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ALSO IN THIS ISSUE

Aripiprazole Lauroxil Reduces Inpatient Admissions for Patients With Schizophrenia

SILAS INMAN

The long-acting injectable (LAI) aripiprazole lauroxil (Aristada) resulted in 25.9% fewer mental health–related inpatient admissions compared with a 6-month baseline assessment for patients with schizophrenia. The lower admissions rate resulted in a decline in costs associated with inpatient services but not an overall reduction in the cost of care, according to new findings.

In the retrospective analysis, mental health–related costs associated with inpatient admission dropped by \$1530 during the follow-up period. However, the costs of outpatient services increased by \$619 and the costs of outpatient prescriptions increased by \$3935, for a total net increase in costs of \$3025 ($P < .001$). This increase was largely driven by the cost of aripiprazole lauroxil, said lead investigator John Lauriello, MD.

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15-Year Study Finds Use of Statins Remains Suboptimal Among Patients Who Need Them Most

DANIELLE MROZ, MA

Statin use among patients in the United States with a history of myocardial infarction (MI), angina pectoris (AP), and stroke remains poor, despite a reduction in overall out-of-pocket (OOP) expenses for patients and the availability of generics, according to the results of a new study. The significant undertreatment of this high-risk group may be contributing to increasing cardiovascular medical costs seen over the past 15 years.¹

As the leading cause of death in the United States for almost a century,² cardiovascular diseases accounted for 647,457 deaths in 2017.³ This number, along with some \$351 billion⁴ in indirect and direct medical costs associated with treating cardiovascular diseases, is expected to rise as the population of the United States grows older. With the goals of improving cardiovascular health in the United States and controlling costs, investigators

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Aripiprazole Lauroxil (Continued from page 1)

"I was surprised that the inpatient savings were not higher. Twenty-five percent seems like a lot to me," said Lauriello, medical director of the Missouri Psychiatric Center, and the Robert J. Douglas, MD, and Betty Douglas Distinguished Professor in Psychiatry, University of Missouri School of Medicine, in an interview with *The American Journal of Managed Care*®. "This is a dilemma for all medicine, in which you may be able to improve the quality of life for patients, but the costs may be higher, and that is often driven by the medication costs."

Patients for the observational study (N = 485) were selected from the IBM MarketScan Multi-State Medicaid Database, from October 1, 2015, to June 30, 2017. The mean age of patients was 35.3 years (± 12.1 years), and 58.1% were male. The mean Deyo-Charlson Comorbidity Index score was 0.6 (± 1.1). In the 60 days prior to entering the study, 44.7% of patients (n = 217) had received an LAI, 40.2% (n = 195) had used an oral antipsychotic, and 15.1% (n = 73) had not used any antipsychotics.

All patients had a diagnosis of schizophrenia; however, other coexisting mental health conditions were also present, including major depressive disorder (33.6%), bipolar disorder (29.1%), and attention deficit hyperactivity disorder (29.1%). At baseline, significant numbers of patients were on antidepressants (65.6%); anxiolytics, hypnotics, or sedatives (51.5%); anticholinergic agents (34.8%); and mood stabilizers (34.2%).

The starting dose for aripiprazole lauroxil was 882 mg for nearly half of patients (48%), with a third receiving a starting dose of 662 mg (35.9%), and the remainder receiving 441 mg (16.1%). The proportion of days covered was 0.76 (± 0.31 days), which resulted in a mean of 136 days of continuous drug exposure (± 56.6 days).

"The doctors tended to start with the highest dose available then," Lauriello said. "This could mean they wised up to the fact that previous antipsychotic regimens may

have been a little underdosed. They were veterans by the time they got to this drug."

The mean number of aripiprazole lauroxil doses received was 4.6 (± 2.1 doses), with 43.5% having received 6 or more doses of the medication, suggesting a high level of adherence. Overall, 34% of patients discontinued treatment in a mean of 56.1 days from initiation of therapy.

"We expected about 6 injections over 6 months, and they averaged about 4.8 injections—close to 5. That doesn't include [instances when] they got it in the inpatient [setting], because that isn't registered by this database," Lauriello said. "That immediately told me that there's a group of patients who stayed on it for 6 months. Surprisingly, a huge number of people who were prescribed this ended up getting all of the shots they could have in the 6 months."

Following treatment with aripiprazole lauroxil, all-cause inpatient admissions declined by 22.4% ($P = .017$), and there were 11.6% more prescription fills per patient ($P < .001$). In addition to 25.9% fewer inpatient admissions for mental health-related causes, there were 13.2% more prescription fills ($P < .001$) and 13.4% fewer mental health-related emergency department (ED) visits ($P = .025$) following administration of aripiprazole lauroxil.

