Pharmacy and Therapeutics (P&T) Committee Meeting Record

Date: November 17, 2017

Time: 9:00 a.m. – 3:30 p.m. **Location:** Idaho Medicaid, 3232 Elder Street, Boise, Idaho, Conference Room D

Moderator: Phil Petersen, M.D.

Committee Members Present: Phil Petersen, MD-Chair; Tami Eide, PharmD; Christopher Streeter, MD; Andrei Rudyi, PharmD; Paul Driver, PharmD; Perry Brown, Jr., MD; Stephen Carlson, PharmD; David Agler, MD; Berk Fraser, RPh; Joseph Weatherly, DO; Jeffery Johnson, PA, PharmD; Brian Crownover, MD.

Committee Members Absent: none

Others Present: Sarah Martinez, PharmD, Magellan Health Services; Jane Gennrich, PharmD, Division of Medicaid; Clay Lord, Division of Medicaid; Ashley Fretwell, Division of Medicaid; Keshia Schneider, Division of Medicaid; Mark England, PharmD, Magellan Medicaid Administration

AGENDA ITEMS	PRESENTER	OUTCOME/ACTIONS
CALL TO ORDER	*Phil Petersen, MD*	*Dr. Petersen called the meeting to order.*
Committee Business		
➢ *Roll Call*	*Phil Petersen, MD*	Dr. Petersen completed the roll call and welcomed the P&T Committee members.
➢ *Reading of Mission and Confidentiality Statements*	*Phil Petersen, MD*	Dr. Petersen read the Mission and Confidentiality Statements.
➢ *Approval of Minutes from October 20, 2017 Meeting*	*Phil Petersen, MD*	The October 20, 2017 minutes were reviewed. The minutes were approved as submitted.
Drug Class Reviews and Committee Recommendations	*Sarah Martinez, PharmD Magellan Health Services*	**Drug Class Reviews and Committee Recommendations** Committee members were asked to base their recommendations for each drug class on the answers to the following questions: 1. Is there comparative evidence to support clinically significant differences in efficacy or effectiveness between agents? If yes, what are the differences? 2. Is there comparative evidence to support clinically significant differences in safety

		between agents? If yes, what are the differences? 3. Are there any agents that the committee feels strongly must be preferred or non-preferred? 4. Are there any recommendations for changes to PA requirements?
➢ *Otic Antibiotics*	*Sarah Martinez, PharmD*	**Otic Antibiotics** Dr. Martinez reviewed the utilization patterns of these agents. There are no new products and no recent clinical information of significance in this class. **Committee Recommendations:** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents.
➢ *Alzheimer's Agents*	*Sarah Martinez, PharmD*	**Alzheimer's Agents** Dr. Martinez reviewed the utilization patterns of these agents. There are no new products and no recent clinical information of significance in this class. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. They recommended that the Department have adequate representation of cholinesterase inhibitors and NMDA Receptor Antagonists on the preferred list.
➢ *Antihyperuricemics, oral*	*Sarah Martinez, PharmD*	**Antihyperuricemics, oral** Dr. Martinez reviewed the utilization patterns of these agents. There are no new products in this class. Dr. Martinez reported on recently released clinical guidelines for the management of acute and recurrent gout from the American College of Physicians (ACP). They recommend corticosteroids, NSAIDs, or colchicine for the treatment of acute gout with corticosteroids considered first-line therapy. They recommend not starting long-term (≥ 12 months) urate lowering therapy in most patients after an initial gout attack or in patients with infrequent attacks (< 2 attacks per year). Practitioners should consider the benefits and risks of the medication along with cost before starting therapy in patients with ≥ 2 attacks per year or those with problematic gout (e.g. tophi, chronic renal disease, urolithiasis). They reported that allopurinol (300 mg daily) and febuxostat (40 mg daily) are equally efficacious at decreasing serum urate levels and that evidence shows therapy reduces the risk for acute gout attacks after 1 year but did not reduce the risk within the first 6 months.

<table>
<tr><td></td><td></td><td>The guidelines state that prophylactic low-dose colchicine or NSAID therapy reduces the risk for acute attacks when starting urate lowering therapy and continuing prophylactic therapy for > 8 weeks was more effective than shorter durations.

The guidelines did not address pegloticase nor lesinurad claiming the medications would unlikely be prescribed by primary care prescribers.

Committee Recommendations
The Committee concluded that there is no comparative evidence to support clinically significant differences in efficacy, effectiveness, or safety between the agents affecting uric acid secretion. It was recommended that authorization of a 3-month supply of colchicine to prevent flare-ups when a secretion inhibitor such as allopurinol is first started be granted. The department will explore whether this can be auto-authorized by the adjudication system with new starts.</td></tr>
<tr><td>Public Comment Period</td><td>Phil Petersen, MD
Keshia Schneider</td><td><u>Public Comment Period</u>

No manufacturer representatives were pre-approved to provide testimony.

