Pharmacy and Therapeutics Committee Meeting Record

Date: 3/18/05 **Time:** 9:00 a.m. – 5:00 p.m. **Location:** 3232 Elder Street, Conference Room D **Moderator:** W. Terry Gipson, M.D.

Committee Members Present: W. Terry Gipson, M.D.; Bob Comstock, RPh; Catherine Gundlach, PharmD; Cindy Bunde, P.A, George Pfoertner, M.D.; Phil Petersen, M.D.; Richard Pines, D.O.; Rick Markuson, RPh; Rick Sutton, RPh; Selma Gearhardt, PharmD.

Committee Members Absent: Stephen Montamat, M.D.; Thomas Rau, M.D.

Agenda Item	Presenter	Outcome/Action
CALL TO ORDER	W. Terry Gipson, MD	
• **Roll Call**	Linda Edson	Ms. Edson called the roll. One voting and one non-voting member were not present.
• **Reading of Confidentiality Statement**		The confidentiality statement was read by Dr. Gipson.
• **Approval of Minutes from January 21, 2005 Meeting**		The minutes from the January 21, 2005, Committee meeting were approved.
• **Discussion of Key Questions for Upcoming EPC Drug Effectiveness Review Studies**	Tami Eide, PharmD	Tami Eide was introduced as the new Pharmacy Services Supervisor for Idaho Medicaid. The draft key questions for Angiotensin II Receptor Antagonists, Atypical Antipsychotics, Newer Antiemetics, Newer Sedative Hypnotics, and Targeted Immune Modulators were discussed.
CLINICAL DATA REVIEW • **Atypical Antipsychotics**	Marian McDonagh, PharmD.	Dr. McDonagh attended via conference call and presented the Oregon Evidence-Based Practice Center's report comparing the atypical antipsychotic drug class. This report was finalized in January of 2005. The Committee accessed and reviewed a copy of the report prior to the meeting.
CLINICAL DATA REVIEW • **Inhaled Corticosteroids**	Richard Hansen Rph.	Richard Hansen attended via conference call and presented the University of North Carolina Evidence-Based Practice Center's report comparing the Inhaled Corticosteroid drug class. This report was finalized in January of 2005. The Committee accessed and reviewed a copy of the report prior to the meeting.
DRUG CLASS REVIEW • **Atypical Antipsychotics**	Tami Eide, PharmD., BCPS, FASHP	Dr. Eide presented a review of atypical antipsychotics including indications, how the drugs work, the drug-drug interactions, availability, and dosing. This review included the following drugs: • Aripiprazole (Abilify®) • Clozapine (Clozaril®) • Olanzapine (Zyprexa®)

		• Quetiapine (Seroquel®) • Risperidone (Risperdal®) • Ziprasidone (Geodon®)
DRUG CLASS REVIEW • **Inhaled Corticosteroids**	Tami Eide, PharmD., BCPS, FASHP	Dr. Eide presented a review of inhaled corticosteroids including indications, how the drugs work, the drug-drug interactions, availability, and dosing. This review included the following drugs: • Beclomethasone dipropionate (QVAR®) • Budesonide (Pulmicort ®) • Flunisolide (AeroBid®) • Fluticasone propionate (Flovent ®) • Triamcinolone acetonide (Azmacort®)
DRUG CLASS REVIEW • **Leukotrienes**	Mary Wheatley, RPh	Ms. Wheatley presented a review of leukotrienes including indications, how the drugs work, the drug-drug interactions, availability, and dosing. This review included the following drugs: • Montelukast (Singulair®) • Zafirlukast (Accolate®)
DRUG CLASS REVIEW • **Inhaled Beta 2 Adrenergic Agonists**	Selma Gearhardt, PharmD	Dr. Gearhardt presented a review of Inhaled Beta 2 Adrenergic Agonists including indications, how the drugs work, the drug-drug interactions, availability, and dosing. This review included the following drugs: <u>Short Acting, for use with nebulizer</u> • Albuterol (generics, Proventil®, AccuNeb®) • Metaproterenol (generics, Alupent®) • Levalbuterol (Xopenex®) <u>Short Acting, hand-held device</u> • Albuterol (generics, Proventil/HFA®, Ventolin/HFA® • Metaproterenol (Alupent®) • Pirbuterol (Maxair/Autohaler®) <u>Long Acting, hand-held device</u> • Salmeterol (Serevent Diskus®) • Formoterol (Foradil®)
DUR COX II PRESENTATION • **Upcoming Asthma Intervention**	Tami Eide, PharmD., BCPS, FASHP	Dr. Eide presented the upcoming DUR educational asthma treatment intervention for prescribers and pharmacists. Included in the intervention is an educational flyer designed to be copied and distributed to asthma patients.
PUBLIC COMMENT PERIOD	W. Terry Gipson, MD	Eleven people were listed to speak during the public comment period. Public comment was received from the following: • Dr. Robert Calder, Merck – Leukotrienes (Singulair)

