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The Impact of Chronic Obstructive Pulmonary Disease on Long-term Disability Costs

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JMCP employs extensive bias-management procedures intended to ensure the integrity and reliability of published work.
Ferdie Pacheco, MD, has been selected as the winning cover artist in JMCP’s 2004 Annual Call for Entries from artists with a pharmaceutical or medical background.

Pacheco has enjoyed a career as colorful as his paintings—he has even been called a “Renaissance man” because of his multiple talents and diverse professions. As disclosed in Pacheco’s biography on his Web site, www.ferdiepacheco.com, “He has been successful as a pharmacist, medical doctor, ‘Fight Doctor’ in boxing . . . working as a corner man for 12 world champions, including Muhammad Ali for 17 years.” He also served as a boxing commentator for NBC, Showtime, and Unvisión, winning two Emmys. During this time, he was the boxing consultant for NBC for 10 years.

He retired from broadcasting after being on air for 25 years. Pacheco has had 14 books published and written articles, columns, and reviews for many of the major newspapers in America. He has appeared as an actor, playing himself in the movie “The Great White Hype.” A movie he wrote for an Italian company, Pico Productions, called “Virtually Yours” has been distributed throughout Europe. A documentary on his life titled “Ferdie Pacheco, The World of the Fight Doctor” was shown on HBO in the summer of 2004.

Pacheco was born in Tampa, Florida, in 1927. His creativity was clearly evident by the age of five, when he began to draw and paint. His interest in art continued during his childhood and adolescence, but by his mid-teens he had decided to pursue a career in medicine. Nonetheless, he remained passionate about art, and he was able to utilize his skills as a cartoonist to finance his education at the University of Miami Medical School. Through medicine, he studied the human form, which, in return, gave his art anatomical integrity.

After receiving his medical degree, Pacheco set up a free medical clinic for indigent blacks in the poor Overtown section of Miami. Later, he opened a similar free medical clinic for Cubans. The young doctor was there to witness the first Cuban exiles as they began streaming into the city during the 1960s. His biography states, “In their stories, he found echoes of his own family’s immigrant roots, as his father was the Cuban-born son of a Spanish consul on the island. These are stories that would stock his repertoire of detail-laden, human anecdotes and inspire splashes of colors that he would transfer onto canvas.”

With Pacheco’s ancestry rooted in Spain, Latin artists as well as European and American artists have influenced his art. They include Mexican artist Diego Rivera, German artist George Grosz, Dutch artist Vincent Van Gogh, and American artist Thomas Hart Benton.

Pacheco has embraced the approach of many of these artists, who usually painted everyday people going about their lives, and through the painter’s brush strokes, a story is told that mere words could not express. This narrative style lends itself particularly well to murals. Pacheco was recently commissioned to paint four historical battle-scene murals.

Pacheco’s cover art, Portrait of Winston Churchill, is a fascinating mosaic of multiple hues and patterns. This semiabstract work successfully combines elements of Cubism and Pop Art. When asked why he chose to paint Churchill, Pacheco simply replied, “I paint my heroes.” There are many more portraits of his heroes, such as Albert Einstein, Franklin Delano Roosevelt, and Mahatma Gandhi, found in the Famous Faces category on Pacheco’s Web site. Other categories include paintings about the Civil War, Miami Cubans in exile, cigar workers, jazz and the arts, boxing and football, Frida Kahlo, Mexico, Spain, and Tampa.

All of his paintings are powerful—with a marvelous mix of bold colors and strong forms. While some are more realistic than others, each one conveys Pacheco’s spirited sense of humor, which brings his art to life.

Painting remains Pacheco’s passion, and the popularity of his work is increasing both in the United States and abroad. He was commissioned by Verizon to illustrate the cover of Tampa’s Yellow Pages, 2000-2001 edition. Another commission, for the West Tampa library, will be installed in early 2005. Pacheco’s art was also chosen to be placed in the permanent collection at the Florida State Capitol in 2004, and his paintings are in the collections of many leading personalities and celebrities. His artistic skills have earned him the Gold Medal and First Prize from the Centre Culturel in Tonneins, France, and First Prize for Best Colorist at Musée Du Luxembourg, Grand Duchy of Luxembourg.

Pacheco’s work is currently available for sale through his Web site, www.ferdiepacheco.com, Deck the Walls in Tampa, the Minds Eye Gallery in Fort Lauderdale, and the Artist in Residence Gallery in the Cocowalk Mall in Coconut Grove, Florida.

Sheila Macho
JMCP Cover Editor

COVER CREDIT

SOURCES
Interview with the artist.
www.ferdiepacheco.com
JMCP Author Guidelines

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3. Journal paginated by issue

4. Book or monograph by authors

5. Book or monograph with editor, compiler, or chairman as author

6. Chapter in a book

7. Government agency publication

8. Dissertation or thesis

9. Paper (or Poster) presented at a meeting

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• certifies that the paper has not been accepted for publication or published previously and that it is not under consideration by any other publication, and
• identifies the nature and extent of any financial interest or affiliation that any author has with any company, product, or service discussed in the manuscript.

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☐ keywords: follows the abstract
☐ references: cited in numerical order as they appear in the text (use superscript numbers) and prepared following modified AMA style, do not include footnotes in the manuscript.
☐ tables and figures (generally no more than a total of 6). Submit referenced tables and figures on separate pages with titles (and captions, as necessary) at the end of the manuscript; match symbols in tables and figures to explanatory notes, if included. May use 10-point font.

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REFERENCE

Prescribing of Antipsychotic Medication in a Medicaid Population: Use of Polytherapy and Off-Label Dosages

STEPHEN J. KOGUT, PhD, MBA; FELIX YAM, PharmD; and ROBERT DUFRESNE, PhD, PhD, BCPS, BCPP

ABSTRACT

OBJECTIVES: To describe the use of atypical antipsychotic medications in a Medicaid-enrolled population composed primarily of elderly and disabled patients. Our analyses focused upon the frequency of use of polytherapy with multiple antipsychotic medications and the prescribing of off-label dosages.

METHODS: We conducted a cross-sectional retrospective analysis of oral antipsychotic medication use, as prescribed for this population in 2003. The unit of analysis was the patient. We determined the prevalence of use of each type of antipsychotic medication according to gender and age group and determined the extent of use of combination therapies with multiple oral antipsychotic medications. Using the dosage ranges described in the product labeling, we identified the percentage of patients prescribed in-range dosages, overall and for each atypical antipsychotic medication studied. Those identified as receiving out-of-range (off-label) dosages were further stratified by gender and age group. The statistical significance of differences between these proportions was assessed using the chi-square test.

RESULTS: Of the 8,616 patients meeting our inclusion criteria, 7,748 (90%) received monotherapy with an oral antipsychotic medication and 888 patients (10%) received polytherapy with multiple oral antipsychotic medications. Approximately 2 of 3 patients receiving atypical antipsychotic medications were prescribed a dosage that was within the range recommended in the product labeling. Dosages lower than recommended in the product labeling were prescribed for 27% of patients receiving atypical antipsychotics, while 6% of patients received an above-range dosage. The frequency of patients receiving in-range dosages varied substantially among medications. Younger patients and female patients were more frequently prescribed below-range dosages of these medications (P<0.001 for both findings).

CONCLUSION: In this subpopulation of Medicaid enrollees who were prescribed antipsychotic medications, we found a 10% incidence of use of antipsychotic polytherapy and a 33% incidence of prescribing of dosages outside the range listed in the product labeling. These findings suggest that physicians commonly prescribe antipsychotic medications in a manner that differs from the recommendations described in the prescribing information. The off-label use of atypical antipsychotic medications raises important questions regarding the purpose and applicability of the product labeling and the role and ability of the pharmacist to provide information regarding the risks and benefits of therapy as commonly prescribed.

KEYWORDS: Antipsychotic, Atypical, Off-label, Polytherapy, Dosage, Prescribing


The atypical antipsychotic medications have rapidly become a leading drug expense category within Medicaid populations, which typically serve lower-income citizens, institutionalized seniors, and the disabled. Many patients within this population have psychiatric illnesses for which antipsychotic medications are commonly prescribed. The U.S. Food and Drug Administration (FDA) has approved the atypical antipsychotic medications for use in the treatment of schizophrenia (all atypicals) and bipolar disease (olanzapine, risperidone, and ziprasidone only), yet these agents are commonly prescribed "off-label" for a variety of other conditions, particularly where psychosis is a feature.

Despite a substantial difference in the direct cost of these medications compared with the conventional antipsychotics, several researchers have found the atypicals to be at least as cost effective as the conventional antipsychotics.6-9 These medications also provide advantages in terms of decreased motoric side effects such as drug-induced parkinsonism, tardive dyskinesia, and akathesia6,7 and improved efficacy in treating negative symptoms of schizophrenia such as avolition (absence of initiative or motivation to begin and maintain behavior in pursuit of a goal) and flat affect.8,10 Also, the newer agents have shown advantages in terms of improvement in health-related quality of life.11,12 These medications have also been shown to be cost effective.13,14 However, pharmacoeconomic studies have evaluated the cost-effectiveness of various atypical agents when administered in dosages used in clinical trials and as approved by the FDA. The cost-effectiveness of the atypical antipsychotics when used in combination therapies or when prescribed at dosages above or below the recommendations described in the product labeling has not been well studied.

While physicians may legally prescribe medication at dosages outside of the parameters recommended in the product

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Methods

We conducted a cross-sectional study of antipsychotic medication use among Rhode Island Medicaid enrollees to describe the use of antipsychotic medications as most recently prescribed for patients during 2003. The state of Rhode Island provides a managed care insurance program that serves a proportion of nonsenior residents who are eligible for the program based upon low income (categorically needy). A majority of Medicaid-eligible senior and nonsenior disabled patients receive their care through a fee-for-service program component that is administered by the state's Department of Human Services. This fee-for-service population comprised the universe of patients available for our study. Our analyses were conducted solely using pharmacy claims data, which included patient age, gender, and information pertaining to the dispensed prescription. The Rhode Island Medicaid pharmacy program does not restrict the use of antipsychotic medications, nor are any particular medications considered preferred.

The unit of analysis was the patient. There were 59,498 patients enrolled in the fee-for-service component and receiving prescription medication during 2003. Seniors (aged 65 years or older) comprised 31% of the population. Among patients receiving prescription medications, 10,470 (18%) received at least 1 dispensing for an oral antipsychotic medication (n=8,761). This total does not include patients receiving an antipsychotic medication in liquid form (n=1,505); these patients were excluded because we could not reliably calculate the dosage prescribed for liquid products given the limitations of our data source. Additionally, we excluded 63 patients who received an injectable product as their most recent dispensing of an antipsychotic medication.

We also attempted to distinguish users of combination antipsychotic therapy (polytherapy) from patients who were switching therapies. Patients were classified as users of polytherapy if they received at least 2 dispensings of the 2 different antipsychotic medications during the 90 days prior to the most recent dispensing. All other patients receiving more than 1 type of oral antipsychotic medication were considered to be recent switchers and were excluded (n=83). The resulting sample

---

### FIGURE 1

Selection of Patients for Analyses of Prescribed Dosages of Atypical Antipsychotic Medications

<table>
<thead>
<tr>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>59,498</td>
<td>Medicaid enrollees in fee-for-service component receiving at least 1 prescription dispensing during 2003</td>
</tr>
<tr>
<td>10,470</td>
<td>Patients receiving at least 1 prescription dispensing for any type of antipsychotic medication</td>
</tr>
<tr>
<td>8,698</td>
<td>Patients receiving at least 3 prescription dispensings for an oral solid (excluding nonliquid) antipsychotic medication</td>
</tr>
<tr>
<td>8,616</td>
<td>Patients who were not recently switching antipsychotic drug therapy (within past 90 days)</td>
</tr>
<tr>
<td>7,759</td>
<td>Patients who were users of risperidone, olanzapine, quetiapine, aripiprazole, or ziprasidone</td>
</tr>
</tbody>
</table>

Higher dosages of atypical antipsychotic medications may provide benefit for a percentage of patients who do not respond to recommended dosages, but the risk associated with using higher dosages of an atypical antipsychotic medication has not been as well studied. Additionally, the use of below-range dosages of the atypical antipsychotics merits examination. Though prescribers may act from concern regarding the use of these potent medications in elderly or frail individuals, the use of low-dose therapy may nevertheless cause adverse effects while failing to elicit a worthwhile therapeutic response.