All-cause inpatient costs dropped by \$2836 ($P < .036$) following aripiprazole lauroxil initiation. However, outpatient prescription costs increased by \$4121 ($P < .001$). Overall, no statistically meaningful difference in all-cause healthcare costs arose following initiation of therapy.

"If you can trade inpatient stays and ED stays with outpatient visits and medication, that's probably a good trade-off because ideally, the patient isn't ending up in the hospital or in crisis in the ED," Lauriello explained. "You're really building on their recovering versus backsliding into admissions."

Following completion of the database analysis in 2017, 2 new dosing strategies were approved for aripiprazole lauroxil. In 2017, the FDA approved a 1064-mg dose

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of the medication that could be given once every 2 months. Then, in 2018, a combination bolus injection-plus-oral dosing strategy for aripiprazole lauroxil, known as Aristada Initio, was approved by the FDA, offering further convenience for patients.

“I think things have changed dramatically since 2015 for this particular drug,” Lauriello said. “Patients have more options now. One is a 2-month injectable, which is probably easier for

patients to take, and also a bolus injection, called Initio, which means that patients don’t need to take any oral medications for the first 3 weeks. These are some [very] nice enhancements.” ●

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Statins (Continued from page 1)

from The Medicines Company conducted a 15-year retrospective analysis of Medical Expenditure Panel Survey data⁵ to understand the prevalence, statin use and adherence, and medical costs of patients with a history of MI, AP, and stroke, or varying risk levels, from 2002 to 2016 in the United States. The investigators were led by Weihong Fan, MS, senior director and statistician, and included Stephanie Plent, MD, executive vice president and chief value officer.

“We are not doing right by [patients with] our treatment of chronic hyperlipidemia [in the United States],” Plent said in an interview with *The American Journal of Managed Care*[®]. “[Focusing on] lowering your cholesterol is like putting money in the bank for retirement. It is a 20-year-plus payoff. Similar to saving for retirement, however, most people don’t do it enough, and it comes back to haunt us later in life. What we wanted to show with our research is that there is a lot of room for improvement.”

For the study, the investigators included individuals who were 21 years and older at the time of the survey and hierarchically categorized them into the following categories:

- Patients with a self-reported history of MI, AP, and/or stroke. Categorized as “ASCVD” [atherosclerotic cardiovascular disease].
- Patients with self-reported diabetes with the absence of MI, AP, or stroke. Categorized as “Diabetes.”
- Patients in the primary prevention population with 3 or more cardiovascular risk factors (CRFs).
- Patients in the primary prevention population with 2 CRFs.
- Patient in the primary prevention population with 1 or 0 CRFs.

CRFs were defined as self-reported hypertension, diagnosed high cholesterol, lack of physical activity, smoking, or a body mass index of 30 or more (obesity), according to the presentation. Those patients in the primary prevention population classified as having 0 or 1, 2, or 3 or more CRFs were analyzed after 2005 because data on high cholesterol was not collected prior to that date.

The investigators defined statin use as the patient having filled at least 1 prescription (or filed 1 claim) for a statin during the survey year, while adherence was determined by the proportion of days covered. Those patients whose proportion of days covered was 80% or higher were determined to be highly adherent. Annual expenditures per individual were captured from various points of service, and all were summarized and adjusted to 2016 dollars.

According to the study results, the total US population increased from 200.9 million in 2002 to 233.0 million in 2016. The average age of the US population increased as well, from 47 years in 2002 to 49 years in 2016. The number of individuals with a history of MI, AP, and stroke increased from 13.3 million in 2002 to 19.7 million in 2016. The prevalence of diabetes (in the absence of ASCVD) increased by 77%, from 10.4 million in 2002 to 18.4 million in 2016.

Annual medical expenditures for individuals with ASCVD increased by 44.5% over that time period, from \$231 billion in 2002 to \$333 billion in 2016. However, annual OOP costs decreased from \$34 billion in 2002 to \$24 billion in 2016.

The investigators postulated that the increase in medical expenditures and decrease in OOP costs may be due, respectively, to an overall increase in the cost of medical care and the introduction of generic versions of statins.

“We have the ability to treat cardiovascular disease with more than just medication—for example, with CABG [coronary artery bypass graft] and angioplasty. The costs of those procedures have risen, whereas with most statins going generic during the course of this study [starting around 2007], out-of-pocket costs have decreased,” Plent explained.

A total of 331,720 individuals were included in the study population. Among these individuals with a self-reported history of MI, AP, and/or stroke, less than half (46.8%) used a statin in 2002. These numbers improved slightly going forward, fluctuating between 53% and 57% in the years between 2004 and 2016.

A little more than half (53%) of individuals with a history of MI, AP, and/or stroke filled prescriptions for statins between 2002 and 2016, falling far short of the threshold to achieve optimal benefit (80%). Statin and medical cost utilization varied depending on the type of cardiovascular event and category of insurance.