		• Rebecca Persing, Sepracor – Beta 2 (Xopenex) • Randy Legg, AstraZenica – Respiratory • Thomas Patterson, MD, Saltzer Medical Group – Respiratory • Debra Richards, PharmD, GlaxoSmithKline – Respiratory • Trina Clark, Lilly – Atypical Antipsychotics • Elham Tabarsi, AstraZeneca – Atypical Antipsychotics • Andrew Bane, PhD, Bristol-Myers Squibb – Atypical Antipsychotics • Richard Ensign, Pfizer – Atypical Antipsychotics • Cynthia Miller, RN, Asceni Behavioral Health – Atypical Antipsychotics • Lee Woodland, NAMI Idaho – Atypical Antipsychotics
COMMITTEE DISCUSSION AND CLINICAL CONCLUSIONS FOR SELECTED THERAPEUTIC CLASSES	W. Terry Gipson, MD	Atypical Antipsychotics The Committee determined that each agent has patient specific efficacy. It was agreed that each drug was effective and needed to be available for use due to their unique therapeutic properties and patient specific responses. Inhaled Corticosteroids The Committee determined that agents in this class are equally efficacious and safe. Patient education on use of inhaled corticosteroid medications to reduce beta agonist usage and hospital visits was advocated. Inhaled Beta 2 Adrenergic Agonists The Committee determined that agents in this class are equally efficacious and safe. Patient education on use of inhaled corticosteroid medications to reduce Inhaled Beta 2 Agonist usage and hospital visits was advocated. Leukotrienes The Committee determined that the two drugs in this class were equally efficacious and safe. Singular® may have some advantages with compliance because of once a day dosing and available dosing options.
PUBLIC MEETING ADJOURNED	W. Terry Gipson, MD	The next classes of agents to be reviewed by the Pharmacy and Therapeutics Committee on May 13, 2005 are: Alzheimer drugs, Estrogens and Urinary Incontinence drugs. A re-review of the therapeutic requirements for the Proton Pump Inhibitor drug class will also be conducted. Dr Gipson adjourned the public portion of the meeting.
SUPPLEMENTAL REBATE INFORMATION *(CLOSED TO PUBLIC)*	Randy May, Medicaid Deputy Administrator	Randy May presented supplemental rebate information to the Committee members for their review and discussion. This review and discussion were closed to the public.
COMMITTEE FINAL RECOMMENDATION FOR THERAPEUTIC CLASSES	W. Terry Gipson, MD	Atypical Antipsychotics The Committee recommends that all agents in this class become designated as preferred agents. The Committee also recommends that all agents in this class become subject to the following prior authorization criteria. ▪ Appropriate diagnosis ▪ Maximum use of two atypical agents concurrently limited to 45 days. ▪ Children 12 and under will require a documented psychiatric consultation

		▪ Children 12 and under will require a signed Informed Consent on record ▪ Maximum dosage limits (as defined by the Department based on FDA guidelines) <u>Inhaled Corticosteroids</u> The Committee recommends that Flovent® and Pulmicort® become designated as preferred agents. All other agents in this class will require prior authorization. <u>Inhaled Beta 2 Adrenergic Agonists</u> The Committee recommends that Albuterol become designated as the preferred short-acting agent for this class. Neither of the long-acting agents, Serevent® nor Foradil®, are superior to the other. All other agents in this class will require prior authorization. <u>Leukotrienes</u> The Committee recommends that Accolate® and Singulair® become designated as Preferred Agents, that all individuals using a Leukotriene have an asthma or allergic rhinitis diagnosis and that individuals over age 16 show documented use and failure of an Inhaled Corticosteroid.

Pharmacy and Therapeutics Committee
Public Comment
March 18, 2005

Dr. Robert Calder, Merck – Leukotrienes (Singulair)

Dr. Calder: Thank you. And again I am Robert Calder from Merck. I'm a physician, epidemiologist. I've been with Merck for fifteen years, prior to that I was state epidemiologist in Florida and before that I was [unintelligible] officer in the army. And Singulair is indicated for both asthma and allergic rhinitis as you heard. It is indicated for asthma in patients 12 months of age and older. The indications have been based on a range of studies in various age groups of people as well as locations and the studies have shown that FED1 has been decreased, daytime symptom scores improved, [unintelligible] improved and total daily Beta [unintelligible] decreased. In addition, in patients taking Singulair with inhaled corticosteroids we've been able to decrease the dose of inhaled corticosteroids or even discontinue them in some cases. You also heard earlier that Singulair is a leukotriene inhibitor, it is an orally active leukotriene inhibitor that binds with high infinity and select[unintelligible] leukotriene receptor inhibiting the affects of leukotriene D4. Which when I went medical school was called slow reacting substance [unintelligible]. And the fact that it is orally active is important because after all efficacy, the over all effectiveness of a product is really a combination of the efficacy and compliance. And so with that in mind we have come up with several dosage forms for Singulair. We have tablets, chewable tablets and oral granules covering the range of people 12 years of age and older. And that's an important point. In the material that was sent to you in our AMCP dossier there is a two page circular comparison for Singulair vs Accolate and I'll just hit a couple of points on that. Singular again is indicated for children 12 months of age and older. Accolate is only indicated for children 5 years and older. Singulair is dosed once daily. It's been clinically shown to be a 24 hour drug and it was approved by the FDA as a once daily medication. Accolate on the other hand is a [unintelligible] medication. Third point Singular is available in a range of dosage forms, Accolate is just tablets. Singular has really fairly minor food interactions, you've heard about the fat [unintelligible] meal, C max is decreased, T max is prolonged with the under the curve remains the same with a high fat meal so there's no dosage adjustment recommended. Where as with Accolate there are definitely food interactions. And also finally you've heard about the [unintelligible] interactions with Accolate that are much more numerous. With Singulair it's just inducers that tend to decrease levels of concentration of Singulair. With that I'll end.

Committee Thank you. I think we have a question.

Committee I just wonder, have you, would you know of any reason to increase the dose above 10 mgs. daily?

Dr. Calder No, there is no reason. We've studied in our dose range and phase 2 studies, we studied higher doses and they weren't found to be more efficacious than the 10 mg. dose.

Committee So you would never recommend going to 20 mgs.?

Dr. Calder Unless the person were taking inducers such as Phenobarbital that would decrease the clasinal levels. That would be the only situation where I could theoretically think that there might be a reason to increase it, but if a person isn't on inducers [unintelligible] I can't think of another reason. Because we look at it in our Phase 2 A studies.