The objective of our study was to assess the manner in which atypical antipsychotic medications are prescribed in a Medicaid population comprising mainly elderly and disabled patients. We sought to determine the extent of use of combination oral antipsychotic therapies and the prevalence of prescribing off-label dosages. We compared dosages of the atypical antipsychotics as prescribed among older and younger patients, among genders, overall, and for specific agents. We did not presume that the prescribing of off-label dosages was inappropriate per se; rather, our aim was to better understand how these medications are prescribed and to identify opportunities for improving and studying the efficacy of the use of these medications in the population.
Prescribing of Antipsychotic Medication in a Medicaid Population: Use of Polytherapy and Off-Label Dosages

of 8,616 patients comprised the population of study for the analyses of frequencies of use of various oral antipsychotic regimens. The sample selection criteria and totals of patients identified are presented in Figure 1.

We determined the prevalence of use of specific antipsychotic medication regimens based upon the most recent dispensing for such products occurring during the study year. Patients identified as receiving antipsychotic polytherapy were categorized as either receiving polytherapy with an atypical plus a conventional antipsychotic medication or polytherapy with 2 different atypical antipsychotic medications. The prevalence of use of polytherapy was stratified by gender and by age group (age less than 18 years, age 18 to 64 years, and age 65 years or older).

The percentage of therapies used in off-label dosage was determined for patients receiving atypical antipsychotic medications, as attributed to the dosage of the most recently dispensed prescription during the year. For this prescription, we calculated the mean daily dose by dividing the quantity of medication dispensed by the days supply received and multiplying this quotient by the strength (in milligrams) of the dispensed medication. Recommended dosages for each atypical medication were identified from the prescribing information as obtained from each manufacturer's Web site (accessed in June 2004). Where the dosage range varied by indication, age, or clinical condition, we used the lowest and highest possible range of dosages that appeared in the product labeling. FDA-recommended in-range dosages as described in the product labeling were as follows—aripiprazole: 10 to 30 mg, quetiapine: 150 to 750 mg, olanzapine: 5 to 20 mg, risperidone: 1 to 8 mg, and ziprasidone: 14 to 160 mg. We did not include patients receiving clozapine in these analyses because we believed that those receiving this medication were more likely to have severe disease and/or have failed other therapies and because this medication was often dispensed in a 1-week supply, a feature that added considerable complexity to the analyses.

Several patients were prescribed "odd" dosages of medication and received different prescriptions for the same medication (e.g., 2 mg of risperidone in the morning and 3 mg at bedtime). Such patients were included in our analyses if the two prescriptions for different strengths of the same medication were received on the same date during the two most recent dispensings. For these 281 patients, we calculated the total dose by adding the daily dosages of the two separate prescriptions.

We determined the frequency and percentage of patients receiving dosages below or above the recommended range, overall, and for users of each particular atypical antipsychotic agent. The frequency and percentage of patients receiving below- or above-range dosages were stratified by gender and age group (seniors versus those younger than 65 years). Differences in the proportions of males and females receiving off-label dosages was evaluated through cross-tabulation, and the statistical significance between differences in these proportions was determined using the chi-square test. Differences in the proportion of senior and nonsenior patients receiving off-label dosages were assessed in the same manner. The level of significance was set at \( P<0.05 \), with a minimum of 5 observations per cell required for reporting probabilities. These analyses were performed using SAS version 8.1 for microcomputers.

Results

Of the 59,498 Medicaid fee-for-service program enrollees receiving prescription medication during 2003, nearly 1 in 5 received a dispensing for an antipsychotic medication. A total of

| TABLE 1 | Frequency and Percentage of Use of Antipsychotic Medications Within a Medicaid Population: Overall Use and Use of Polytherapy, Stratified by Gender and Age Group |
|----------------|-------------------------------------------------|--------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Patients Prescribed Antipsychotic Medication* | % Using Polytherapy† | % Using Polytherapy: Atypical + Conventional | % Using Polytherapy: Atypical + Atypical |
| Gender | n | % | n | % | n | % | n | % |
| Male | 3,685 | 42.8 | 455 | 12.3 | 93 | 2.5 | 362 | 9.8 |
| Female | 4,931 | 57.2 | 413 | 8.4 | 87 | 1.8 | 326 | 6.6 |
| Age (years) | | | | | | | | |
| <18 | 554 | 6.4 | 25 | 4.5 | 4 | 0.7 | 21 | 3.8 |
| 18-64 | 5,477 | 63.6 | 710 | 13.0 | 152 | 2.8 | 558 | 10.2 |
| 65+ | 2,585 | 30.0 | 133 | 5.1 | 24 | 0.9 | 109 | 4.2 |
| Total | 8,616 | 100 | 868 | 10.1 | 180 | 2.1 | 688 | 7.9 |

* Received at least 3 dispensings for an oral antipsychotic medication during 2003. † Polytherapy = concomitant use of 2 or more different antipsychotic medications.

| TABLE 2 | Frequency and Percentage of Use of Atypical Antipsychotic Medications and Conventional Antipsychotics Prescribed as Monotherapy or Polytherapy |
|----------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| n | % |
| Monotherapy | | |
| Risperidone | 2,283 | 26.5 |
| Olanzapine | 2,275 | 26.4 |
| Quetiapine | 1,756 | 20.4 |
| Aripiprazole | 382 | 4.4 |
| Clozapine | 346 | 4.0 |
| Ziprasidone | 195 | 2.3 |
| Conventional agent | 511 | 16.0 |
| Subtotal =7,748 | | |
| Polytherapy | | |
| Atypical + conventional | 180 | 2.1 |
| Atypical + atypical | 688 | 8.0 |
| Subtotal =868 | | | |
| Total | 8,616 | 100 |
8,616 patients met our criteria of receiving at least 3 dispensings for any oral, nonliquid antipsychotic medication during the year, a majority of which were nonsenior adults (64%). The use of polytherapy with multiple antipsychotic agents was more frequent among males for both polytherapy with atypical or conventional agents. The use of polytherapy was also more frequent among nonsenior adults than among seniors (13% versus 5%). These results are presented in Table 1.

Of the patients meeting our study criteria, 7,748 (90%) were identified as receiving monotherapy with an antipsychotic medication, and 7,327 (94%) of these patients were receiving monotherapy with an atypical antipsychotic medication. Approximately three quarters of patients receiving antipsychotic medication were users of monotherapy with risperidone, olanzapine, or quetiapine. Of the approximately 10% of patients identified as receiving polytherapy, the majority (688 of 868, or 79.3%) received 2 atypical antipsychotic drugs, while 2.1% of all patients received polytherapy with an atypical plus a conventional antipsychotic medication (21% of patients who received polytherapy) (Table 2).

Figure 2 presents dose range categories for the prescribed dosages of atypical antipsychotic medications regardless of whether the medication was used alone or in polytherapy with another antipsychotic agent. Overall, approximately 1 in 3 patients was prescribed an atypical antipsychotic medication at a dosage that was below the range recommended in the product labeling. The majority of off-label dosing was for below-range dosages, as 27% of patients received medication at a dosage that was below the range recommended in the product labeling. In-range dosing was more frequent among users of aripiprazole (94%) and ziprasidone (85%) as compared with the other atypical antipsychotic medications. Quetiapine was prescribed within the recommended range least frequently; users of this medication received below-range dosages as frequently as they received in-range dosages (47%). Use of below-range dosages was next most frequent among users of risperidone (25%) and then olanzapine (17%), with 7% of ziprasidone users and 5% of aripiprazole users receiving below-range dosages.

Use of above-range dosages was much less frequent than the use of below-range dosages. Overall, 6% of patients received medication at dosages that were higher than recommended in the product labeling. The percentage of patients receiving above-range dosages was 9.5% for olanzapine, 8% for ziprasidone, 6% for quetiapine, 3% for risperidone, and 2% for aripiprazole.

For patients receiving above- or below-range dosages, we determined if the use of such dosages was more frequent among particular age groups or by gender. These stratifications are presented for those receiving above- and below-range dosages in Figures 3 and 4, respectively. Patients receiving above-range dosages were overall more frequently male and younger than 65 years (P<0.001 for both). Male and younger patients were also more frequently prescribed above-range dosages of olanzapine and quetiapine as compared with female or senior patients, respectively. Each of these findings was statistically significant.

The use of above-range dosages of risperidone, ziprasidone, or aripiprazole did not differ in statistical significance among age...
groups or by gender, though in most cases these subgroups were too small to analyze.

In contrast to patients receiving above-range dosages of these medications, users of below-range dosages were more frequently female and above age 65 years ($P < 0.001$ for both). Quetiapine, the agent most frequently prescribed in below-range dosages, was prescribed in below-range dosages for 72.5% of seniors using this medication. While seniors were more frequently prescribed below-ranges dosages of quetiapine as compared with nonsenior patients (72.5% versus 40%, $P < 0.001$), the percentage of males (47%) and females (50%) prescribed below-range dosages of this medication did not differ in statistical significance. For each of the atypical antipsychotics, seniors were more frequently prescribed below-range dosages than nonsenior patients, though the percentage of use of below-range dosages among seniors varied considerably among medications. Slightly more than half of senior patients (51%) receiving risperidone were prescribed a dosage that was below the recommended range. This proportion was substantially greater than the percentage of below-range dosages prescribed for seniors using ziprasidone (21%) or aripiprazole (12%). Use of below-range dosages of quetiapine, ziprasidone, and aripiprazole was similar among males and females, while females were more likely than males to receive below-range dosages of olanzapine or risperidone ($P < 0.001$ for both findings).

**Discussion**

In this population of Medicaid-enrolled seniors and disabled patients, we found a high rate of prescribing of antipsychotic medications in off-label dosages. Most of such prescribing was for dosages below the recommended range, though approximately 6% of patients received dosages that were above the range recommended in the product labeling.

As may be expected, seniors were more frequently prescribed below-range dosages, while above-range dosages were more frequently prescribed for nonsenior patients. This trend, observed for all of the atypical antipsychotic agents prescribed, may likely be mainly attributed to the condition for which the medications were prescribed. It is probable that younger patients were more frequently prescribed these medications for the treatment of schizophrenia or bipolar disorder, while older patients may have more frequently received these medications for off-label conditions such as psychosis or agitation, where lower dosages are commonly prescribed. We note, however, that we did not possess information describing patient diagnoses, and, hence, this interpretation is largely speculative. While we did not examine diagnosis codes to attempt to determine the conditions for which these medications were prescribed, our primary objective was to quantify the extent of off-label dosing regardless of the condition being treated. Furthermore, the reliability of using diagnosis codes from medical claims to identify schizophrenia and related disorders may be questionable.$^{29,29}$

Though not specifically recommended in the product labeling or in current treatment guidelines for schizophrenia$^{30}$ or bipolar disorder,$^{31}$ the use of polytherapy with multiple atypical antipsychotic medications has been identified as an increasingly common practice.$^{15,17,32,33}$ Thus, we were not surprised to find that many patients were receiving multiple antipsychotic medications concomitantly. Indeed, the use of antipsychotic polytherapy was quite common in the population, particularly among younger patients. Roughly 1 in 10 nonelderly patients received therapy with multiple atypical antipsychotics. It is possible that some of these patients were transitioning to different therapies, though we did attempt to exclude patients who were switching therapy, as described above.

Though several reports from smaller trials provide evidence to support the potential effectiveness of antipsychotic polytherapy for patients with treatment-resistant disease,$^{21,22,34}$ no atypical antipsychotic has gained FDA approval for use in combination with other atypicals. Furthermore, the American Psychiatric Association’s treatment guidelines for schizophrenia$^{30}$ do not support the use of polytherapy as routine practice. While the use of antipsychotic polytherapy was found to be fairly common in the population studied here, limited information is available regarding the safety of using multiple antipsychotic medications concomitantly. When used as monotherapy, these agents are known to cause potentially significant adverse effects. Many of these agents have been found to increase plasma glucose levels,$^{35}$
The atypical antipsychotic medications are associated with other problematic side effects. To varying degrees, these agents can cause sedation, anticholinergic side effects, and QTc prolongation. However little is known about the prevalence and severity of these side effects when atypicals are used in greater than recommended dosages or in combination with each other. At the very least, the benefit-to-risk ratio should be reconsidered when polytherapy is initiated. However, there is a paucity of larger and long-term clinical trials of the use of antipsychotic medications in higher dosages or in combination.