Although the data used did not include reasons why patients who should be on statins were not taking them, Plent pointed to a recent article in the *Journal of the American Heart Association* that found more than half of patients (59.2%) were not offered a statin even if they were eligible to be on one. Of those who refused or discontinued treatment, concerns over adverse effects were the leading reasons for not taking a statin.⁶

“When you have a silent disease like this—one that doesn’t hurt, requires long-term medication, and takes years to develop—[some patients] have apathy to it. Adherence is very hard to change when you are dealing with a silent disease,” Plent added. “Studies have shown that when healthcare practitioners are active in calling patients and reminding them, and explaining the risk factors, it has an impact on whether they take their statins, long-term. Incentives within the healthcare system should ensure this happens as well. However, as a society, we are very bad at prevention for long-term chronic diseases.”

Some limitations of the study include that ASCVD, diabetes, and patient risk factor status data were self-reported, and that the trend results were not age-adjusted. Furthermore, because MEPS data do not include reported LDL cholesterol levels from blood samples, the risk level was categorized based on CRFs. In addition, the number of days in each statin prescription was not available until 2010, and dosing was not included. Also, data on high cholesterol were not collected until 2005.

Based on these results, the investigators stated that strategies need to be developed to improve statin use.

“Our elderly population is going to keep on costing us enormous amounts of money unless we treat them earlier,” Plent said. “There is a sense that since the cardiovascular death rate has dropped since the 1960s, that we have somehow solved the cardiovascular problem, but in fact, what we have done is kicked the can down the road. It is still the number-1 killer around the world.” ●

This research was sponsored by The Medicines Company, of which Dr Plent and Mr Fan are employees and shareholders.

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Costs of Living With HIV Can Be Mitigated by Rapid Initiation of ART Post Diagnosis

CHRISTINA MATTINA

The results of a trio of posters indicate that high healthcare utilization leads to substantial costs among individuals living with HIV, but prompt initiation of antiretroviral therapy (ART) regimens after diagnosis can help contain costs in both Medicaid-covered and commercially insured patients.

In a poster describing an analysis of multistate Medicaid data combined with results of a literature review, investigators estimated the costs of healthcare resource utilization among patients living with HIV in the United States.¹ These total costs included costs per inpatient day and per each emergency department (ED) and outpatient visit. Outpatient care included services from general care providers and specialists, HIV care (including medications), and procedural and social services.

In an interview with *The American Journal of Managed Care*[®], Keith Dunn, PharmD, BCPS, of Janssen, senior author of the 3 posters, explained that the investigators combined the results of a literature review with the Medicaid claims data analysis because while they had claims data from more than 21,000

enrollees living with HIV in the Medicaid database, those data came from only 6 states in that particular database. As such, the team used the targeted literature review to compare the administrative costs identified from the Medicaid claims data with those of a more diverse population.

From the 21,513 Medicaid claims analyzed, the investigators found that mean costs were \$2035 per inpatient day, \$212 per ED visit, and \$85 per outpatient visit. Within the 7 US studies identified by the targeted literature review, mean costs for those 3 types of utilization ranged from \$1849 to \$3451, \$704 to \$828, and \$130 to \$417, respectively.

Because the literature review was not limited to Medicaid data, the authors noted that mean costs for inpatient days were similar in both the Medicaid data and the broader US population; however, Medicaid-insured patients had lower costs for outpatient and ED visits. This “could be related to changes in treatment guidelines and in the provision of healthcare services, as well as improvements in overall health” in this population, they wrote.

“Combining both sources provided a robust range of costs for [people living with HIV], which is important for decision makers,” the authors concluded. They suggested that further research could explore the financial effects of changing treatment guidelines and of the use of new single-tablet regimens.

“Understanding the differences between the administrative claims data and the data in the public domain through the targeted literature review is important, because when we look at costs associated with healthcare resource utilization in different data sets or clinical trials, we may be able to use the range to conduct various sensitivity analyses, as costs can vary across payer channel,” Dunn added.

Another poster explored healthcare costs of Medicaid patients with HIV, specifically focusing on how quickly they began ART after being diagnosed with HIV-1.² Rapid initiation (RI) was defined as being started on treatment prior to having full laboratory results or resistance testing records available.

According to Dunn, the investigators looked at the economic impacts of RI because “previous studies have shown that when you start patients rapidly, they have a higher rate of retention in care (ie, coming back to see the doctor); improvements in virologic outcomes, such as decreased time to virologic suppression; and decreased rates of morbidity and mortality.”

The 627 eligible patients were separated into 4 cohorts based on their time to ART initiation post diagnosis: 20.4% were rapid initiators (RIs; ≤ 14 days), 36.4% were moderately rapid initiators (mRIs; 15-60 days), 26.0% were moderately delayed initiators (mDIs; 61-180 days), and 17.2% were delayed initiators (DIs; 181-360 days).