One person signed up to speak during the public comment period. Public testimony was received from the following speaker:

<table>
<tr><th>Speaker</th><th>Representing</th><th>Agent</th><th>Class</th></tr>
<tr><td>Robert T. Wechsler, MD</td><td>The Epilepsy Foundation and the St. Luke’s Epilepsy Center</td><td>All</td><td>Anti-convulsants</td></tr>
</table>

Testimony transcript attached.</td></tr>
<tr><td>➢ Anticonvulsants</td><td>Sarah Martinez, PharmD</td><td><u>Anticonvulsants</u>
Dr. Martinez reviewed the utilization patterns of these agents. There are no new products and no recent clinical information of significance in this class.

Dr. Martinez reported on the following product updates.
• Qudexy XR is now approved for use as prophylaxis for migraine headache in adults and adolescents 12 years of age and older.
• Trokendi XR is now approved for the treatment of migraine headache in adults and</td></tr>
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		adolescents 12 years of age and older. • GlaxoSmithKline has made a business decision to remove Potiga from the market. • Fycompa is now approved as monotherapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 12 years of age and older. • Aptiom is now approved for the treatment of partial-onset seizures in pediatric patients, ages 4-17 years old. Pediatric dosing is weight-based and taken once daily. • Briviact is now approved as monotherapy for partial-onset seizures in patients 16 years of age or older. The recommended dosage is the same when used for mono- or combination therapies. Dr. Martinez reported on the International League Against Epilepsy (ILAE) revised seizure classifications. The new classification is based on 3 key features: seizure origin in the brain, level of awareness during the seizure, and other seizure features. Generalized seizures were previously called primary generalized. Focal onset seizures may or may not affect awareness, and are further broken down as "aware" and "impaired awareness." The classification system also describes movement and other symptoms and applies to generalized, focal and unknown onset seizures. A seizure is described as non-motor if other symptoms, such as changes in sensation, emotions, and thinking occur. The generalized tonic-clonic seizure term is still used to describe seizures with stiffening (tonic) and jerking (clonic). Terms the ILAE no longer uses include: complex partial, simple partial, partial, psychic, dyscognitive, and secondarily generalized tonic-clonic. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents within the indications of epilepsy or pain and mood disorders. They recommended that if current preferred agents went to non-preferred status that patients be grandfathered and criteria should not exceed one failure for most agents if designated non-preferred. The committee recommended that the Department explore the feasibility of allowing coverage of injectable midazolam for intranasal administration as a rescue medicine. Risk evaluation of diversion was recommended as part of that evaluation.

➢ *Antipsychotics, Atypical*	*Sarah Martinez, PharmD*	**Antipsychotics, Atypical** Dr. Martinez reviewed the utilization patterns of these agents. There are no new products in this class. Dr. Martinez reported the following product updates: • Saphris is now indicated for maintenance monotherapy in adults with bipolar I disorder (previously indicated for schizophrenia, acute bipolar I disorder). • Latuda is now indicated for use in adolescents ≥ 13 years for the treatment of schizophrenia (previously indicated for schizophrenia and bipolar depression in adults only). • There was a class wide labeling revision to include a warning that antipsychotics may cause somnolence, postural hypotension and motor/sensory instability which can lead to falls. • The FDA has approved a new formulation of Aristada (1,064 mg suspension in a single-use prefilled syringe) for every 2-month intramuscular administration for the treatment of schizophrenia. • The FDA has approved Abilify Maintena for maintenance monotherapy of bipolar I disorder in adults. The recommended maintenance dose is 400 mg IM once monthly (no sooner than 26 days after last dose). Tolerability to oral aripiprazole should be established prior to initiating Abilify Maintena. **Committee Recommendations** The committee concluded that the evidence did not support significant differences in efficacy or effectiveness between the agents. They noted that there were differences in safety specifically with olanzapine. They noted that having agents preferred that were indicated for both schizophrenia and bipolar was useful. They noted that Aristada and long-acting injectables in general removed barriers to long-term compliance and should be preferred unless cost prohibitive. The committee recommended that Zyprexa Relprev remain non-preferred due to safety concerns.
➢ *Antipsychotics, Typical*	*Sarah Martinez, PharmD*	**Antipsychotics, Typical** Dr. Martinez reviewed the utilization patterns of these agents. There are no new products and no recent clinical information of significance in this class. **Committee Recommendations** The committee requested additional data on this class, specifically to see how many patients

