment may be especially crucial in the early or acute phases of schizophrenia to minimize harm to self or others. Residential treatment settings, group homes, or day hospital programs may be an option for the more stable patient. Individual or group psychotherapy may also be utilized to help the patient understand their illness and need for treatment, as well as to help identify trigger factors that influence symptoms, and to develop strategies to effectively deal with the illness. Family therapy sessions can help the families of schizophrenic patients to understand the illness, and influence their judgment of the affected individual, which may minimize negative impacts. For the stabilized patients, social skills training and vocational rehabilitation may help schizophrenic patients return to a more productive and normal life.

The American Psychiatric Association does not recommend a specific first line agent. Pharmacologic treatment selection should be based upon severity of illness and whether it's an acute phase treatment or somatic treatment. Acute phase treatment includes consideration of parenteral or rapidly dissolving formulations of first and second generation antipsychotics in conjunction with benzodiazepines. For somatic treatment, the following factors should be considered:

- Prior degree of symptom response
- Past experience of side effects
- Side effect profile of prospective medications
- Patient's preferences for a particular medication, including route of administration
- Available dosage forms

Diagnosis of Bipolar Disorders[7]

Bipolar disorder is a heterogeneous group of disorders characterized by cyclical disturbances in mood, cognition, and behavior. The diagnosis requires a history of mania for at least 1 week, or hypomania for at least 4 days. Bipolar I disorder refers to patients who have had at least one episode of mania. Bipolar II disorder refers to patients with a history of hypomania and major depressive episodes. Cyclothymia refers to patients with chronic mood swings (at least 2 years in duration) that fluctuate between hypomania and minor but not major depression.

Treatment of Manic or Mixed Episodes associated with Bipolar I Disorders[8]

Lithium has been shown to be the mood stabilizer of choice for the treatment of bipolar disorders[9]. For severe manic or mixed epidsodes, Lithium or valproate alone or used in conjunction with an antipsychotic is recommended by the American Psychiatric Association. Carbamazepine or oxcarbamazepine in conjunction with lithium or valproate may also be an alternative. Monotherapy with lithium, valproate, or an antipsychotic may be sufficient for less severe episodes. Short term adjunctive treatment with benzodiazepines may also be helpful.

Atypical antipsychotics are now recommended over first generation antipsychotics due to the belief that atypical antipsychotics possess the propensity for a lower incidence of neurologic adverse effects. Over the past decade, with more clinical evidence that emerged in support of the use of atypical antipsychotics for acute manic episodes, the use of atypical antispychotics for this indication has increased.[10] However, the maintenance treatment of Bipolar Disorders with atypical antipsychotics has not been as intensively studied as with schizophrenia, and currently there are only three atypical antipsychotics indicated for maintenance therapy. Many patients are started on antipsychotics when hospitalized for the acute episode, and subsequently left on the antipsychotic medication after discharge.[11]

EFFICACY AND SAFETY OF ATYPICAL ANTIPSYCHOTICS

The safety and efficacy of the atypical antipsychotics have been an important issue of interest since the introduction of the first atypical antipsychotic, clozapine. During the last decade, as more atypical antipsychotics have been added to this class, major research efforts have focused on comparing the advantages of safety vs. efficacy and costs between the older antipsychotics and the newer atypical antipsychotics as well as comparisons between the atypical antipsychotics. However, caution should be used when interpreting results of clinical trials specifically for this class of medications due to the following reasons[12]:

- Patients with severe symptoms of mental illness will often not be included in trials because of their inability or refusal to provide consent.
- Often, efficacy studies also exclude patients who have comorbid diseases, meaning diseases other than the one studied, which does not reflect real life conditions.
- They often examine the short-term effects of drugs that are used for much longer periods of time in practice.
- They tend to use objective measures of effects that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.
- Many studies were found only in abstract form, with no subsequent full article publication.
- The number of authors employed by pharmaceutical companies was unusually high for this category. In some cases, a pharmaceutical company employed all the authors of the publication; however, these publications do not address the additional potential for bias when there is no independent authorship.

COMPARISON OF EFFECTIVENESS

The majority of atypical antispychotic efficacy trials are designed to show that the atypical agent is as effective as the older first generation antipsychotic, typically haloperidol. Very few trials aim to show superior efficacy. The exception lies with clozapine, which has been demonstrated to be superior to first generation antipsychotics in the treatment of positive and negative symptoms of schizophrenia. It remains to be the treatment of choice for patients with high risk of suicide, or for patients refractory to treatment.[13] Among the atypical antipsychotics, there are few head to head trials

comparing the efficacy of one agent over another. Most comparative efficacy data are derived from meta-analysis or Cochrane systematic reviews, which up to this point, only shows a slight and variable advantage of the second generation antispychotics in terms of efficacy, rate of relapse, and discontinuation due to adverse effects.[14]

The CATIE[15] trial, sponsored by the National Institute of Mental Health, is the first study to actively compare the efficacy of all available atypical antipsychotics and of atypical antipsychotics against a first generation antipsychotic. This trial compared the first generation antipsychotic, perphenazine, with the atypical antipsychotics olanzapine, quetiapine, risperidone, and ziprasidone in 1,493 schizophrenic patients. The trial started January 2001 and ended December 2004. Aripiprazole was added after its FDA approval in 2002, and clozapine was reserved for phase two of the trial for patients who failed treatment with one of the phase I medications. The following are the results from phase 1 of the CATIE study:

- Patients with chronic schizophrenia, regardless of the medication treatment group, discontinued their antipsychotic medications at a high rate (64-82%) due to inefficacy, intolerable side effects, or for other reasons.
- Within the limited range of effectiveness, there were no significant differences in effectiveness between the atypical antipsychotics and perphenazine, except olanzapine, which appeared to be slightly more effective than the other agents.
- There were no significant differences among the medications in the time until discontinuation due to intolerable side effects. However, olanzapine was associated with greater weight gain and increases in glycosylated hemoglobin, cholesterol, and triglycerides. These changes may have serious implications with respect to medical morbidity such as the development of the metabolic syndrome.

Discontinuation due to any cause is a significant indicator of tolerability, which greatly influences efficacy and is the primary outcome measured in the trial. The phase I results of the CATIE study indicated that there was no significant difference in efficacy between atypical antipsychotics or the first generation antipsychotic, perphenazine.

It cannot be concluded from the currently available data that the atypical antipsychotics are a safer, more effective treatment for schizophrenia. However, it is clear that this class of newer medications offers the clinician more choices in the treatment of schizophrenia, realizing that each agent possesses a different adverse effect profile that must be weighed and considered in light of patient characteristics and comorbid conditions.

The **CUtLASS[16] trial** is similar to the CATIE trial and was sponsored by the National Health Service (England). It was a noncommercially funded, pragmatic, multisite, randomized controlled trial to test the hypothesis that in people with schizophrenia requiring a change in treatment, second generation antipsychotics other than clozapine are associated with improved quality of life across 1 year compared with first generation antipsychotics. The results of the CUtLASS trial showed there was no clinical advantage for use of atypical antipsychotics over first generation antipsychotics. The results refute the hypothesis that the use of atypical antipsychotics is superior to the use of first generation antipyschotics in terms of quality of life at 1 year as there was no significant difference in change of Quality of Life Scale between the two arms. Clinical superiority had been defined a priori as a 5-point difference in the QLS score.

The **TEOSS[17] study** is a double-blind, randomized trial comparing olanzapine, risperidone, and molindone in 119 pediatric patients with early-onset schizophrenia and schizoaffective disorder. The primary outcome was response to treatment, defined as a Clinical Global Impression improvement score of 1 or 2, and at least a 20-percent reduction in the total score on the Positive and Negative Syndrome Scale after eight weeks of treatment. No significant differences were found among treatment groups in response rates (molindone: 50 percent; olanzapine: 34 percent; risperidone: 46 percent) or magnitude of symptom reduction. Olanzapine and risperidone were associated with significantly greater weight gain. Molindone was associated with more self-reports of akathisia.

These studies show there are few differences in effectiveness between first-generation antipsychotics and atypical antipsychotics in nonrefractory patients. This conclusion runs counter to the impressions of many clinicians and previous studies suggesting marked superiority of the newer agents. However, these results are generally consistent with numerous meta-analyses[18,19,20,21,22,23,24,25,26,27,28,29] performed during the past decade seeking to find a definitive answer regarding comparative effectiveness of these agents. The strength and availability of such evidence indicates the non-superiority of the atypical antipsychotics, and should have wide-ranging effects on policies and clinical practice.

COMPARISON OF SAFETY

The atypical antipsychotics are generally perceived as possessing a more favorable side effect profile compared with conventional antipsychotic medications. Through increasing use and experience with the novel medications, it is clear that atypical antipsychotics have their own unique side effect profiles. The metabolic adverse effects of the atypical antipsychotics have been viewed by some to be the tardive dyskinesia equivalent of the first generation antipsychotic medications and include cardiovascular irregularities, metabolic disturbances, and dyslipidemias that can lead to long term health consequences, such as diabetes and coronary artery disease.

To understand the magnitude of these adverse effects and its impact on the healthcare of the schizophrenic population, there must first be an understanding of the incidence of cardiovascular comorbidities in patients with schizophrenia. Coronary heart disease is by far the leading cause of mortality in developed countries, but this incidence and the incidence of related comorbidities are disproportionately higher in the schizophrenic population. The following table shows a comparison between the general population and the schizophrenic population[30]:

	General Population	Population with Schizophrenia
Cigarette smoking	**25%**	**75%**
Hypertension	**15%**	**19%**
Obesity	**27%**	**42%**
Diabetes	**7%***	**1.5-2.0 fold greater**
Absolute risk of death from CHD	**33%**	**50-75%**
Life expectancy	**76 years (72-men, 80-women)**	**61 (57-men, 65-women)**

* statistics came from the American Diabetes Association.

The relative risk of weight gain associated with atypical antipsychotic use is higher when compared to first generation antipsychotics and is greatest for clozapine and olanzapine[31]. The health implications of long-term therapy with atypical antipsychotics, which has been shown to significantly increase the risk of treatment emergent diabetes mellitus[32], is a growing concern especially when compounded by the obesity epidemic that is widespread among both the adult and adolescent U.S. population. A recently published article[33] assessed the cardiometabolic risk of atypical antipsychotic medications during first-time use in children and adolescents. The following are the comparative results of weight gain among use of various antipsychotics compared with an untreated group after 11 weeks:

Medication	Average Weight Gain
aripiprazole	10 lbs
risperidone	12 lbs
quetiapine	13 lbs
olanzapine	19 lbs
untreated	0.42 lbs

Other cardiovascular risks include hypotensive effects, hypertensive effects, and QTC prolongation resulting in tachycardia and sudden cardiac death. The QTC prolongation effect is present in both older and newer antipsychotics. The increased risks of death and cerebral ischemia or stroke among elderly patients receiving therapy for psychotic disorders or agitation associated with dementia was of particular concern. Based on the findings of 17 placebo controlled trials involving a total of 5,106 elderly patients with dementia-related psychosis, the FDA issued a black box warning requirement in 2005 for all antipsychotics regarding the 1.6 to 1.7 fold increase in risk of death associated with the use of these agents.

In addition to metabolic disturbances and increased cardiovascular risk, atypical antipsychotics possess adverse effects that are also present in first generation antipsychotics. EPS, akathisia, and movement disorders are present and are found to be dose related. In clinical trials, it's often common to see comparisons between moderate doses of atypicals vs. large doses of potent first generation antipsychotics. A meta-analysis by Leucht et al found that at low doses, chlorpromazine or its equivalent had no higher risk of EPS than atypical antipsychotics[34]. This is further evident as the CATIE trial results showed that there were no significant differences between atypical antipsychotics and perphenazine

in the incidence of EPS, akathisia, or movement disorders, although the incidence of discontinuation of treatment due to these adverse effects were nonsignificantly more prominent for the perphenazine group. The following are other adverse effects of concern with the atypicals:

- Sedation and risk of neuroleptic malignant syndrome
- Anticholinergic side effects such as dry mouth, constipation, increased intraocular pressure, and urinary retention

Comparison of Atypical Antipsychotic Side Effect Profiles

	Clozapine[b] (Clozaril®)	Risperidone (Risperdal®)	Olanzapine (Zyprexa®)	Quetiapine[c] (Seroquel®)	Ziprasidone (Geodon®)	Aripiprazole[d] (Abilify®)
EPS/TD	0[a]	+	0[a]	0[a]	0[a]	0[a]
Increased Prolactin Level	0	+++	0	0	+	0
Glucose Abnormality	+++	++	+++	++	0	0
Lipid Abnormalities	+++	++	+++	++	0	0
QTc Prolongation	0	+	0	0	++	0
Weight Gain	+++	++	+++	++	0	0
Sedation	+++	+	+	++	0	+
Hypotension	+++	+	+	++	0	0
Anticholinergic	+++	0	++	0	0	0

Adapted from Table 3 of Treating Schizophrenia: A Quick Reference Guide.[35]

[a] Possible exception of akathisia, side effect may be dose dependent.

[b] May also cause agranulocytosis, seizures, and myocarditis.

[c] Also carries warning about potential development of cataracts

[d] Also causes nausea and headache.

COST EFFECTIVENESS OF ATYPICAL ANTIPSYCHOTICS

Although clozapine was the first atypical antipsychotic, there was not a rapid shift to atypical antipsychotic use until the introduction of risperidone, olanzapine, and quetiapine during the 1990s. Atypical antipsychotics have largely replaced first generation antipsychotics in utilization, and with costs of the atypical medications considerably more than the first generation antipsychotics, spending has substantially increased for both private and public payor systems. A study by the Lewin[36] group found that prescriptions for atypical antipsychotics in the Medicaid system increased overall by 20% from 1995 – 1998, but resulted in a disproportionate 160% increase in costs. A point of interest with antipsychotics is that while the Medicaid program pays for only 18% of all prescriptions filled in the U.S., Medicaid pays for nearly 75% of all antipsychotic medications.[37] Although the cost data is alarming, payer systems have held on to the hope that the newer agents will decrease total mental healthcare costs by increasing compliance, which should increase efficacy and decrease relapse, and also decrease adverse effects such as EPS, which may require a patient to be in a care facility.

The drawback is that outcomes such as rate of relapse, hospital readmission, improvements in occupational and social functionality, and costs have been minimally assessed in clinical trials. Among the atypical antipsychotics, one retrospective study[38] based on administrative claims data from 46 U.S. commercial health plans compared the mental health resources utilized by patients with bipolar disorder treated with risperidone, olanzapine, or quetiapine. The results showed that total charges for mental health services other than the study drug were not different between the three medications. However, when prescription costs were included, olanzapine appeared to be considerably more costly at an equivalent daily dose than risperidone or quetiapine. Findings from studies that examine the relationship between the use of atypical antipsychotics vs. first generation antipsychotics and total healthcare spending yielded mixed results such as the one by Glazer et al[39] which found reduced expenditures and one by Coley et al[40] which found the opposite result. One Cochrane systematic review[41] yielded inconclusive results.

Rosenheck et al[42] conducted a 12 month, prospective, double blinded, randomized, controlled trial to evaluate the effectiveness and cost impact of olanzapine compared to haloperidol in the treatment of schizophrenia. The study found no statistically or clinically significant advantages of olanzapine on measures of compliance, symptoms, or overall quality of life; nor did it find evidence of reduced inpatient use of healthcare resources or total costs. Olanzapine use did modestly reduce akathisia and tardive dyskinesia, and improved measures of memory and motor functions. However, the cognitive gains were insufficient to improve quality of life functioning or employment earnings.

Another study by Duggan[43] examined the trends in total mental healthcare costs paralleled by the increase in atypical antipsychotic usage in a 20% sample of California fee for service Medicaid population to see if the atypical antipsychotics "pay for themselves" as was the hypothesis. From 1993 to 2001 spending on antipsychotic drugs increased by 610% with the most significant increase occurring around 1997. However, from 1993 to 2001, there was no decline in average spending on inpatient or outpatient care, with the cost trend greatly increasing after 1997. As a result of the increase in mental healthcare spending and medication costs, the growth rate of Medicaid spending for individuals diagnosed with schizophrenia increased from an annual rate of just 1.6% per year from 1993-1997 to 9.3% per year during the 1997-2001 time period. An analysis of the time period 1993-2001 also showed that the incidence in diagnosis of tardive dyskinisia and EPS declined, but was countered by an increase in prevalence of diabetes and related metabolic disorders.