Dunn noted that the 7-day mark is the widely accepted definition of RI in sources such as the World Health Organization guidelines, but the investigators’ use of the 14-day mark to define RI in this cohort was due to longer times to initiation seen among Medicaid patients.

“We actually had to change the window in which we defined rapid initiation in the Medicaid population, from 7 days to 14 days, because there were so few patients starting treatment within 7 days,” Dunn said.

Medical costs increased across all follow-up time points after diagnosis, but they were always greater among the DI group than the RI group (6 months, \$9124 vs \$7757; 12 months, \$15,989 vs \$10,836; 24 months, \$27,797 vs \$16,220; 36 months, \$43,067 vs \$23,447, respectively). DI patients had lower pharmacy costs, and the medical costs of the DI/mDI patients accounted for more than half of their total healthcare costs, whereas the RI/mRI patients had pharmacy costs that were higher than their medical costs.

By the time of follow-up at 36 months post diagnosis, the increased pharmacy costs in the RI group were offset by lower medical costs, resulting in lower total healthcare costs compared with their DI counterparts (DI, \$83,157; RI, \$74,093). These results highlight “the long-term economic benefits of rapid ART initiation post HIV-1 diagnosis,” the authors wrote.

To make RI the standard of care, and to potentially lessen downstream spending by Medicaid, the authors suggested that future efforts should focus on “reducing barriers to treatment initiation, such as time spent waiting for test results and [for] counseling.”

Finally, another poster looked at characteristics of and healthcare costs among commercially insured US patients with HIV who were treated within 60 days of diagnosis.³ This was among the first studies to specifically examine the financial implications of ART initiation timeliness in patients with commercial insurance; such patients compose a larger proportion of the population with HIV than do Medicaid patients, yet the latter are more commonly examined in similar cost-focused studies.

“ Medical costs were always greater among the delayed initiation group than the rapid initiation group.”

In this study, the RI group was defined as patients who started an ART regimen within 7 days of diagnosis, whereas the mRI group included those who started between 8 and 60 days after diagnosis.

Of the 6743 eligible patients, 18.3% were RIs and 81.7% were mRIs. Nearly three-fourths (74.3%) were started on single-tablet regimens. RI patients were more likely to start on protease inhibitor-based regimens, whereas mRI patients were more likely to start on integrase strand transfer inhibitor-based regimens. The groups were equally likely to start nonnucleoside reverse transcriptase inhibitor-based regimens. Total healthcare costs, defined as the sum of medical and pharmacy costs, were lower in the RI group than in the mRI group (\$109,456 vs \$116,870, respectively) over the 36 months after diagnosis.

The authors pointed to opportunities for improvement in ART initiation, including increasing the percentage of patients who start therapy within 7 days. They also noted that many of the RI patients used agents that are considered “suboptimal” due to the agents’ “low rather than high genetic barrier to resistance, demonstrating a need to optimize HIV treatment with antiretrovirals having high genetic barrier to resistance.” They suggested that “opportunities exist to educate healthcare providers about which antiretrovirals have a high genetic barrier to resistance, have fewer testing barriers, and can provide adherence benefits through their availability in single-tablet form.”

The message that rapid initiation of ART was associated with lower healthcare costs “is really important, because some payers are looking at formulary management and trying to contain access to various regimens,” Dunn said.

“These findings highlight the importance of starting treatment rapidly after diagnosis and should hopefully encourage payers to provide unrestricted access to HIV treatment options that are recommended for rapid initiation per national and international treatment guidelines,” said Dunn. “If active management strategies are put in place, like prior authorization or preferred tiering, that may result in further delayed receipt of care and inhibit really rapid initiation from taking place.”

Dunn noted that these newly published cost data will be used to inform the results of the ongoing phase 3 DIAMOND study, which is “evaluating the efficacy and safety of rapidly starting Symtuza [darunavir, cobicistat, emtricitabine, and tenofovir alafenamide], which is a single-tablet regimen that can be utilized in treatment by these patients and certain virologically

suppressed patients. In this particular study, we are looking to examine the efficacy and safety of Symtuza in patients who rapidly start treatment.” ●

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Oral Oncolytic Initiation Diminishes Medication Adherence for Comorbid Conditions

SILAS INMAN

Adherence to oral therapies to treat chronic conditions declined in patients initiating treatment with an oral oncolytic for chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), or multiple myeloma (MM), according to findings from a retrospective, observational cohort study.

In the database analysis, adherence to a lipid-lowering agent declined by 10.7 to 15.6 percentage points after initiating an oral oncolytic, which was the greatest level of decline seen in the study. Adherence to antihypertensives declined by 7.0 to 12.0 percentage points and adherence to antidiabetics declined by 12.5 to 13.1 percentage points. The findings highlight the need for better medication management strategies, according to senior author Justin Gatwood, PhD, MPH.