		are using these short-term vs those who have been stable on them long-term. They would like to see how many are being used for other indications outside of psychosis. The committee concluded that the evidence did not support differences in efficacy, or effectiveness. They did conclude there were difference in safety between the agents based on high versus low potency subclasses.
➢ *Stimulants and Related Agents*	*Sarah Martinez, PharmD*	**Stimulants and Related Agents** Dr. Martinez reported on new products and formulations in this class. Cotempla XR-ODT (metylphenidate) is approved for the treatment of ADHD in pediatric patients 6 to 17 years of age. She reviewed the dosing, contraindications, warnings and adverse reactions which are similar to other available methylphenidate products. Mydayis (mixed amphetamine salts) is approved for the treatment of ADHD in patients 13 years of age and older. She reviewed dosing, contraindications, warnings and adverse reactions which are similar to other amphetamine products in the class. Dr. Martinez reported on the following product updates: • Vyvanse now available as a chewable tablet that may be substituted on a milligram per milligram basis with the already approved capsule formulation • All strengths of Metadate CD have been discontinued by the manufacturer • Strattera is now available generically as atomoxetine. • Methylin chewable tablets have been discontinued by the manufacturer, but are available as generic methylphenidate chewable tablets. **Committee Recommendations** The committee concluded that there was no evidence of differences in efficacy or effectiveness between the stimulants. Some of the committee members related that they had clinically found methylphenidate to be better tolerated than amphetamine based products in their individual patient base. The committee recommended making the age range for both methylphenidate, dexmethylphenidate and mixed amphetamine salts the same. The committee concluded that there was no difference in efficacy, effectiveness or safety between the non-stimulant ADHD drugs and similarly no differences between the narcolepsy-specific agents.
➢ *Sedative Hypnotics*	*Sarah Martinez, PharmD*	**Sedative Hypnotics** Dr. Martinez reviewed the utilization patterns of these agents. There are no new products and no recent clinical information of significance in this class. Dr. Martinez reported on the recently issued guidance from the American Academy of Sleep

		Medicine (AASM) on pharmacologic therapy of chronic insomnia in adults. Cognitive behavioral therapy (CBT) continues to be the first line recommendation. If patients do not respond to CBT, AASM recommends (strength of recommendation is weak) 8 drugs for sleep onset and/or maintenance (doxepin, eszopiclone, ramelteon, suvorexant, temazepam, triazolam, zaleplon, zolpidem). Diphenhydramine, melatonin, tiagabine, trazodone and others are not recommended. She also reported that the American College of Physicians (ACP) released 2016 clinical practice guidelines on the management of chronic insomnia disorder in adults. Their guidelines state that the FDA has approved medications for short-term use (4 to 5 weeks), and patients should not continue taking them for extended periods of time. Patients should be further evaluated if insomnia does not remit within 7 to 10 days of treatment. **Committee Recommendations** The committee concluded that there was not comparative evidence showing differences in efficacy, effectiveness or safety among the agents. They recommended actions emphasizing appropriate use for maximum therapeutic effect and safety over PDL choice. Suggestions included limiting the first prescription to 14 days with no refill; monthly limit so not taking every night; limits on concurrent opioid use and an educational letter on appropriate use. They recommended preferring non-controlled agents over controlled agents and listing doxepin 10 mg as a preferred alternative.
➢ *Anti-Parkinson's Agents/Restless Leg Syndrome*	*Sarah Martinez, PharmD*	**<u>Anti-Parkinson's Agents/Restless Leg Syndrome</u>** Dr. Martinez reported on a new product in this class, Xadago (safinamide) which is indicated as an adjunct to levodopa/carbidopa in patients with Parkinson's disease experiencing 'off' episodes. Dr. Martinez review contraindications, dosing, adverse effects and drugs interactions as well as clinical trials for approval. She reported that Azilect is now available generically (rasagiline). **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents within the subclasses. They recommended that the COMT inhibitors as add-on therapy be non-preferred.
➢ *NSAIDs*	*Sarah Martinez, PharmD*	**<u>NSAIDs</u>** Dr. Martinez reviewed the utilization patterns of these agents. There are no new products in this class. Dr. Martinez reviewed updated guidance from the American College of Physicians (ACP).

		They recommend non-pharmacological therapy (e.g., heat, massage) as first line treatment of acute/subacute low back pain lasting 12 weeks or less. NSAIDs or skeletal muscle relaxants may be used but acetaminophen is no longer recommended. For chronic pain, first-line therapy is also non-pharmacological. NSAIDs may be added if needed, then tramadol or duloxetine. Opioids should only be considered if prior therapy fails and potential benefits outweigh risks. She reported that labeling was updated to add a warning against substituting Duexis with the single-ingredient components. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. It was recommended that the department consider expanding the indications of diclofenac topical preparations to help limit use of opioids.
➢ *Pain, Other*	*Sarah Martinez, PharmD*	**Pain, Other** Dr. Martinez reviewed the utilization patterns of these agents. There are no new products in this class. Dr. Martinez reported that the American Diabetes Association (ADA) has updated their 2005 position statement on prevention, treatment and management of diabetic neuropathy. Pregabalin or duloxetine are recommended as initial therapy for the treatment of pain. Gabapentin is also recommended in select patients. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. The committee recommended easing restrictions and opening up access of these agents if financially feasible with the goal of making them alternatives before prescribing opioids.
➢ *Colony Stimulating Factors*	*Sarah Martinez, PharmD*	**Colony Stimulating Factors** Dr. Martinez reviewed the utilization patterns of these agents. There are no new products and no recent clinical information of significance in this class. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents.