Committee Individually there could be one individual that might just metabolize faster and you wouldn't know ahead of time. I mean if your looking at this one patient you can have one patient changes too. From a group you'd never see that.

Committee Thank you very much Dr.

Rebecca Persing, Sepracor – Beta 2 (Xopenex)

Ms. Persing: Thank you for having me here. My name is Rebecca Persing. I'm a medical liaison with Sepracor. Obviously I represent Xopenex. My background is slightly different. I'm a trained Molecular Biologist in the area of asthma and respiratory diseases. I've come today to talk to you a little about Xopenex. I want to go over a little bit of background and then highlight of the things that might have been lacking form the [unintelligible] and I'd like to just go over just a small amount of data. First of all Xopenex is, with the exception of Xopenex all the marketed forms of [unintelligible] versions of Albuterol and they contain a 50/50 mix between the R and the F[unintelligible]. Xopenex however, just contains the R [unintelligible] pointed out and it's the therapeutic reactive component of the drug. Where as the F[unintelligible] previously being considered to be biologically inert. However there is a growing body of evidence that suggests that this may have negative affects on lung function and [unintelligible] in the long term. So, just to point out a couple of things about the therapeutic class summary from Regence Group. First, I would just like to say that obviously as you pointed out it is sort of out of date. The only publication that was sighted for Levalbuterol was published in 1998 and since then we have had 70 additional articles that have been published. That includes over 15 clinical trials, 2 head to head comparisons and some other studies that were pre[unintelligible] and include many exposed adults and children with asthma and [unintelligible]. So many of these studies were large prospective studies and demonstrate that lower doses of Levalbuterol provide equal or better [unintelligible] dilatation compared with [unintelligible] and have a longer duration [unintelligible], end quote. [Unintelligible] packaging [unintelligible] labeling for 8 hours worth of [unintelligible]. On page two table, ah page three a table two a summary approved indications say that Levalbuterol ages restriction is stated as above 12 years of age. But actually that is wrong in the package insert it's greater than six. We received approval on Friday for the Xopenex HFANDI last week and that has been approved for the treatment of and prevention of [unintelligible] in adult and children above the age of four. And that is in the MDI form. For these reasons it seems [unintelligible] accept some of the conclusions from the class summary. And so just to go into a little bit of the data. On the chronic dosage, briefly, some of the pivotal settings have been highlighted, and obviously these were sponsored by Sepracor, were the Nelson study in 1998, Millburn study in 2001 and in December 2004 Dr. Plescow published another double blind randomized placebo controlled trial. And they concluded over thousand patients evaluated chronic dosing in lab. vs rats. But as you know this isn't typically how [unintelligible] is administered [unintelligible] are not chronically administered. So even though in these studies Levalbuterol and it's a lower dose compared with Resimic had similar [unintelligible] dilation. As you know based on the guide lines they short acting Beta Agonists are used as rescue med. and so, but in spite of that we found that Levalbuterol had a greater change in FED 1 compared to the other treatments. And a more pronounced improvement was found in the most severe subjects. There are two stages of drug administration of second [unintelligible] Beta Agonists, which is self administration as a rescue med. and [unintelligible] high dose nebulized Albuterol. [Unintelligible] for that reason it is inappropriate to have only one Beta Agonist available on this EDL because some of these patients need to be using strips.

Committee One minute.

Dr. Persing So I guess I want to point out a couple of things. First is that Levalbuterol by last fall was received from the CMS it was recognized as a unique chemical and indeed by awarding it it's own Jcode we have, they did that because they stated that they recognized clinical differences and efficacy in outcome compared to Resimic Albuterol and Xopenex utilization in the state of Idaho according to the Kaiser Foundation shows that children of primary beneficiaries who are the primary beneficiaries of the enhanced efficacy reduced side affects constitute 61% of Idaho Medicaid. Yet surprisingly on consume 8% of the Idaho drug expenditures which is well below drug averages which is 24%. Across the board only two prescriptions per year for Xopenex are

filled with an average of 48 units per year. So is it appropriate in light of such patterns to restrict access to clinicians and patients for medication that may have significant therapeutic benefits and reduce [unintelligible] side affects at lower doses. Thank you.

Committee Randy Legg.

Randy Legg, AstraZenica – Respiratory

Mr. Legg: Thanks for letting me come here. My name is Randy Legg. I'm a PharmD. I live in Spokane WA. And I work in medical [unintelligible]. And one thing I wanted to address is there was a discussion about Rolf studies inhaled steroids. And for the record one of the studies is highlighted there, and Agratalk paper was a 9.2 year study of kids taking and average of 420 mg. of Fidesinite for nine years. And what they found was in the first year there was about 1.1 centimeter of growth drop. But by the second and subsequent years they caught up. So [unintelligible] growth height was not changed. And then also there is another Camp paper that looked at the use of [unintelligible] for kids and that was a 4 year study [unintelligible]. Are there anymore questions about growth studies? I just had a few points to share with you. Both [unintelligible] have the only category B pregnancy rating of inhaled steroid class that's available. [Unintelligible] inhaler also has a once a day dosing. Homecarbespules is age 12 months and up and is the only nebulized Corticosteroids available as of right for 12 months to 8 years of age. In the packet I gave you is recent publications since the Oregon dossier was written about a year ago. So it's all recent literature. In the packet there are two safety trials on [unintelligible] inhaler and one out come paper. In the Comacartrespules section there are three safety papers in addition to one outcome paper. And in addition to [unintelligible] paper. The final thing I want to highlight is the start paper is steroid treatment as regulated therapy paper. It was 7, 221 ages 5 to 66 with mild persistent asthma. And they got 200 to 400 mg. of Dedesinite per day for three years. And on the outcome side of that paper they had an increase of symptom free days of 14 per year, a decrease in hospitalizations by 69%, a decrease of ER visits by 67%, a decrease in office visits by 36%, and decrease in school day missed by 37%.