While high doses of atypical antipsychotic agents may be incrementally effective for treatment-resistant patients, the evidence supporting this use is primarily drawn from smaller studies that do not adequately assess the frequency and extent of adverse events likely to be experienced. For example, Lerner et al. describes the effectiveness of high-dose olanzapine as prescribed for 3 patients with treatment-resistant schizophrenia, while Brotman et al. presents a case series of 8 patients receiving high-dose therapy. High-dose therapy may be a useful option for selected patients, yet the relative lack of information pertaining to the safety of such dosages is of concern. It was encouraging in our study to find a small percentage of elderly patients (less than 1%) who received higher dosages of antipsychotic medications, but nearly 8% of nonelderly patients received atypical antipsychotic medication in dosages above the recommended range. This suggests that the use of high-dose therapy in younger adult patients is fairly common, at least within this Medicaid subgroup.

Though the use of below-range dosages may be of lesser concern in terms of the safety and risks of therapy, one may question the rationale for using these medications in potentially subtherapeutic dosages. The in-range dosages applied in our analyses included dosages recommended for frail and elderly patients. As such, patients identified as using below-range dosages were prescribed medication in dosages that were below what was found to be efficacious in the clinical trials upon which the FDA-approved labeling is based (though such trials generally do not include frail and/or elderly patients). Perhaps prescribers were merely exerting caution when using these agents in elderly patients. Lower dosages of atypical antipsychotics are associated with a reduced incidence of motoric side effects such as tardive dyskinesia, but placebo-controlled trials demonstrating the efficacy of low-dose therapy in the treatment of schizophrenia or bipolar disease are lacking.

It is possible that many elderly patients in the population we studied received these medications in low dosages for off-label indications such as agitation or insomnia. This may be particularly true for the use of quetiapine, which was prescribed in below-range dosages for nearly 3 of 4 seniors receiving this medication. We also considered the possibility that patients receiving low-dose therapy may have been more likely to be users of polytherapy. However we found the converse to be true—patients prescribed below-range dosages of atypical antipsychotics were less likely to be receiving multiple antipsychotic agents than were users of higher dosages (6% versus 13%, P < 0.001).

Overall, these findings provide evidence that the FDA-approved labeling describing the indications and recommended dosages of these agents appears to correspond poorly with how atypical antipsychotics are prescribed in practice. Yet it is important to note that our findings do not necessarily indicate that medications were prescribed inappropriately. It may be argued that the off-label use of medications reflects emerging knowledge and that the product labeling may fail to keep pace with new findings pertaining to the scope or utility of medications.

The FDA’s supplemental new drug approval (sNDA) process provides a mechanism for updating the product labeling to include new indications and updated dosages. However, the costs associated with the submission of an sNDA may present a disincentive to manufacturers, especially when a new indication or dosage pertains to a smaller subpopulation of potential medication users. Furthermore, the efficacy of the medication for a new use or dosage may fail to be substantiated when subjected to the rigorous study required for submission of an sNDA, creating a disincentive for manufacturers to submit such an application. The need for a manufacturer to obtain an sNDA is lessened further when physicians rely upon personal experience and the opinions of others when prescribing medications. Thus, at least partially as a consequence of the above considerations, there exists a complex dynamic between the FDA-approved usage of a medication versus published evidence from recent trials and experience gained from prescribing a medication in practice.

The off-label prescribing of these medications presents important issues from the perspectives of the practicing pharmacist and for those responsible for the pharmacy benefit. The practicing pharmacist must be aware that the risks described in the product labeling directly pertain to the use of the medications for approved indications and when prescribed at recommended dosages. The use of polytherapy with multiple antipsychotic medications or the prescribing of above-range dosages warrants careful consideration of the potential for benefits and risks. The dispensing pharmacist can provide a service to prescribers and other members of the health care team by making them aware of patient cases in which the prescribed therapy is considered to be off-label and by alerting providers to the need for increased attention to monitoring for effectiveness and signs of adverse reactions.

The implications for those responsible for providing the pharmacy benefit are less straightforward. The atypical antipsychotics are an expensive class of medications, but these drugs have become common in the care for patients with psychosis, and can be cost effective when used appropriately. How then should these medications be used most appropriately within a population? Some may interpret “appropriate use” as the prescribing of these products only for labeled indications...
Prescribing of Antipsychotic Medication in a Medicaid Population: Use of Polytherapy and Off-Label Dosages

and at recommended dosages. Formulating policy upon such an interpretation may prove to be difficult given the extent of off-label usage as described here and by others. Most importantly, such a policy is not likely to benefit patients when off-label uses offer a therapeutic advantage. Nevertheless, one may question if the pharmacy benefit should provide for the use of expensive therapies that have not been assessed for safety and effectiveness. The use of such therapies may be justified where off-label regimens benefit patients more than they harm them, but it is often not possible to know a priori when this might be the case.

Analyses such as the type described here can provide the basis for interventions designed to align prescribing within appropriate dosing parameters, as determined through review of the available evidence, and by collaborating with clinicians having expertise in the use of these medications. Such interventions may potentially include provider profiling, academic detailing, or other educational initiatives designed to inform prescribers about the risks and benefits of the off-label use of these medications.

Another approach is to require that appropriate diagnoses exist prior to initial prescription. Policy makers must be careful when developing criteria for such a strategy, since the use of atypical antipsychotic medications for off-label conditions may offer a meaningful therapeutic benefit for certain patients.

Lastly, we note that on-screen edits alerting the pharmacist to the prescribing of off-label dosages can be helpful for identifying dosage errors and prompting the pharmacist to contact the prescriber to ensure that the proper medication dosage is prescribed. While the prescriber may ultimately decide which medication dosage is employed, a clinically sound and prescribed. While the prescriber may ultimately decide which dosage errors and prompting the pharmacist to contact the prescribing of off-label dosages can be helpful for identifying which medications for off-label conditions may offer a meaningful therapeutic benefit for certain patients.

Limitations

Our research included several limitations that should be acknowledged. Most important, pharmacy claims were our sole data source, and we did not determine the conditions for which these medications were prescribed. It is possible that our results may be biased by inaccuracies in the pharmacy claims data. For example, since we did not audit or otherwise verify the dosages of medication prescribed (e.g., through review of medical charts), it is possible that inaccurate values in pharmacy claims for the days supply or quantity of medication dispensed were a source of error. Also, we did not determine the duration of use of these medications and dosages.

Though our inclusion criteria specified that patients must have received at least 3 dispensings of antipsychotic medication, it is possible that some patients receiving below-range dosages would have eventually been titrated upward to an in-range dosage.

Additionally, we did not examine other factors that may have further explained our findings. For example, dosReis et al. found that African-American Medicaid enrollees more frequently received higher dosages of antipsychotic medications than other racial groups, while Galletly and Tsourtos found that schizophrenic patients receiving lithium, carbamazepine, or benzodiazepines were more likely to receive higher dosages of antipsychotic medications. Finally, we should note that our findings apply only to this population of aged or disabled Medicaid enrollees. Generalizations to other populations should be made with caution.

Conclusion

In this subpopulation of Medicaid enrollees, we found that many patients (33%) were prescribed atypical antipsychotic medications in off-label dosages, and many patients (10%) received multiple antipsychotic medications. These findings suggest that physicians commonly prescribe antipsychotic medications in a manner that differs from the recommendations described in the prescribing information. Pharmacists have an important role in working with the health care team to ensure that the risks and benefits associated with the off-label use of antipsychotic medications are carefully considered and that patients are appropriately monitored. From a policy perspective, the off-label use of atypical antipsychotic medications raises important questions regarding the purpose and applicability of the product labeling, particularly in the context of current prescribing practices.

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REFERENCES


The Impact of Chronic Obstructive Pulmonary Disease on Long-term Disability Costs

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ABSTRACT

OBJECTIVES: Chronic obstructive pulmonary disease (COPD) as a cause of disability with subsequent costs remains poorly recognized. The small, growing body of literature on COPD shows that it is one of the leading causes of missed work—greater than asthma or diabetes. However, much less is known about the impact of COPD on long-term disability (LTD). Because the health care burden for disabled, working-age patients will fall heavily on managed care organizations, better estimates of the economic and pharmacoeconomic costs of COPD are required. We seek to improve understanding of the burden of COPD on several national LTD programs.

METHODS: We reviewed occupational health and disability literature and government statistics to determine how long-term, respiratory-related disability is addressed by disability pension programs in 8 developed countries (Canada, France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States). We then applied respiratory-specific disability definitions to country-specific population and pension information to estimate the potential burden of COPD on LTD insurance programs in each country.

RESULTS: Comprehensive, relevant data to evaluate respiratory-related disability are lacking. Of the study countries, only the United States has explicit respiratory-specific criteria for disability eligibility, which are based solely on spirometry. We estimate that the total burden of COPD in the study countries may range from $5 billion to as high as $25 billion per year if all persons who met U.S. eligibility criteria for respiratory-related disability were granted compensation.

CONCLUSION: The potential burden of COPD on LTD programs may be large. The lack of standard criteria for respiratory-related disability may lead to under-recognition of COPD’s true potential impact. Further work is needed to develop consistent and cost-effective ways to measure the impact of COPD and to assist in disability determination for COPD patients.

KEYWORDS: Chronic obstructive pulmonary disease, Disability insurance, Costs and cost analysis

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Chronic obstructive pulmonary disease (COPD) is a prevalent disease whose management incurs very high expenditures and exacts significant economic losses worldwide. In the United States, the age-adjusted prevalence of COPD is estimated at 60 per 1,000 persons above the age of 25 years.1 Internationally, reports of prevalence rates vary from 4% to 11%.2 Worldwide, the burden of COPD in disability-adjusted life years was estimated to be twelfth highest (29.1) in 1990 and is projected to rise to fifth place by 2020.3 Prevalence of the disease increases with age, and it is associated with certain risk factors of which the most important is smoking. Passive smoking, exposure to occupational dust and chemicals, infections, and genetic predisposition are other less strongly associated factors.1 COPD places a substantial burden on patients by causing decreased lung function and associated symptoms.4-6 Individuals with COPD have significantly poorer functional health than the average adult.7 In addition, acute exacerbations of COPD lead to further erosion of quality of life, absenteeism, and greater use of health care resources.4,8 COPD is preventable but not fully reversible (GOLD definition9). The slow, inexorable decline in health toward the terminal phase plays a role in creating a prolonged period of need for compensation and appropriate health care. In the United States, the burden of providing care for disabled, working-age patients will fall heavily on managed care organizations; better estimates of the economic and pharmacoeconomic costs of COPD are required.

These costs will likely be substantial. In the United States, the total economic burden of COPD was estimated to be $32.1 billion in 2002, with direct medical costs accounting for $18 billion. Disability and premature death due to COPD cost the United States an additional $14.1 billion in lost income.1 Disability payments to incapacitated workers by national governments alone are quite large, averaging nearly 1% of national gross domestic product for the 8 countries reviewed in this report.9 Further, an economic analysis of data from a large-scale international survey conducted in 7 countries (Canada, France, Italy, the Netherlands, Spain, the United Kingdom, and the United States) estimated the total economic burden of COPD to be $5,646 annually per patient.10

Although the drivers of direct medical cost expenditures are increasingly recognized throughout the world, the impact of COPD on worker disability is less well understood. A recent study of California adults showed that COPD has a much greater impact than asthma on absence from work, perceived inability to work, and perceived limitation in type or amount of work.11 The prevalence of current employment among adults
The Impact of Chronic Obstructive Pulmonary Disease on Long-term Disability Costs

with COPD was 46.5%, whereas current employment among those with asthma was 67.6%. The risk for someone with COPD experiencing a prolonged absence from work was almost 3 times that of a normal population (OR 2.92). This is not the case for asthma or any other respiratory disease. Adults with COPD were also more likely to indicate a perceived inability to work (OR = 12.90). Such individual-level outcomes translate into significant productivity losses at the national level. In the United States, COPD is the sixth leading cause of lost workdays after back problems, mood disorders, motor vehicle accidents, acute respiratory infections, and arthropathies.

This paper estimates the impact of COPD on the national long-term disability (LTD) programs, the primary source of compensation for LTD, in 8 countries. There is no strict definition of LTD that can be applied uniformly to all 8 study countries; nonetheless, LTD is generally defined as an inability to engage in full-time employment for 6 months or more due to a medical condition. Despite the large burden that COPD poses, the magnitude of LTD due to COPD still remains largely unrecognized. There is very little available literature to document how COPD impacts LTD insurance programs. Moreover, efforts to increase the recognition and diagnosis of COPD* can be predicted to increase patient awareness, and the future impact of COPD on LTD may be even greater. For instance, Danish researchers found that over a 20-year period (1977-1996), the mean FEV₁ (forced expiratory volume in 1 second) of COPD patients seeking a disability pension increased from 45% of predicted normal to 53% of predicted normal (P < 0.05), suggesting that, over time, more and healthier people are seeking compensation.