“Adherence to lipid-lowering agents had the greatest decline after patients started an oral oncolytic.”

“This is a prime opportunity for pharmacists to get even better engaged,” said Gatwood, assistant professor, Clinical Pharmacy, University of Tennessee Health Science Center College of Pharmacy in Memphis, Tennessee. “We have oncology pharmacists who can assist with the oncolytic. They could form a team where the oncology pharmacists who came up with the regimen for the cancer could work hand-in-hand with the ambulatory or community-based pharmacist who can better manage the lipid-lowering, antidiabetic, and antihypertensive medicines.”

Data for the observational study were selected from the 2013-2016 Truven Health MarketScan Commercial Claims and Medicare Supplement databases. Adherence was determined using proportion of days covered (PDC), with less than 80% coverage determined to be nonadherence. A total of 1378 patients were selected from the databases with CML, 1126 with CLL/SLL, and 3527 with MM.

Treatments in the CML group included imatinib (Gleevec), dasatinib (Sprycel), nilotinib (Tasigna), bosutinib (Bosulif), and ponatinib (Iclusig). CLL and SLL treatments consisted of ibrutinib (Imbruvica) and idelalisib (Zydelig). MM therapies included thalidomide, lenalidomide (Revlimid), and pomalidomide (Pomalyst).

In the CML arm, most patients had a commercial payer (78.5%) whereas other groups had a more even split between commercial and Medicare. The most common place to fill the prescription was at a retail store for most patients; however, approximately 23% of patients with CML and MM used mail order services. Only 0.5% used these services in the CLL/SLL cohort. Copay amounts were similar across groups.

Adherences to antidiabetics dropped from 89.8% at baseline to 77.3% at 180 days following initiation of oral oncolytic therapy for patients with CML ($n = 130$; -12.5% change; $P = .004$). For those with CLL/SLL, adherence to antidiabetics declined from 86.5% to 73.4% ($n = 98$; -13.1% change; $P = .002$) and from 87.6% to 74.8% for those with MM ($n = 361$; -12.8% change; $P < .0001$).

At baseline, 88% of patients with CML were adherent to lipid-lowering agents compared with 74.9% at 180 days ($n = 273$; -13.1% change; $P < .0001$). Lipid-lowering agent adherence was 89.4% at baseline and 78.7% at 180 days for those with CLL/SLL ($n = 222$; -10.7% change; $P = .01$). The rates were 87.6%

and 72%, respectively, for those with MM (n = 709; -15.6% change; $P < .0001$).

Declines in adherence to antihypertensives were relatively modest compared with other oral therapies for comorbid conditions, with the exception of patients with MM. In this group, 90.6% were adherent to antihypertensives prior to the initiation of oncolytic therapy compared with 78.6% after starting therapy (-12.0% change, $P < .0001$). For those with CLL/SLL the difference was 7.8 percentage points (91.2% vs 83.4%; $P < .01$) and for those with CML the difference was 7.0 percentage points (90.9% vs 83.9%; $P < .001$).

“Theoretically, one would think that perhaps the focus of the patient’s attention is shifting from their chronic disease management to what they perceive to be the most likely thing they need to focus on, which is their oral oncolytic therapy,” Gatwood said. “[However,] it would be a shame for them to survive their cancer, or highly adhere to [oncolytics], and then end up having a heart attack because they did not follow their other regimens.”

For those enrolled in the study, the mean PDC for oral oncolytic adherence was 83.8% in the CML group, 83.3% in the CLL/SLL group, and 69.8% in the MM arm. The patients who

were not adherent to their oral oncolytic were also more likely to be nonadherent to oral therapies for comorbid conditions.

In those who were nonadherent to their oral oncolytic (PDC, <80%), adherence to a lipid-lowering agent declined by 17.1 to 22.0 percentage points. Adherence to antihypertensives declined by 11.3 to 13.9 percentage points and adherence to antidiabetics declined by 9.4 to 18.9 percentage points. However, these findings were statistically significant in only a few of the groups, specifically for antihypertensives in those with CML and CLL/SLL, and for lipid-lowering agents in those with CLL/SLL.

Most current research focuses on “the overarching adherence for oncolytics. The focus for this study was on what happens to the chronic conditions,” Gatwood said. “We’re trying to better understand in other work which level they need to adhere to the oral oncolytic to get a sense for how high we need to drive the adherence.” ●

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Majority of Elderly Patients Receiving Inappropriately Prescribed Antipsychotics

DANIELLE MROZ, MA

More than 99% of outpatient prescriptions for antipsychotics in elderly patients are inappropriate, according to the results of new research.¹

US Census data indicate the population of US adults who are 65 years or older will double by 2060.² This continuing shift in the age of the US population is expected to lead to a jump in the prevalence of neurological disorders and accompanying behavioral disturbances. Often, patients suffering from behavioral disturbances are prescribed antipsychotics, but these treatments are not recommended in the American Geriatrics Society Beers Criteria³ (Beers) for use in elderly patients because they carry an increased risk of stroke and mortality.