Duggan concludes that from the standpoint of pharmacoeconomics, the the high cost of the atypical antipsychotic medications are not justified as a decrease has not been shown in total mental healthcare spending. The Medicaid system is the major payer bearing the brunt of these costs, and in this kind of system, there is little incentive for prescribers or patients to consider cost as the copay remains relatively the same regardless of the medication prescribed.

OFF LABELED USE OF ATYPICAL ANTIPSYCHOTICS

Dementia Related Psychosis in the Elderly

Dementia is prevalent in 13% of the elderly population 71 years of age and older and may reach 37% in those 90 years of age or older.[44] It may be a result of a primary psychotic disorder such as schizophrenia, or may be secondary to other medical conditions such as Alzheimer's disease, Lewy Body Dementia, and/or Parkinson's disease. Antipsychotics have been commonly used off-label to treat dementia-related psychosis. Atypical antipsychotics have been associated with an increased risk of stroke and sudden cardiac death when used in elderly patients suffering from dementia-related psychosis. The etiology of this risk has not been determined, but most of the death that occurred appear to be cardiovascular (cardiac failure, sudden death) or infectious (i.e. pneumonia) in nature. Since 2005, all antipsychotics are required to have a black box warning regarding the increased mortality when used in this population as mentioned earlier. In addition, the findings of the CATIE-AD[45] trial in 2006 also concluded that adverse effects offset advantages in efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease. However, these drugs are still prescribed in this population, mostly for their sedative effects in the treatment of aggressive behavior or as an adjunctive sleep aid.

Pervasive Developmental Disorders, Disruptive Behavior, or ADHD[46]

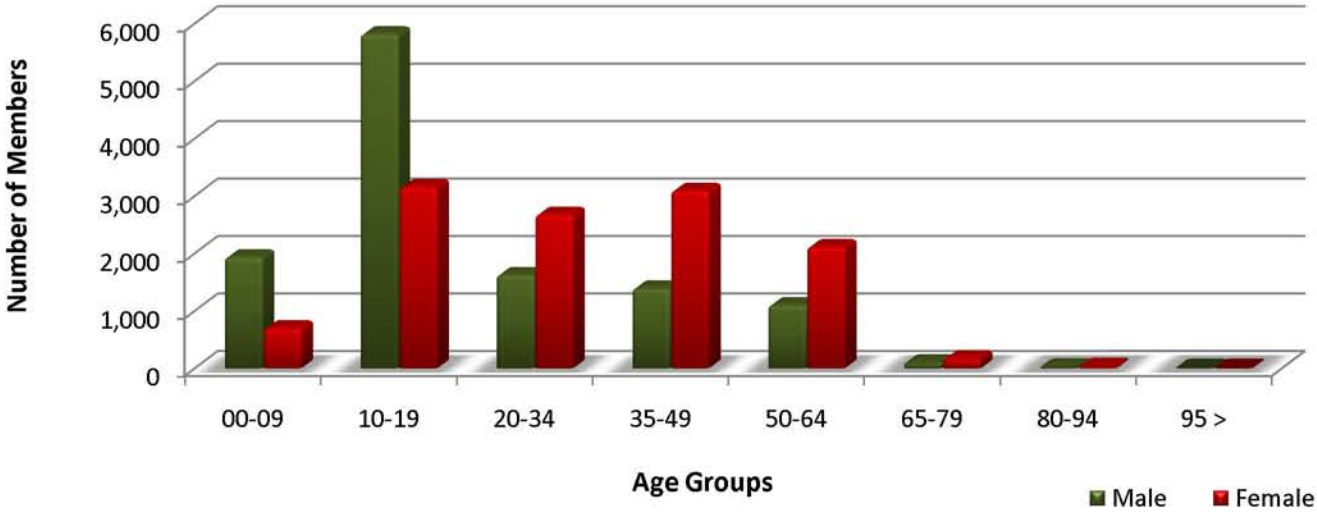
Atypical antipsychotics are increasingly used off-label for diagnoses such as autism, disruptive behaviors, or attention deficit hyperactivity disorders (ADHD). Clinical trials supporting the use of atypical antipsychotics for these indications are few and of poor quality. Of the atypical antipsychotics, only five fair-quality, short term placebo-controlled trials were available and results showed superior efficacy when used in autism and disruptive behaviors compared with placebo. There were no head to head trials, only one small study with an active comparator showed olanzapine to be similar in efficacy to haloperidol when used for autism. Currently, no trials have evaluated the use of atypical antipsychotics for ADHD.

Trends in Utilization of Atypical Antipsychotics

Fiscal Year	Members*	Claims	Paid	Paid/Claim	Perdiem	Units	Days
2007	21,469	155,139	$49,125,723.19	$316.66	$10.19	6,833,197	4,819,323
2008	22,549	168,501	$58,682,908.63	$348.26	$11.22	7,288,590	5,230,079
2009	24,043	174,195	$60,211,839.62	$345.66	$11.24	7,405,071	5,358,373
% Change	12.00%	12.30%	22.60%	9.20%	10.30%	8.40%	11.20%
Change	2,574	19,056	$11,086,116.43	$29.00	$1.05	571,874	539,050

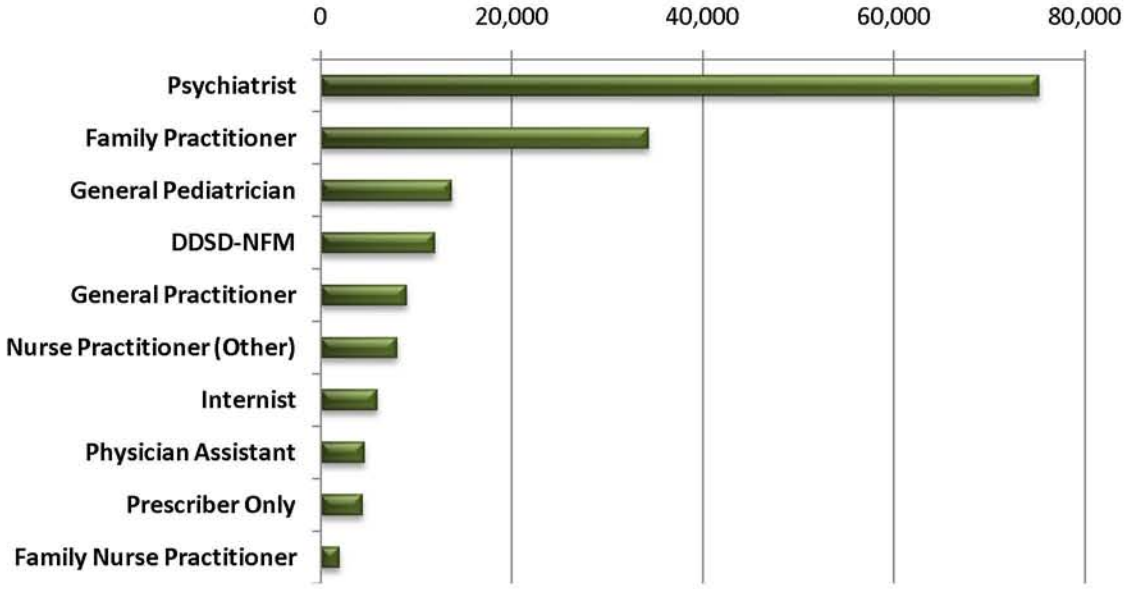
* Total number of unduplicated members.

Demographics of Members Utilizing Atypical Antipsychotics: FY 2009

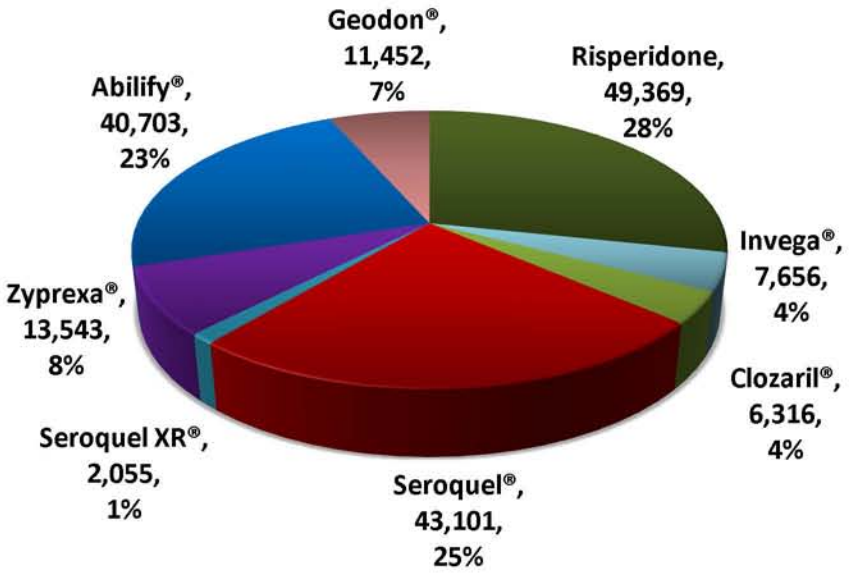


Of the 24,043 total members, 608 members were categorized as Advantage Waiver and 1,293 members were in nursing homes or other care facilities.

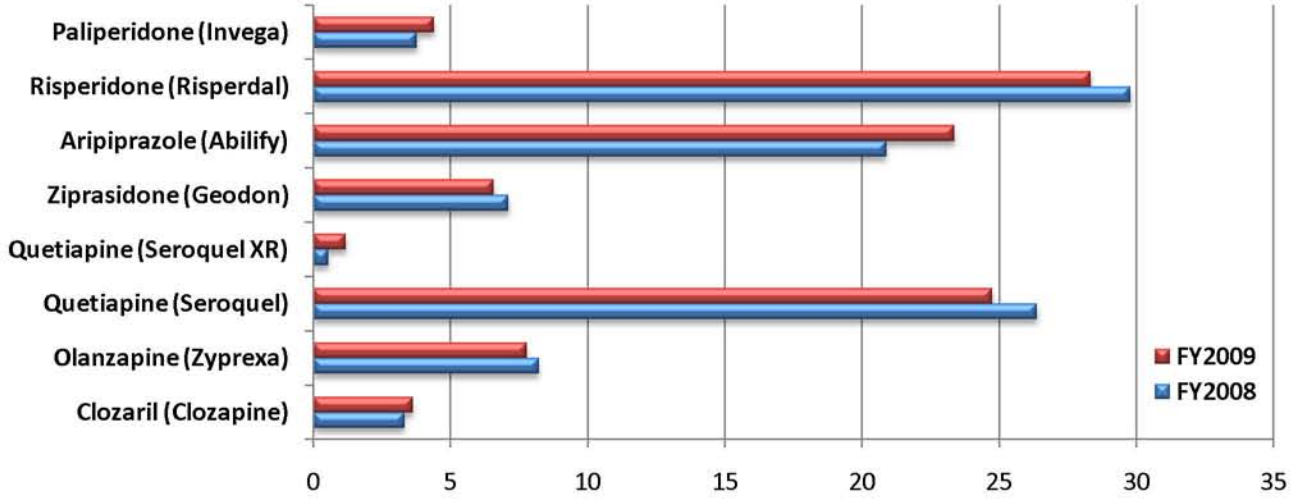
Top 10 Prescriber Specialty by Claims: FY 2009



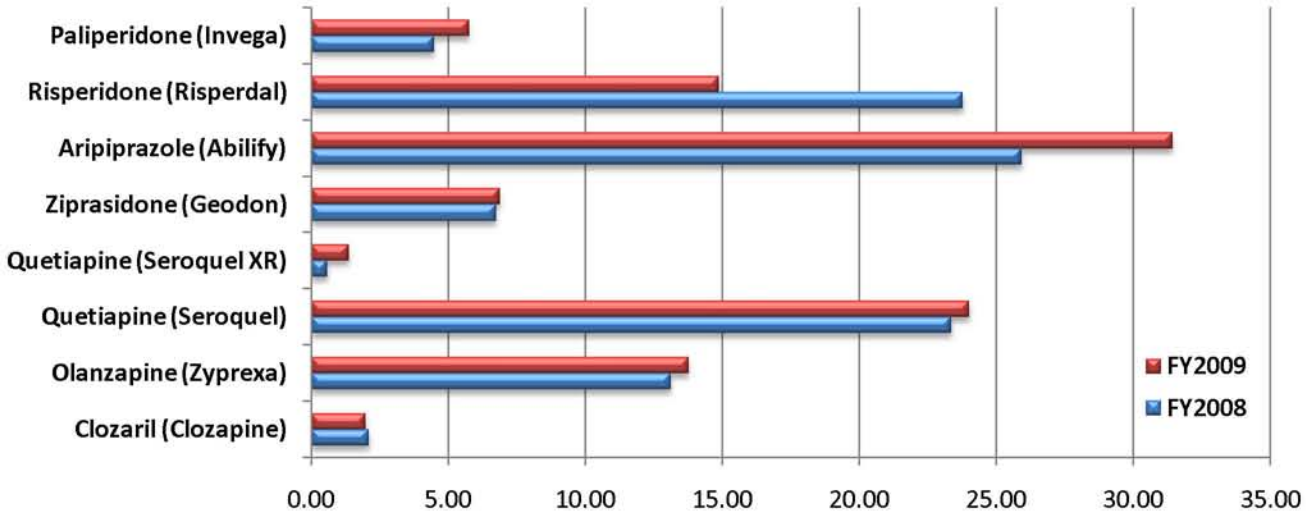
Market Share by Claims: FY 2009



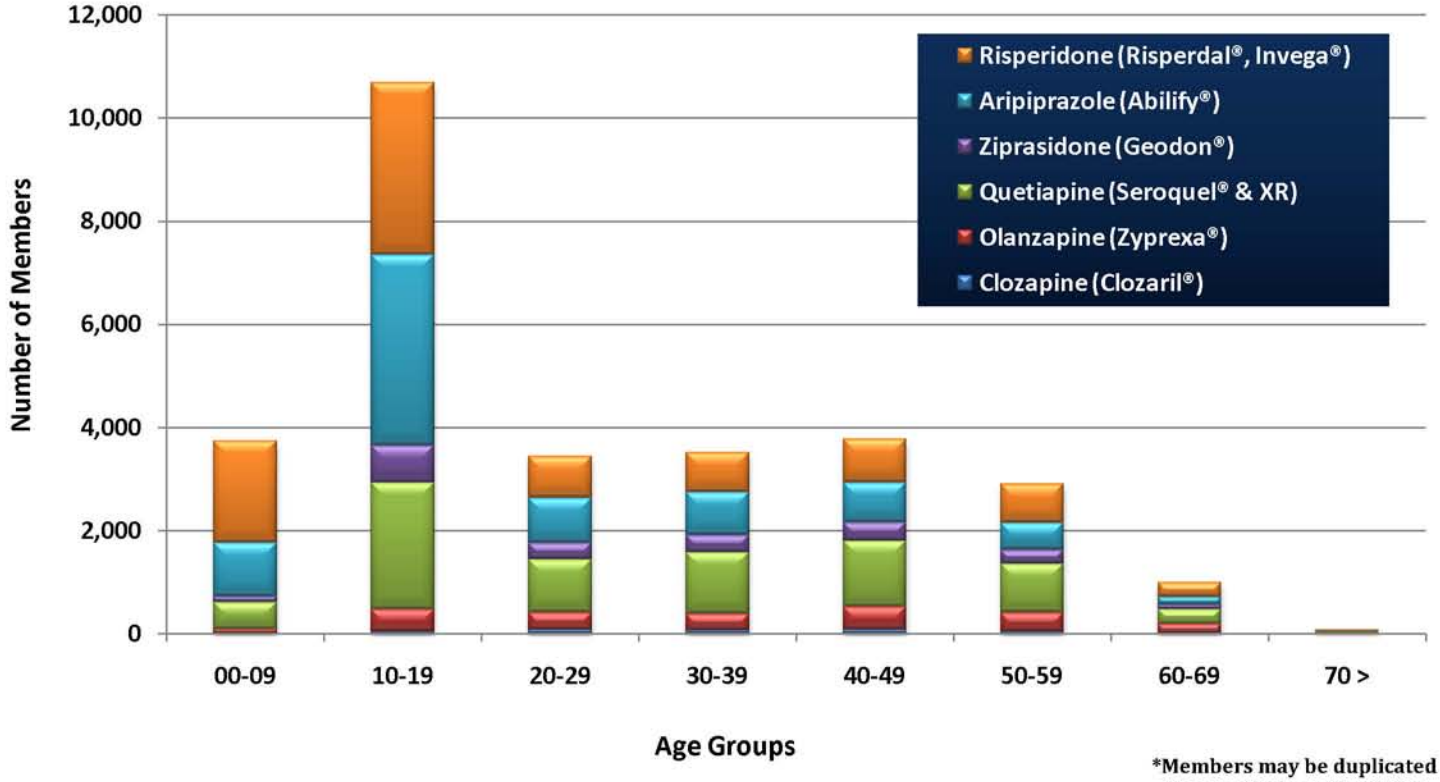
Change in Percent of Total Claims: FY 2009 vs. FY 2008