To better understand the linkage between COPD and LTD insurance, this study seeks to answer the following:

- How is respiratory-related LTD assessed and defined in several developed countries?
- What is the potential financial impact of COPD on LTD pensions in these countries?

**Methods**

The analysis consisted of a 2-phase approach. First, we performed a review of the international occupational health and disability literature (available in the English language) to identify all articles that addressed respiratory-related disability, with a particular focus on COPD. This literature was supplemented with review and assessment of published government statistics for the 8 developed countries of interest for this analysis: Canada, France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States. These countries were selected for inclusion because of the availability of English-language literature and the presence of large national pension programs.

Second, based upon the information from the above review, we calculated a standardized estimate of the financial burden of COPD due to LTD for each nation. These estimates were derived by multiplying (1) an estimate of the number of working-age persons with respiratory disability by (2) the LTD compensation rates for each country. Reflecting the very limited availability of data on this subject, this method was necessarily simplistic and subject to a number of assumptions as detailed below. The steps in the cost estimation were as follows:

1. We used the U.S. Social Security Administration (SSA) spirometry guidelines as a standard to estimate the number of persons eligible for respiratory-related disability. Our review of the English-language literature and government statistics indicated this was the only objective, respiratory-specific criterion used in definition of disability due to respiratory impairment. An objective measure such as this was essential for estimation of the number of persons in our calculations. The SSA criteria for disability eligibility are listed in Table 1.

2. We determined the proportion of the U.S. working-age population (20-64 years) that meets these spirometric criteria using the individual-level data on height and spirometry from the U.S. Third National Health and Nutrition Examination Survey (NHANES III). A complete description of the NHANES III survey methodology has been previously published. The age range of 20 through 64 years was chosen to be consistent with population data for other countries (which use age 20 as a lower cutoff point and the common retirement age of 65 as the upper cutoff point). Regarding that proportion as the maximum number of potentially eligible persons, we further searched government statistics to find the number of people who actually receive compensation. We regarded this as the minimum number of eligible persons.

3. The SSA spirometric criteria are only one component of the disability determination decision in the United States; not all persons falling below the FEV₁ threshold for their height will be granted disability compensation. As such, we view these criteria as generating an upper bound on the estimated number of persons granted compensation. This upper bound was 0.54% of the population between the ages of 20 and 64 years, or 896,500 persons. The number of persons granted LTD compensation by the SSA in 2002—178,300—represents the lower-bound estimate in our calculations.
The ratio between the lower- and upper-bound estimates is approximately 1 to 5.

- The maximum and minimum estimates reflect different aspects of disability determination. The maximum is an estimate of all persons eligible for disability based upon SSA spirometric criteria alone. Thus, it is strongly associated with the prevalence and severity of COPD in a particular country. The lower-bound figure estimates the current number of persons granted disability as being the same as in the United States and thus reflects administrative procedures and the multifactor nature of physical disability.

4. Sensitivity analyses were performed on the estimated numbers of persons eligible for disability compensation using data on COPD prevalence in study countries. Halbert et al. recently summarized estimated prevalence of COPD in many countries. They found wide variation in methods, representativeness of study samples, and final prevalence estimates. We used prevalence estimates from studies with the most representative samples and objective measurement techniques available. Estimated numbers of disabled persons were adjusted in this analysis based on the measured prevalence of COPD in study countries relative to its prevalence in the United States. For example, if the prevalence in Country A was 50% lower than the prevalence of COPD in the United States, the estimated number of disabled persons was reduced by 50%. COPD prevalence estimates used are reported in Table 2.

5. Finally, we calculated maximum and minimum expected payments using the estimated eligible persons and the average benefit levels for each country. Total payments were also calculated for the estimates adjusted for COPD prevalence. We calculated total payments at a national level and respiratory-related disability payments per person of working age. All results were presented in U.S. dollars (USD) by converting local currencies into USD using the exchange rate prevailing July 1 of the reference year; except where noted, the reference year is 2002.

### Results

#### Disability Programs

Benefits paid to those disabled by respiratory conditions are part of much larger social insurance programs administered by various government agencies. In many countries, employers bear a significant financial burden for national disability pension programs. Table 3 provides a synopsis of funding sources and benefit levels of national disability pensions in each of the study countries.

Disability pension program similarities across the 8 countries include the following:

- Governments often provide substantial support for the programs from general funds, with the exception of Spain. In the United States, a variable contribution is made from U.S. treasury general revenues toward income supplements. The primary burden is financed through social security payroll taxes paid by workers and their employers. The Japanese government makes the greatest contribution, with up to one third of program costs. The United Kingdom’s treasury may subsidize the program by up to 17% of total benefits payments; this is in addition to costs of means testing (determining individual eligibility) for the program.

- Benefits vary according to one or more of the following: age, years of contributions, and average earnings for a fixed time period prior to disability. Average benefits range from 21% (Japan) to 73% (United Kingdom) of average private-sector wages. This wide variation appears to depend on the social welfare ideology of the nation under consideration, as our results showed only a weak correlation with percentage...
conditions that may lead to disability. Rather, they rely on overall assessments of the impact a medical condition has on a person's ability to perform productive work. Only Japan and the United States have respiratory-specific criteria for establishing eligibility for respiratory-related disability (Table 4).

The Japanese respiratory criteria are subjective categorizations of restrictions to activities in home and social environments. Such measures appear to be related to quality-of-life measures such as the physical and social functioning indices of the Short Form 36 Health Survey. In addition, while criteria are defined as respiratory-specific, they are relevant to virtually any disease state.

The SSAs “Blue Book” provides explicit spirometric criteria to evaluate respiratory-related impairment. These criteria are minimum FEV1 thresholds for given height ranges. The criteria do not account for normal variations in gender, age, or race or nonlinearities with height, as would be possible when using established spirometric reference values.

**Estimated Impact of COPD on LTD Programs**

We found no studies in the international English-language literature to adequately quantify the impact of COPD on LTD programs. Accurate epidemiological data that could be used to quantify such impact has been described as difficult and expensive to collect for several reasons. First, determination of disability due to COPD is not objectively codified in most countries. This makes extracting data difficult. Second, COPD is usually only diagnosed in its end stages; therefore, its role in disability compensation prediagnosis cannot be correctly assessed. Third, COPD has been recognized as not just one disease but as a group of diseases with multiple differential diagnoses; therefore, diagnosis is variable and imprecise, and morbidity and ensuing disability are difficult to quantify. Finally, it is a disease more likely to be cited as a contributory rather than an underlying cause of mortality. In many instances, it is not quoted at all. Thus, we applied a deterministic model (described under “Methods”) for estimating a range of the potential burden of COPD on LTD.

By applying the SSA respiratory-specific disability eligibility criteria to the U.S.-based NHANES data, we estimated that 0.54% of the working-age population are potentially eligible for respiratory-related disability. Table 5 lists the derived minimum and maximum estimates of working-age persons in each study country who would be eligible for respiratory-related LTD.

Figure 1 illustrates our estimates for the potential financial impact of COPD on government-administered LTD programs. The maximum potential burden of COPD, corresponding to the maximum number of persons eligible for disability, and the minimum estimated burden, corresponding to the minimum number of eligible persons, are depicted. Bars representing variation due to differences in COPD prevalence are also shown. In summing up the results of Figure 1, it can be said that the total estimated burden of COPD-attributable disability in the

**TABLE 3 National Disability Program Funding Sources and Benefit Levels**

<table>
<thead>
<tr>
<th>Country</th>
<th>Private Sector Contributions</th>
<th>Government Funding</th>
<th>Average Benefit/ Month (U.S. $)</th>
<th>% of Average Wage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>3.5</td>
<td>Means testing and cost of basic pension</td>
<td>532</td>
<td>24</td>
</tr>
<tr>
<td>France</td>
<td>6.55</td>
<td>Variable subsidies</td>
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<td>Germany</td>
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<td>Subsidies for shortfalls</td>
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<td>58</td>
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<td>8.89-9.9</td>
<td>Means testing and subsidies for shortfalls</td>
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<td>38</td>
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<td>8.675</td>
<td>Administrative costs and up to 33% of total benefits</td>
<td>539</td>
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<td>Spain</td>
<td>4.7</td>
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<td>53</td>
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<tr>
<td>United Kingdom</td>
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<td>6.2</td>
<td>None</td>
<td>976</td>
<td>28</td>
</tr>
</tbody>
</table>

- Disability is defined broadly in terms of a substantial inability to maintain gainful employment (Table 4). Many countries define more than one category of disability based on the percentage of work capacity that is limited and linked to benefit levels. However, we focus only on those qualifying for 100% LTD compensation.

**Disability Criteria**

The procedure by which a worker seeking disability is declared eligible is similar across countries. The procedure typically begins with an individual making an application to the responsible agency. A medical exam is performed to determine the level of physical impairment. Following the medical assessment, an administrative review is conducted that generally considers type of employment, work history, medical records, and recent medical examinations. Interviews with the person seeking disability coverage are often conducted prior to final disability eligibility determination.

The determination of disability is based on multiple criteria; medical assessments of physical impairment are just one component of that judgment. Most countries do not have specific physiological criteria established for the large number of...
8 countries studied is substantial. If disability enrollment rates are comparable to those in the United States in 2000, the total burden in all study countries is estimated at $5 billion annually. The burden could be as high as $25 billion annually if all persons estimated to meet U.S. eligibility criteria are granted disability compensation.

As shown in Figure 2, on a per capita basis, France is estimated to bear the greatest financial burden of about $14.30 to $74 per person of working age per year. This is due largely to the generous benefits paid by the French disability program—about 44% of the average private sector wage. Coupled with relatively high wage rates, France leads in this category. Germany ($12.80 to $66.50), the United States ($12.20 to $63.20), and Spain ($11.40 to $59.10) also have high estimated per capita costs. Despite low benefit levels of 26% of private sector wages, the United States has high private sector wages, thus balancing the relatively low benefit levels.

Discussion

Public policy decisions regarding allocation of scarce health care resources are increasingly reliant on the results of economic analyses. Thus, the definition of potential financial impact of COPD on LTD pensions in these 8 countries is a major concern. Our estimates suggest that the total burden in these countries could range from $5 billion to as high as $25 billion per year if all persons potentially eligible for respiratory-related disability were granted compensation. Thus, COPD-related disability could result in significant expenditures for payers.

Spirometric criteria for disability, used by SSA guidelines, have the advantage of being based on objective measurements obtained by simple spirometry. However, pulmonary function testing (PFT) has since been criticized as a measure of disability due to the limited correlation between PFT and actual physical impairment. In fact, our results show a 5-fold difference between the “potential” number of eligible persons using the SSA criteria and the “actual” number of eligible persons from SSA records; this difference suggests that spirometric criteria may not be particularly useful in making the disability determination.

More recently, cardiopulmonary exercise testing (CPET) has been called the “gold standard” for assessing impairment primarily because of the limitations of spirometry testing. The rationale behind this is that if the physical demands of work are put in terms of oxygen consumption, CPET is a better proxy for oxygen consumption than is PFT. The main drawbacks to cardiopulmonary exercise testing are that (1) it is not commonly available, (2) it is not easily performed, and (3) it is relatively costly.

There is as yet no explicit consideration of respiratory symptoms in disability determinations. However, European guidelines for medical assessments of physical impairment touch on symptoms as they correspond to an inability to work. In addition, some recent research indicates stronger links between respiratory symptoms and measures of impairment.

More cost-effective indicators of disability have been suggested but are not widely accepted. Bestall et al. conclude that the Medical Research Council dyspnea scale may be a simple and inexpensive method for evaluating physical impairment. The strong correlations between Medical Research Council scores and quality-of-life indices suggest that the St. George Respiratory Questionnaire (SGRQ) and the Nottingham Extended Activities of Daily Living (EADL) scale may also be cost-effective indicators of physical impairment. These findings are especially relevant in light of the fact that the ability to work is not dependent on oxygen consumption alone. Symptoms such as chronic cough, sputum production, and dyspnea that interfere with communications or cause respiratory-related drowsiness may render workers effectively disabled.