Committee Thank you.

Committee Thomas Patterson

Thomas Patterson, MD, Saltzer Medical Group – Respiratory

Dr. Patterson: I'm Tom Patterson [unintelligible] Saltzer Medical Group in Nampa and I have a particular interest in asthma as I have it, my wife has it, my 10 month old baby has it and I treat a ton of patients with asthma. I'm glad you all have the message that Corticosteroids is the number one treatment for all persistent levels of asthma and that delighted me to hear. In terms of what are our choices for corticosteroids my own personal choice is Fluticasone. It has a lot of advantages in terms of how you get it to the patient, in terms of dosing comes in a variety of dose amounts allowing you to give a very small number of puff per day for the small children verses some of the other inhaled corticosteroids where you have to give six, seven puffs a day to get an efficacious dose to control their asthma. Compliance goes up I think when you decrease the number of puffs [unintelligible] with my 10 month old too. Is giving him a puff of Albuterol which is quite a challenge with a spacer and a mask so to do that once or twice a day is OK, but to do it four times a day or a bunch of doses in a row isn't an issue. The other thing that about [unintelligible] in terms of safety is the [unintelligible] through the liver so your not worried about the metabolic byproducts being active and [unintelligible], so in my mind Fluticasone is the one I go to the most. I was trained at the University of Arizona and that is what our, Fernando Martinez, [unintelligible] are still teaching and taught when I was there, eight, nine, ten years ago. Any questions at all?

Committee Who [unintelligible] Xopenex [unintelligible]

Dr. Patterson Zofanex is something I am excited about the MDI form coming out. I have a few patients in my practice that have absolutely confirmed to me that there are some people that [unintelligible] isomer that is not biological active is detrimental. I have a few kids in my practice where I've given them regular Albuterol and have them have such incredible bronchial spasm that it scared me. And these kids I think are going to benefit from Xopenex in an MDI form. I don't think everybody needs it, but I think there is a percentage of the population that we don't know exactly who they are yet, that are going to get incredible benefit for Xopenex because of that [unintelligible] isomer form.

Committee Excuse me Dr. Patterson, it's common for a clinical to identify whether you came on your own behave or as a request of a pharmaceutical company.

Dr. Patterson I came on behalf of advocating for children with asthma. It's one of those things that I think that we need to advocate for children, I been to speak at the American Academy of Pediatrics on Asthma, I've done education in schools, I do speak for GlaxoSmithKline, but I'm not here for that purpose, but rather my own purpose and representing Saltzer Medical Group Pediatrics.

Committee Thank you very much for that clarification. Any comments for Dr. Patterson?

Committee Debra Richards

Debra Richards, PharmD, GlaxoSmithKline – Respiratory

Dr. Richards: Hello. Thank you for the opportunity to allow me to testify in front of you today. I'm Debra Richards, PharmD. I'm a respiratory [unintelligible] medical scientist with GlaxoSmithKline and part of the [unintelligible] division and I too would like to speak today Fluticasone and the treatment of respiratory diseases as well as Somederal. First I would like to point out [unintelligible] highlight the [unintelligible] presented earlier this morning regarding Fluticasone. [Unintelligible] when looking at comparative efficacy and safety there were some end points where the results favored Fluticasone. We also noted that the number of puffs for some of the products to reach equal potent doses could be very substantial. So when medium to high doses of inhaled corticosteroid are need to provide asthma control there higher doses of Priticizon for those patients. And so this allows most patients to take 2 puffs per dose maximum 4 puffs per day. There was also a Cochrane collaboration in year 2000 of Fluticasone and it concluded that most patients with mild to moderated asthma experience similar results with low dose Fluticasone verses high dose Fluticasone. So practically speaking that means that optimizes the risk [unintelligible] ratio using the lower dose is well as it may provide some cost savings to the patients. Another approach to assessing drug affectedness is to retrospectively get helpline data. And in 2001 there was a heath line data base study in respiratory medicine and it compared the monthly cost of Fluticasone at the lowest strength available verses other inhaled corticosteroids. Annual asthma care verses annual health care charges where significantly lower with Fluticasone verses the other inhaled corticosteroids. And another point that I want to bring to your attention is that Fluticasone is currently available on the regions formulary. So in summary, there is some conclusive clinical evidence favoring Fluticasone and also there are three available strengths of Fluticasone which provides an effective way to deliver the needed dose without increasing the number of doses substantially [unintelligible]. And finally, there is a data base analysis which suggests that as [unintelligible] total health care costs may be lower for patients filling Fluticasone lower strength prescriptions verses other inhaled corticosteroids. So I want to switch topics now and talk to you about Serevent. Any questions?

Committee I would ask, when you say it is available on Regence formulary what tier is it?

Dr. Richards I don't know that. I'm sorry. Do you know?

Audience Member I can't answer that. I went to the website last night to double check and it was on, but I didn't check the tier, I'm sorry.

Committee OK, thank you.

Audience Member [unintelligible] question.