Change in Percent of Total Cost: FY 2009 vs. FY 2008

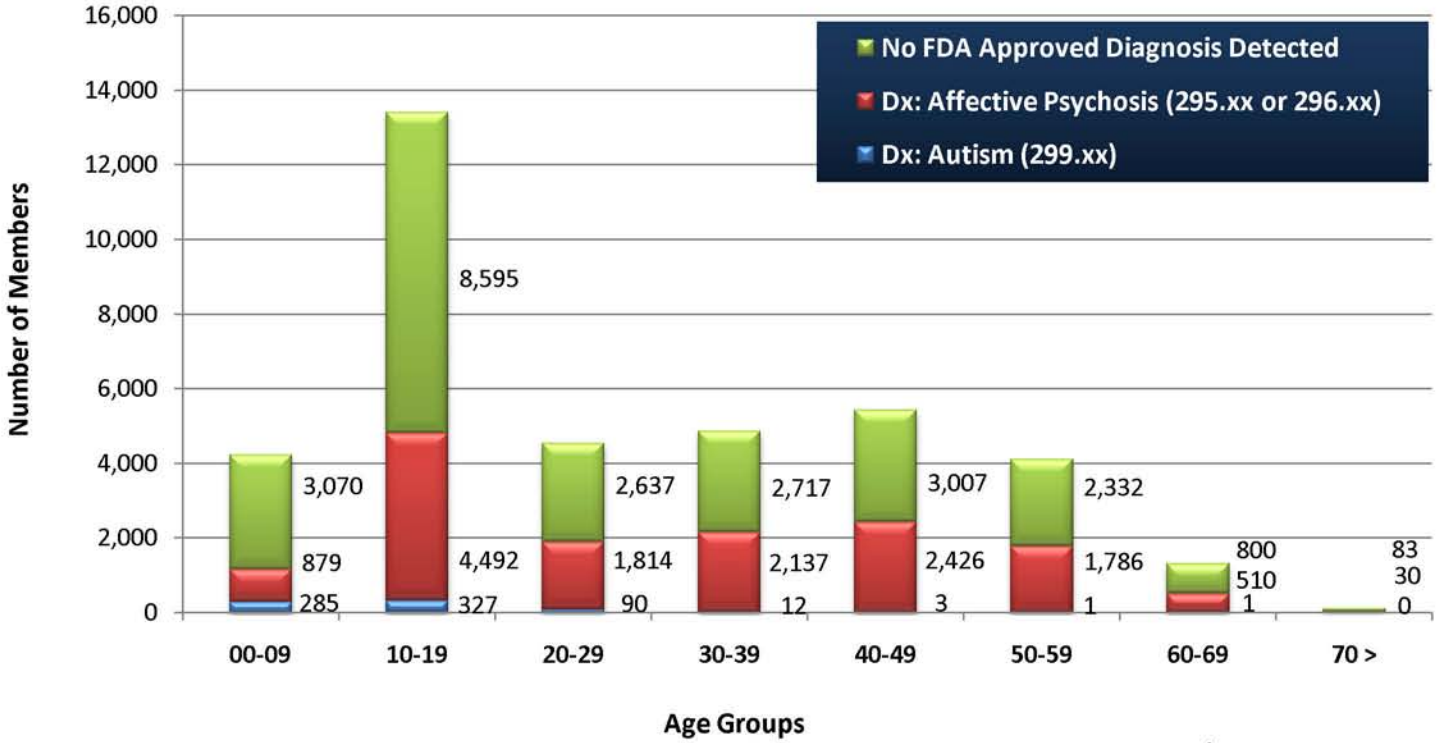


Trends in Demographics of Members* Utilizing Atypical Antipsychotics: CY 2008



*Members may be duplicated if on multiple medications.

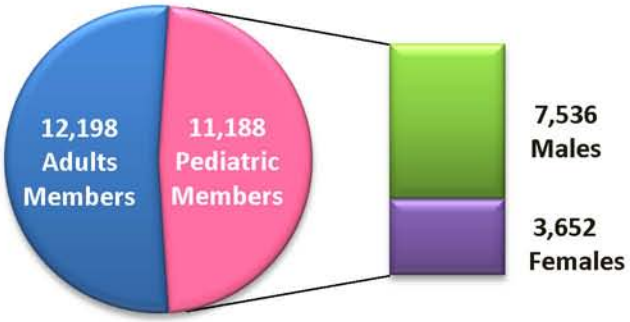
Demographics of Members† Utilizing Atypical Antipsychotics with Select Diagnoses: CY 2008

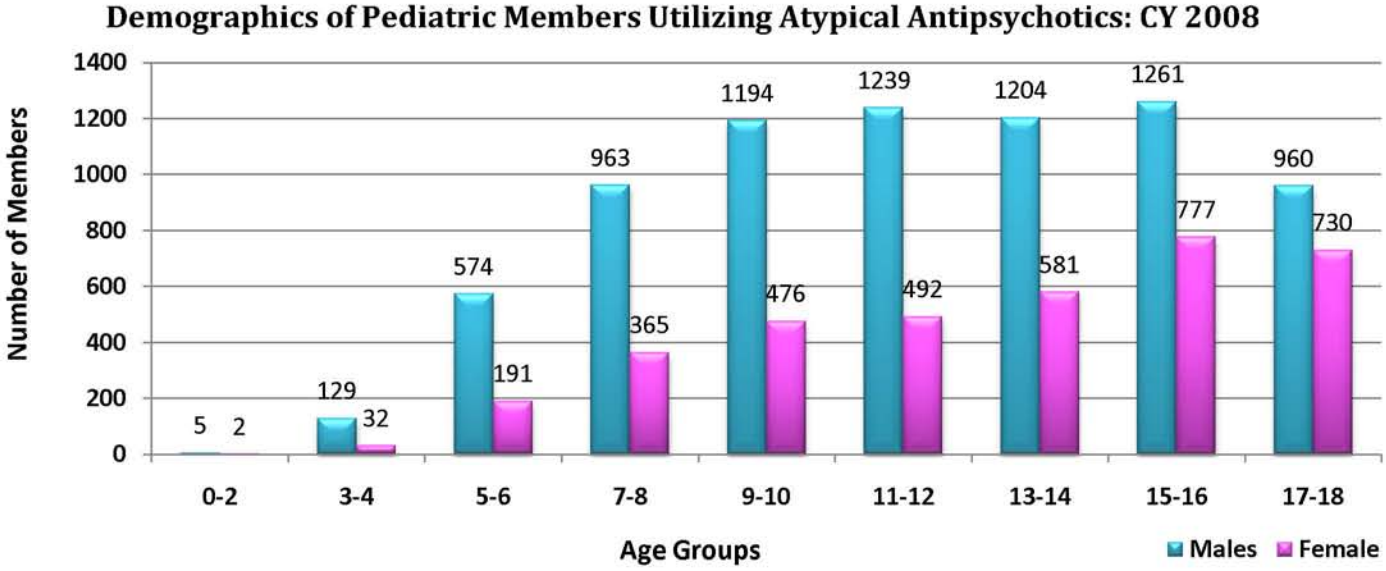


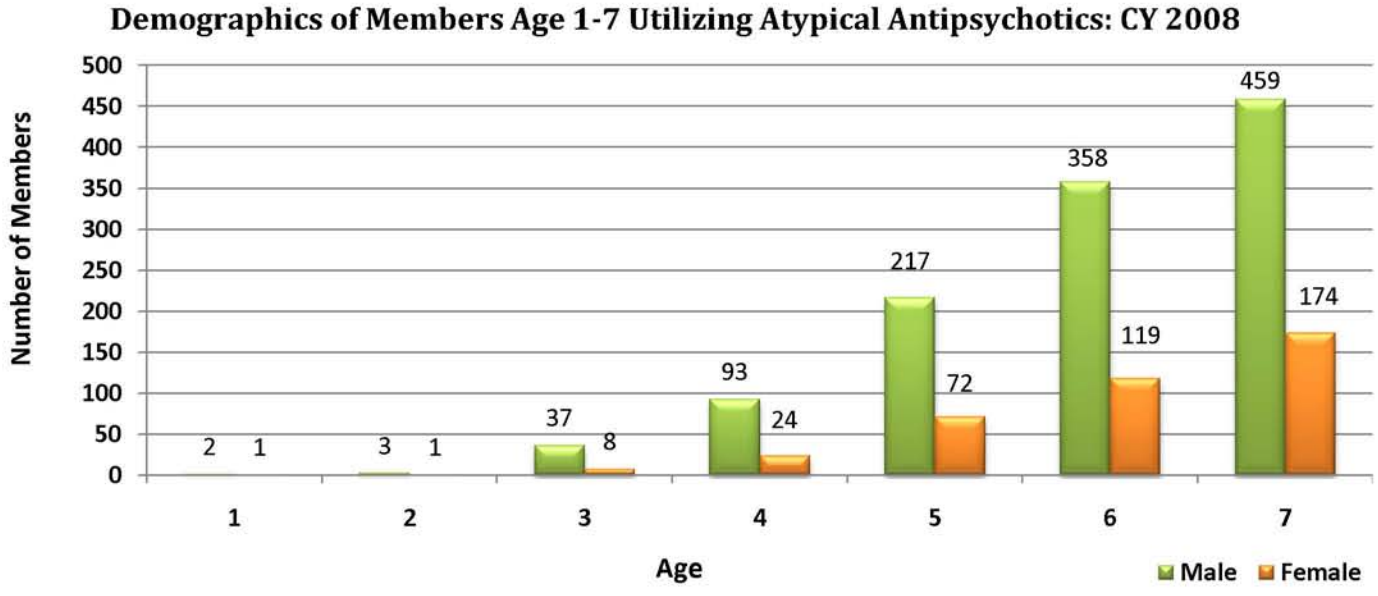
†Members not duplicated.

Demographics of Pediatric Members Utilizing Atypical Antipsychotics: CY 2008

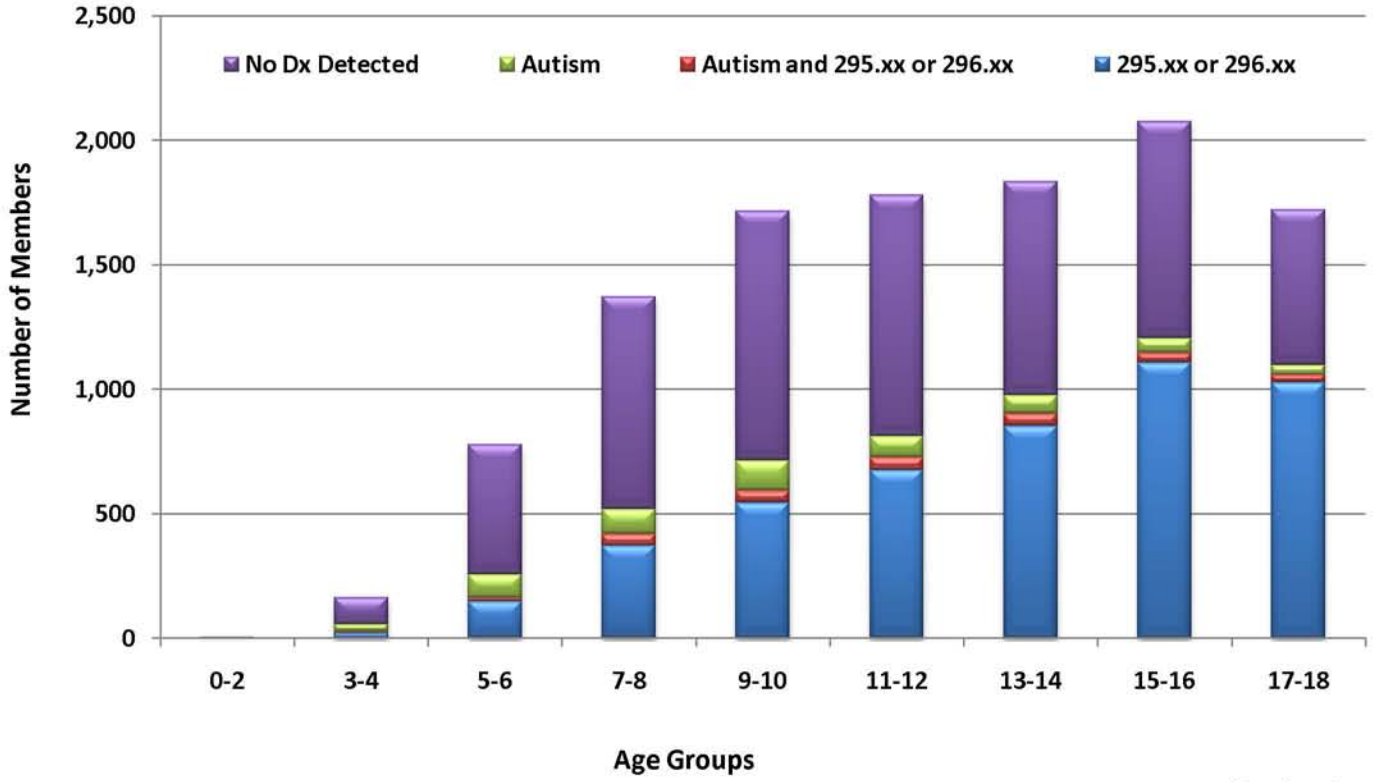
Of the 23,386 members who utilized atypical antipsychotics during calendar year 2008, 47% were pediatric members. The following charts show the breakdown of the pediatric demographics.