There is also evidence that recognition of respiratory-related disabilities may be on the rise among those affected. Combined with the effects of antidiscrimination legislation and patients' rights movements, the financial impact of COPD-related disability on health care utilization may also become a concern. For example, the Rehabilitation Act of 1973 and the Americans with Disabilities Act of 1990 have been in place in the United

---

**TABLE 4** Definitions of Disability Relevant to Respiratory Disease

<table>
<thead>
<tr>
<th>Country</th>
<th>Definitions of Respiratory Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>Eligibility is not based on a list of any specific disabilities, disease states, or body system impairments. Rather, eligibility is based on conformity to Canada Pension Plan's definitions.</td>
</tr>
<tr>
<td>France</td>
<td>An assessment of disability is not based on the physical incapacity itself, but, rather, it is based on the impact of the physical incapacity on the worker's earnings. The assessment of disability is based on a review of the gravity and nature of physical incapacity in conjunction with the age of the worker, physical/mental capacity, vocational training, etc.</td>
</tr>
<tr>
<td>Germany</td>
<td>The question of whether an illness exists within the meaning of labor law has to be judged from the circumstances in each particular case, especially the nature and severity of the condition and the type of work performance due.</td>
</tr>
<tr>
<td>Italy</td>
<td>None specific</td>
</tr>
<tr>
<td>Japan</td>
<td>Level of disability pension payment is based on grade of disability. Grades of impairment of respiratory organs:</td>
</tr>
<tr>
<td></td>
<td>• Grade 1: Daily activity in the home is significantly limited</td>
</tr>
<tr>
<td></td>
<td>• Grade 2: Daily social activity is significantly limited</td>
</tr>
<tr>
<td>Spain</td>
<td>None specific</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Disability is based in part on a medical assessment</td>
</tr>
<tr>
<td>United States</td>
<td>Chronic obstructive pulmonary disease due to any cause, with FEV1 equal to or less than the values specified in Table 1.</td>
</tr>
</tbody>
</table>

---

*Note*: FEV1 refers to forced expiratory volume in the first second, a measure of lung function.
States for some time. Nonetheless, the extent to which they may increase health care utilization among those with physical disabilities is still uncertain, as they have been little tested in the courts. Moreover, while these statutes may tend to increase health care utilization by guaranteeing access to care, at the same time, they tend to decrease pension burdens by emphasizing rights to employment.

The present analysis is necessarily based on limited respiratory-specific eligibility criteria data. GOLD guidelines define spirometry as essential to diagnosis of COPD. They categorize spirometry results for assessment of severity and monitoring of COPD but do not attempt to categorize symptoms (except respiratory failure). These guidelines have been designed only as a very general approach to management, but their deficiency makes it evident that measures need to be developed and evaluated for COPD disability evaluation. In contrast, National Institute for Clinical Excellence guidelines assert there is no single diagnostic test for COPD. They describe spirometry as a poor predictor of disability and quality-of-life assessment in COPD sufferers and recommend that clinical judgment rather than pulmonary function test results should form the basis of management.

Most notably, our current understanding of the national-level financial impact of COPD on LTD could be improved by development of clear eligibility criteria to facilitate data collection. A codification of symptoms combined with physical status could achieve this. Strong correlations between Medical Research Council scores and the quality-of-life indices suggest that SGRQ or EADL may be combined with spirometry to create a cost-effective indicator of disability in COPD.

We structured our estimates to include only the national LTD programs. This method made 2 things possible: (1) consistency of program aims and covered populations across all study countries and (2) availability of readily accessible English-language sources. We did not attempt to describe the entire universe of disability programs that may cover COPD-related disability. Other programs may also provide funds for disability due to COPD. In the United States, for example, there are private sources (including various LTD policies supported by employer contributions and individually purchased plans) and other public programs for specific populations such as the United Mine Workers Fund. A similar constellation of public and private programs provides funds that may supplement national LTD programs. However, gathering consistent information across all programs and countries was beyond our aims for this assessment.

### Conclusion

The potential burden of COPD on LTD is quite large, but the lack of available data results in substantial uncertainty internationally about what the actual burden is. In the face of limited information, U.S. managed care organizations may have difficulty estimating future pharmacoeconomic and total economic costs of care for this patient population. Internationally, the lack of standard criteria to identify patients with respiratory-related disability may lead to under-recognition of COPD’s true impact by hampering the ability to estimate the current impact and project the burden into the future. In addition, cross-country comparisons are severely limited. Further work is needed to develop consistent and more cost-effective ways to measure the impact of COPD and to ensure equitable access to compensation.
for COPD patients. Establishing the link between symptoms and worker disability may hold promise. The wide disparity we observed between the number of persons in the United States who meet SSA spirometric criteria for disability and the number (one fifth) who actually obtain disability compensation confirms the idea that pulmonary function tests, while objective, alone may not be an appropriate criterion for assessment of disability. We propose that CPET and the SGRQ or EADL questionnaires be combined with spirometry to create more useful respiratory-specific disability criteria.

DISCLOSURES

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Part of the material in this article was presented as a poster at the 13th Annual Congress of the European Respiratory Society in Vienna in September 2003. The sponsor organization assisted in the critical review of this manuscript. Tinkelman served as principal author of the study. Study concept and design were contributed by Tinkelman, Nordyke, and Isonaka. Analysis and interpretation of data were contributed by all authors; statistical expertise was contributed by Nordyke. Drafting of the manuscript was the work of Nordyke, Isonaka, and DesFosses, and its critical revision was the work of all authors.

REFERENCES

38. E-mail communication between Keith DesFosses and Human Resources Development Canada, Old Age Security and Canada Pension Plan Office; November 11, 2002.
Clinical Monograph for Drug Formulary Review: Systemic Agents for Psoriasis/Psoriatic Arthritis

VICKI S. FISHER, BS, PharmD

ABSTRACT

BACKGROUND: Significant advances in the pharmacologic treatment of psoriasis, most notably the introduction of the biologic agents efalizumab and alefacept, have occurred recently. In addition, another biologic agent, etanercept, was recently approved for the treatment of psoriasis and psoriatic arthritis, thus adding to the list of biologic agents approved for the treatment of these disease states. A review was conducted by the Drug Information Service of a pharmacy benefits manager (PBM) to determine the relative merits and place in therapy of commonly used systemic agents for the treatment of psoriasis and psoriatic arthritis.

OBJECTIVE: To provide readers with a comprehensive clinical monograph on psoriasis and psoriatic arthritis agents, written with a managed care perspective, as used in actual drug formulary decision making by a PBM.

METHODS: The drug formulary of this PBM is designed to provide health plans with an evidence-based review of drugs, therapeutic classes, and disease states with a managed care focus. For each therapeutic class or disease review, an extensive and thorough literature search of MEDLINE is conducted for efficacy, safety, effectiveness, and humanistic and economic data. Drug/disease-state databases (UpToDate online, MICROMEDEX), U.S. Food and Drug Administration clinical reviews, key Internet sites, medical/pharmacy-related news sites, clinical guidelines, and AMCP dossiers are also reviewed. Formulary drug monographs produced by the Drug Information Service of the PBM include a critical analysis and summary of disease-oriented and patient-oriented clinical outcomes, effectiveness, and humanistic data. Additional data considered and included in the formulary review process are clinical attributes, patent expirations/generic competition, off-label or pending indications, and pharmaco-economic data.

RESULTS: The biologic agents do not appear to be as efficacious as traditional systemic therapies but are associated with fewer long-term toxicities that often limit treatment duration with traditional systemic agents. Although no head-to-head comparisons between alefacept and efalizumab exist, efalizumab appears to offer slightly higher efficacy rates, while alefacept has a longer duration of action. Etanercept at the higher approved dose appears more efficacious compared with efalizumab or alefacept for the treatment of psoriasis, and it is the only biologic currently approved for the treatment of psoriatic arthritis. Efalizumab and alefacept are generally well tolerated, but rebound flare of psoriasis is associated with efalizumab, thus requiring continuous treatment to avoid a flare in disease. Efalizumab and etanercept can be self-administered by the patient, while alefacept and infliximab require administration by a health care professional.

CONCLUSIONS: Systemic therapy is reserved for patients with moderate-to-severe psoriasis or patients with psoriatic arthritis. The biologic agents are not as efficacious as traditional therapies but, due to better tolerability, are gaining acceptance in the treatment of psoriasis and psoriatic arthritis. The biologic agents differ in efficacy rates and are generally well tolerated. Clinical attributes, overall efficacy, and economic costs associated with the biologic agents will be significant factors in selecting agents for the treatment of psoriasis and psoriatic arthritis.

KEYWORDS: Psoriasis, Psoriatic arthritis, Alefacept, Efalizumab, Etanercept, Inflixizumab, Methotrexate, Acitretin, Cyclosporine, Sulfasalazine, Drug monograph, Outcomes-based formulary, Evidence-based medicine


Editor's Note: This article contains the information presented in nearly identical facsimile to the Pharmacy and Therapeutics (P&T) committee for the pharmacy benefit manager (PBM) and its health plan clients. Only the cost data have been updated, and the P&T committee sees actual cost and utility data for the PBM during its deliberations. Part of the purpose of this article is to present for readers an example of the information that is actually reviewed in contemporary P&T processes in managed care today.

I. Introduction

Psoriasis

An immune-mediated chronic skin disease, psoriasis is characterized by red, thickened, scaly plaques that are the result of hyperproliferation and incomplete terminal differentiation of the epidermis, vascular changes, and migration of activated neutrophils and T lymphocytes into the dermis and the epidermis. There is a genetic association with psoriasis in that 40% of patients have a family history of psoriasis. Not all patients with the gene develop psoriasis, but it is thought that triggers such as emotional stress, skin injury, infection (human immunodeficiency virus [HIV] or streptococcal infection), or a reaction to a drug may cause a psoriasis outbreak. Notably, patients with HIV may have a higher incidence of psoriasis or it may be more severe in these patients.

Psoriasis is one of the most common chronic skin diseases, with prevalence in the general population of 1% to 3%. It affects approximately 4.5 million Americans (2.1%), and 1 million (0.5%) have psoriatic arthritis. Approximately 250,000 new cases are diagnosed each year. Of those patients diagnosed with psoriasis, 1.5 million, or one third, have moderate-to-severe psoriasis. Psoriasis is more common in individuals of European descent, with Asians and Africans at lowest risk. This condition is not specific to age or gender, but it is slightly more prevalent in women than in men. The average age of onset is 28 years (range of 15-35 years), but psoriasis can actually develop at any age. Approximately 20,000 children under the age of 10 years are diagnosed with psoriasis.

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annually. The annual cost to treat psoriasis was estimated to be more than $3 billion in 1993, and it can substantially impact quality of life for sufferers.¹

Psoriasis may be typed as plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, pustular psoriasis, nail psoriasis, scalp psoriasis, and/or inverse psoriasis. These forms of psoriasis vary in severity and respond differently to treatment. Although a patient can have 2 types of psoriasis at one time, normally patients have only one type, but one type can convert to another type. The most common type of psoriasis is plaque psoriasis, accounting for approximately 80% of cases.¹ The degree of skin involvement may range from just a few lesions to total skin involvement, and it is usually symmetrically distributed.² Disease of the scalp is common and may be the only site affected.¹ Plaque psoriasis can appear on any skin surface, but the most common areas are the knees, elbows, scalp, trunk, and nails. The majority of patients have mild disease, with approximately 30% of psoriasis patients progressing to moderate-to-severe disease.

Severity has typically been based on the amount of body surface area (BSA) affected; however, the current line of thinking is that severity of disease should also take into account quality-of-life (QOL) issues.⁴ For example, a patient with psoriasis involving primarily the hands or feet may be classified as severe even though BSA affected is low, due to the impact on the patient's ability to function normally. A recent survey found that 75% of patients with moderate-to-severe psoriasis felt it had a moderate-to-large impact on their daily living.¹ Studies have documented that psoriasis has a profound effect on health-related quality of life (HRQOL).⁵ Approximately 25% of patients stated that it caused them to alter or stop normal daily activities, 40% stated that it affected their clothing choices in that they chose clothes to cover arms and legs, and 36% stated that it affected sleeping or caused them to bathe more than normal. One study showed that psoriasis impacts HRQOL to the same degree as cancer, arthritis, hypertension, diabetes, and depression.⁶ Severe psoriasis has also been shown to be associated with a higher incidence of depression and suicidal ideation compared with the general population.⁷

Psoriatic Arthritis

Psoriasis is associated with psoriatic arthritis, with 10% to 30% of patients having psoriasis developing psoriatic arthritis.¹ Psoriatic arthritis occurs in approximately 1 million (0.5%) Americans, typically developing in patients between the ages of 30 to 50 years. Psoriasis usually appears approximately 10 years before psoriatic arthritis, but, rarely, some patients do present without psoriasis.