Investigators led by Qian Ding, PhD, assistant professor of pharmaceutical sciences at Ferris State University College of Pharmacy in Big Rapids, Michigan, examined data from the most recent Medicare Current Beneficiaries Survey⁴ to determine the prevalence of inappropriate outpatient antipsychotic prescribing in elderly patients. The team defined inappropriate prescribing as a case where either the *International Classification of Diseases (ICD), Ninth Revision* or *Tenth Revision* code was not consistent with Beers criteria for the recommended use of antipsychotic medications in the elderly for conditions such as schizophrenia (codes 295.X, F20.X, F25.X), bipolar disorder (codes 296.X, F31.X), or short-term therapy for chemotherapy-induced nausea and

vomiting (codes 787.01, V58.11, V67.2, Z51.1, R11.2, T45.1x5), or if the ICD code was missing.

In an interview with *The American Journal of Managed Care*[®], Ding explained that the team extracted encounters with patients 65 years and older who were prescribed at least 1 antipsychotic medication. Data on their diagnoses were analyzed using χ^2 tests for categorical variables (gender, ethnicity, marital status, annual household income, patient location, and provider type) and 2-sample *t* tests for continuous variables (age, average income, total expenditure, and out-of-pocket expense).

“ The population of US adults who are 65 years or older is expected to double by 2060, leading to an increase in the prevalence of neurological disorders. ”

Of a total 31,379 patient encounters that were evaluated, just 271 cases (0.86%) had a diagnosis that was consistent with appropriate use of antipsychotics; the remaining 31,108 cases (99.14%) indicated inappropriate use. The most common ICD codes identified in encounters in which psychotherapeutic medications were prescribed included severe recurrent episode

of major depressive affective disorder without mention of psychotic behavior (n = 113, 41.7%); antineoplastic chemotherapy, short-term antiemetic during chemotherapy (n = 51, 18.82%); short-term antiemetic during chemotherapy, nausea with vomiting (n = 33, 12.18%); and unspecified schizophrenia (n = 27, 9.96%).

An evaluation of patient demographic information showed that the majority of patients who were inappropriately prescribed antipsychotics were white versus nonwhite (89.62% vs 80.24%; $P = .000$), female versus male (70.39% vs 53.89%; $P = .000$), had an annual income more than \$50,000, and lived in a metropolitan area.

Patients who were prescribed antipsychotics inappropriately were about 6 years older than those patients who had claims for antipsychotics with appropriate ICD codes (mean 78.7 years; 95% CI, 78.6-78.8; $P = .0000$).

Medical doctors were responsible for nearly three-fourths (n = 9023; 71.34%) of claims that did not include an ICD code indicating appropriate use, while psychologists were responsible for 1.69% of inappropriate claims (n = 214). Notably, the number of antipsychotic prescriptions attributed to podiatrists (n = 534; 4.22%) is more than the number attributed to psychologists in total. Ding indicated that this surprising finding may be due to data entry error.

Based on these results, the investigators concluded that inappropriate prescribing of antipsychotics in elderly patients is a significant healthcare issue. Ding hopes that the results will raise public awareness of potentially unsafe use of antipsychotic medications in the elderly. In addition, she hopes the study will stimulate behavioral change among healthcare providers to focus increased attention on their prescribing practices. ●

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Keeping an Eye on Increasing Competition in the Specialty Drug Pipeline

CHRISTINA MATTINA

With all of the changes in the pharmaceutical development landscape from year to year, there is at least 1 constant: Aimee Tharaldson, PharmD, will be on hand to make sense of the specialty drug pipeline and its implications for the managed care market. As she does every year, Tharaldson, a senior clinical consultant in emerging therapeutics for Express Scripts, presented her look at the development pipeline.¹

“About \$24 billion in opportunity lies within the group of specialty drugs that have upcoming generics through 2023.”

Tharaldson explained that her assessment of the specialty drug pipeline could be distilled into 3 broad themes: increased competition, cancer drug development, and orphan drug development.

More competition will result in more opportunities for cost savings, Tharaldson said, with many specialty drugs going generic in the next few years and biosimilar approvals increasing. About \$24 billion in opportunity lies within the group of specialty

drugs that have upcoming generics through 2023, compared with \$14 billion in the 2015-to-2018 period.

In the biosimilar landscape, she noted that, although 18 biosimilars have been approved, 7 are still pending a launch, mostly due to patent litigation. These biosimilars often have limited indications compared with their reference drugs because some of the originators' indications are still protected by orphan drug exclusivity. The impact of legal hurdles has been exemplified by the uncertainty around the launch of the etanercept biosimilar Erelzi. If a court rules in favor of the biosimilar's maker, Sandoz, it could hit the market as soon as this year; if Amgen, which makes the reference Enbrel, succeeds, the biosimilar's entry could be delayed until 2028 or 2029.