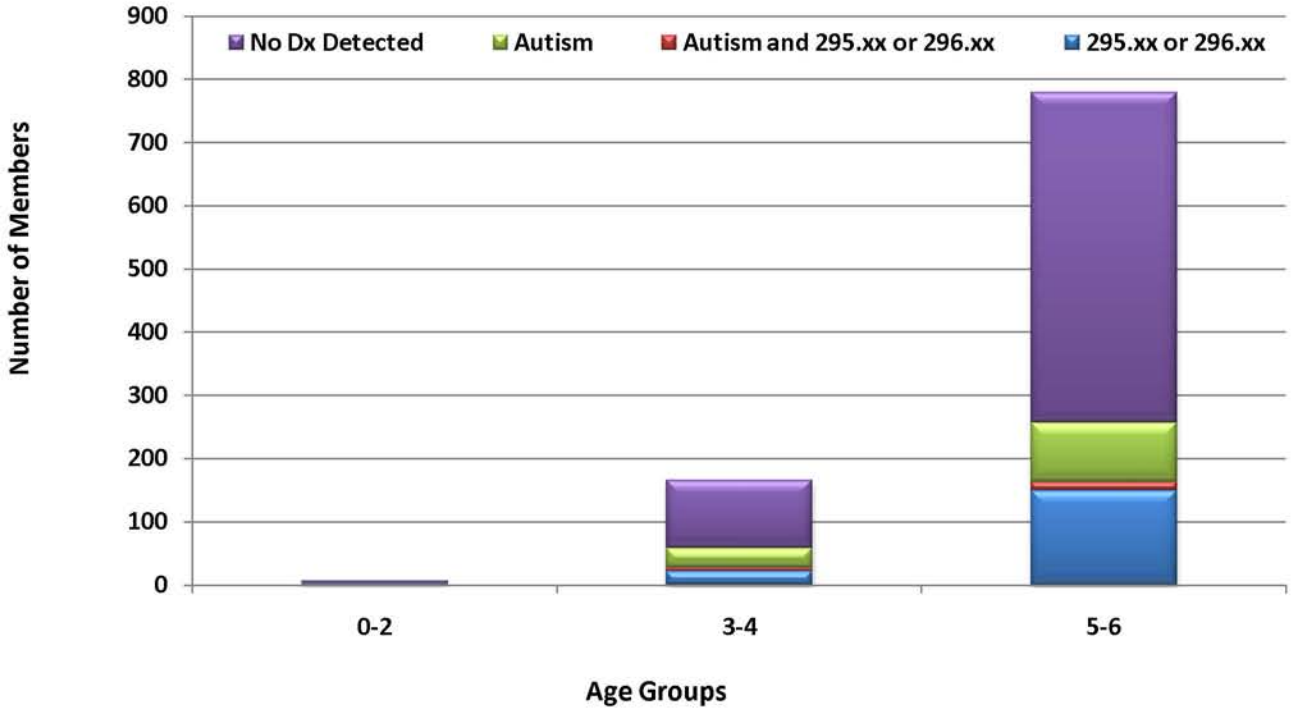


Detected Diagnosis of Pediatric Members 0-18: CY 2008



295.xx = Schizophrenic DO
296.xx = Bipolar I DO

Detected Diagnosis of Pediatric Members 0-6: CY 2008

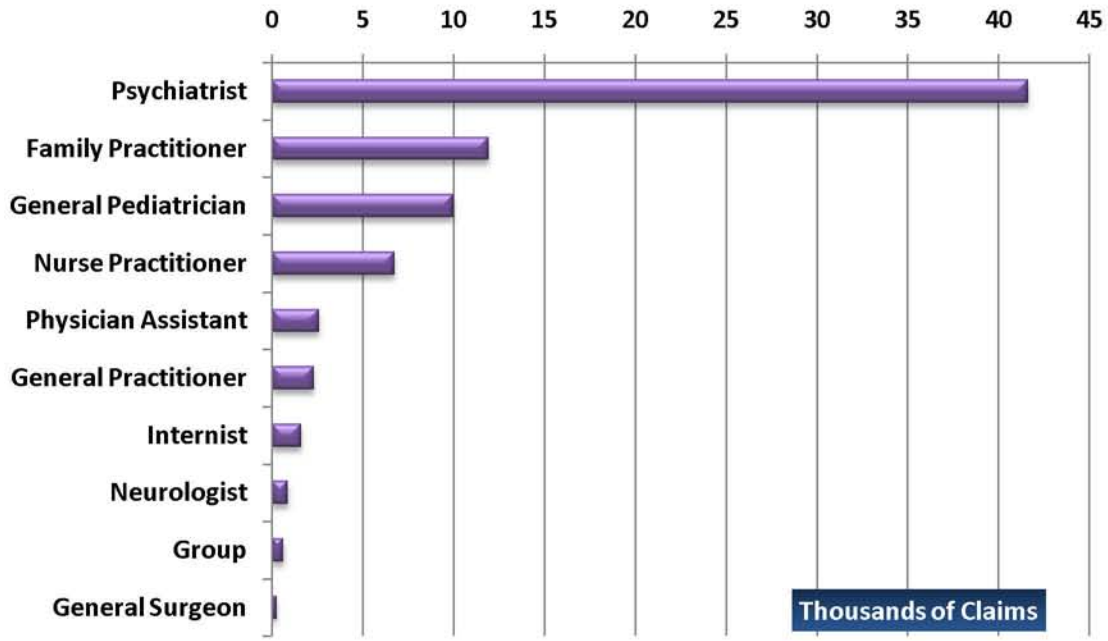


There were 7 members under the age of 3 with claims for at least one atypical antipsychotic. The following chart shows what other mental health drugs each member also has in their claims history during calendar year 2008 and what diagnosis the drugs may have been used for.

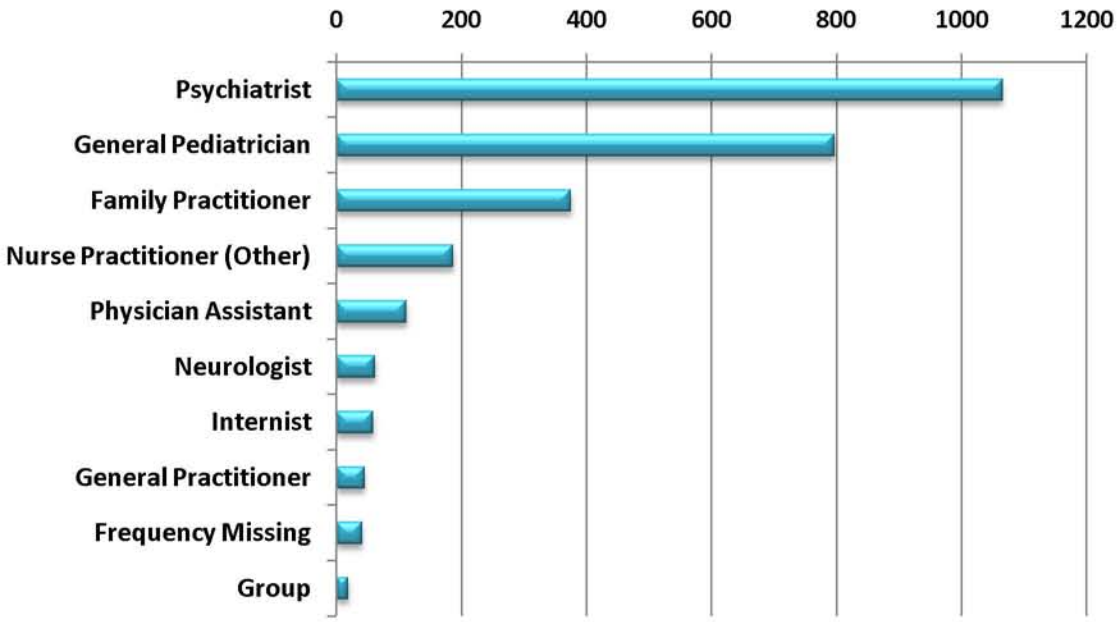
Age	Sex	Possible Diagnosis detected from Med/Hosp Claims	Number of Claim(s) for CNS Medication
0	M	Schizophrenia unspecified, Spina Bifida unspecified region w/out hydrocephalus	1 Sertraline, 1 Abilify®, 1 Benztropine, 1 Haloperidol, 1 Citalopram, 1 Seroquel®, 1 Trazodone
1	M	Neurotic DO, MDD, Bipolar DO, Manic Depressive DO, Adjustment Reaction DO	5 Seroquel®, 1 Hydroxyzine, 5 Paroxetine, 1 Risperidone, 1 Geodon®, 9 Clonazepam
1	F	Delay in development	1 Geodon®
2	M	Developmental coordination DO, Disturbance of conduct, Early childhood psychosis current or active	2 Risperidone syrup, 2 Clonidine
2	M	ADHD	3 Risperidone
2	F	Convulsions	5 Valproic acid syrup, 1 Abilify®
2	M	Delay in Development	1 Risperidone syrup

PRESCRIBERS OF ATYPICAL ANTIPSYCHOTICS IN THE PEDIATRIC POPULATION

Top 10 Prescriber Specialty by Claims in Pediatric Members 0-18: CY 2008



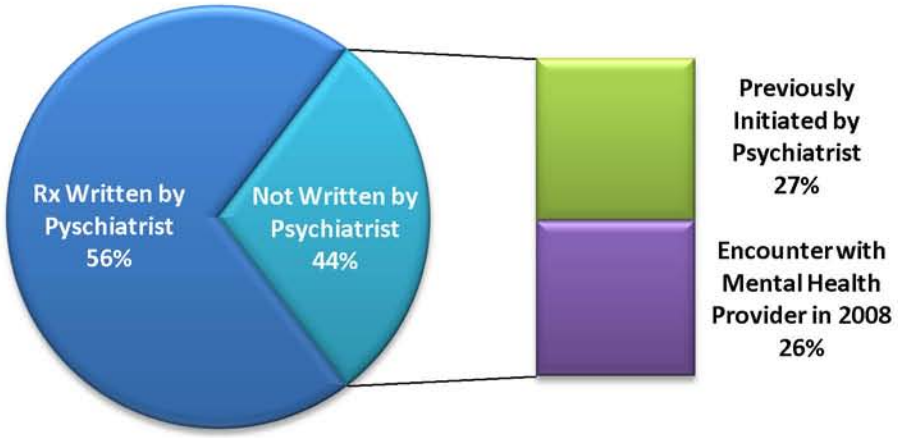
Top 10 Prescriber Specialty by Claims in Pediatric Members 0-5: CY 2008



Prescriptions written by Psychiatrists

A sample was taken to determine the percentage of prescriptions written by non-psychiatrists had been previously initiated by a psychiatrist. All atypical antipsychotic claims for 2008 were collected, and pharmacy claims for December were reviewed to detect any atypical antipsychotic medication claim(s) written by a prescriber with the primary specialty of psychiatrist.

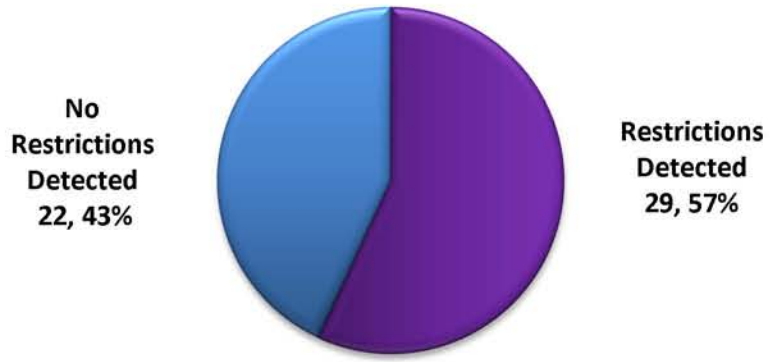
This analysis revealed that 56% of the members had a prescription for an atypical antipsychotic written by a psychiatrist. However, 44% of the sample did not. The claims for the previous 11 months were then reviewed for the members whose claims were not written by a psychiatrist. Approximately 27% of these members had a claim from a psychiatrist earlier in the year. Next, all medical claims with some type of mental health provider coding were pulled for these members, and the results showed that 47% of the members still did not have any type of psychiatrist or mental health provider encounter. It is important to note that the prescriber specialty is self-reported to OHCA and some psychiatrists may not be coded as such.



OPTIONS IMPLEMENTED BY OTHER STATE PLANS

A review of publicly available information regarding other state Medicaid plans shows that more than half the state Fee for Service Medicaid programs have implemented certain restrictions on the category of atypical antipsychotic medications. All state Medicaid websites, including that of the District of Columbia, were included in the search. Six states did not have their preferred drug list (PDL) available online or were not accessible by the public.

29 out of 51 Medicaid agencies have a PDL or Quantity Limit



Number of Agencies	Summary of Options Implemented
29 out of 51	Have Restrictions
27 out of 51	Have PDLs
17 out of 51	Have QLs
6 out of 51	No information available

Options Implemented by other Medicaid State Programs include:

- **Preferred Drug Lists** with prior authorization required for Tier 2 medications
- **Preferred Drug Lists** with prior authorization required for Tier 1 and Tier 2 medications
- **Preferred Drug Lists** with **Age Limits** on Tier 1 and/or Tier 2 medications
- **Age Limits** requiring prior authorization and clinical review
- **Quantity Limits** based on maximum recommended daily doses for each medication
- **Duration Limits** for special formulations
- **Input of Diagnosis Code** for pharmacy claims

Idaho State Medicaid is implementing a unique academic detailing program at the same time they are implementing their preferred drug list. The goal of the academic detailing program is to provide up-to-date, non biased information, and to supply tools for patient care that busy practitioners might not otherwise have time to access. The program will focus on appropriate use of medications to treat ADHD, depression, bipolar disorder, psychosis, and insomnia. The Idaho Project's goal is to reach a minimum of 85 practitioner visits by December 2009.

Washington State Medicaid has just recently implemented their Antipsychotic Drug Initiatives in March of 2009 also known as the "Second Opinion" program. This new initiative is designed to safeguard pediatric members 17 years of age or younger who receive specific antipsychotic medications. The program details age limits and doses of each antipsychotic medication. A second opinion must be obtained when a prescriber starts a new antipsychotic prescription for children under the age limit or when a new dose above the dosing limits is prescribed. The second opinion is required before the authorization request is submitted for approval. The prior authorization unit will require additional clinical information and the recommendations of the Medicaid-designated Mental Health Specialist from the Second Opinion Network Provider that has been established.

Arkansas State Medicaid has just recently implemented their antipsychotic clinical edits in July of 2009 which include:

Patients 18 years or older

- For oral liquids and ODTs patient must have an NPO code in the past year (posted list of ICD codes)
- Oral capsules and tablets are approved

Patients less than 18 years of age

- Typical and Atypical Antipsychotics
  - One therapeutic duplication for a change in therapy between two antipsychotics with > 25% remaining on the last fill on different dates of service allowed per 93 days
  - PA required through manual review for members < 5 years of age
- Oral Liquids and ODTs
  - Patient must have an NPO code in the past year or be < 7 years of age AND meet criteria for atypical antipsychotics.

Additional dose criteria also applies

CONCLUSIONS

- The second generation antipsychotics, also referred to as the atypical antipsychotics, were developed in response to concerns with older first generation antipsychotics such as troublesome adverse effects.
- The atypical antipsychotics were originally reserved for the treatment of schizophrenia and acute manic or mixed episodes associated with Bipolar I disorders. However, off-label use has propelled this class to the top therapeutic class in the United States by sales and this trend is expected to further increase.
- Clinical trials and meta-analysis show there are few differences in effectiveness between first-generation antipsychotics and atypical antipsychotics, and between atypical antipsychotics agents in non-refractory patients.
- Atypical antipsychotics have their own unique side effect profiles. The adverse effects of the atypical antipsychotics differ by agent and include cardiovascular, metabolic disturbances, and dyslipidemias that can lead to long term health consequences.
- Government payer systems bear the brunt of the costs associated with this class of medications; however, there is a lack of definitive evidence to show these agents decrease total mental healthcare spending to justify the high medication costs.
- Adverse effects of antipsychotics often offset the advantages in efficacy of these drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease and there is a black box warning against the use of these agents for dementia-related psychosis.
- Atypical antipsychotics are increasingly used off-label for non-FDA approved diagnoses such as autism, disruptive behaviors, or attention deficit hyperactivity disorders (ADHD), however, among these diagnoses there is only fair clinical evidence to support efficacy of risperidone for autism and disruptive behaviors.
- Although the cost trends have slowed between FY 2008 and 2009, it is expected to increase along with an increase in the total lives covered by SoonerCare and due to newly approved indications.
- Demographic utilization trends are consistent with the makeup of the SoonerCare population.
- Prescriber specialty is somewhat consistent with the disease state involved.
- The introduction of a generic product in the category curbed the increase in cost, however, utilization trends show there is a positive shift to branded products and a negative shift in use of the generic product. With more patented products expected to enter the market, it is anticipated that the cost for this category will be driven by use of newer agents.
- The lack of FDA-labeled indications detected in members utilizing this category of medications suggests high off-label use in both the adult and pediatric population.