Dr. Richards It's been available in the US since 1994. There a [unintelligible] published evidence regarding its safety and efficacy and as described in the presentation earlier verses Salmeterol and Formoterol they've been compared in several clinical trials. And while the on set of action from Formoterol is faster there's been no significant differences in efficacy [unintelligible] in the studies. Both treatments were well tolerated without significant differences in adverse events. The rapid on set of action of Formoterol is unlikely to be of clinical significance. Since long acting Beta-Agonists are intended to be used clinically for main stream treatment and not rescue therapy. In addition there is a concern that the rapid on set of Formoterol may cause some patient confusion between the long acting and Beta-Agonists with the potential of over use and increased morbidity. Of the Beta-Agonists, Salmeterol is the highest Beta 2 activity. It's two hundred times more selective for Beta 1 than Beta 2 receptors, as it was talked about earlier Beta 1 is mainly in the lungs, Beta 2 is mainly in the heart. For the package inserts there are also so differences in the administration that you were saying was important on a practical basis. So for [unintelligible] the patient has to open the blister packet, they have to put it into the device, close it, pierce the device and then they have to inhale, and then they open it, and if there is anything left in the little blister capsule then they have to repeat the process. Whereas with Serevent this is a discus and it is an enclosed device and there are three steps, you open it, and then breathe in. So, it's one, two, three. It's much simpler process. One, two, three. So the difference in device and dosage administration may have an impact on the patient's ability to use the medication and may impact compliance as well. So in summary, Serevent has been available in the US since 1994, has a large body of evidence regarding it's safety and efficacy, the molecule of greater selectivity for Beta 2 receptors than Formoterol and it is delivered via discus in three easy steps and I would also like you to consider, if the patient is already on a [unintelligible] that it behooves the patient and health care system to allow them to remain on those medications.

Committee Thank you. Questions?

Audience Member I just checked, its tier 2.

Committee Thank you.

Dr. Richards No more question?

Audience Member What does tier 2 mean?

Committee The way the commercial side controls their pharmacy costs is to tier a drug so you pay a copay of say 10.00 for generic, a tier 2 might be a 20.00 copay, tier 3 might be a 40.00 copay. And some of the commercial folks have a really pricy tier that you pay a significant amount for a branded product that their pharmacy has taken to the [unintelligible] more efficacious than a tier 1 or 2. It's a way of controlling costs and of course in not accessible to Medicaid in terms of being able to drive the utilization to those products that have proven equal efficacy.

Committee Trina Clark

Trina Clark, Lilly – Atypical Antipsychotics

Ms. Clark: Ms. Clark: Good afternoon. My name is Trina Clark and I am an outcomes liaison with the medical division of Eli Lilly and Company and I thank you for the opportunity to provide comment regarding the per [unintelligible] preferred drug list for the Atypical Antipsycotics. I would like to share with you some important information today that was not included in the Oregon evidence based practice [unintelligible] review. And this is evidence around the safety and effectiveness of implementing a preferred drug list in a population with schizophrenia and bipolar disorder. I'll first begin with the safety question. Given that these diseases are sever disorders of mood and thought the severely mentally ill are not as able as the general population to negotiate prescription denial as well as to navigate a complex prior authorization process. This increases the opportunity for treatment failure and relapse. These relapses may be associated with delayed treatment response and a permanent lose of functioning. Research has reported that brain injury occurs in close association with schizophrenia crises. In 27% of patients persistent symptoms remain after the first event. This number increases to 47% following the fourth crisis event. Additionally, time to treatment response may progressively increase with subsequent relapses. One study showed a steady increase in time to response of 48, 58 and 85 days for the first, second and third psychotic episode respectively. Basically this means that the more relapses the patient has the more treatment resistant a patient becomes and the poorer the patient outcome. I would also like to point out that denial of medication are not the only requirement for relapse, but delays on receiving medication are all the are necessary. There was an independent study done by a large PBM that looked at their prior authorization process and found that half of those that obtained a PA indicated that it took five or more days. In schizophrenia we know that short delays of treatment of just a few days, a 1 to 10 day gap in therapy doubles the risk of psychiatric hospitalization. It doesn't take very many relapsing patients to wipe out the perceived saving from a preferred drug list. Moving on to the effectiveness literature. Independent studies done in Tennessee, New Hampshire and a pooled [unintelligible] of several states revealed that even seemingly minor restrictions, such as caps on the number of prescriptions, can negatively effect [unintelligible] on medication, continuity of care and the need for mental health services, basically increasing hospitalization and nursing home use. Finally, I would like to share with you one states experience in implementing a prior authorization [unintelligible] for atypical antipsychotics. To the states credit they did commission a report to look at the impact of this prior authorization program and concluded that the restriction had minimal impact on cost control and actually cost per prescription increased by 2.3 percent. Unfortunately the harm to patients was not evaluated. In summary given the grave consequences of any interruption in care of the severely mentally ill, as well as experiences from other states, we believe it is both clinically and fiscally appropriate to make all the atypical antipsychotics available as a [unintelligible] option. Thank you for your time.

Committee Any questions?

Committee What state are you referring to that has prior authorization?

Ms. Clark The state of Kentucky.

Committee I guess what I'm hearing you advocate is, "leave us alone."

Ms. Clark Well, I'm advocating for the patient that in this population it is different from someone with hypertension or someone with upper GI distress who might be able to navigate a complex prior authorization process that when they leave the pharmacy without a medication they will come back to the pharmacy, where in this population we know there is a very high percentage of patients that will attempt and commit suicide.

Committee That's a given. To take that and extrapolate that we shouldn't follow some guide lines in terms of, because you also made the comment that restricting dosages, and I think there is consensus, and will address that at a later time, but I just needed to get clarification because it troubled me a little bit.

Ms. Clark I think there are other alternatives and I think you mentioned restricting dosages, is that what I heard you say, and I think there is other alternatives that other states are looking at and that's focusing on appropriate prescribing of these medications.

Committee I agree. Thank you.

Committee I cannot pronounce this next name but the representative from AstraZeneca.