➢ *Erythropoiesis Stimulating Proteins*	*Sarah Martinez, PharmD*	**Erythropoiesis Stimulating Proteins** Dr. Martinez reviewed the utilization patterns of these agents. There are no new products in this class. She reported that REMS requirements had been eliminated for Aranesp, Epogen and Procrit when used in cancer patients. Prescribers and hospitals no longer need to be certified to prescribe and/or dispense to patients with cancer. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents.
Second-generation Antidepressants	*Gerald Gartlehner, MD, MPH* *Pacific Northwest Evidence-based Practice Center*	**Second-generation Antidepressants** Dr. Gartlehner of the Pacific Northwest Evidence-based Practice Center reported via conference call on the DERP targeted evidence review on levomilnacipran, vilazodone, and vortioxetine compared to other second-generation antidepressants. He reported the following from the systematic evidence review. • For major depressive disorder, there were no eligible studies for most direct comparisons of the drugs with one another or with other second-generation antidepressants (SGAs). Based on network meta-analyses, there were similar response rates between the drugs and other SGAs. • There was no eligible evidence on quality of life, hospitalizations, time to onset of efficacy, and prevention of relapse and recurrence. • For general anxiety disorder based on one randomized control trail with a rating of low strength of evidence, there were numerically lower response and remission rates for vortioxetine than duloxetine. • Vilazodone and citalopram had similar risks for adverse events and overall discontinuation. • Vortioxetine led to similar risks of overall adverse events as duloxetine and venlafaxine. • There were similar overall discontinuation rates between vortioxetine and duloxetine or venlafaxine XR. • There were no eligible studies that assessed differences in subgroups.
➢ *Antidepressants, Other*	*Sarah Martinez, PharmD*	**Antidepressants, Other** Dr. Martinez reviewed the utilization patterns of these agents. There are no new products and no recent clinical information of significance in this class. She reported that Pristiq is now available generically.

		Committee Recommendations The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. They specifically pointed out that the newer agents had little advantages over currently available agents.
➢ *Antidepressants, SSRI*	*Sarah Martinez, PharmD*	**<u>Antidepressants, SSRI</u>** Dr. Martinez reviewed the utilization patterns of these agents. There are no new products and no recent clinical information of significance in this class. **Committee Recommendations** The committee concluded that evidence did not support difference in efficacy or effectiveness. They did conclude that paroxetine had more safety issues particularly with anti-cholinergic adverse effects and should be non-preferred. They recommended grandfathering current paroxetine users.

Summary Review Benzodiazepines	*Mariam McDonagh, PharmD*
	Pacific Northwest Evidence-based Practice Center
		Summary Review Benzodiazepines
		Dr. McDonagh presented the DERP summary review of benzodiazepines via conference call. This is the first time for this evidence review.
		
		The conclusions from the evidence review were:
		
		• For short-term use of 2 to 8 weeks (no long-term studies met inclusion criteria)
		  ○ Benzodiazepines had similar efficacy to antidepressants in generalized anxiety disorder
		  ○ Older benzodiazepines showed no difference to typical antipsychotics for schizophrenia
		  ○ Alprazolam has less efficacy than antidepressants in patients with depression
		  ○ Temazepam was no different than placebo for patients at risk for post-traumatic stress disorder
		  ○ Benzodiazepines resulted in fewer panic attacks or better response than antidepressants (most studies were with tricyclic antidepressants)
		  ○ Benzodiazepines had lower rates of study discontinuation or adverse events
		• Evidence for concurrent use with opioids was limited, but indicated increased risk of mortality with methadone.
		• Evidence on tapering benzodiazepines

		○ While any intervention was better than usual care, tapering in combination with another intervention was most effective. ○ Abrupt medication substitution was inferior. ○ Dose and duration did not affect success. ○ Withdrawal symptoms were common, but not serious.
➢ *Benzodiazepines*	*Sarah Martinez, PharmD*	**Benzodiazepines** This is the first time this class has been reviewed. There was no recent information of significance to report on. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. The committee had concerns about the safety and inappropriate use of this drug class in general. They recommended that all benzodiazepines be non-preferred and the non-benzodiazepine anxiolytic buspirone be preferred. The exception would be those specifically indicated for seizure disorders and in some cancer patients. The committee recommended using interventions similar to those currently being used for opioids. Initially they recommend a limit duration of 14 days for initial prescriptions with no refill followed by hard stops at point of sale when given concurrently with opioids. They suggested targeting people at high risk first with interventional educational provider letter including information on treatment of choice being a SSRI or SNRI for generalized anxiety disorder. The Drug Utilization Review Board will continue to gather utilization data and present findings at future P&T meetings.
➢ *Movement Disorders*	*Sarah Martinez, PharmD*	**Movement Disorders** This is the first time this drug class has been reviewed. Dr. Martinez discussed the indication of these drugs for chorea associated with Huntington's disease and tardive dyskinesia and reviewed those conditions. She discussed contraindications, adverse effects and drug interaction potential of the individual agents. She also discussed mechanism of action and the specific dosing of each agent as well as available clinical trial information. Dr. Gennrich reviewed proposed criteria for each agent. **Committee Recommendations** The committee concluded that the evidence did not support differences in efficacy, effectiveness or safety between the agents. They recommended implementing the proposed criteria with a suggested change to a more specific movement disorder scoring system.
Other Committee Business	*Tami Eide, PharmD*	**Other Committee Business** The meeting adjourned at 3:17 PM. Next meeting will be on April 20, 2018.