RECOMMENDATION

The College of Pharmacy recommends the addition of the Atypical Antipsychotics class to the Product Based Prior Authorization program. The following Tier-1 drug list has been reviewed and determined to be an acceptable combination for use as initial therapy for the majority of members. The College of Pharmacy recommends this list to the Drug Utilization Review Board based on cost and clinical effectiveness for approval before referral to the Oklahoma Healthcare Authority. The following are the recommendations for this category:

- Children less than 5 years of age will require a "second opinion" prior authorization to be reviewed by a child psychiatrist, unless already prescribed by a child psychiatrist. Current users will be allowed to remain on current medication until the petition is submitted and reviewed.
- For all members on atypical antipsychotics, after six months of use, a questionnaire will be sent to the prescriber to be filled out and returned for continuation of therapy.
- In addition, the College recommends the following tier structure and approval criteria:

Atypical Antipsychotics*		
Tier 1	**Tier 2**	**Tier 3†**
risperidone (Risperdal®) **clozapine (Clozaril®)**	**Supplemental Rebated Tier-3 medications**	**olanzapine (Zyprexa®)** **quetiapine (Seroquel®)** **ziprasidone (Geodon®)** **aripiprazole (Abilify®)** **paliperidone (Invega®)** **quetiapine ER (Seroquel XR®)** **asenapine (Saphris®)** **clozapine (Fazaclo®)**

***Mandatory Generic Plan Applies**
†May be rebated to Tier 2 status only

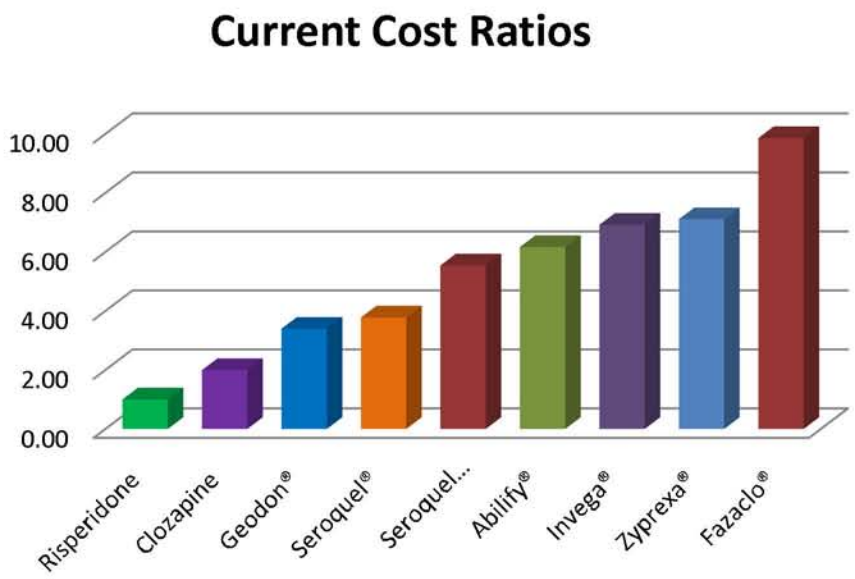
Approval Criteria for Tier 2 Medication:

1. FDA approved diagnosis
    a. For aripiprazole a diagnosis of depression requires current use of an antidepressant, and previous trials with at least two other antidepressants.
2. A trial of risperidone, at least 14 days in duration, titrated to recommended dose, that did not yield adequate response or resulted in intolerable adverse effects.
3. Members currently stabilized on a higher tiered medication while inpatient or as defined by paid claim(s) for the higher tiered medication in the past 90 days will be grandfathered.
4. Clinical exceptions include potential medication interactions or clinical conditions contraindicated with risperidone.

Approval Criteria for Tier 3 Medication:

1. FDA approved diagnosis
    a. For aripiprazole a diagnosis of depression requires current use of an antidepressant, and previous trials with at least two other antidepressants.
2. A trial of risperidone, at least 14 days in duration, titrated to recommended dose, that did not yield adequate response or resulted in intolerable adverse effects.
3. A trial of all available Tier 2 medications, at least 14 days in duration, titrated to recommended dose, that did not yield adequate response or resulted in intolerable adverse effects.
4. Members currently stabilized on a higher tiered medication while inpatient or as defined by paid claim(s) for the higher tiered medication in the past 90 days will be grandfathered.
5. Clinical exceptions include potential medication interactions or clinical conditions contraindicated with risperidone or all available Tier 2 medications.

The following graphs show the ratios of the net unit costs (reimbursement – federal rebate) for the currently available products. The lowest net unit cost is a 1:1 ratio and is reflected as a 1.00 on the graph. The other bars indicate the ratio of each product's net unit cost to the product with the lowest net unit cost. The ratios do not reflect actual dollar amounts but provide a visual comparison of the net unit cost of each product to the lowest net unit cost.



Potential Administrative Costs

Due to the importance of uninterrupted therapy for this class, the cost calculations have been based on potential new starts and time to discontinuation data found in the literature.[13, 44, 45] Based on the number of potential new starts approximately 5,000 to 8,000 members annually would be effected by the proposed tier structure. The number of members requesting a prior authorization (new starts requesting a higher tiered product) is estimated to be approximately 4,000. The proposed tier changes would affect approximately 16% of the total population for this PBPA category.

Previously, it has been theorized that total cost per petition to the *healthcare system* (includes cost to physicians, pharmacists, and program) is between $7.63 and $14.82. Total cost for prior authorization to the *healthcare system* is estimated to be between $30,520 and $59,280 annually. Anticipated actual administrative cost to the program is projected to be less than $30,000.

Potential Program Savings

Potential net ingredient savings to the program based on recommended tiers and potential new starts is estimated to be between 8 % and 16 % of the FY 2009 total reimbursement to pharmacies for this category of drugs.

Percent of Current Reimbursement	**8 % to 16 %**

Utilization Details of Atypical Antipsychotics

Chemical Name	Brand Name	Claims	Members	Paid Amount	Units/ Day	Claims/ Member	PerDiem	% Paid
Paliperidone	INVEGA TAB 3MG	2,248	680	$853,933.68	1.03	3.31	$12.03	1.42%
Paliperidone	INVEGA TAB 6MG	3,933	973	$1,761,710.18	1.21	4.04	$14.09	2.93%
Paliperidone	INVEGA TAB 9MG	1,475	376	$843,439.79	1	3.92	$17.76	1.40%
	Subtotals	**7,656**		**$3,459,083.65**	**1.12**	**3.76**	**$14.21**	**5.75%**
Risperidone	RISPERIDONE TAB 0.25MG	3,726	958	$341,811.09	1.59	3.89	$3.01	0.57%
Risperidone	RISPERDAL TAB 0.25MG	315	189	$58,410.64	1.64	1.67	$6.34	0.10%
Risperidone	RISPERIDONE TAB 0.5MG	9,667	2,373	$903,806.22	1.48	4.07	$3.08	1.50%
Risperidone	RISPERDAL TAB 0.5MG	771	468	$145,262.69	1.47	1.65	$6.16	0.24%
Risperidone	RISPERIDONE TAB 1MG	12,584	2,777	$1,302,217.21	1.47	4.53	$3.34	2.16%
Risperidone	RISPERDAL TAB 1MG	1,100	642	$227,947.65	1.55	1.71	$6.80	0.38%
Risperidone	RISPERIDONE TAB 2MG	7,494	1,686	$1,195,080.56	1.45	4.44	$5.05	1.98%
Risperidone	RISPERDAL TAB 2MG	706	444	$241,124.76	1.42	1.59	$10.49	0.40%
Risperidone	RISPERIDONE TAB 3MG	4,372	882	$871,344.88	1.51	4.96	$6.17	1.45%
Risperidone	RISPERDAL TAB 3MG	465	278	$203,211.54	1.54	1.67	$13.62	0.34%
Risperidone	RISPERIDONE TAB 4MG	2,724	538	$645,691.75	1.38	5.06	$7.07	1.07%
Risperidone	RISPERDAL TAB 4MG	330	207	$189,988.21	1.36	1.59	$15.99	0.32%
	Subtotals	**44,254**		**$6,325,897.20**	**1.48**	**3.07**	**$4.58**	**10.51%**
Risperidone	RISPERIDONE SOL 1MG/ML	475	110	$132,897.98	2.06	4.32	$9.00	0.22%
Risperidone	RISPERDAL SOL 1MG/ML	394	99	$135,256.89	2.22	3.98	$11.17	0.22%
Risperidone	RISPERDAL M TAB 0.5MG	397	109	$75,939.88	1.47	3.64	$6.62	0.13%
Risperidone	RISPERIDONE TAB 0.5MG OD	51	27	$8,605.46	1.23	1.89	$5.36	0.01%
Risperidone	RISPERDAL M TAB 1MG	354	91	$65,454.11	1.28	3.89	$6.35	0.11%
Risperidone	RISPERIDONE TAB 1MG ODT	13	10	$2,429.28	1.28	1.3	$6.36	0.00%
Risperidone	RISPERDAL M TAB 2MG	286	62	$99,357.57	1.4	4.61	$11.93	0.17%
Risperidone	RISPERIDONE TAB 2MG ODT	75	31	$23,605.85	1.33	2.42	$10.91	0.04%
Risperidone	RISPERDAL M TAB 3MG	65	16	$33,409.09	1.78	4.06	$18.75	0.06%
Risperidone	RISPERIDONE TAB 3MG ODT	11	8	$4,838.82	1.58	1.38	$16.40	0.01%
Risperidone	RISPERDAL M TAB 4MG	34	11	$22,485.36	1.39	3.09	$20.15	0.04%
Risperidone	RISPERIDONE TAB 4MG ODT	6	4	$2,827.84	1.29	1.5	$18.13	0.00%
Risperidone	RISPERDAL INJ 12.5MG	24	9	$6,387.03	0.07	2.67	$9.71	0.01%
Risperidone	RISPERDAL INJ 25MG	816	159	$336,121.00	0.07	5.13	$19.74	0.56%
Risperidone	RISPERDAL INJ 37.5MG	737	131	$471,159.37	0.07	5.63	$29.75	0.78%
Risperidone	RISPERDAL INJ 50MG	1,377	162	$1,205,189.35	0.07	8.5	$38.48	2.00%
	Subtotals	**5,115**		**$2,625,964.88**	**0.89**	**3.63**	**$20.30**	**4.36%**
Clozapine	CLOZAPINE TAB 25MG	382	45	$8,624.68	2.77	8.49	$1.34	0.01%
Clozapine	CLOZARIL TAB 25MG	12	3	$1,330.72	2.35	4	$3.87	0.00%
Clozapine	CLOZAPINE TAB 50MG	137	10	$2,339.94	1.73	13.7	$1.86	0.00%
Clozapine	CLOZAPINE TAB 100MG	2,663	206	$230,596.11	4.34	12.93	$4.39	0.38%
Clozapine	CLOZARIL TAB 100MG	182	15	$123,457.28	4.72	12.13	$27.12	0.21%
Clozapine	CLOZAPINE TAB 200MG	40	1	$2,002.12	2	40	$5.50	0.00%
Clozapine	FAZACLO TAB 25MG	754	66	$77,439.12	4.1	11.42	$7.88	0.13%
Clozapine	FAZACLO TAB 100MG	2,146	164	$746,296.78	4.17	13.09	$21.66	1.24%
	Subtotals	**6,316**		**$1,192,086.75**	**4.14**	**14.47**	**$10.86**	**1.97%**

Chemical Name	Brand Name	Claims	Members	Paid Amount	Units/ Day	Claims/ Member	PerDiem	% Paid
Quetiapine	SEROQUEL TAB 25MG	3,968	1,127	$492,019.21	1.69	3.52	$4.05	0.82%
Quetiapine	SEROQUEL TAB 50MG	5,686	1,675	$1,039,342.66	1.51	3.39	$5.97	1.73%
Quetiapine	SEROQUEL TAB 100MG	10,127	2,794	$1,924,842.05	1.45	3.62	$6.01	3.20%
Quetiapine	SEROQUEL TAB 200MG	8,583	2,137	$3,060,681.81	1.46	4.02	$11.32	5.08%
Quetiapine	SEROQUEL TAB 300MG	9,357	2,053	$4,926,106.30	1.64	4.56	$16.75	8.18%
Quetiapine	SEROQUEL TAB 400MG	5,380	1,101	$3,008,742.26	1.48	4.89	$17.75	5.00%
	Subtotals	**43,101**		**$14,451,734.29**	**1.53**	**4.00**	**$10.71**	**24.01%**
Quetiapine	SEROQUEL XR TAB 50MG	70	54	$8,842.45	1.07	1.3	$4.22	0.01%
Quetiapine	SEROQUEL XR TAB 150MG	110	82	$25,534.65	1	1.34	$7.18	0.04%
Quetiapine	SEROQUEL XR TAB 200MG	372	174	$99,617.72	1.07	2.14	$8.09	0.17%
Quetiapine	SEROQUEL XR TAB 300MG	701	297	$278,788.68	1.29	2.36	$12.82	0.46%
Quetiapine	SEROQUEL XR TAB 400MG	802	244	$405,876.67	1.38	3.29	$16.26	0.67%
	Subtotals	**2055**		**$818,660.17**	**1.26**	**2.09**	**$12.66**	**1.35%**
Olanzapine	ZYPREXA TAB 2.5MG	722	208	$162,893.84	1.02	3.47	$7.33	0.27%
Olanzapine	ZYPREXA TAB 5MG	2,025	581	$594,493.01	1.07	3.49	$9.15	0.99%
Olanzapine	ZYPREXA TAB 7.5MG	355	79	$121,076.68	1.01	4.49	$10.62	0.20%
Olanzapine	ZYPREXA TAB 10MG	3,316	833	$1,450,930.42	1.03	3.98	$13.40	2.41%
Olanzapine	ZYPREXA TAB 15MG	1,946	443	$1,398,904.80	1.13	4.39	$22.01	2.32%
Olanzapine	ZYPREXA TAB 20MG	4,039	730	$3,801,568.94	1.08	5.53	$27.77	6.31%
	Subtotals	**12,403**		**$7,529,867.69**	**1.07**	**4.23**	**$18.49**	**12.50%**
Olanzapine	ZYPREXA INJ 10MG	23	14	$2,407.77	1.53	1.64	$40.81	0.00%
Olanzapine	ZYPREXA ZYDI TAB 5MG	200	75	$66,635.11	1.22	2.67	$11.62	0.11%
Olanzapine	ZYPREXA ZYDIS 5MG TAB	3	2	$1,204.01	1.92	1.5	$18.52	0.00%
Olanzapine	ZYPREXA ZYDI TAB 10MG	353	106	$157,764.08	1.07	3.33	$14.72	0.26%
Olanzapine	ZYPREXA ZYDIS 10MG TAB	4	3	$1,400.60	1	1.33	$14.01	0.00%
Olanzapine	ZYPREXA ZYDI TAB 15MG	184	50	$148,270.05	1.36	3.68	$28.04	0.25%
Olanzapine	ZYPREXA ZYDI TAB 20MG	373	87	$376,871.49	1.11	4.29	$30.24	0.63%
	Subtotals	**1140**		**$754,553.11**	**1.16**	**2.63**	**$21.92**	**1.25%**
Aripiprazole	ABILIFY TAB 2MG	3,961	1,356	$1,642,070.56	1.01	2.92	$13.64	2.73%
Aripiprazole	ABILIFY TAB 5MG	10,980	3,634	$4,596,202.00	1	3.02	$13.62	7.63%
Aripiprazole	ABILIFY TAB 10MG	9,882	3,018	$4,268,691.98	1.02	3.27	$13.79	7.09%
Aripiprazole	ABILIFY TAB 15MG	6,753	1,893	$2,797,815.79	0.95	3.57	$12.85	4.65%
Aripiprazole	ABILIFY TAB 20MG	4,601	1,200	$2,813,367.47	1	3.83	$19.21	4.67%
Aripiprazole	ABILIFY TAB 30MG	4,259	896	$2,669,891.42	0.98	4.75	$18.78	4.43%
	Subtotals	**40,436**		**$18,788,039.22**	**0.99**	**3.56**	**$14.75**	**31.20%**
Aripiprazole	ABILIFY SOL 1MG/ML	163	49	$77,208.99	5.47	3.33	$16.23	0.13%
Aripiprazole	ABILIFY INJ 9.75MG	5	3	$211.57	0.44	1.67	$4.81	0.00%
Aripiprazole	ABILIFY DISC TAB 10MG	59	24	$30,682.34	0.96	2.46	$15.77	0.05%
Aripiprazole	ABILIFY DISC TAB 15MG	40	10	$23,127.05	1.2	4	$19.26	0.04%
	Subtotals	**267**		**$131,229.95**	**3.69**	**2.87**	**$16.52**	**0.22%**
Ziprasidone	GEODON CAP 20MG	1,400	452	$365,841.03	1.45	3.1	$8.50	0.61%
Ziprasidone	GEODON CAP 40MG	2,407	740	$700,126.55	1.58	3.25	$9.41	1.16%
Ziprasidone	GEODON CAP 60MG	2,532	721	$971,510.80	1.7	3.51	$12.32	1.61%
Ziprasidone	GEODON CAP 80MG	5,088	1,028	$2,094,283.10	1.8	4.95	$13.07	3.48%
	Subtotals	**11,427**		**$4,131,761.48**	**1.69**	**3.70**	**$11.59**	**6.86%**

Chemical Name	Brand Name	Claims	Members	Paid Amount	Units/ Day	Claims/ Member	PerDiem	% Paid
Ziprasidone	GEODON INJ 20MG	25	14	$2,961.23	1.25	1.79	$15.34	0.00%
	TOTALS	**174,195**	**24,043***	**$60,211,839.62**	**1.38**	**7.25**	**$11.24**	**100.00%**

***Total number of unduplicated members.**

REFERENCES

[1] Prien RF, Cole JO. **High dose chlorpromazine therapy in chronic schizophrenia: report of National Institute of Mental Health–psychopharmacology research branch collaborative study group.** Arch Gen Psychiatry. 1968;18:482–495.