Although some biosimilars have struggled to capture market share, Tharaldson foresees significant cost savings opportunities in the coming years, especially with 8 biosimilars pending approval this year and new FDA policies encouraging biosimilar development as well as providing more clarity around naming conventions.

Regarding the second trend of cancer drug development, Tharaldson noted that, despite the fact that the FDA approved a record 17 new cancer drugs in 2018, there haven't been

subsequent reductions in cost: Many of these drugs launch at around \$150,000 per year.

Orphan drug development represents a particularly lucrative segment, as the average costs of these drugs are 5 times those of other drugs; 30% are considered “blockbusters,” indicating more than \$1 billion in sales. A little more than half of the drugs in the specialty pharmacy pipeline (53%) are for orphan diseases.

In light of the 4 specialty drug approvals so far this year, Tharaldson said 2019 was off to a “slow start,” but she noted that the drug mechanisms and disease states covered by these approvals represent promising strides in areas without many alternatives. One example is brexanolone (Zulresso) to treat severe postpartum depression, a condition that affects 11% of new mothers. The treatment starts working within 48 hours, whereas oral antidepressants may take weeks to show effects. For treatment-resistant depression, eskatamine (related to ketamine) is a breakthrough therapy. Its distribution and use will be monitored carefully; however, the drug promises relief for at least some of the large market of about 5 million patients who do not respond to conventional treatments for depression. Looking to agents currently moving up the pipeline, Tharaldson discussed 7 classes of specialty drugs to watch. These included treatments for:

- **Inflammatory disease.** Drugs to treat diseases like rheumatoid arthritis and ulcerative colitis are the leading class by per-member-per-year spending. With 5 upcoming drugs targeting approval in 2019 or 2020, we will see indications expand and competition increase in this market, especially as new products are demonstrating improvements over existing drugs in clinical trials.
- **Multiple sclerosis.** Five new oral drugs (4 in 2019; 1 in 2020) will potentially join disease-modifying drugs already on the market. Four treat the relapsing form of the disease and the other is for secondary progressive multiple sclerosis. These new agents offer improved safety profiles compared with existing drugs.
- **Oncology.** Of the 8 cancer drugs pending approval in 2019, 7 are oral and 1 is intravenous. These drugs will treat a range of cancer types from urothelial cancer to solid or giant cell tumors to myelofibrosis. Some are breakthrough therapies, and some apply to patients with specific gene types. They also have different prospects for approval. Tharaldson thought selinexor, for instance, was unlikely to be approved in July because an FDA panel voted to wait for more data on it, but she said that pexidartinib might be approved even before its August action date.
- **HIV.** The HIV market is dominated by single-tablet regimens because adherence to antiretroviral therapy is key for achieving viral suppression. One new oral drug could

be approved in 2019, and 2020 could see the entry of an intramuscular injection drug, another oral drug, and a subcutaneous injection drug. The intramuscular injection presents an alternative to daily pill regimens, but the pain associated with injection may limit its uptake.

- **Nonalcoholic steatohepatitis.** “A lot of buzz” surrounds this disease class, says Tharaldson, with many drugs in development. Three oral drugs are in phase 3 trials and could gain approval by 2020, and several more are slated for approval after 2020. Drug manufacturers are drawn to this class because analysts expect it could represent a market of \$20 billion annually, but “there are many unknowns at this point,” Tharaldson said. “We don’t know what combos are going to be effective and safe; we don’t know long-term clinical benefits of these medications; and we don’t know how much they’re going to cost.”
- **Alzheimer disease.** The search for a drug that can modify the disease course instead of temporarily improving its symptoms has suffered disappointing setbacks, but prospects are on the horizon. Three drugs that affect anti-amyloid- β antibodies are in the pipeline and could be approved in 2021 or 2022 or beyond; drugs acting on anti- τ antibodies would take even longer. “It will be several years, unfortunately, before we see disease-modifying drugs available [for this disease state],” Tharaldson said.
- **Hemophilia.** With 7 drugs in the pipeline that could be approved from 2020 to 2022, Tharaldson sees opportunity in the early promising results of gene therapy via 1-time infusions, which seem to be well tolerated and could potentially eliminate the need to use clotting factors.

Other interesting drugs in the pipeline with approvals expected within the first half of 2019 included the breakthrough therapy onasemnogene, a 1-time intravenous infusion for treating babies who have the highly fatal disease known as type 1 spinal muscular atrophy. Videos of improvements in treated patients have been “very impressive,” Tharaldson said, adding that she thinks the drug has a chance of being approved before its May action date.

