

# MedPAC Backs Bundled Pay for Hospitalizations

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WASHINGTON — The Medicare Payment Advisory Commission has given its backing to bundling payment for hospitalization, which would essentially give hospitals and physicians an incentive to control costs and avoid readmissions.

At its April meeting, the commission (MedPAC) unanimously voted to include a bundling recommendation in its June

report to Congress. As a first step, physicians and hospitals should be required to report to the Centers for Medicare and Medicaid Services (CMS) on resource use and readmissions during an “episode of care,” which is proposed to include the first 30 days post hospitalization. The data would be confidential initially, but by the third year, should be made public, MedPAC commissioners recommended.

Once the resource and readmission data are in hand, CMS should start adjusting payment to hospitals, according to the recommendation. There would be the possibility for gain-sharing among hospitals and physicians. The commissioners also voted to direct CMS to study the feasibility of “virtual”

bundling. With virtual bundling, the payment would be adjusted based on aggregate use of services over an entire episode of care.

Finally, MedPAC voted to recommend that CMS create a voluntary pilot to test

share in any savings, according to MedPAC staff.

The pilot represents Medicare’s ultimate goal—making bundled payments, said MedPAC chairman Glenn Hackbarth who is a health care consultant in Bend, Ore.

The data collection and adjusting payment based on readmission are interim steps aimed at getting providers to collaborate to improve care and cut costs, said Mr. Hackbarth.

Commissioner Ronald Castellanos, a urologist in private practice in Fort Myers, Fla., said he thought it would take 5 or 10 years to make collaboration work, but that he agreed that it was the ultimate end point. ■

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## LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%), Anorgasmia (2% and <1%). \*Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo  $\geq$  Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflamed injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=225 Lexapro; N=188 placebo). †Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). **TABLE 3: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder\* (Lexapro (N=225) and Placebo (N=188))**

**Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%). **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder† (14% and 2%); Anorgasmia‡ (6% and <1%); Menstrual Disorder (2% and 1%). \*Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo  $\geq$  Lexapro: inflamed injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). †Denominator used was for females only (N=477 Lexapro; N=222 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of  $\geq 5\%$  in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the incidence of common adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (66%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4: Incidence of Common Adverse Events\* in Patients with Major Depressive Disorder Receiving Lexapro (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125) and Placebo (N=383):** Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). In Females Only: Lexapro (N=737) and Placebo (N=636): Libido Decreased (3% and 1%); Anorgasmia (3% and <1%). There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priligal has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=327) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in **Tables 2 & 3**, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; Cardiovascular - Frequent: palpitation, hypertension, infrequent: bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders - Frequent: light-headed feeling, migraine, infrequent: tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tic, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, hiccups, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - Frequent: heartburn, abdominal cramp, gastroenteritis. Infrequent: gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - Frequent: allergy, pain in limb, fever, hot flushes, chest pain. Infrequent: edema of extremities, chills, lightness of chest, leg pain, asthma, syncope, malaise, anaphylaxis, fall. Hemic and Lymphatic Disorders - Infrequent: bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - Frequent: increased weight. Infrequent: decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - Frequent: arthralgia, myalgia. Infrequent: jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - Frequent: appetite increased, lethargy, irritability, concentration impaired. Infrequent: jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, anorexia, anxiety attack, bruising, carbohydrate craving, confusion, depression/agitation, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female - Frequent: menstrual cramps, menstrual disorder. Infrequent: menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. \*% based on female subjects only. N= 905 Respiratory System Disorders - Frequent: bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. Infrequent: asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders - Frequent: rash. Infrequent: pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. Special Senses - Frequent: vision blurred, tremors. Infrequent: taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - Frequent: urinary frequency, urinary tract infection. Infrequent: urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, alkalosis, allergic reaction, anger, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, echymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoesthesia, hypoglycemia, hypokalemia, IRR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leukopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, pruritus, procloniaemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

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## GENOMIC MEDICINE

### Old Drugs, New Tricks

As a former gene therapy researcher, I must confess that to me, nearly all attempts at gene therapy for genetic disorders have been disappointing. The sad fact is that our immune system is its own worst enemy as far as gene therapy goes, clearing attempts to use vectors to introduce new genetic material into cells and organs without breaking a sweat.