[2] May PR, Tuma AH, Dixon WJ, Yale C, Thiele DA, Kraude WH. **Schizophrenia: a follow-up study of the results of five forms of treatment.** Arch Gen Psychiatry. 1981;38:776–784.

[3] **U.S. Prescription Drug Sales Grow Slowly; Hydrocodone Most Prescribed.** IMS Health. Accessed at: http://seekingalpha.com/article/128003-u-s-prescription-drug-sales-grow-slowly-hydrocodone-most-prescribed

[4] **The Numbers Count: Mental Disorders in America.** NIMH. Accessed at: http://www.nimh.nih.gov/health/publications/the-numbers-count-mental-disorders-in-america/index.shtml

[5] Jacobson: **Psychiatric Secrets, 2nd Ed.** Copyright 2001 Hanley and Belfus. Pg 51-55.

[6] American Psychiatric Association: **Practice Guidelines for the Treatment of Patients with Schizophrenia. 2nd Ed.** February 2004.Available online at www.phsyc.org

[7] Ibid.

[8] Ibid.

[9] Bauer MS, Mitchner L. **What is a "mood stabilizer"? An evidence based response.** *American Journal of Psychiatry*. 161(1); 3-18, January 2004.

[10] Yatham, Lakshmi N. **Efficacy of Atypical Antipsychotics in Mood Disorders.** *Journal of Clinical Psychopharmacology*. Vol 23(1). June 2003.

[11] Jacobson**: Psychiatric Secrets, 2nd Ed.** Copyright 2001 Hanley and Belfus. Pg 51-55.

[12] Oregon Evidence-Based Practice Center Authors. **Drug Class Review of Atypical Antispsychotics. Final Report Update 2.** June 2008. Accessed at: http://derp.ohsu.edu/final/AAP_final_report_update_27.pdf

[13] Geddes J, Freemantle N, Harrison P, Bebbington P. **Atypical antipsychotics in the treatment of shizophrenia: systematic overview and meta-regression analysis.** *BMJ.* 2000; 321:1371-6.

[14] Emsly R, Oosthuizen P. **The new and evolving pharmacotherapy of schizophrenia.** *Psychiatr Clin N Am.* 26(2003): 141-163.

[15] Lieberman JA, Stroup TS, et al. **Effectiveness of Antipsychotic Drugs in Patiens with Chronic Schizophrenia. *NEJM*.** 353(12);1209-1223: September 2005.

[16] Peter B Jones, et al. **Randomized Controlled Trial of the Effect on Quality of Life of Second- vs First-Generation Antipsychotic Drugs in Schizophrenia. Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1).** *Arch Gen Psychiatry.* 2006;63:1079-1087.

[17] Sikich L, Frazier JA, McClellan J, Findling RL, Vitiello B, Ritz L, Ambler D, Puglia M, Maloney AE, Michael E, De Jong S, Slifka K, Noyes N, Hlastala S, Pierson L, McNamara NK, Delporto-Bedoya D, Anderson R, Hamer RM, Lieberman JA**: Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the Treatment of Early Onset Schizophrenia Spectrum Disorders (TEOSS) study**. Am J Psychiatry 2008; 165:1420–1431

[18] Leucht S, Pitschel-Walz G, Abraham D, Kissling W. **Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomized controlled trials.** Schizophr Res. 1999;35:51–68.

[19] Geddes J, Freemantle N, Harrison P, Bebbington P. **Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis.** BMJ. 2000;321:1371–1376.
[20] Bagnall A, Lewis RA, Leitner ML, Kleijnen J. **Ziprasidone for schizophrenia and severe mental illness. Cochrane Database Syst Rev.** 2000;(2):CD001945
[21] Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B. **Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials.** Am J Psychiatry. 2001;158:518–526.
[22] Adams CE, Fenton MK, Quraishi S, David AS. **Systematic meta-review of depot antipsychotic drugs for people with schizophrenia.** Br J Psychiatry. 2001;179:290–299.
[23] Leucht S, Barnes TRE, Kissling W, Engel RR, Correll C, Kane JM. **Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials.** Am J Psychiatry. 2003;160:1209–1222.
[24] Leucht S, Wahlbeck K, Hamann J, Kissling W. New **generation antipsychotics vs low-potency conventional antipsychotics: a systematic review and meta-analysis.** Lancet. 2003;361:1581–1589.
[25] Rummel C, Hamann J, Kissling W, Leucht S. **New generation antipsychotics for first episode schizophrenia. Cochrane Database Syst Rev.** 2003;(4):CD004410
[26] Srisurapanont M, Maneeton B, Maneeton N. **Quetiapine for schizophrenia. Cochrane Database Syst Rev.** 2004;(2):CD000967
[27] Jayaram MB, Hosalli P. **Risperidone vs olanzapine for schizophrenia. Cochrane Database Syst Rev**. 2005;(2):CD005237
[28] Adams CE, Rathbone J, Thornley B, Clarke M, Borrill J, Wahlbeck K, Awad AG. **Chlorpromazine for schizophrenia: a Cochrane systematic review of 50 years of randomized controlled trials.** BMC Med. 2005;3:15
[29] Duggan L, Fenton M, Rathbone J, Dardennes R, El-Dosoky A, Indran S. **Olanzapine for schizophrenia. Cochrane Database Syst Rev.** 2005;(2):CD001359
[30] Hennekens CH, Hennekens AR, et al. **Schizophrenia and increased risks of cardiovascular disease.** *Am Heart J.* 150:1115-21. 2005.
[31] Wirshing DA, Wirshing WC Kysar L, et al. **Novel Antipsychotics: Comparisdon of weight gain liabilities.** *J Clin Psychiatry.* 1999;60:358-363.
[32] Citrome, Leslie. Jaffe, Ari. Levine, Jerome. Allingham, Baerbel. Robinson, James. **Relationship between Antipsychotic Medication Treatment and New Cases of Diabetes among Psychiatric Inpatients.** Psychiatric Services. September 2004. Vol. 55. No. 9.
[33] Christoph U. Correll, MD; Peter Manu, MD; Vladimir Olshanskiy, MD; Barbara Napolitano, MA; John M. Kane, MD; Anil K. Malhotra, MD. **Cardiometabolic Risk of Second-Generation Antipsychotic Medications During First-Time Use in Children and Adolescents.** *JAMA.* 2009;302(16):1765-1773.
[34] Leucht S, Wahlbeck K, Hamann J, Kissling W. **New generation antipsychotics vs. low-potency conventional antipsychotics: a systematic review and meta-analysis.** *Lancet.* 361 (9369): 1581-9, May 2003.
[35] American Psychiatric Association: **Practice Guidelines for the Treatment of Patients with Schizophrenia. 2nd Ed.** February 2004.Available online at www.phsyc.org
[36] The Lewin Group. **Access and Utilization of New Antidepressant and Antipsychotic Medications.** Available online at http://aspe.hhs.gov/search/health/reports/psychmedaccess/index.htm#TOC. 2000.
[37] Duggan M. **Do new prescription drugs pay for themselves?** *Journal of Health Economics.* 24(1):1-31, 2005 Jan.
[38] Gianfrancesco F, Pesa J, Wang RH. **Comparison of mental health resources used by patients with bipolar disorder treated with risperidone, olanzapine, or quetiapine.** *Journal of Managed Care Pharmacy.* 11(3):220-30, 2005 April.
[39] Glazer WM. Johnstone BM. **Pharmacoeconomic evaluation of antipsychotic therapy for schizophrenia.** *Journal of Clinical Psychiatry. 58 Suppl 10:50-4, 1997.*
[40] Coley KC. Carter CS. DaPos SV. Maxwell R. Wilson JW. Branch RA. **Effectiveness of antipsychotic therapy in a naturalistic setting: a comparison between risperidone, perphenazine, and haloperidol.** *Journal of Clinical Psychiatry. 60(12):850-6, 1999 Dec.*
[41] Rummel C, Hamann J, Kissling W Leucht S. **New generation antipsychotics for first episode shizophrenia.** *Cochrane databse of Systematic Reviews.* (4): CD004410, 2003.
[42] Rosenheck R, Perlick D, Bingham S, et al. **Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial.** *JAMA.* 2003;290:2693–2702.
[43] Duggan M. **Do new prescription drugs pay for themselves?** *Journal of Health Economics.* 24(1):1-31, 2005 Jan.
[44] Plassman, B.L., et al. **Prevalence of Dementia in the United States: the Aging, Demographics, and Memory Study.** *Neuroepidmiology*. 2007.; 29 (1-2): 125-132.
[45] Schneider, Lon et al. **Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease. CATIE-AD** *NEJM.* October 2006. Vol 355:1525-1538.
[46] Oregon Evidence-Based Practice Center Authors. **Drug Class Review of Atypical Antispsychotics. Final Report Update 2.** June 2008. Accessed at: http://derp.ohsu.edu/final/AAP_final_report_update_27.pdf

Appendix H

Safety

Norpramin (desipramine hydrochloride) - Dear Healthcare Professional Letter

Audience: Psychiatric healthcare professionals

[Posted 12/02/2009] Sanofi-Aventis and FDA notified healthcare professionals of changes to the Warnings and Overdosage sections of the Prescribing Information for Norpramin (desipramine hydrochloride), indicated for the treatment of depression. The new safety information states that extreme caution should be used when this drug is given to patients who have a family history of sudden death, cardiac dysrhythmias, and cardiac conduction disturbances; and that seizures precede cardiac dysrhythmias and death in some patients.

[December 2009 - Dear Healthcare Professional Letter - Sanofi-Aventis]

News & Events

FDA NOTE TO CORRESPONDENTS

For Immediate Release: Nov. 25, 2009

Media Inquiries: Karen Riley, 301-796-4674, Karen.Riley@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA's Woodcock Discusses Pain Management and Drug Safety in Nov. 26, 2009 Issue of The New England Journal of Medicine

An article by Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research, titled "A Difficult Balance – Pain Management, Drug Safety, and the FDA," appears in the Nov. 26, 2009 issue of The New England Journal of Medicine.

In the article, Woodcock discusses FDA efforts to strike a balance between access to pain medication for those who need it and managing the risks posed by various analgesics. As examples, she cites recent FDA actions on acetaminophen, the low-potency opioid propoxyphene, and high-potency opioids such as Oxycontin.

These actions are part of the FDA's ongoing Safe Use Initiative, aimed at reducing the likelihood of preventable harm from medication use. Millions of people are harmed every year from inappropriate medication use. Many injuries occur as a result of incomplete access to information about a drug, a patient, or the patient's condition. Other preventable sources of harm include unintentional misuse of medications, medication abuse, and attempts at self harm.

For more information

FDA Web Page on Safe Use Initiative
http://www.fda.gov/Drugs/DrugSafety/ucm187806.htm

The New England Journal of Medicine
http://content.nejm.org/

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RSS Feed for FDA News Releases [what is RSS?]

For Consumers

Tablet Splitting: A Risky Practice

Search Consumer Updates

Some pharmacists have reported that patients have changed the way they take medications because of the downturn in the economy, according to a recent survey by the American Pharmacists Association. This includes skipping doses and splitting tablets in an effort to save money. Regarding the practice of splitting tablets, the Food and Drug Administration (FDA), the American Medical Association, and other medical organizations advise against it unless it's specified in the drug's labeling.

Tablet splitting often involves buying higher strength tablets and then breaking the tablets in half or quarter doses as a way to lower drug costs. For instance, a 30 mg tablet may cost the same amount as the 15 mg tablet. So a patient may try to save money by buying the 30 mg tablets and splitting them all in half. This might seem like a smart money-saving strategy, but the practice can be risky.

Why Splitting Tablets is Risky

- **You might get confused about the correct dose.** There have been cases when people have purchased higher strength tablets intending to split them, but then they forgot to split them. Instead, they took the whole tablet. This led to accidentally taking too much medicine.
- **Equal distribution of medicine in split tablets is questionable.** Studies have shown that the actual dose in each half of a split tablet often is different. So while the two halves may look the same, they don't necessarily contain equal amounts of medicine. Even if the tablet is scored with a line that runs down the middle, one half may actually have more medicine than the other.
- **Some tablets are hard to split.** Some tablets are too small to split, may have an unusual shape that makes them hard to split, or may crumble more easily when split. Also, some people may not be able to split tablets correctly. These factors make it difficult to accurately split a tablet.
- **Not all pills are safe to split.** Patients may mistakenly think that any pill can be split. But some pills, such as capsules and time-released drugs, should always be taken whole. For example, some tablets are coated with a substance that helps to release the medicine slowly. Splitting these

tablets destroys the coating, which means you might absorb the medicine too fast or not at all.

What if You Still Want to Split a Tablet?

FDA has approved drugs where tablet splitting is part of the manufacturer's drug application. "If the tablet is approved for splitting, the information will be provided in the drug's professional prescribing information," says Mansoor Khan, Ph.D., director of the Division of Product Quality Research in FDA's Office of Pharmaceutical Science.

"FDA does not encourage the practice of tablet splitting unless it's specified in the drug's professional prescribing information. If a patient is considering splitting a tablet, FDA recommends that the patient get advice directly from his or her doctor or pharmacist to determine whether it is appropriate or not for a particular drug."

This article appears on FDA's Consumer Updates page, which features the latest on all FDA-regulated products.

Date Posted: July 21, 2009

For More Information

- Best Practices for Tablet Splitting
- Are You Taking Medication as Prescribed?
- Opinion Survey by the American Pharmacists Association

Drugs

Best Practices for Tablet Splitting

At some point your healthcare or managed care company may have recommended tablet splitting for reasons such as to adjust the dosing of your medication or to reduce costs. In such cases, it is your healthcare professional's responsibility to monitor the impact of risks associated with the practice of tablet splitting. You should always talk to your healthcare professional before splitting a tablet and not be afraid to ask him or her questions if you are considering splitting tablets.

When considering whether to split a tablet, you and your healthcare professional should bear in mind the following:

- If a tablet is FDA-approved to be split, this information will be printed in the "HOW SUPPLIED" section of the professional label insert and in the patient package insert. Also, the tablet will be scored with a mark indicating where to split it.
- If a tablet does not include such information in the label, FDA has not evaluated it to ensure that the two halves of a split tablet are the same in weight or drug content or work the same way in the body as the whole tablet. You should discuss with your healthcare professional whether to split this type of tablet.
- If your healthcare professional asks you to split your tablets, do not split the entire supply of tablets at one time and then store them for later use. That is, make sure that both halves are taken before splitting the next tablet. This is important because split tablets may be affected by factors such as heat, humidity and/or moisture content. For example, a split tablet stored in a damp environment such as in a bathroom medicine cabinet could be affected.
- Your healthcare professional may be able to recommend the best method by which to split a tablet. In many cases, a tablet splitter may be appropriate. However, some tablets may not be suitable for this method because of their unique shape and size—even if they appear to be scored. It is important to discuss this issue with your healthcare professional to determine what is best for you.
- Most sustained, controlled, or timed release medications are not meant for splitting. In those rare instances where splitting is recommended for this type of medication, such information will be printed in the "HOW SUPPLIED" section of the professional label insert and in the patient package insert and will be scored.
- When you switch from one brand of medicine to another, you and your healthcare professional should confirm whether the newly prescribed

tablet is splitable, even if the original tablet could be split. The same medications can be manufactured differently, thus may not have been developed to be split.