Pharmacy and Therapeutics Committee Meeting
Public Comment

Dr. Robert T. Wechsler

Thank you very much and thank you for the opportunity to speak. Who am I? I'm a neurologist. I specialize in Epilepsy. I founded the Epilepsy Center at Saint Luke's about 12 years ago, but I'm still in private practice. Within my practice, I do a lot of clinical trial work. I've been an investigator on most of the epilepsy studies that have been done in the last 10 or 12 years. I'm also very involved with the Epilepsy Foundation of Idaho. I'm board president of that organization. So, for anyone that's wondering, I absolutely work with companies. I work with all of them, and I'm not representing any one of them when I come talk to you guys, which I try to do as often as I can. What I am representing is the Epilepsy Center and the epilepsy patients. Epilepsy is super common, it's one out of twenty-six people will get a diagnosis of epilepsy at some point in their life. One out of ten people will have a seizure at some point in their life. I actually really was interested hearing you guys talk about some of these other conditions because all I ever think about is epilepsy and I think one of the challenges that folks like yourselves will face dealing with medications for epilepsy is that it's not one condition, really. It's really kind of a family of conditions that have the final, or common feature, of seizures, and broadly we divide them into the genetically-determined, generalized epilepsies and the focal-localization related epilepsies. And that makes it very difficult because we have twenty-four molecules that we can use in the treatment of epilepsy. About 2/3 of them are reasonable medications that we might commonly prescribe. We have very little head to head data just to point to one as superior to another, with very few exceptions. And what works for one person might be the very worst thing for the very next person. We have a number of medications that are approved that will actually make generalized seizures worse, but can help focal seizures. So, it makes a challenge for how you sort these things. I like to organize the medications into kind of three generations. The literature still talks about 2 generations, but I'll tell you how I justify it.

The first generation is everything that came out before 1982, and they were all drugs that were discovered through serendipity and have a lot of potential long-term health consequences and are falling out of favor more and more. Phenytoin is still commonly prescribed in the United States, but in the rest of the world it's really not used very much. The second generation of drugs are the ones that came out in the 90's most of which are now available as generics, and they were born of investigations in animal models of epilepsy, but again a lot of serendipity in there, not a lot of thought about mechanism of action, and some of them, when they got approved, we had no idea how they actually worked. What I like to think of as the third generation of drugs are the drugs that have

come out in the last, oh, 10-15 years for the most part, where there's been a little bit more of a rational approach. Send the scientist into the laboratory with a specific goal in mind. Sometimes that goal is come up with a better variation of an existing theme. You know, I like this mechanism of action, but bring me a molecule that has a higher binding affinity for the target, or I like this mechanism of action, but let's find a way to get the terminal metabolite into a pill rather than the pro drug, basically. What I can you tell you is that while we have very little comparative data, as I said, the newer drugs by and large tend to have pretty decent tolerability, and I think that's one of the big advantages of some of the newer products. And I also am excited when something comes out that has a legitimate new mechanism of action because… I tell people all the time, in treatment of hyper-tension you never try two beta-blockers in combination when one failed. So, why would it make sense that in epilepsy you're going to try two sodium channel drugs together? So, obviously that's where the most excitement is with the epilepsy drugs. You guys run into issues with particularly the brand name drugs, the newer drugs. We've got a few that are still brand name in epilepsy that generate a lot of concern about cost. And 2017 is an interesting year because it's the year of extrapolation. Someone showed me a cute cartoon that said, 'there's two types of people. Number one, those who can extrapolate from an incomplete data set. So, the FDA has come to recognize it's an undue hardship on the industry and it delays time to access to therapies for patients when we're forced into doing studies for which we can probably predict the outcome. And so, we have four brand name drugs for which the indications have changed in the last year based on extrapolation of data. For eslicarbazepine acetate (Aptiom) and for lacosamide (Vimpat), they're now approved in pediatric use based on extrapolation from the adult studies. And for perampanel (Fycompa) and for brivaracetam or Briviact, we now have indication for monotherapy use based on extrapolation from the adjunctive studies.

Those of you who know me, I prescribe a lot of these drugs because you know in 2005 when I came to Boise, I was the only one prescribing levetiracetam and I looked so smart. And now everyone prescribes levetiracetam and I get to figure out what to do next when levetiracetam doesn't work. So, I have a pretty good familiarity with these products. I think they all have their place. And I do appreciate the access to them and being able to use them as I see fit because, gosh, if I could give you a list of five drugs that would be, that would work for just about everyone and that ought to be tried before the next thing gets tried, I would do that, but… that's just not the case. There's too many different versions of epilepsy so we need broad access to medications to be able to make people better. We can get them seizure free 70% of the time with medication. So, I appreciate the access and I'd be happy to answer any questions, if anybody has any questions about epilepsy or about any individual products.

Dr. Peterson: "Are there any agents that you think are unsafe enough that barriers should be put in place?"