Psoriatic arthritis is similar to rheumatoid arthritis, but it is typically milder. It can be difficult to diagnose and can be confused with rheumatoid arthritis, osteoarthritis, gout, Reiter's syndrome, and ankylosing spondylitis. It is generally diagnosed by a process of elimination using x-rays of the affected joints, medical history, physical examination, and blood tests.⁸ Because it is difficult to diagnose, approximately 50% of patients already have bone loss by the time they are diagnosed. Symptoms of the disease include stiffness, pain, swelling, and tenderness of joints and surrounding soft tissue; decreased range of motion; morning stiffness and tiredness; pain and redness of the eye; and nail changes (pitting or lifting of the nail) are common. The joints most commonly affected are the wrist, knees, ankles, lower back, and neck. Interestingly, a link between psoriasis and Crohn's disease has also been suggested.¹

There are 5 types of psoriatic arthritis, with the most common types being symmetric and asymmetric. Less commonly occurring forms are distal interphalangeal predominant (DIP),

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**TABLE 1** Monograph Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Formulary Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>(Rheumatrex - Stada Pharma, various generics)</td>
</tr>
<tr>
<td>Actinmetin</td>
<td>(Solana - Roche)</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>(Hydra, Droxia - BMS; various generics)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>(Neoral - Novartis; various generics-cyclosporine modified; Gengraf - Abbott)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>(Imuran - Prometheus; various generics)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>(Azulfidine - Pharmacia-Upjohn; various generics)</td>
</tr>
<tr>
<td>Auranofin</td>
<td>(Ridaura - Promethus)</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>(Depen - MedPointe Pharm; Cuprimine - Merck &amp; Co.)</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>(Aralen - Sanofi Pharm; generic)</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>(Plaquenil - Sanofi Pharm; various generics)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>(Enbrel - Amgen)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>(Remicade - Centocor)</td>
</tr>
<tr>
<td>Alefacept</td>
<td>(Amevive - Biogen)</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>(Raptiva - Genentech/XOMA)</td>
</tr>
</tbody>
</table>

**TABLE 2** Evidence-Based Medicine Terms

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-oriented evidence (DOE)</td>
<td>Refers to surrogate markers associated with a specific disease state such as blood pressure reduction or glucose and cholesterol lowering</td>
</tr>
<tr>
<td>Patient-oriented evidence (POE)</td>
<td>Also referred to as patient-oriented evidence that matters (POEM) and refers to clinical events associated with a disease such as myocardial infarction, stroke, and death</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>Evaluation of beneficial effects of a treatment when assessed under the usual conditions of clinical practice, also referred to as efficacy measured in a real-world setting</td>
</tr>
<tr>
<td>Humanistic</td>
<td>Measures of quality-of-life, functional status, patient satisfaction, and symptom scores</td>
</tr>
<tr>
<td>Economic</td>
<td>Measures of direct (hospitalization, physician visits, drug costs) and indirect costs (work loss, restricted activity days)</td>
</tr>
</tbody>
</table>

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Clinical Monograph for Drug Formulary Review: Systemic Agents for Psoriasis/Psoriatic Arthritis
II. Pathophysiology

Psoriasis and psoriatic arthritis are similar in that both diseases are immune-mediated chronic diseases with a genetic link. Psoriasis is caused by a hyperproliferative state, characterized by increased numbers of epidermal stem cells and numbers of cells undergoing DNA synthesis, keratinocytes undergoing a shortened cell cycle compared with normal skin (36 hours versus 311 hours), and a decrease in the turnover time of the epidermal skin layer compared with normal skin (4 days versus 27 days). The presence of T lymphocytes and neutrophils in the epidermal and dermal layers, activation of growth factors (epidermal growth factor and transforming growth factor-alpha), and cytokines including interleukin-8 (IL-8), IL-6, IL-2, and interferon-gamma support immune regulation as a factor in psoriasis. Psoriasis is characterized by patches of red, scaly, flaky skin that can be associated with intense itching and burning.

Similar to psoriasis, psoriatic arthritis is linked to the presence of cytokines, including tumor necrosis factor (TNF)-alpha, IL-1beta, IL-2, IL-10, and interferon-gamma found to be present in the synovial tissue. These cytokines stimulate the inflammatory process in the skin and synovium, thus leading to migration of activated T cells through the epidermal skin layer compared with normal skin (4 days versus 27 days). The presence of T lymphocytes and neutrophils in the epidermal and dermal layers, activation of growth factors, and cytokines including interleukin-8 (IL-8), IL-6, IL-2, and interferon-gamma support immune regulation as a factor in psoriasis.

It is not clearly defined which patients should be considered to have mild, moderate, or severe psoriasis, which is important in determining the optimal therapy for treatment. The National Psoriasis Foundation position paper provides some guidance in defining severity using QOL-based definitions in the absence of standardized criteria. (See Table 3.)

### TABLE 3 | Quality-of-Life–Based Definitions of Severity of Psoriasis From the National Psoriasis Foundation

<table>
<thead>
<tr>
<th>Severity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>No alteration in patient QOL; patient can manage impact of disease and may not need treatment; treatments selected are not associated with any serious risks; BSA &lt; 5%.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Some alteration in patient QOL; patient requires therapy to improve QOL; treatments selected are associated with only minimal health risks in the short or long term; BSA = 2% to 20%.</td>
</tr>
<tr>
<td>Severe</td>
<td>Alteration in patient QOL; disease unresponsive to treatments associated with minimal risks; patient is willing to accept life-altering adverse effects to improve disease or clear disease; BSA &gt; 10%. Also takes into consideration location of disease such as hands, feet, face; symptoms (pain, tightness, bleeding, or severe itching); presence of arthralgias or arthritis.</td>
</tr>
</tbody>
</table>

QOL = quality of life; BSA = body surface area.

### TABLE 4 | Pharmacology of Biologic Response Modifiers

<table>
<thead>
<tr>
<th>Biologic Response Modifier</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alefacept</td>
<td>Dimeric fusion protein consisting of the extracellular CD2-binding portion of the LFA-3 that is linked to the Fc portion of IgG1. It works by inhibiting lymphocyte activation by binding to CD2 on T and NK cells. Decreases lymphocyte count (CD2 and memory cells). Studies have shown alefacept to exert greater effects on CD4+ memory cells, than CD4+ naive cells.</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>Recombinant humanized IgG1 monoclonal antibody that binds to the CD11a (subunit of the LFA-1) and prevents adhesion to ICAM-1, thus inhibiting T-cell activation and migration.</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Dimeric fusion protein consisting of the extracellular ligand-binding portion of the TNF receptor linked to the Fc portion of IgG1. It exerts its effect by binding TNF and prevents interaction with cell surface TNF receptors, thus inhibiting the inflammatory process.</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Humanized monoclonal antibody to TNF-alpha that neutralizes the activity of TNF-alpha, thus preventing induction of IL-1 and IL-6, inhibiting leukocyte migration, induction of acute phase reactants, and tissue-degrading enzymes.</td>
</tr>
</tbody>
</table>

Ig = immunoglobulin; IL = interleukin; LFA-1 = leukocyte function antigen-1; LFA-3 = leukocyte function antigen-3; ICAM-1 = intercellular adhesion molecule-1; NK = natural killer cells; TNF = tumor necrosis factor.
traditional agents are primarily administered orally.

In one study evaluating the pharmacokinetic/pharmacodynamic effects of alefacept, the Psoriasis Area Severity Assessment Index (PASI) and Physician Global Assessment (PGA) were correlated with increasing alefacept serum levels. Dose-dependent decreases in peripheral CD4+ memory cells occurred during treatment with alefacept, which was shown to correlate with improvements in psoriasis. It is this specificity for reducing CD4+ memory cells that has been attributed to the sustained efficacy observed with this agent.

The pharmacokinetics of etanercept in treating psoriasis are similar to what is observed in patients treated with etanercept for rheumatoid arthritis. The pharmacokinetics were similar whether patients were treated with 25 mg twice weekly or 50 mg once weekly, supporting that this dose would be efficacious in treating psoriasis patients. Long-term treatment was also shown to result in similar pharmacokinetics regardless of whether treatment was continuous or intermittent, thus suggesting the potential efficacy of etanercept when used in a sequential or rotational dosing scheme (Table 5).

**TABLE 5 Pharmacokinetics of Systemic Therapies**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability</th>
<th>Elimination Half-Life</th>
<th>Protein Binding (%)</th>
<th>Metabolism</th>
<th>Primary Route of Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>60% (&lt;30 mg/m2) dose-dependent</td>
<td>3-10 hours</td>
<td>50</td>
<td>Liver</td>
<td>Renal</td>
</tr>
<tr>
<td>Acitretin</td>
<td>72%</td>
<td>49 hours</td>
<td>99.9</td>
<td>Liver</td>
<td>Feces (34%-54%) and urine (16%-53%)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Variable (30% conventional formulation; 43% oral emulsion)</td>
<td>8.4-27 hours</td>
<td>90-98</td>
<td>Liver</td>
<td>Biliary (6% urine)</td>
</tr>
<tr>
<td>Infliximab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>58% (SC)</td>
<td>102+ 30 hours (SC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efalizumab</td>
<td>50% (SC)</td>
<td>25 days (mean)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alefacept</td>
<td>63% (IM)</td>
<td>IV- 270 hours (11 25 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IM- 289+123 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IV = intravenous; SC = subcutaneous; IM = intramuscular.

Methotrexate reduces the synthesis of tetrahydrofolate (by binding to dihydrofolate reductase) and subsequently inhibits pyrimidine synthesis. These actions result in a reduction in DNA synthesis, inhibition of mitosis, and a decrease in the proliferation of rapidly dividing cells. Methotrexate is known to decrease T and B cell function and suppress the secretion of cytokines (IL-1, interferon-gamma, TNF).

Acitretin is an oral retinoid with anti-inflammatory, antiproliferative, and keratolytic activity. Acitretin is the active metabolite of etretinate, previously known as Tegison. While etretinate takes years to be eliminated from the body, acitretin elimination takes several months. However, alcohol may precipitate conversion of acitretin back to etretinate, resulting in prolonged elimination. Because of the prolonged action of acitretin and teratogenic effects, women must avoid pregnancy during and for 3 years after discontinuing treatment.

**Cyclosporine**

Cyclosporine is an immunosuppressant that binds with the immunosuppressant-binding protein cyclophilin. The immunosuppressive effects of cyclosporine result from the inhibition of cytokine promoters, which eventually inhibits the transcription and processing of cytokines (IL-2, interferon-gamma) within the T cells and decreases T-cell growth and migration. Cyclosporine absorption is variable and incomplete, although a newer emulsion formulation of cyclosporine has better absorption, at 43%.

**Additional Agents**

Several additional agents have been used in the treatment of psoriasis/psoriatic arthritis but are not U.S. Food and Drug Administration (FDA)-approved for these indications. Hydroxyurea is an antineoplastic agent that inhibits DNA synthesis, which slows basal cell replication in the epidermis. Hydroxyurea also inhibits vascular proliferation in the dermis; lowers the neutrophil count, which decreases pustule and papule formation; and reverses abnormal keratin formation. Sulfasalazine is an anti-inflammatory agent that is thought to work by inhibiting prostaglandin synthesis and interfering with the arachidonic pathway. Azathioprine is an immunosuppressive agent that metabolizes to 6-mercaptopurine and inhibits DNA and RNA synthesis. The mechanism of action of auranofin in treating psoriatic arthritis is unclear, but it is thought to work by reducing T-cell activity and inhibiting neutrophil migration. Similarly, it is unclear how penicillamine exerts its effects in
psoriatic arthritis; however, it has been theorized to inhibit complement binding to immunoglobulins and may inhibit helper T-cell activity. It is unclear how chloroquine and hydroxychloroquine work in the treatment of psoriasis/psoriatic arthritis.