Elham Tabarsi, AstraZeneca – Atypical Antipsychotics

Ms. Tabarsi: Ms. Tabarsi: Good afternoon. I'm Elham Tabarsi. I'm a medical determination scientist for AstraZeneca. I appreciate having the opportunity of speaking to you today about [unintelligible] antipsychotic agents and also [unintelligible]. First on behave of AstraZeneca I would like to know that we are in full support of making open access for the class of atypical antipsychotics. Open access is important because different people respond to different medications and we need to ensure that mental health patients receive appropriate medical care. In the atypical antipsychotic drug class each product has its own [unintelligible] receptor binding properties and [unintelligible] as well as [unintelligible] dosing schedule [unintelligible]. Physicians should be able to consider these factors in prescribing the most appropriate product for the need of this patient. Treatment of people with mental illness is very individualized; they are not an aveage medicaid recipient. Untreated or inadequately treated mental illness is often resulted in expensive community consequences which are law enforcement [unintelligible], ER treatment, hospitalization, homelessness, and suicide. Statistically [unintelligible] is indicated for the treatment of [unintelligible] episodes associated with bipolar 1 disorder [unintelligible] therapy and for the treatment of schizophrenia. [Unintelligible] has demonstrated significant improvement in [unintelligible] both schizophrenia and bipolar mania. Since it launching in 1997 [unintelligible] continues to be effective and well tolerated in more than 8 million patient exposures. A principle cause of non compliance of antipsychotic medications is related to the side affects of these medications. Therefore it is the only atypical that has demonstrated [unintelligible] including [unintelligible] across the entire dosage range in clinical trials for both schizophrenia and bipolar mania. [Unintelligible] also demonstrated [unintelligible] at placebo level [unintelligible] profile and a favorable [unintelligible] profile. Individual clinical trials [unintelligible] due to weight gain. Additionally in the Serico clinical trials there was no difference in the mean change of random glucose measurements between circle and [unintelligible] placebo or with the [unintelligible] compared to other antipsychotics. There was also no significant difference [unintelligible] difference in a proportion of patients experiencing potential [unintelligible] EKG [unintelligible] changes. Furthermore, there is no association between the occurrence of [unintelligible] either serious or non serious [unintelligible] treatment. In both the schizophrenia and bipolar mania Serico patient remain on treatment. In clinical trials for schizophrenia there was a 4% discontinuation in treatment due to side effects verses 3% discontinuation for placebo. In bipolar mania there was no difference between Serico and placebo for treatment discontinuation due to side effects. [Unintelligible] conducted a patient [unintelligible] patients were switched for Serico from previous antipsychotic medications. 97% preferred Serico to previous treatment. AstraZeneca strongly urges the state to refrain from implementing policy or regulations that reduce access to atypical antipsychotics. In addition, AstraZeneca feels that based upon its safety and efficacy profile, Serico must remain available as an important treatment option for physicians and their patients who have schizophrenia and/or acute bipolar mania. Thank you for your time.

Committee Thank you for your comments. Questions?

Committee Andrew Bane

Andrew Bane, PhD, Bristol-Myers Squibb – Atypical Antipsychotics

Dr. Bane: Mr. Chairman, members of the committee, thanks for the opportunity to address you today. My name is Andrew Bane. I'm medical science liaison for Bristol-Myer Squibb in aeroscience and hold a PhD. in behavioral aeroscience. I would just like to make a couple of comments if I might, regarding the evidence Center for Evidence Based Policy and their report. A number of these shortcomings were noted in the meeting today. One is there were a number of studies that were excluded in particular the [unintelligible] patient studies [unintelligible] important information particularly for a compound like ours that has only been on the market since November of 2002. In addition, those studies that were included in the report were rated by the center as being of fair or poor quality. And at least the majority of them were and I would encourage you that if you're going to make any decisions based upon data like this that maybe you could postpone these decisions until studies like the Katie study or, are you all familiar with the Katie study? This is an NIH funded study so it is not a [unintelligible] sponsored study so it is an MINH sponsored study, [unintelligible] study, and it stands for the Clinical Antipsychotic Trial of Intervention Effectiveness. This trial is put together to compare antipsychotics directly head to head in a real world setting and I know committee members, or really committees in your situation are waiting for the results of trials like that before they make any conclusions. With regard to Aripiprazole in particular, let me just mention that it is the only antipsychotic on the market to have a different mechanism of action, [unintelligible] as all other antipsychotics with a typical or atypical are antagonist [unintelligible]. [unintelligible] has a unique finding, safety tolerability profile and [unintelligible] treatment of schizophrenia, acute and manic episodes associated with bipolar disorder, and just recently in the maintenance treatment of acute and manic episodes associated with bipolar 1 disorder only the second antipsychotic to receive that [unintelligible]. That concludes my statements. Are there any questions that I can answer?

Committee Thank you. This study that MINH is funding, do you know if, for how many years and where are they currently…

Dr. Bane It included about 1500 patients and is a multi site study that was done with a number of sites across the nation, the results, the first of the results I think will be published in June and I don't know the length of time of the study, but [unintelligible] and actually the last time I heard Marion speak said this will most likely be the best evidence to date when it arrives on the scene. So it might be worth waiting for.

Committee And all atypicals are included in that.

Dr. Bane Yes, Aripiprazole was just coming out at the time the study was designed so they did make an adjustment for Aripiprazole to be included [unintelligible] but there will be information [unintelligible].

Committee 1500 patients sounds like a small for drawing those kinds of serious conclusions about such a complex class of…

Dr. Bane The design of the study [unintelligible]

Committee Thank you. Other comments?