Dr. Weschler: You know, I think a lot of the barriers are already there. GSK ended up pulling Potiga off the market due to safety concerns. I actually had a few patients doing great with it, and I thought that was probably them choosing to leave the disease state rather than do the hard work of monitoring the safety. Vigabatrin is very difficult to prescribe because you got to track the vision

outcomes, but that's regulated already so that's not difficult to do. Beyond that we haven't seen much in the way of safety signals, you know. I've used a lot of lacosamide in my practice. They're up to 600,000 exposures world wide. No signal of safety has emerged. Perampanel just hit their 100,000 exposures, which, at least in neurology, 100,000 exposures is the magic number for, 'this might be an okay drug to use more broadly'. So, yeah, I can't think of any specific drug that I have safety concerns about that would require special barriers.

Dr. Carlson: "Is there a mechanism of action that has more than two medications in it that is not represented on the first list?"

Dr. Weschler: You know, off the top of my head I don't know what your first list is. I tell everybody, my job is to figure out what's best for the patient, my office staff's job is to make it happen. And so, I don't keep track of that very much. We certainly have several families of drugs where there's a shared mechanism, right. So, the sodium channel drugs are a great example. I think lacosamide is a little bit of a different sodium channel drug in that it enhances the slow inactivation of voltage gated sodium channels. All the other sodium channel drugs tend to enhance the fast inactivation of the channel. Within that family, if you cornered me at a party and said, 'If you had to put your kids on one of those drugs, which one would you pick?', I would actually pick eslicarbazepine over oxcarbazepine and carbamazepine and phenytoin, just from a tolerability standpoint. And again, they don't have comparative data, but I've treated a lot of patients. From the standpoint of, and, within that family also lamotrigine is kind of a distant cousin in that family because it has some mixed mechanisms, but that's definitely one of them. And it has some added benefits in terms of mood stabilization, so it's one we use a lot. Within the, you know, levetiracetam is the go to for everybody these days out of the ER and now there's brivaracetam, and everyone says, 'Do we really need another SV2A drug?', and I point back to my primary [cough] and I say, would you be satisfied if I limited you to just one beta-blocker? My best guess is that levetiracetam and brivaracetam have the same mechanism, but slightly different binding sites. The reason I say that, is in the first two studies they did, they allowed levetiracetam as a background drug, and the combination had no added benefits so it's actually in their label for brivaracetam that you shouldn't use it in combination with levetiracetam, there's no added benefit. But in the third study, the one that I was an investigator in, they excluded levetiracetam from the list of background drugs, but a past lev-failure was allowed. More than half the patients were past lev-failures, and lev-failure did not predict briv-failure. So, what I'm assuming is they must be binding to the same target if putting the two together doesn't make any additional benefit, but if one can work where the other has failed, then they're not 100% identical either. So, with that molecule or with that mechanism, I think there's a role for both. In an ideal world, I'd like to see at least one drug from every mechanism included in, on a short list. I've been using a lot of perampanel because it's the only AMPA receptor blocker we've got in the epilepsy world. The sodium channel area is the one where we have the most drugs that share a mechanism. Benzos is the other one. I use a lot of clobazam, as you guys may have noticed. I was actually involved in a retrospective study that was sponsored by the company, but it was initiated by a colleague of mine at University of Wisconsin, looking for any evidence of tolerance to the effect of clobazam and the open label extension study of the Lennox-Gastaut program, and after two years we didn't see any dose

creep up or increase in seizures or increase in the use of dose or number of background medications. So, the conclusion of that review was that perhaps it's not as prone to tolerance as some of the other benzos historically have been thought to be. Although, interestingly, when we looked into the literature to find evidence of tolerance with benzos, what we got was while everyone knows that benzos cause tolerance, but not a lot of actual science to prove it. So, I do like that benzo ahead of the others if I can get it. Not really any other specific comparisons.

Dr. Driver: "Of the newer agents, is there any signals of any cognitive type of issues in kids?"

Dr. Weschler: Not as far as we know. As far as, so we've got the –

Dr. Driver: "Newer' meaning in the past 15 years."

Dr. Weschler: Yeah, so obviously we have less data because they've not been around as long. Let's see, with perampanel, I can tell you that their pivotal trials went down to age 12 and they're up to 100,000. There's not been any reports of anything like that. With eslicarbazepine, I doubt that there will be such a signal because it's, actually from a mechanism of action and efficacy standpoint, but I think it's pretty similar to oxcarbazepine. I think the tolerability is maybe a little but better with escli, but it's really, they both end up in the same metabolite. And lacosamide, again, lacosamide is going generic next year in Europe, to 600,000 exposures. There's not been a signal for any cognitive concerns in kids.

Dr. Driver: "So for kids, then, it would be you have no preference other than tolerability?"