## IV. Clinical Efficacy

### Efficacy Measures

Various measures have been used to evaluate efficacy, including changes to BSA coverage, the Salford Psoriasis Index (SPI), PASI, self-administer PASI (SPASI), Psoriasis Disability Index (PDI), and various QOL scales. The PASI is the most frequently encountered scale in the trials that follow and describes overall psoriasis severity and coverage, based on the amount of skin and degree of itching and scaliness involved in 4 defined body sections. A PASI75 is defined as a 75% improvement from baseline in PASI score and PASI50 is a 50% improvement in PASI score. Achievement of PASI50 is considered a clinically significant improvement. The PASI is a measure primarily used in clinical trials to demonstrate efficacy for FDA approval, but because it is both time-consuming to administer and complex, it is not commonly used in the clinical setting. New tools for measuring response are being developed that will take into consideration the effect on QOL in determining severity of disease and response to treatment. Little information is available about recurrence or length of remission rates among various treatment approaches. The variable outcome measures should be considered when comparing outcomes from one trial to the next.

### Treatment Strategies

A number of treatment options are available for treating psoriasis, both topical and systemic. Selection of treatment is dependent on the areas affected, type, severity level, and risk-to-benefit ratio of treatments. In general, first-line therapy for patients with mild disease consists of topical agents such as topical emollients, topical corticosteroids with or without coal tar, or calcipotriene. Second-line topical therapies include anthralin and tazarotene. For mild-to-moderate disease, low- to mid-potency corticosteroids are generally the first choice of therapy. Usually, more potent corticosteroids, other topical agents, or systemic therapies are used for more severe disease or on areas of thicker skin. For thinner skin areas and for maintenance, a low-potency corticosteroid can be used. Low-potency products or noncorticosteroid agents are generally preferred in infants and elderly patients. For patients with more severe disease that is unresponsive to topical therapies, systemic therapies are generally used.

### Systemic Therapies for Psoriasis

For more severe disease unresponsive to topical agents or that involves large areas, phototherapy, with or without a topical agent or with methoxsalen, has been used. In addition, oral agents, such as acitretin, cyclosporine, and methotrexate, may be used as first-line therapy in patients with severe disease. Ultraviolet B (UVB) was considered a therapy of choice used alone or in combination with topical or oral agents; however, inconvenience and costs associated with this therapy have led to decreased use. Psoralen plus ultraviolet A (PUVA) light is an effective therapy that has been shown to induce remission in patients; additional maintenance therapy adds to the high efficacy rates of 80% with this therapy. However, long-term use can result in an increased risk of nonmelanoma and potentially melanoma skin cancer that may persist even after therapy is discontinued, which is a potential concern.

In addition, PUVA treatment can be inconvenient for the patient either because of a lack of availability of PUVA equipment in close proximity to the patient or because of a requirement for frequent treatments in the physician’s office. This may limit patient acceptance of this very effective therapy. PUVA is often combined with acitretin, an oral retinoid, to increase efficacy and decrease the amount of UVA energy required. Combination therapy has been shown to be superior to PUVA alone, with clearance rates of 80% for PUVA compared with 96% with combination therapy, and was associated with a 42% reduction in the mean cumulative dose of UVA. This combination is thought to potentially decrease toxicity and costs associated with use of either agent alone.

Spuls et al. conducted a systematic review of 5 systemic treatments for psoriasis. A total of 665 studies involving systemic therapies—methotrexate, retinoids, cyclosporine, UVB, or PUVA—were identified. Patient series, focusing on treatment outcome, were used as the unit of analysis. After application of exclusion criteria, a total of 129 patient series (13,677 patients) were included in the analysis. The largest number of patient series evaluated PUVA; however, no studies on methotrexate remained in the analysis following exclusion. Two outcomes were evaluated—clearance and treatment response—defined as good (75% - 100% improvement), moderate (50% - 75% improvement), poor (< 50% improvement), and clearance (100% improvement). Good response was seen in 83% of patients treated with PUVA, 68% with UVB, 64% with cyclosporine, 56% with etretinate, and 56% with acitretin. The percentage of patients achieving clearing in each group was 70%, 44%, 13%, 22%, and 9%, respectively. The incidence of adverse events was also lowest with PUVA (0.6%). The authors suggested that phototherapy may be the first choice of systemic therapy for patients with severe psoriasis. A potential limitation of this review is that the exclusion rate was high due to concomitant use of other psoriasis agents, outdated dosages, or inadequate documentation in these studies. Of 821 patient series identified, 692 were excluded, for an inclusion rate of only 19%. This is primarily attributed to the fact that these agents have been used for many years, with many studies published as far back as 1958 for methotrexate, the 1970s for PUVA, and early 1980s to 1990s for many of the other agents.
thus study design was not as stringent for the older agents.

In a systematic review by Griffiths et al., sufficient evidence from randomized controlled trials (RCTs) was identified to support the efficacy of cyclosporine, systemic retinoids in combination with PUVA, photochemotherapy, phototherapy, combinations of topical vitamin D3 analogues, and topical steroids in combination with photochemotherapy or phototherapy and fumarates. In contrast, there was a lack of RCTs to support the use of methotrexate, hydroxyurea, azathioprine, and sulfasalazine. Because methotrexate was approved prior to the requirement of RCTs for approval, limited RCTs are available.

Lebwohl et al. reviewed the use of cyclosporine in the treatment of psoriasis, concluding that it is best reserved for patients with severe psoriasis that have failed first-line therapies. Typically, an induction dose up to 4 mg/kg/day (titrated) is used to treat a flare-up of psoriasis, then once the patient is clear or nearly clear of lesions, a lower maintenance dose can be used. In one study of 457 patients with severe psoriasis, treatment with cyclosporine 5 mg/kg/day resulted in 88% of patients achieving a 75% reduction in PASI (PASI75), with 52% of patients taking cyclosporine 2.5 to 3 mg/kg/day, and 24% of patients taking cyclosporine 1.25 mg/kg/day achieving PASI75 or greater. Short-term, sequential, or rotational use is preferred because of potential risks associated with long-term therapy (renal toxicity and hypertension). For sequential or rotational therapy, cyclosporine is used to achieve remission, then patients are transitioned to acitretin for maintenance.

A recent comparative trial evaluated methotrexate and cyclosporine in patients with moderate-to-severe chronic plaque psoriasis, many of whom had failed topical, phototherapy, photochemotherapy, or acitretin. Eighty-eight patients were randomized to methotrexate 15 mg/week titrated up to 22.5 mg/week or cyclosporine 3 mg/kg/day titrated up to 5 mg/kg/day if there was an inadequate response after 4 weeks of therapy. After 16 weeks of treatment, 40% of methotretaxate-treated patients achieved a PASI90 compared with 33% of cyclosporine-treated patients, which was considered an almost complete remission. Partial remission or a PASI75 was achieved in 60% of methotretaxate-treated patients compared with 71% of cyclosporine-treated patients. Duration of therapy was approximately 4 weeks for both treatments, indicating treatment must be continued for optimal effects. There was no significant difference in efficacy between agents, but more patients discontinued methotretaxate (12 patients due to liver enzyme elevations) compared with only 1 patient discontinuing cyclosporine due to adverse effects.

Several small studies have shown hydroxyurea in doses of 0.5 grams to 1.5 grams per day to be efficacious in improving psoriasis in patients refractory to or failing conventional therapies. Recently it was shown to be efficacious and safe in treating psoriasis in a patient with psoriatic arthritis when used in combination with infliximab.

Systemic Therapies for Psoriatic Arthritis
In a Cochrane Database Systematic Review of treatments for psoriatic arthritis, parenteral high-dose methotrexate and sulfasalazine were the two agents found to have the most data published demonstrating efficacy in treating psoriatic arthritis. Of the 20 RCTs identified, 6 studies of sulfasalazine, 2 each of auranofin and etretinate, and 1 each of azathioprine, colchicine, fumaric acid, and low, pulse-dose methotretaxate were included. A parenteral high-dose methotretaxate study was also included. All agents were shown to be better than placebo, but only parenteral high-dose methotretaxate, sulfasalazine, azathioprine, and etretinate reached statistical significance. It was also noted that patients receiving placebo improved over baseline, thus suggesting that noncontrolled trials are limited in their findings when evaluating treatments for psoriatic arthritis. The overall poor quality of studies limited the inclusion of studies and, thus, these findings.

Low-dose methotretaxate (maximum 15 mg/week) was compared with cyclosporine (3 - 5 mg/kg/day) in treating 35 patients with psoriatic arthritis. Both agents significantly improved measures of disease activity—physician and patient assessments of disease activity at 6 and 12 months. More patients withdrew on cyclosporine therapy, while increases in liver enzymes were significantly more common with methotretaxate, thus indicating the potential tolerability issues with each agent. In a study comparing cyclosporine (3 mg/kg/day) with sulfasalazine (2,000 mg/day) plus standard therapies or standard therapies alone (nonsteroidal anti-inflammatory drugs [NSAIDs], prednisone 5 mg/day, analgesics), cyclosporine was more efficacious overall compared with sulfasalazine or standard therapies, with only mild reversible kidney dysfunction reported more commonly with cyclosporine therapy. Overall, sulfasalazine was superior to standard therapy alone in improving PASI, spondylitis functional index, and improved erythrocyte sedimentation rate but not in pain measures. Response to cyclosporine occurred at 8 weeks versus 34 weeks with sulfasalazine. In 3 studies evaluating the efficacy of sulfasalazine in treating psoriatic arthritis, although superior to placebo, efficacy was minimal, with high response rates reported in placebo patients.

Several small studies have evaluated the efficacy of auranofin (oral gold) and gold sodium thiomalate (injectable gold). In general, the studies were small and not controlled, but results indicate that, while injectable gold is more potent in efficacy compared with oral gold, tolerability is better with oral gold. Data were not consistent across all studies, but, overall, they suggested superiority of gold compounds over placebo/control in improving symptoms of psoriatic arthritis. However, results of one study indicate gold compounds do not prevent progression of joint damage.

Data are limited regarding the safety and efficacy of antimalarial agents (chloroquine/hydroxychloroquine) or penicil-
TABLE 6 Placebo-Controlled Trials of Biologic Agents for the Treatment of Psoriatic Arthritis With or Without Psoriasis

<table>
<thead>
<tr>
<th>ETANERCEPT</th>
<th>Mease et al., 2000</th>
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| Study design: R, DB, PC trial in pts. with active psoriatic arthritis (>3 swollen joints and >3 tender/painful joints and failed NSAIDs) and psoriasis (n = 60). Additional TXs allowed: (MTX<25 mg/wk if stable for 4 wks, corticosteroids < prednisone 10 mg, stable NSAIDs therapy)
| Treatment(s): ETA 25 mg SC twice weekly or placebo for 12 weeks.
| OUTCOMES: ACR response at week 12: ETA 73% vs. placebo 13% (P<.001; NNT = 2); ACR50—ETA 50% vs. placebo 3% (P=.001; NNT = 2); ACR70—ETA 13% vs. placebo 0% (P=.04; NNT = 8). Improvements in psoriasis: % pts. achieving PASI50 at week 12: ETA 47% vs. placebo 18% (P=.003; NNT = 5). Improvements in disability (HAQ): ETA 83% vs. placebo 3% (P<.0001; NNT = 1). Tolerability: ETA was well tolerated with similar AEIs vs. placebo. Mild/moderate injection site reactions and upper respiratory infections were the most common AEIs.
| Comments: Limitation: small study size. 63% of pts. (n = 38) had > 3% BSA affected by psoriasis.

Study design: R, DB, MC trial in pts. with active psoriatic arthritis (>3 swollen or >3 tender joints; failure to conventional therapy) (n=205). Additional TXs allowed: (MTX<25 mg/wk if stable for weeks, corticosteroids < prednisone 10 mg; stable NSAIDs therapy).
| Treatment(s): ETA 25 mg SC twice weekly or placebo for 24 weeks.
| OUTCOMES: Improvement in psoriatic arthritis: Primary efficacy measure for psoriatic arthritis was % pts. meeting ACR20 at week 12: ETA vs. placebo (P<.001; NNT = 3). ACR50 at week 12: ETA 38% vs. placebo 4% (P<.001; NNT = 3); ACR70 at week 12: ETA 11% vs. placebo 0% (P<.001; NNT = 9). Tolerability: ETA was well tolerated with similar AEIs vs. placebo. HAQ were significantly lower with ETA beginning at week 4 - 12.
| Comments: Full study not published.