REMEMBER: Tablet splitting should be done *only* under the supervision of a healthcare professional.

Additional Information

- Tablet Splitting: A Risky Practice
  FDA Consumer Update
- Ensuring Safe Use of Medicine

Drugs

Information for Healthcare Professionals: Update to the labeling of Clopidogrel Bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC)

[11/17/2009]

FDA is alerting the public to new safety information concerning an interaction between clopidogrel (Plavix), an anti-clotting medication, and omeprazole (Prilosec/Prilosec OTC), a proton pump inhibitor (PPI) used to reduce stomach acid. New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole. The updated label for clopidogrel will contain details of new studies submitted by Sanofi-Aventis and Bristol-Myers Squibb, the manufacturer of Plavix (clopidogrel).

Omeprazole inhibits the drug metabolizing enzyme (CYP2C19) which is responsible for the conversion of clopidogrel into its active form (active metabolite). The new studies compared the amount of clopidogrel's active metabolite in the blood and its effect on platelets (anti-clotting effect) in people who took clopidogrel plus omeprazole versus those who took clopidogrel alone. A reduction in active metabolite levels of about 45% was found in people who received clopidogrel with omeprazole compared to those taking clopidogrel alone. The effect of clopidogrel on platelets was reduced by as much as 47% in people receiving clopidogrel and omeprazole together. These reductions were seen whether the drugs were given at the same time or 12 hours apart.

Other drugs that are potent inhibitors of the CYP 2C19 enzyme would be expected to have a similar effect and should be avoided in combination with clopidogrel. These include: cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine. Since the level of inhibition among other PPIs varies, it is unknown to what amount other PPIs may interfere with clopidogrel. However, esomeprazole, a PPI that is a component of omeprazole, inhibits CYP2C19 and should also be avoided in combination with clopidogrel.

FDA is aware there are studies, such as the Clopidogrel and Optimization of Gastrointestinal Events (COGENT) study, that might provide information about the effect of this interaction on clinical outcome. Although the FDA has not fully

reviewed the study results, the applicability of these data is limited because of the study design and follow-up. Therefore, based on the current scientific information, the clopidogrel label has been updated with new warnings on omeprazole and other drugs that inhibit the CYP2C19 enzyme that could interact with clopidogrel in the same way. In addition, the manufacturer of Plavix (clopidogrel) is conducting follow-up studies to explore this and other drug interactions.

Considerations for Healthcare Professionals

- The concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel's active metabolite levels and anti-clotting activity. Patients at risk for heart attacks or strokes, who are given clopidogrel to prevent blood clots, may not get the full protective anti-clotting effect if they also take prescription omeprazole or the OTC form (Prilosec OTC).
- Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.
- Other drugs that should be avoided in combination with clopidogrel because they may have a similar interaction include: esomeprazole (Nexium), cimetidine (which is available by prescription Tagamet and OTC as Tagamet HB), fluconazole (Diflucan), ketoconazole (Nizoral), voriconazole (VFEND), etravirine (Intelence), felbamate (Felbatol), fluoxetine (Prozac, Serafem, Symbyax), fluvoxamine (Luvox), and ticlopidine (Ticlid).
- At this time FDA does not have sufficient information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to make specific recommendations about their co-administration. Healthcare professionals and patients should consider all treatment options carefully before beginning therapy.
- There is no evidence that other drugs that reduce stomach acid, such as most H2 blockers ranitidine (Zantac), famotidine (Pepcid), nizatidine (Axid), except cimetidine (Tagamet and Tagamet HB - a CYP2C19 inhibitor) or antacids interfere with the anti-clotting activity of clopidogrel. Ranitidine and famotidine are available by prescription and OTC to relieve and prevent heartburn and antacids are available OTC to relieve heartburn.
- Talk with your patients about the OTC medicines they take. Be aware that patients may be taking non prescription forms omeprazole and cimetidine.

FDA will continue to investigate other drug interactions with clopidogrel. FDA plans on presenting this issue at the next meeting of FDA's Drug Safety Oversight Board in November. The Agency will communicate any further recommendations or conclusions once additional information is available.

Related Information

- Information on Clopidogrel Bisulfate (marketed as Plavix)
- Public Health Advisory: Updated Safety Information about a drug interaction between Clopidogrel Bisulfate (marketed as Plavix) and Omeprazole (marketed as Prilosec and Prilosec OTC)
  11/17/2009
- Follow-Up to the January 26, 2009, Early Communication about an Ongoing Safety Review of Clopidogrel Bisulfate (marketed as Plavix) and Omeprazole (marketed as Prilosec and Prilosec OTC)
  11/17/2009
- Early Communication about an Ongoing Safety Review of clopidogrel bisulfate (marketed as Plavix)
  1/26/2009

Labeling and Regulatory History from Drugs@FDA

- Clopidogrel Bisulfate (marketed as Plavix) - Prescribing and Label Information

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FLUVIEW
A Weekly Influenza Surveillance Report Prepared by the Influenza Division

2009-2010 Influenza Season Week 46 ending November 21, 2009

All data are preliminary and may change as more reports are received.

Synopsis:

During week 46 (November 15-21, 2009), influenza activity continued to decrease in the U.S.

- 1,880 (20.5%) specimens tested by U.S. World Health Organization (WHO) and National Respiratory and Enteric Virus Surveillance System (NREVSS) collaborating laboratories and reported to CDC/Influenza Division were positive for influenza.
- Over 99% of all subtyped influenza A viruses being reported to CDC were 2009 influenza A (H1N1) viruses.
- The proportion of deaths attributed to pneumonia and influenza (P&I) was above the epidemic threshold for the eighth consecutive week.
- Thirty-five influenza-associated pediatric deaths were reported. Twenty-seven of these deaths were associated with 2009 influenza A (H1N1) virus infection, seven were associated with an influenza A virus for which the subtype was undetermined, and one was associated with a seasonal influenza A (H1) virus infection that occurred in March.
- The proportion of outpatient visits for influenza-like illness (ILI) was 4.3% which is above the national baseline of 2.3%. All 10 regions reported ILI above region-specific baseline levels.
- Thirty-two states reported geographically widespread influenza activity, Puerto Rico and 17 states reported regional influenza activity, the District of Columbia and one state reported local influenza activity, and Guam and the U.S. Virgin Islands reported sporadic influenza activity.

National and Regional Summary of Select Surveillance Components

	Data for current week			Data cumulative for the season						
HHS Surveillance Regions*	**Out-patient ILI†**	**% positive for flu‡**	**Number of jurisdictions reporting regional or widespread activity§**	**A (H1)**	**A (H3)**	**2009 A (H1N1)**	**A (unable to sub-type)¥**	**A (Subtyping not performed)**	**B**	**Pediatric Deaths**
Nation	Elevated	20.5 %	50 of 54	24	41	53,291	400	17,552	162	172
Region 1	Elevated	37.0 %	6 of 6	5	2	2,557	8	404	9	4
Region 2	Elevated	27.3 %	3 of 4	1	5	852	0	859	3	5
Region 3	Elevated	47.0 %	5 of 6	3	6	9,446	34	1,354	14	11
Region 4	Elevated	19.5 %	8 of 8	0	3	5,808	89	3,840	37	37
Region 5	Elevated	35.4 %	6 of 6	6	16	8,073	45	1,222	11	19
Region 6	Elevated	11.5 %	5 of 5	0	3	2,580	19	4,251	27	58
Region 7	Elevated	19.7 %	4 of 4	4	1	3,162	148	903	3	3
Region 8	Elevated	23.2 %	5 of 6	3	1	9,173	0	3,569	50	11
Region 9	Elevated	25.7 %	4 of 5	0	3	7,273	44	968	6	15
Region 10	Elevated	40.6 %	4 of 4	2	1	4,367	13	182	2	9

*Influenza season officially begins each year at week 40. This season data from week 35 will be included to show the trend of influenza activity before the official start of the 2009-10 influenza season.
**HHS regions (Region 1 CT, ME, MA, NH, RI, VT; Region 2: NJ, NY, Puerto Rico, US Virgin Islands; Region 3: DE, DC, MD, PA, VA, WV; Region 4: AL, FL, GA, KY, MS, NC, SC, TN; Region 5: IL, IN, MI, MN, OH, WI; Region 6: AR, LA, NM, OK, TX; Region 7: IA, KS, MO, NE; Region 8: CO, MT, ND, SD, UT, WY; Region 9: AZ, CA, Guam, HI, NV; and Region 10: AK, ID, OR, WA).
† Elevated means the % of visits for ILI is at or above the national or region-specific baseline
‡ National data are for current week; regional data are for the most recent three weeks
§ Includes all 50 states, the District of Columbia, Guam, Puerto Rico, and U.S. Virgin Islands
¥ The majority of influenza A viruses that cannot be sub-typed as seasonal influenza viruses are 2009 A (H1N1) influenza viruses upon further testing

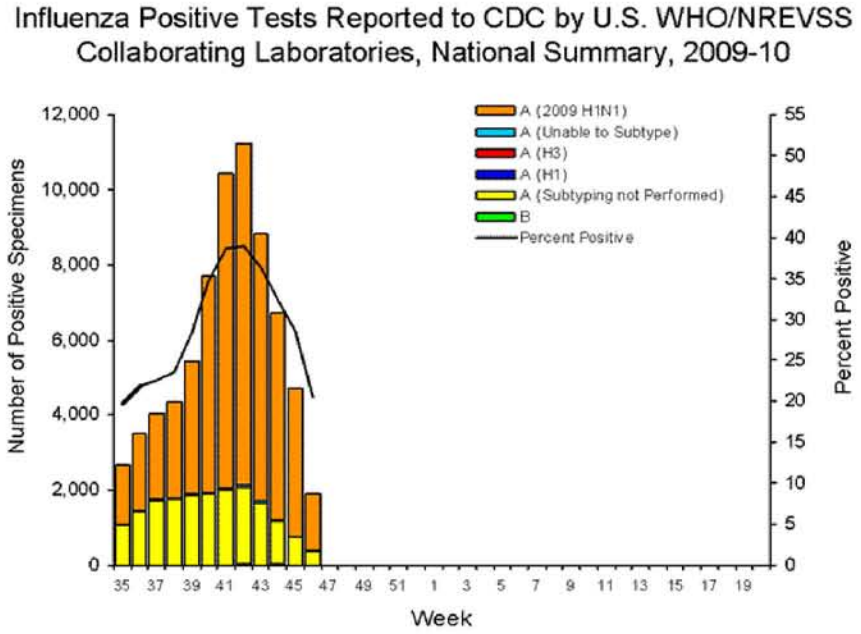
U.S. Virologic Surveillance:

WHO and NREVSS collaborating laboratories located in all 50 states and Washington D.C., report to CDC the number of respiratory specimens tested for influenza and the number positive by influenza type and subtype. The results of tests performed during the current week are summarized in the table below.

	Week 46
No. of specimens tested	9,159
No. of positive specimens (%)	1,880 (20.5%)
Positive specimens by type/subtype	
Influenza A	1,874 (99.7%)

A (2009 H1N1)	1,478 (78.9%)
A (subtyping not performed)	372 (19.9%)
A (unable to subtype)	23 (1.2%)
A (H3)	0 (0.0%)
A (H1)	1 (0.1%)
Influenza B	6 (0.3%)

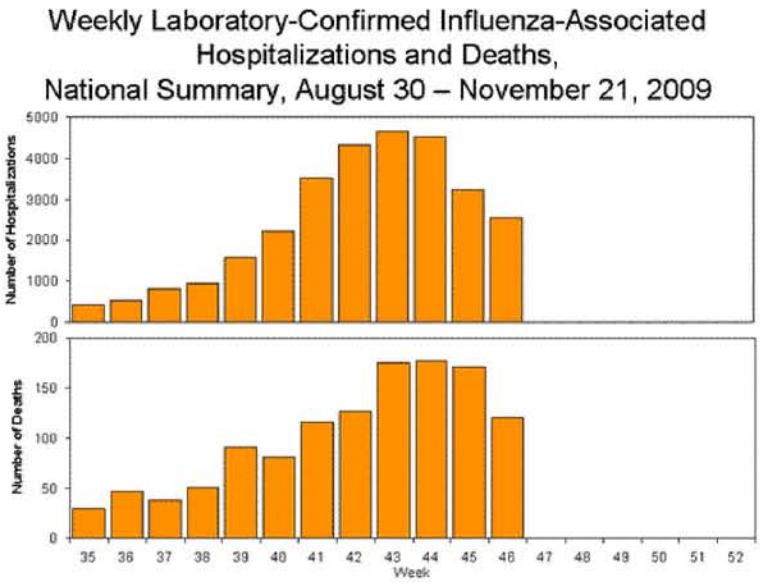
During week 46, seasonal influenza A (H1N1) and influenza B viruses co-circulated at low levels with 2009 influenza A (H1N1) viruses. Over 99% of all subtyped influenza A viruses reported to CDC this week were 2009 influenza A (H1N1) viruses.



View WHO-NREVSS Regional Bar Charts | View Chart Data | View Full Screen | View PowerPoint Presentation

Pneumonia and Influenza Hospitalization and Death Tracking:

This new system was implemented on August 30, 2009, and replaces the weekly report of laboratory confirmed 2009 H1N1-related hospitalizations and deaths that began in April 2009. Jurisdictions can now report to CDC counts of hospitalizations and deaths resulting from all types or subtypes of influenza, not just those from 2009 H1N1 influenza virus. To allow jurisdictions to implement the new case definition, counts were reset to zero on August 30, 2009. From August 30 – November 21, 2009, 29,348 laboratory-confirmed influenza-associated hospitalizations and 1,224 laboratory-confirmed influenza-associated deaths were reported to CDC. CDC will continue to use its traditional surveillance systems to track the progress of the 2009-10 influenza season.



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Antigenic Characterization:

CDC has antigenically characterized one seasonal influenza A (H1N1), three influenza A (H3N2), four influenza B, and 412 2009 influenza A (H1N1) viruses collected since September 1, 2009.

One seasonal influenza A (H1N1) virus was tested and is related to the influenza A (H1N1) component of the 2009-10 Northern Hemisphere influenza vaccine (A/Brisbane/59/2007).

The three influenza A (H3N2) viruses tested showed reduced titers with antisera produced against A/Brisbane/10/2007, the 2009-2010 Northern Hemisphere influenza A (H3N2) vaccine component, and were antigenically related to A/Perth/16/2009, the WHO recommended influenza A (H3N2) component of the 2010 Southern Hemisphere vaccine formulation.

Influenza B viruses currently circulating globally can be divided into two distinct lineages represented by the B/Yamagata/16/88 and B/Victoria/02/87 viruses. The influenza B component of the 2009-10 vaccine belongs to the B/Victoria lineage. The four influenza B viruses tested belong to the B/Victoria lineage and are related to the influenza vaccine component for the 2009-10 Northern Hemisphere influenza vaccine (B/Brisbane/60/2008).

Four hundred eleven (99.8%) of 412 2009 influenza A (H1N1) viruses tested are related to the A/California/07/2009 (H1N1) reference virus selected by WHO as the 2009 H1N1 vaccine virus and one virus (0.2%) tested showed a reduced titer with antiserum produced against A/California/07/2009.

Annual influenza vaccination is expected to provide the best protection against those virus strains that are related to the vaccine strains, but limited to no protection may be expected when the vaccine and circulating virus strains are so different as to be from different lineages. Antigenic characterization of 2009 influenza A(H1N1) viruses indicates that these viruses are only distantly related antigenically and genetically to seasonal influenza A(H1N1) viruses, suggesting that little to no protection would be expected from vaccination with seasonal influenza vaccine. It is too early in the influenza season to determine if seasonal influenza viruses will circulate widely or how well the seasonal vaccine and circulating strains will match.