Committee Richard Ensign

Richard Ensign, Pfizer – Atypical Antipsychotics

Mr. Ensign: My name is Richard Ensign I'm a Pharmacy with Pfizer Pharmaceuticals, manufacturer of Ziprasidone or Geodon. I would like to echo some of the comments that were provided earlier just briefly about open access to medications. This is a patient population that is difficult to treat, many of whom have tried multiple medications in the past and have responded to on particle dosing regime. So I think it is very important for the providing prescriber that we give them all the options that are available out there. We can't at the same time ignore the cost of these medications. One of the recommendations that I have for the committee is to help utilize the services of the other aspects of Medicaid and that is the DUR board. And [unintelligible] the people from Idaho State University. In most states the DUR board and P&T board are one in the same. Idaho is think one of the rare ones where you have the P&T board and you have the DUR board. So I think it would be a great opportunity for the DUR board to look at the appropriate use of the atypical antipsychotics and look at some of the metabolic outcomes to see what is actually happening in your state. Maybe some of the members of the committee are actually here today, and I think that would actually be a good overlap to look at these agents. Just to comment briefly on the OSU report I would like to highlight as mentioned previously about some of the deficiencies in the report. I think the key questions are good, but there are many exclusion that left out a lot of evidence. Particularly they reference acute illness, first episode of schizophrenia inpatient studies that were not included. There was a lot of good data that can add to the body of evidence that was excluded from this study. In addition there's another observational and switch studies that again can add addition evidence that were not included. It sounds like there are being revised and will hopefully give us more information later, but you don't have that information with you today. From Pfizer's prospective there are at least two studies head to head inpatient studies published in the last year that look at Ziprasidone verses Asperidol and Alansopine both showed similar efficacy but significant difference in some of [unintelligible] metabolic parameters. I think that brings me to my last point, although we did talk a little bit about weight gain, diabetes, I think one omission was cholesterol. I didn't see any discussion on the affect of these drugs on cholesterol and I think there are significant differences and hopefully that is something that will be included in future reports as well. It was mentioned early the consensus guidelines from the American Diabetes and American Psychiatric Assoc., this was published over a year ago and they reference significant differences between the agents in diabetes and weight gain and the effects on serum cholesterol. So hopefully the discussion for the committee would be why consensus guidelines would have different recommendations or different conclusions than the Oregon report. In summary I would hope that you would look at all the evidence but most of all provide open access for these medications. Any questions?

Committee Thank you.

Committee Cynthia Miller

Cynthia Miller, RN, Asceni Behavioral Health – Atypical Antipsychotics

Ms. Miller: Hi. I'm Cindy Miller. I'm a register nurse and one of the owners of Asceni Behavioral Health Services in Meridian. We are one of the fewer private psychiatric providers that use [unintelligible] care for Medicaid patients on a regular basis and I am here today as a representative [unintelligible] and to [unintelligible]. I want to address the fact that experience has shown us that the greatest cause to the psychiatric population, at least [unintelligible] associated with medication, non compliance. And the current data shows that only 41% of patients routinely take their medications as prescribed. And as a result those non adherent patients are 2 ½ times more likely to be hospitalized. Those patients who are partially adherent or are access fillers are 80% more likely to be hospitalized. Those relapsed result in multiple providers providing multiple medications and often result in some of the often kind of crazy

medication reschemes that we often see in our setting here today. In addition, medication non compliance also results in psychiatric instability that results in higher doses being required to maintain that patient outside of the hospital. And so I really encourage you to look beyond traditional cost containment measures that we typically see and recognize that medication compliance really is the key here and the use of psycho-educational interventions that focus on medication education, symptom management, weight management, understanding your illness, that those notably improve the outcomes and that these are very cost effective strategies that result in significant long term savings. I too, believe that open access to antipsychotic therapy is really a critical element and [unintelligible] quality treatment and that efficacy is what really does drive [unintelligible]. But as a practioner, daily I see the combination of therapies, which include behavioral and educational interventions, is really the key to our patient's success. Thank you.

Committee Thank you for you advocacy. Questions?

Committee Lee Woodland

Lee Woodland, NAMI Idaho – Atypical Antipsychotics

Ms. Woodland: I'm here today on behalf of the consumer [unintelligible] ask you when you are looking at the medication to [unintelligible] make sure that the people [unintelligible]. I've been with NAMI many years and this time I've seen new medications come out that have really made the lives of the consumer far better and we're just asking you that you make sure that they have the best. Thank you.

Committee Thank you very much. Thank you for the work of NAMI. We will now move to that time where we will have an open discussion with the audience present relative to clinical conclusions on the selective therapeutic classes and how would we best serve their preference for taking anything in specific order. You have heard a lot of information. And based with the decision of looking at the specifics as we usually do when we take a drug class is there any one of these that stands out as being any efficacious than another. Realizing that the spectrum of mood and thought disorders for which these drugs are used is a pretty broad spectrum. So it is hard to talk in generalities relative to the range of disorders from major depressive disorder to manic depressive disorder to schizophrenia and then to those non schizophrenic psychotic disorders that may or may not be associated with the previous two that I mentioned, major depressive disorder, bipolar disorder or not otherwise specified, if you will, psychotic disorders that can occur particularly in late life. So who wants to begin?

Audience Member For me I would like to have Dr. Pines help me make sense of this mismash of data that I got and a specific question for me that was not addressed is, Is there significant individual variability in response to difference agents? Dr. Pines perspective on the data that we got because this is his field but again the argument that I heard from all of the stuff that came, the written comment before, but then the testimony today is we need to have all these available and ask him do people respond to one specific one and not another one which would be the main reason to me why we would need to have them all available.