Tharaldson also mentioned 4 therapies—tafamidis (for the treatment of transthyretin amyloid cardiomyopathy), afamelanotide (for the treatment of erythropoietic protoporphyria), fenfluramine (for the treatment of Dravet syndrome), and golodirsen (for the treatment of Duchenne muscular dystrophy)—that could be approved later in the summer. ●

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Tardive Dyskinesia Severity Alone Underestimates Number of Patients Requiring Treatment

SILAS INMAN

The involuntary movement disorder tardive dyskinesia (TD), which manifests following prolonged use of antipsychotics, was associated with a significant negative impact on health-related quality of life (HRQoL), with significant deficits in mobility and self-care, according to findings from the real-world RE-KINECT study.

Patient-rated TD impact and severity was most closely associated with findings from the EuroQoL 5-Dimensions 5-level questionnaire (EQ-5D-5L), as compared with clinician assessment. In general, clinicians consistently provided lower overall severity scores compared with patients, resulting in a lack of correlation between their assessment and EQ-5D-5L findings (sum severity score 2.3 for clinicians vs 2.7 for patients; $P = .023$). These findings suggest a potential underestimation of TD severity, resulting in undertreatment.

“Patients’ ratings of their symptom severity was more reliable than their physician’s assessment.”

“[Some of the differences between severity ratings] might be due to the patient’s ability to suppress the symptoms,” said investigator Charles Yonan, PharmD, senior director of health economics and outcomes research at Neurocrine Biosciences, in an interview with *The American Journal of Managed Care*®. “We had a series of investigator meetings in which clinicians from the study told us that they had patients who were in the study who they had been caring for years who they did not realize had TD. The patients can sit on their hands, or they can come in to the appointment chewing gum, to distract [from it]. When thinking of the clinician assessment of severity, it is just a snapshot of the day.”

A growing number of treatments are now available for patients with TD. In April 2017, the FDA approved the first agent specifically for the disorder, valbenazine (Ingrezza), and in August 2017, the FDA also approved deutetrabenazine (Austedo) for the treatment of TD. However, following these approvals, identifying the correct patients for treatment remains a challenge, and clinician-assessed severity alone is often used as a measure.

“The payers have struggled with who should get these therapies,” Yonan said. “They have focused their restrictions on severity versus impact. These findings could allow for better alignment around patient selection and better utilization.”

The RE-KINECT study included 654 patients who were receiving antipsychotic treatment in outpatient psychiatry

practices. In cohort 1 ($n = 450$), patients did not show any signs of involuntary movement suggestive of TD while cohort 2 enrolled those with possible TD symptoms ($n = 204$). All patients had received antipsychotics for 3 months or more.

In cohort 2, regression analysis was conducted to assess the potential impact of TD on EQ-5D-5L scores, both by clinician measures and patient-rated severity. Clinicians and patients each rated TD severity across 4 body regions, and an overall assessment was the sum of the 4 regions. Patients also provided ratings for their perceived impact of TD on 7 individual daily activities. An overall impact on the ability to carry out daily activities was also calculated using the sum of the 7 activities.

The differences in HRQoL between groups remained consistent when adjusting for age, gender, and the type of psychiatric diagnosis. The mean utility score in those with TD ($n = 197$) was 0.71, compared with 0.78 in patients without possible TD symptoms ($n = 442$), representing a meaningful difference between the groups (adjusted $P < .0001$). Additionally, health state visual analogue score was lower in those with TD compared with those without (mean 66.8 vs 70.4; adjusted $P = .0134$).

A higher percentage of patients in cohort 2 noted having moderate (score 3) to severe or extreme (score 4 and 5) dimension scores on the EQ-5D-5L questionnaire, when compared with cohort 1, particularly for self-care and mobility ($P < .01$). For self-care, 9.9% of patients had a score of 3 and 5.9% had a score of 4 or 5 in cohort 2 compared with 4.3% and 2.5% for these scores, respectively, in cohort 1. Similarly, for mobility, 12.4% had a score of 3, and 9.0% had a score of 4 or 5 in cohort 2, compared with 8.3% and 3.8% for these scores, respectively, in cohort 1.

The largest differences in utility score between cohorts were seen in patients who noted having “a lot” of TD symptom severity and impact on activities of daily living. In the study, patients’ ranking of “a lot” was more reliable than the physician’s assessment, calling for greater doctor–patient communication for ascertaining severity.

“We found that when you asked about the impact, and did not focus on the severity, that was by far the biggest correlation with the quality-of-life measures,” Yonan explained. “We’re trying to shift the way practice goes so that, rather than looking through a window and trying to determine whether you’re severe or not, we just ask you.”

When patients provided utility scores of “a lot” there was a statistically significant difference between cohort 1 and cohort 2. Once adjusted for confounders, those with a clinician-indicated rating of “a lot” had a nonsignificant 0.044-point lower utility