Dr. Weschler: I think it really comes down to tolerability, comorbidities, what mechanisms that maybe tried and failed, and drug interactions. And the other thing for me that's really important, I think, is how quickly we can start a drug. You know, there was an expert consensus on antiepileptic drugs published a couple of years ago, and one of the drugs that was listed as the "preferred" for first-line was lamotrigine. Which I thought was just nutty, I'm not sure who these experts were that they interviewed; I didn't get the survey. But lamotrigine takes two to three months to titrate up. I think it's a great second-line drug because it has its definite advantages, but you're limited in how fast you can titrate it because of the rash. And so, I would not think of it as a first-line drug if it's going to take me weeks or a couple of months to get to a therapeutic dose, right? So, from that standpoint, that's why I think you see a lot of utilization of levetiracetam, lacosamide, because you can get started quickly and because it's available in IV form. That always helps. I tease the ER physicians that even if something has a peak plasma of an hour after oral dose they still use the IV because it makes them feel better that they were able to inject something. And they typically will chuckle and go, "Okay, yeah, that's true." So, for me an important feature is to look at how long it takes to get to at least a minimum therapeutic dose. And even with

something that we would typically do a slow titration like perampanel, you're still looking at being able to achieve a therapeutic does within a couple of week. Whereas with topiramate, zonisamide, lamotrigine, I'm looking at you know, 6 to 8 weeks to get to a therapeutic dose in most cases.

Dr. Eide: "When I look at our utilization, we still have a high use of phenytoin. Do you think that's just waiting until these people age out type of thing or are people still starting people on phenytoin?"

Dr. Weschler: You know, I am fascinated by the whole phenytoin thing. If any of you have ever seen me speak, I quote C. Everett Koop, who once said, "The medicines don't work in the people who don't take them", and I have a corollary to Dr. Koop's rule which is that the medicines don't work if the doctors don't prescribe them. And I use that as, and I talk about market share… over the years I've gotten people at various companies to share with me some of the market share data that they're not supposed to show me and I've kind of made some graphics about it. It's looking like phenytoin utilization is definitely dropping, but it's still in the top 3 or the top 5% of prescribed drugs in the United States by market share depending on where you get your data. I think a lot of that is either primary care or older physicians who, that's still what they're comfy with, and they… I ran into a physician in the hallway at Saint Luke's. He said, "Oh I just tried someone on that new drug Keppra – works really good!" This was just two years ago, so I think there's definitely an element of that. I think, interestingly, even though the textbooks will say, if they're seizure free for a couple of years and the EEG looks normal, it's okay to stop coming off medicine and see what happens. In Idaho, we have a lot of patients who chose not to do that because of the potential associated driving restriction. Not that we have a law, it's whatever the doctor says, but everyone's dependent on cars for transportation here and so the prospect of having to refrain from driving for 3 months in a deal breaker. They'd rather stay on their medicine. So, I think that might be part of it. I got one of our local pharmaceutical people to show me prescribing data for physicians in Idaho, and the top prescribing neurologist of phenytoin in Idaho will look you in the eye and tell you that he never prescribes it. And I don't know if he just doesn't realize it's kind of auto-refills being generated by his office or if he's just not comfy sharing the fact that he still uses it. So, it's dropping off, it is, but I think everyone runs to it because it's what they learn in their training. I was on the phone with the emergency room the other day and they said, "I've got this patient being followed by Dr. Kashirny. He's in here with a bunch of seizures and they're on levetiracetam and we gave him some lorazepam and they're still having seizures so I'm going to load him with fosphenytoin." And I said, "Well, why not load him with the drug they're already on? Maybe they missed some doses. Why not give them a couple of grams of levetiracetam and then see if you need to go to something else? And if you need to go to something else, why would you go to phenytoin?"

Dr. Driver: "Well there is a protocol up in my area, Northern Idaho, I can't remember if it comes from Spokane or Seattle, but the ER Docs are being recommended to use fosphenytoin."

Dr. Weschler: Worst thing that ever happened to status epilepticus management was when Dave Triman published his VA cooperative study on status epilepticus because before we had that study, it was a little bit of a free for all, you could use your clinical judgement. Now everyone points to the Triman study and says, well, this is what we should do. And all the seizure emergency protocols are derived from that. In that study, he had four arms; he had phenobarbital, he had benzo, he had a benzo followed by phenytoin, he had phenytoin alone. And of the four arms, the benzo followed by phenobarbital did slightly better than the other three arms. And that's where, where all of our seizure emergency protocols are born. You start with a benzo, and if that doesn't work you go to phenytoin.

Dr. Driver: "This protocol's actually recommending that they use fosphenytoin?"

Dr. Weschler: One of my favorite references that I point people to from a couple of years ago, there's this, Thomas Bleck, is a neurocritical care guy back East, and he published a review in a journal called Continuum, which is the CME journal of the Academy of Neurology. Read the book and fill out the questionnaire, and you get your CME. He did this great review of the newer antiepileptic drugs and he said, if they're used correctly, they're just as effective as phenytoin in seizure emergencies. The problem is that they're not used correctly because we don't have guidelines and people get nervous. So, when an ER physician tells me they're going to load levetiracetam and I ask, "How much are you going to give?" Invariably, invariably they'll say a gram and I'll say, "Why?" The answer is, "because that's what we do when we load phenytoin." Which doesn't make sense, but that's way they come to that dose, right? So, what Dr. Bleck's review article said is levetiracetam can work in those seizure emergencies if you load 3 or 4 grams, but that's not what people are doing. Same thing with lacosamide. When I'm on call at Saint Luke's and I'm dealing with seizure emergencies, I still go to a benzo first. I typically will follow it up with IV lev- or IV lacosamide, and with lacosamide, if you load 3-400 milligrams, it'll be just as, you'll have just as much success. Problem is, people get nervous because they're not as comfy with it so they'll load 100, and of course that's not, you know, it's not going to be as effective. We under dose the benzos too, by the way. Triman's recommendation for status was 0.1 milligrams per kilogram for, for lorazepam. Alright, so the average 70 kilo person, we're talking 7mg of lorazepam to stop the status. What do we do, typically? What do our ERs do? "I gave them – we gave them one. When they were still seizing we gave them another 0.5mg." You know, they're dripping it in, and it's not working effectively.