Dr. Pines I think, first of all just going through this data, I'm not really impressed with a lot of the evidence based information, I don't think there is a lot here. The point that I was trying to make when we spoke with the pharmacist on the phone was that a lot of these studies are rated either fair or poor and there is not a lot out there that is giving me as a practicing psychiatrist [unintelligible] already know. A couple of studies have shown one drug be superior in certain cases but there is nothing in here that just strikes me as being really impressive of any of this research. And I think there is a lot lacking in this area in terms of research just like in a lot of the other drug classed we've looked at, it's kind of disappointing that there aren't more head to head trials of these different medications and more data on long term usage and on switching

medications and on dosing. From a practical clinical standpoint I use, as a child psychologist, I use all five of the medicines except for Closeril and Closipine, Closipine I just don't use in children, I've probably used it twice. Just because of the risk and the [unintelligible]sytosis and the frequent blood draws. So I don't have a lot of experience with Closipine. The other five medicines I use, some more than others in certain situations, it is kind of based on my own clinical experience and comfort with the different medications in terms of which one I am going to choose, but I, as a practicing psychiatrist would like to have all five available, or all six I guess available based on the type of patient and the presenting symptoms, I'm not going to get into details of why I choose one over the other, I'm just saying that I use all five of them. The thing that I have concern about is seeing medicines dosed inappropriately and in very high doses in terms of multiple antipsychotics being used at the same time. I reviewed some the information before I came today to this meeting, there is no real data out there about using two or more of these medicines at the same time that it's any better and there are probably are increased risks of side effects and things and so most of my concerns are around, how much medication is being given to a specific patient and using more than one of these medications together. I've seen kids come in on three of these all at once on doses well above what I would think is safe. And that is kind of what my interest level is on focusing on at this committee today and helping to kind of making some decisions on that. I'm not being real specific, but that's pretty much what I think.

Committee I would like to clarify something. We do not have a formulary every drug is available. So we are not limited in that any drug would be available. As far as open access, that's were we are at now and if you looked at our use of the antipsychotics were anyone of us that work here could tell you how inappropriate and inadequate and of poor quality of what is happening with the way those drugs are being used. I think we need to keep that in mind. That is what open access has done to us.

Audience Member So it may not be limiting them from a specific medication, we may need to look at indications, amounts of medication being prescribed, how many of these medications are being used at once and I don't see any data on that in the evidence based. I don't thing it is clear cut that we say we are going to approve Ziprexa and Ceraquil as the preferred agents. I think it is more complicated than that in terms of how these medicines [unintelligible] how many are being used at the same time, or what are the indications.

Audience Member I almost hear an implication that we should perhaps have a prior authorization above a certain dose or prior authorization if you have to use more than one. Is that what I'm kind of hearing?

Audience Member Anything is possible, I don't think there is ever much of an indication to use more than one at the same time unless I am cross tapering from one to the other. I do have problems with what is called with drawl disconesia which was not talked about today. We talked a lot about [unintelligible] disconesia and about this tonic reaction, but in a lot of these medications, especially in children, if they are taken for a long period of time, a year or two, couple years, three, four years, and the efficacy starts to wane and you want to switch them to another medication and you take them off the original atypical I had a lot of problems with kids having bad movement problems. Then I like to do that over a six month period verses a three week period so that I can see that there may be some time when there are two used at once. And I don't work with adults, I talked with some of adult colleges about using two at the same time and there are rare instances when maybe once in awhile they might use two of these medicines at once, but I would never do that unless I am cross tapering.

Audience Member I think kind of a follow up to what Phil was saying, how often do you change atypical antipsychotics on a patient?

Audience Member That's another thing to look at.

Audience Member Do you personally change them, does the average patient have to go through three before they find the right one?

Audience Member I tend to say, again I'm a tertiary Doc. I often get kids for the Region or the State that have failed.

Audience Member Who have already been on three before they come in.

Audience Member Who may have been on lots of medications, so my patient population is complicated and I get them and they have been on meds. already, I may have to retry a medicine, but they are probably more difficult to treat and I probably switch medicines more often because these kids are more complicated. So I often will have to go through one or two medications over a six month period of sooner if they are going to have a side effect or a problem and switch medicine.

Audience Member No one time where, this one always works pretty good it's just individual.

Audience Member I kind of look at the patient and I decide what I think is the best, where I think is the best place to start based on their constellation of symptoms. And most of the kids I treat aren't psychotic we using these for mood stabilizing agents, as treatment for extreme aggression, conduct disorder symptoms, impulse control problems and depending on that child I also look at the body. If it is an over weight kid I'm not going to use Resredol or Ziprexa, I'm going to pick something else. So I make decisions on what their body [unintelligible] before I prescribe the medication, so a lot factors.

Committee Rich, when you get these complex cases that have been on three or four antipsychotic medicines, either typical or atypical, is your impression that the trials of the medicines have been rational in terms of starting out with doses that are reasonable and gradually progressing to a maximum dose before making a switch?

Audience Member The thing that I see happening a lot is I see low doses of multiple medications being used or high doses of multiple medications. So you might start somebody on atypical X and put them on it for a couple of weeks at a low dose and instead of tytrading up the dose, another medication is added. Or I see maxing out doses on meds. getting up to 800 mgs. of Serapolen then adding another atypical verses cross tapering. So I see it from both ends of the spectrum.

Committee I think the best practice guidelines in several different formats allow for a 45 day period of time as cross over. I think most conscientious practioners accept as the one condition where two atypicals could be appropriately used at the same time. Now what do you do for conformed consent for these children for these children where, these are drugs that are effecting the pituitary function, these are growing kids, we really don't have data, what do you tell the parents?

Audience Member Well, I have a pretty exhaustive (tape ends).