When I was a graduate student, I was fond of saying (probably not originally) that with gene therapy we were attempting to treat disorders we didn't understand, in systems we didn't understand, using gene vectors we didn't understand. At that time, many expected that, like a medical “Hail Mary,” something good would come out of the considerable efforts directed at gene replacement-based therapies.

Moving forward, the prospects for successful primary gene therapy for most disorders remain distant. However, remarkable gains—fueled by discoveries in genomics—have been made in understanding the pathophysiology of many genetic disorders, and they are yielding therapeutic breakthroughs.

A particularly compelling story is the evolution of our understanding of Marfan syndrome (MFS), one of the classic autosomal dominantly inherited disorders that is characterized by tall stature, disproportionately long limbs, dislocated lenses, and other connective tissue abnormalities.

The most devastating consequence of MFS is a predisposition to aortic root dilatation and aneurysm formation that all too frequently leads to death in early adulthood. Unfortunately, the disorder is not that rare, affecting about 1 in 5,000 individuals (as a benchmark, cystic fibrosis affects about 1 in 2,500 whites). It is caused by mutations in the fibrillin-1 gene, which

encodes the protein fibrillin-1, a constituent of the extracellular matrix in connective tissues and blood vessel walls.

Until recently, most investigators thought that MFS was a nearly hopeless case for targeted therapeutic interventions, largely because the defect was in a structural protein, rather than in an enzyme.

In general, it is comparatively easy to come up with rational ways for treating disorders with enzyme replacement; however, it is much harder to conceptualize treating a disorder if the cause is a structural element defect. MFS patients were therefore relegated to risky surgical correction of developing vascular abnormalities, or marginally beneficial use of  $\beta$ -blockers to slow blood vessel dilatation.

However, investigators were not satisfied that a classic structural protein defect could explain all of the features of MFS, and a few years ago, they made a vital discovery: Defects in fibrillin-1 cause dysregulation of transforming growth factor  $\beta$  (TGF- $\beta$ ) signaling in affected tissues.

By using mouse models for MFS and TGF- $\beta$ -neutralizing antibodies, investigators were able to show rescue of the blood vessel abnormalities. This alone would be a remarkable scientific finding, but delivering antibodies over a long period to patients isn't a much more appealing clinical solution than the prospects of gene therapy.

Then something bordering on magical happened. One group of investigators recognized that an already commonly used antihypertensive in the class of drugs known as angiotensin II type 1 receptor blockers (ARBs) also interfered with TGF- $\beta$  signaling, so they tried the drug in the mouse Marfan model.

The results were nothing short of spectacular: The vascular consequences of

MFS could be prevented in the mouse model system (Science 2006;312;117-21).

This success, coupled with the grave prognosis for MFS and the known safety profile of the ARB drugs, has led to a large prospective human clinical trial funded by the National Heart, Lung, and Blood Institute.

The trial, comparing the effectiveness of losartan and atenolol in a pediatric to young adult (aged 6 months–25 years) population, will have as its primary outcome measurement of body surface-adjusted aortic root dilatation, with measurement at 2, 12, 24, and 36 months. The preliminary results are due out soon, and many in the field expect that the trial will show clear, major benefits from the use of ARBs.

It is interesting—and probably prophetic—that MFS treatment might soon be revolutionized through a careful tweaking of a formerly unrecognized but important pathway rather than through brute-force correction of the underlying genetic defect.

Expect that this will be the model for other trivalent genetic disorders, not the least of which appears to be cystic fibrosis, for which a drug targeting patients with a particular genetic variant (unfortunately not the most common) has shown promising results in phase II trials in recent months.

Although almost 12 years have passed since I was a grad student, gene therapy remains the genomic medicine equivalent of a “Hail Mary”—a play not to be counted on or out. The difference today is that the ground game is fundamentally sound: Those 4-yard gains might carry the contest for a variety of disorders. ■

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