So, I think that we're not likely to have real comparative data on the antiepileptic drugs in seizure emergencies anytime soon. What I point out to people is, it's not just, I mean, yeah, we want to stop the seizures, right? But above and beyond stopping those seizures, we want to have the patient recover quickly. Right? So, in that protocol, it typically says you do 20mg per kilogram of fosphenytoin after the benzo, and if that doesn't work, you can give another 10mg per kilo, and if that doesn't work, you should go to a pentobarb coma. Well, but if you're going to go to the barbs for coma, your patient's going to be in the ICU for a heck of a long time after you've stopped the seizures, right? So, a lot of use are now going to, to midazolam or, if they're well into their seizures, then the benzos are probably not doing much anymore, maybe do propofol. More and more I've been using ketamine.

Dr. Driver: "We've used that too."

Dr. Weschler: And, and there's some good anecdotal evidence that might be a good way to go. But, gosh, I haven't, I've gotten a pretty good reputation over the last 12 years of being the go-to guy for seizures. I've helped out a lot of people. I haven't had a lot of catastrophes. And I've not used fosphenytoin. I can't tell you the last time I used it in a seizure emergency and I haven't prescribed phenytoin in the outpatient clinic… I think I have one patient who's on it who refuses to come off.

Dr. Crownover: "You mentioned that Aptiom would be your preferred sodium channel agent, but it's roughly, even best coupon price, 20 times the cost of Trileptal. One, why would you say Aptiom is preferred, and two, do you think it's worth the extra "

Dr. Weschler: You know, I think that if they're really in need of that mechanism, I think it has an advantage in tolerability. They did a tiny little study, and I don't know how they found patients for this, they did a study where they had in-dwelling LP catheters in patients and they gave them oxcarbazepine, because remember with Aptiom we're talking about eslicarbazepine acetate first pass metabolism you get eslicarb, right, which is half of the monohydroxy derivative of oxcarb. So, when you're doing oxcarb, you're mostly getting, eventually, once oxcarb gets metabolized, what you've got is a mix of eslicarbazepine and R-licarbazepine. So, they gave people oxcarbazepine, eslicarbazepine and arlicarbazepine, and they measured their serum levels and their CSF levels at various points after normal dose. And with oxcarb, they got an oxcarb peak about an hour or two after normal dose, which coincides of when you get the side effects. The best example I have for this side effect, I hired a number of my patients. My PA has temp lobe epilepsy and when I hired her, when she moved back to Boise, she was on oxcarb. And this is a pearl that I got from her. When she started working for me, her seizures were controlled, but she'd wait until she got to work to take her morning medicine and with oxcarb she's taking it twice a day. And I said, "That's fine, but just out of curiosity, why?" And she said, "Well, if I take my oxcarb first thing in the morning, I get diplopia so bad that I can't drive to work, but I can deal with the diplopia when I'm seeing patients." And I thought, what a terrible way to have to live your life every day, right? I have a colleague who's had a mid-level diplopia that's fantastic, she can see twice as many patients.

So, I think that, that aspect… I used to say quality of life. Now you have official quality of life measures and everyone gets all nervous if you say 'quality of life' without having data on quality of life. These patients, when they're seizure free, and 70% of them are seizure free without medication, they have to get up every day and go to work or go to school in the morning, right? If they can be on a drug that has a long half-life where they can take it all at night and get the worst of the dose-dependent side effects while they're in bed, then they can get up and go to work, go to school without those issues, that's a huge up for that patient, right? So, I'm not as skeptical as the extended release products as some of my colleagues in the academic world are because of that. So, I think with not

getting the CSF peak of oxcarb, the cone size with when people get their dizziness and diplopia with oxcarb, I have a little bit of evidence, science, that says that this might be a better tolerated product. I certainly have a lot of patients that tell me it's a better tolerated product. And the fact that it has that longer half-life and it's legitimately a once-a-day drug that you can give in the evenings is a big plus.

Dr. Peterson: "Any other questions? I think you've talked more than any guest speaker in a long time."

Dr. Weschler: Well, and I appreciate it because you know if you didn't have a big hook to pull me off of here we could talk epilepsy all day. But I just want to thank you guys for the opportunity to speak and for the collaborative relationship that we've had these 12 years. It's been fantastic and from the standpoint of my patients I want to thank you.

Dr. Peterson: "Thank you."