Antiviral Resistance:

Since September 1, 2009, five influenza A (H3N2), one influenza B, and 402 2009 influenza A (H1N1) virus isolates have been tested for resistance to the neuraminidase inhibitors (oseltamivir and zanamivir), and 1,007 2009 influenza A (H1N1) original clinical samples were tested for a single known mutation in the virus that confers oseltamivir resistance. In addition, two influenza A (H3N2) and 207 2009 influenza A (H1N1) virus isolates have been tested for resistance to the adamantanes (amantadine and rimantadine). Additional laboratories perform antiviral testing and report their results to CDC. The results of antiviral resistance testing performed on these viruses are summarized in the table below.

Antiviral Resistance Testing Results on Samples Collected Since September 1, 2009.

	Samples tested (n)	Resistant Viruses, Number (%)	Samples tested (n)	Resistant Viruses, Number (%)	Sample
		Oseltamivir		Zanamivir	
Seasonal Influenza A (H1N1)	0	0 (0)	0	0 (0)	
Influenza A (H3N2)	5	0 (0)	0	0 (0)	
Influenza B	1	0 (0)	0	0 (0)	

2009 Influenza A (H1N1)	1,409	12†‡ (0.9)	402	0 (0)

*The adamantanes (amantadine and rimantadine) are not effective against influenza B viruses.
†Two screening tools were used to determine oseltamivir resistance: sequence analysis of viral genes or a neuraminidase inhibition assay.
‡Additional laboratories perform antiviral resistance testing and report their results to CDC. One additional oseltamivir resistant 2009 influenza A (H1N1) virus has been identified by these laboratories since September 1, 2009, bringing the total number to 13.

Over 99% of all of the subtyped influenza A viruses reported during week 46 were 2009 influenza A (H1N1) viruses, and the majority of 2009 H1N1 viruses tested since April 2009 have been resistant to the adamantanes (amantadine and rimantadine).

Antiviral treatment with oseltamivir or zanamivir is recommended for all patients with confirmed or suspected influenza virus infection who are hospitalized or who are at higher risk for influenza complications. Additional information on antiviral recommendations for treatment and chemoprophylaxis of influenza virus infection is available at http://www.cdc.gov/h1n1flu/recommendations.htm.

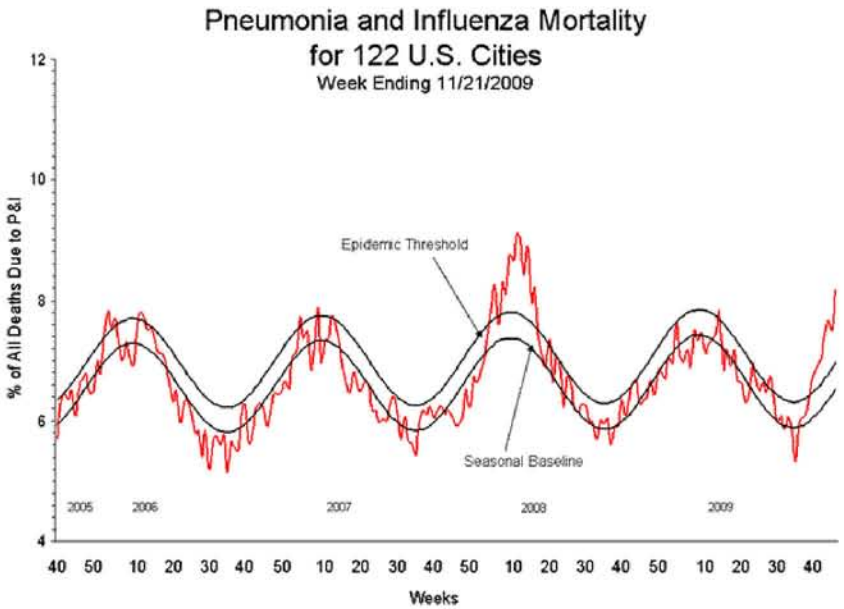
2009 influenza A (H1N1) viruses were tested for oseltamivir resistance by a neuraminidase inhibition assay and/or detection of genetic sequence mutation, depending on the type of specimen tested. Original clinical samples were examined for a single known mutation in the virus that confers oseltamivir resistance in currently circulating seasonal influenza A (H1N1) viruses, while influenza virus isolates were tested using a neuraminidase inhibition assay that determines the presence or absence of neuraminidase inhibitor resistance, followed by the neuraminidase gene sequence analysis of resistant viruses.

The majority of 2009 influenza A (H1N1) viruses are susceptible to the neuraminidase inhibitor antiviral medication oseltamivir; however, rare sporadic cases of oseltamivir resistant 2009 influenza A (H1N1) viruses have been detected worldwide. A total of 23 cases of oseltamivir resistant 2009 influenza A (H1N1) viruses have been identified in the United States since April 2009. In specimens collected since September 1, 2009, 13 cases have been identified in the United States, including two newly identified cases since last week. The proportion of oseltamivir-resistant 2009 H1N1 viruses does not represent the prevalence of oseltamivir-resistant 2009 H1N1 in the U.S. Most cases were tested because drug resistance was suspected. All tested viruses retain their sensitivity to the neuraminidase inhibitor zanamivir. Of the 23 cases, 13 patients had documented exposure to oseltamivir through either treatment or chemoprophylaxis, nine patients are under investigation to determine exposure to oseltamivir, and one patient had no documented oseltamivir exposure. Occasional development of oseltamivir resistance during treatment or prophylaxis is not unexpected. Enhanced surveillance and increased availability of testing performed at CDC are expected to detect additional cases of oseltamivir resistant 2009 influenza A (H1N1) viruses, and such cases will be investigated to assess the spread of resistant strains in the community.

To prevent the spread of antiviral resistant virus strains, CDC reminds clinicians and the public of the need to continue hand and cough hygiene measures for the duration of any symptoms of influenza, even while taking antiviral medications (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5832a3.htm).

Pneumonia and Influenza (P&I) Mortality Surveillance

During week 46, 8.2% of all deaths reported through the 122-Cities Mortality Reporting System were due to P&I. This percentage was above the epidemic threshold of 7.0% for week 46. Including week 46, P&I mortality has been above threshold for eight consecutive weeks.



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Influenza-Associated Pediatric Mortality

Thirty-five influenza-associated pediatric deaths were reported to CDC during week 46 (California, Colorado, Florida [3], Illinois [3], Indiana, Kentucky, Massachusetts, Minnesota, Missouri, New Hampshire, New Mexico [8], New York, North Carolina [2], Pennsylvania [2], Rhode Island [2], South Carolina [2], Tennessee, Texas [2], and Washington). Twenty-seven of these deaths were associated with 2009 influenza A (H1N1) virus infection, seven were associated with an influenza A virus for which the subtype is undetermined, and one was associated with a seasonal influenza A (H1) virus infection. The deaths reported during week 46 occurred between March 8 and November 21, 2009.

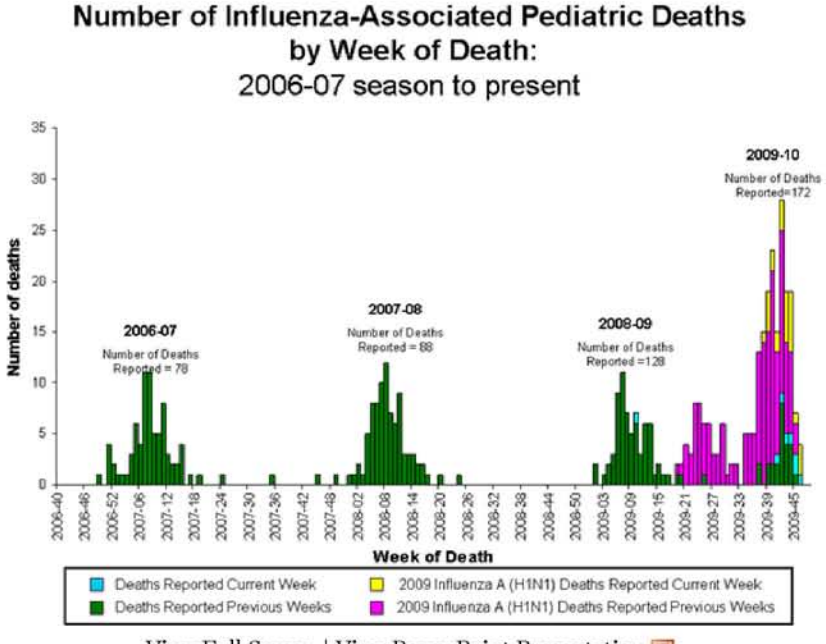
One death associated with seasonal influenza A (H1) virus infection reported during week 46 occurred in March during the 2008-09 season, bringing the total number of reported pediatric deaths occurring during that season to 128.

Since August 30, 2009, CDC has received 172 reports of influenza-associated pediatric deaths that occurred during the current influenza season (30 deaths in children less than 2 years old, 18 deaths in children 2-4 years old, 65 deaths in children 5-11 years old, and 59 deaths in children 12-17 years old). One hundred forty (81%) of the172 deaths were due to 2009 influenza A (H1N1) virus infections, and the remaining 32 were associated with influenza A virus for which the subtype is undetermined. A total of 198 deaths in children associated with 2009 influenza A (H1N1) virus infection have been reported to CDC.

Among the 172 deaths in children, 84 children had specimens collected for bacterial culture from normally sterile sites and 26 (31.0%) of the 84 were positive; Staphylococcus aureus was identified in eight (30.8%) of the 26 children. One S. aureus isolate was sensitive to methicillin, six were methicillin resistant, and one did not have sensitivity testing performed. Seventeen (65.4%) of the 26 children with bacterial coinfections were five years of age or older, and seven (26.9%) of the 26 children were 12 years of age or older.

Laboratory-Confirmed Influenza-Associated Pediatric Deaths by Date and Type/Subtype of Influenza.

Date	2009 H1N1 Influenza	Influenza A-Subtype Unknown	Seasonal Influenza	Total
Number of Deaths REPORTED for Current Week – Week 46 (Week ending November 21, 2009)	27	7	1	35
Number of Deaths OCCURRED since August 30, 2009	140	32	0	172
Number of Deaths OCCURRED since April 26, 2009	198	35	1	234



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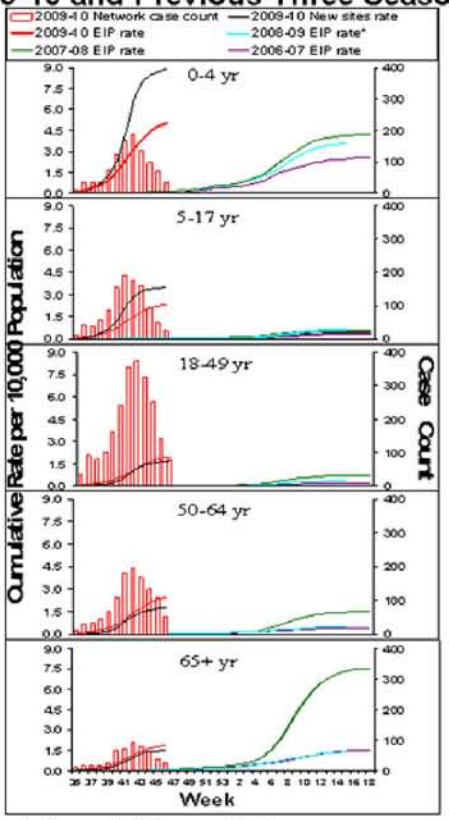
Influenza-Associated Hospitalizations

Laboratory-confirmed influenza-associated hospitalizations are monitored using a population-based surveillance network that includes the 10 Emerging Infections Program (EIP) sites (CA, CO, CT, GA, MD, MN, NM, NY, OR and TN) and 6 new sites (IA, ID, MI, ND, OK and SD).

During September 1, 2009 – November 21, 2009, the following preliminary laboratory-confirmed overall influenza associated hospitalization rates were reported by EIP and the new sites *(rates include influenza A, influenza B, and 2009 influenza A (H1N1)):*

Rates [EIP (new sites)] for children aged 0-4 years and 5-17 years were 5.0 (8.9) and 2.3 (3.5) per 10,000, respectively. Rates [EIP (new sites)] for adults aged 18-49 years, 50-64 years, and ≥ 65 years were 1.9 (1.6), 2.4 (1.7) and 1.9 (1.5) per 10,000, respectively.

EIP Influenza Laboratory-Confirmed Cumulative Hospitalization Rates, 2009-10 and Previous Three Seasons*



*The 2008-09 EIP rate ended as of April 14, 2009 due to the onset of the 2009 H1N1 season.

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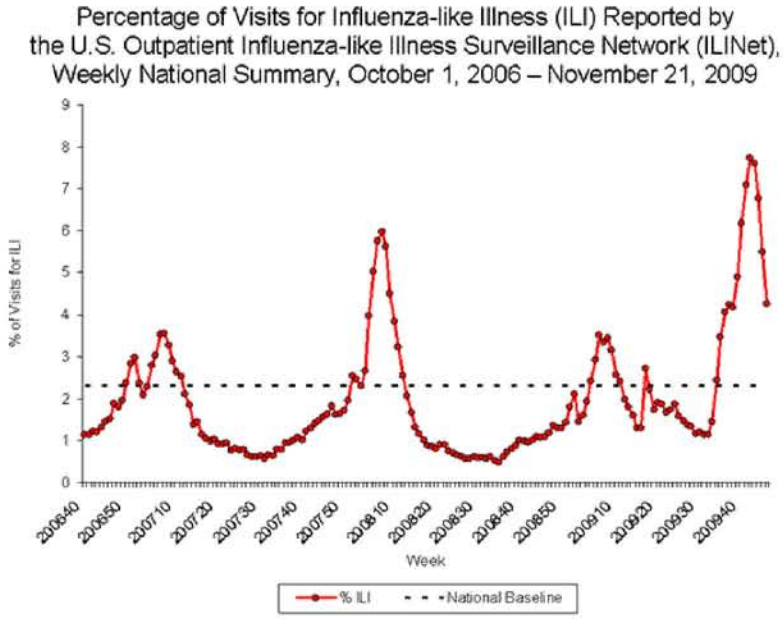
Outpatient Illness Surveillance:

Nationwide during week 46, 4.3% of patient visits reported through the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet) were due to influenza-like illness (ILI). This percentage is above the national baseline of 2.3%.



View ILINet Regional Charts | View Chart Data | View Full Screen | View PowerPoint Presentation

On a regional level, the percentage of outpatient visits for ILI ranged from 2.0% to 6.1% during week 46, and decreased in all 10 surveillance regions compared to the previous week. All 10 regions reported a proportion of outpatient visits for ILI above their region-specific baseline levels.

Geographic Spread of Influenza as Assessed by State and Territorial Epidemiologists:

The influenza activity reported by state and territorial epidemiologists indicates geographic spread of both seasonal influenza and 2009 influenza A (H1N1) viruses and does not measure the severity of influenza activity.

- During week 46, the following influenza activity was reported:
  - Widespread influenza activity was reported by 32 states (Alabama, Alaska, Arizona, California, Connecticut, Delaware, Florida, Idaho, Illinois, Indiana, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, Tennessee, Utah, Vermont, Virginia, and West Virginia).
  - Regional influenza activity was reported by Puerto Rico and 17 states (Arkansas, Colorado, Georgia, Hawaii, Iowa, Louisiana, Minnesota, Mississippi, Missouri, Montana, Nebraska, North Dakota, South Carolina, South Dakota, Texas, Washington, and Wisconsin).
  - Local influenza activity was reported by the District of Columbia and one state (Wyoming).
  - Sporadic influenza activity was reported by Guam and the U.S. Virgin Islands.

Flu Activity data in XML Format | View Full Screen

A description of surveillance methods is available at: http://www.cdc.gov/flu/weekly/fluactivity.htm

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Page last reviewed: November 30, 2009
Page last updated: November 30, 2009
Content source: Centers for Disease Control and Prevention

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