ACR=American College of Rheumatology score; AEs=adverse events; BSA=body surface area; DB=doubt blind; ETA=etanercept; HAQ=Health Assessment Questionnaire; MC=multicenter; MTX=methotrexate; NNT=number needed to treat; NSAIDs=nonsteroidal anti-inflammatory drugs; PASI=Psoriasis Area Severity Index; PC=placebo-controlled; PsARC=Psoriatic Arthritis Response Criteria; Pts.=patients; R=randomized; SC=subcutaneous; SF-36=Short-Form 36 Health Survey; TX=treatment.

lamine in treating psoriatic arthritis. Several small studies evaluated the efficacy of chloroquine and hydroxychloroquine in treating psoriasis, indicating potential efficacy; however, conflicting data indicating the potential to exacerbate psoriasis limit the use of these agents. Although penicillamine is approved for use in the treatment of rheumatoid arthritis, limited data are available to support efficacy and safety in treating psoriatic arthritis.

However, the availability of biologic agents for the treatment of psoriasis and psoriatic arthritis may change how these chronic diseases have been managed in the past. Tables 6 through 8 summarize the studies evaluating the efficacy of biologic agents in the treatment of psoriasis and psoriatic arthritis.

V. Humanistic Outcomes

The impact of psoriasis on patient QOL is well documented. Several QOL measures have been used in assessing humanistic outcomes in psoriasis patients, including the Dermatology Life Quality Index (DLQI), PDI, and the Short-Form 36 Health Survey (SF-36). The DLQI is commonly used, but it is a general measure for dermatologic QOL. Thus, a new QOL instrument is being developed and validated that is specific to psoriasis, the Psoriasis Quality of Life Questionnaire, which should help differentiate between levels of disease severity and clinically important improvements with topical and systemic therapies. Several studies have evaluated improvements in QOL associated with the newest biologic agents.

Alefacept

Significant improvements in HRQOL were noted in 229 patients with moderate-to-severe psoriasis treated with alefacept. Patients treated with alefacept administered intravenously experienced significantly greater improvements in dermatology-specific QOL measures compared with patients treated with placebo. Significant improvements in the DLQI and the Dermatology Quality of Life Scales (DQOLS) were
**TABLE 7** Placebo-Controlled Trials of Biologic Agents for the Treatment of Psoriasis

<table>
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<tr>
<th>Study design (n):</th>
<th>R, DB, PC, MC trial in pts. with moderate-to-severe chronic plaque psoriasis (&gt;1 year and BSA &gt;10%), age &gt;18 years, who were candidates for phototherapy or systemic therapy (n = 507).</th>
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<tr>
<td>Treatment(s): ALE 10 mg, ALE 15 mg, or placebo IM once weekly for 12 weeks, then followed up for 12 weeks.</td>
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<td>OUTCOMES: Primary end point: % of pts. with PASI75 or greater at 2 weeks post-TX was 1% with ALE 15 mg vs. 5% with placebo (P &lt;0.01; NNT=6). Overall response after TX course 1: PASI75 or greater at 2 weeks with ALE 15 mg and 28% with placebo (P &lt;0.01; NNT=5-7). PASI50 or greater at 3 weeks with ALE 10 mg and 53% with placebo. PGA clear/ almost clear 24% with ALE 15 mg and 22% with ALE 10 mg vs. 8% with placebo (P &lt;0.01; NNT=6-7). Tolerability: overall. ALE was well tolerated, with headache (typically single event) and mild injection site reactions (pain, pruritis, and inflammation—mild, transient that did not cause withdrawal from study) reported most commonly. No significant infections, reductions in CD4+ counts, serious drug-related AEs, or increases in malignancy were noted. AST elevations up to 3 times the ULN were noted in 8%-13% of ALE pts. vs. 9% in placebo pts., primarily in pts. with a history of hepatic illness or taking hepatotoxic drugs. No other alterations in liver function were noted. Antialefacept antibodies detected in 4% (14 pts.), but were low titers, did not increase, and were not neutralizing.</td>
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<td>Comments: Similar baseline characteristics, median duration of disease was 19 years (range 2-77 years), median BSA 21%. Pts. with more severe disease and pts. with no prior history of systemic therapy had higher response rates.</td>
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<tr>
<th>Study design (n):</th>
<th>R, DB, PC, MC trial in pts. with chronic plaque psoriasis (&gt;1 year and BSA &gt;10%), age &gt;18 years, who were candidates for phototherapy or systemic therapy (n = 553).</th>
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<tr>
<td>Treatment(s): ALE 7.5 mg IV once weekly for 12 weeks then placebo for 12 weeks, ALE 7.5 mg IV once weekly for 12 week courses, or placebo for 12 weeks, then ALE 7.5 mg IV once weekly for 12 weeks. There was a 12-week TX-free follow-up period after each TX course. Additional TXs allowed: low-potency corticosteroids allowed, but not for 12 hours before efficacy evaluation; moderate-potency corticosteroids; vitamin D analogs; topical retinoids; keratolytics; and coal tar allowed on groin, scalp, palms, and soles only.</td>
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<tr>
<td>OUTCOMES: Primary end point: % of pts. achieving PASI75 or greater at 2 weeks after course 1. TX course 1: 14% of ALE pts. achieved PASI75 or greater vs. 4% placebo pts. (P &lt;0.01; NNT=10) at 2 weeks, overall response rate 28% of ALE pts. vs. 8% of placebo pts. (P &lt;0.01; NNT=5). PASI 50 or greater overall response rate, 56% of ALE pts. vs. 24% with placebo (P &lt;0.01; NNT=3). PGA (clear/almost clear) overall response rate, 23% with ALE vs. 11% placebo (P &lt;0.01; NNT=8). TX course 2: PASI75 or greater overall response rate, 37% with ALE vs. 19% with placebo (P &lt;0.01; NNT=6). PASI50 or greater overall response rate, 64% with ALE vs. 49% with placebo (P &lt;0.05; NNT=7). PGA (clear/almost clear) overall response rate, 30% with ALE vs. 18% with placebo (P &lt;0.05; NNT=8). Duration of response: Pts. achieving PASI75 during or after TX, without phototherapy or systemic therapy, maintained PASI 50 or greater for 7 months (216 days) following 1 course of TX and beyond 48 weeks (379 days) for pts. following 2 courses of TX. Tolerability: Chills occurred more commonly with ALE, which occurs within 24 hours of dose and decreased with a subsequent course of therapy. Increased ALT &lt;3 times normal occurred more commonly with ALE vs. placebo (17% vs. 8%) with second course of TX, but mild with no other alterations in liver function. Dose reduction required in 10% of ALE pts. due to increased CD4+ lymphocyte counts. Antialefacept antibodies detected in &lt;1% (n = 5) of pts.</td>
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<td>Comments: 87% of pts. (482/553) completed course 1 TX; 89% of pts. (401/449) completed course 2 TX. Full effects not observed during TX. Maximal improvement occurred at 8 weeks post-TX. Overall response rate included pts. achieving end point at any time during 12-week TX or 12-week follow-up period. No rebound disease detected with discontinuation.</td>
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<tr>
<th>Study design (n):</th>
<th>R, DB, PC, MC trial in pts. with chronic plaque psoriasis (&gt;1 year and BSA &gt;10%), age &gt;18 years, who were candidates for phototherapy or systemic therapy (n = 229).</th>
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<tr>
<td>Treatment(s): ALE 0.025, 0.075, 0.150 mg/kg IV (30 second injection) or placebo once weekly for 12 weeks with follow-up for 12 weeks after TX. Additional TXs allowed: emollients, but not for 12 hours before efficacy evaluation; moderate-potency corticosteroids; vitamin D analogs, topical retinoids, keratolytics, and coal tar allowed on groin, scalp, palms, and soles only.</td>
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<tr>
<td>OUTCOMES: Primary end point: % of pts. achieving PASI75 or greater at 2 weeks post-TX was 1% with ALE 15 mg vs. 10% (P &lt;.02; NNT=4-9). PASI50: ALE 36%-60% vs. 27% placebo (P &lt;.001; NNT=3-11). At 12 weeks post-TX: PASI75: ALE 19%-33% vs. 11% (P &lt;.02; NNT=5-13). PASI50: ALE 42%-63% vs. 32% placebo (P &lt;.02; NNT=3-10). Tolerability: ALE was well tolerated. Accidental injury, dizziness, nausea, chills and cough were slightly more common with ALE vs. placebo, but all AEs were mild. The incidence of infection was similar between TX groups.</td>
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<tr>
<td>Comments: No cases of rebound or flare of psoriasis were observed after ALE TX ended. improvements in PASI and PGA were correlated with increasing ALE serum levels. Dose-dependent decreases in CD4+ memory cells were noted. Dose-dependent decreases in CD4+ memory and naïve cells were correlated with improvements in psoriasis.</td>
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| AE = adverse events; ALE = alefacept; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSA = body surface area; DB = double-blind; DLQI = Dermatology Life Quality Index; EFA = efalizumab; ETA = etanercept; IM = intramuscular; INF = infusion; IV = intravenous; MC = multicenter; NNT = numbers needed to treat; OL = open label; PASI = Psoriasis Area Severity Index; PC = placebo-controlled; PGA = Physician Global Assessment; Pts. = patients; QOL = quality of life; R = randomized; SC = subcutaneous; TX = treatment; ULN = upper limit of normal; VAS = Visual Analog Scale. |

(Continued on next page)
PLACEBO-CONTROLLED TRIALS OF BIOLOGIC AGENTS FOR THE TREATMENT OF Psoriasis

**TABLE 7**

**Krueger GG, Ellis CN, 2002** (follow-up to Ellis et al., 2001 study)

| Subgroup analysis: R, DB, PC, MC trial in pts. with chronic plaque psoriasis (>1 year and BSA >10%), age >18 years, who were candidates for phototherapy or systemic therapy (n=229). |

| Treatment(s): ALE 0.025, 0.075, 0.150 mg/kg IV (30-second injection) or placebo once weekly for 12 weeks with follow-up for 12 weeks after TX. |

| OUTCOMES: Follow-up evaluation of Ellis et al., 2001 study. Primary objective was to evaluate the remission period following TX with ALE. Of the 148 pts. completing TX with ALE, 118 (80%) required no additional TX for up to 3 months after stopping therapy. Of the 118 pts., 16 pts. were clear or almost clear for 3 months post-TX. Twenty-six of the ALE pts. subsequently were treated with a second course of ALE. Pts. did not require re-TX for several months, with a mean time between TXs of 10 months (range 6-18 mos.). |

| Comments: This study suggests a long duration of efficacy with ALE TX. |

| Low et al., 2003 |

| Interim report of ongoing trial: OL, MC, re-TX study in pts. previously treated in Phase II trials with ALE or placebo, requiring additional systemic TX. |

| Treatment(s): ALE 7.5 mg IV bolus once weekly for 12 weeks. Re-TX course 1 (n=170), Re-TX course 2 (n=50). Additional TXs allowed after wash-out period: low-potency corticosteroids allowed, but not for 12 hours before efficacy evaluation; moderate-potency corticosteroids, vitamin D analogs, topical retinoids, keratolytics, and coal tar allowed on groin, scalp, palms, and soles only. |

| OUTCOMES: Re-TX course 1: % of pts. achieving overall response—PGA of clear or almost clear 29%, PASI75 or greater 39%, PASI 50 or greater 66%. |

| Comments: Pharmacodynamic data showed selectivity for CD4+ memory cells over CD4+ naives cells. Additional data are being collected in pts. receiving a third re-TX course. |

**ETANERCEPT**

| Leonardi et al., 2004 |

| Study design: DB, R, PC, MC trial in pts. with moderate-to-severe stable plaque psoriasis (PASI of 10, BSA>10%; candidate for systemic therapy) (n=652). |

| Additional TXs allowed: stable doses of low or moderate potency corticosteroids allowed to scalp, axillae, or groin. |

| Treatment(s): ETA (Low dose) 25 mg SC once weekly, ETA (medium dose) 25 mg SC twice weekly, ETA (high dose) 50 mg SC twice weekly, or placebo for 24 weeks. After 12 weeks, patients in the placebo group received ETA 25 mg SC twice weekly in a double-blind fashion. |

| OUTCOMES: Primary measure: % pts. achieving PASI75 or greater at week 12: ETA low dose 14%, ETA medium dose 34%, ETA high dose 49% vs. 4% placebo (P<0.001 vs. placebo for all ETA groups; NNT=2-10). % pts. achieving PASI75 or greater at week 24: ETA low dose 25%, ETA medium dose 44%, ETA high dose 59%. No placebo group at week 24, as these pts. had begun ETA medium dose at week 12, and 33% of these pts. had achieved PASI75 or greater at week 24. % pts. achieving PASI50 or greater at week 12: ETA low dose 41%, ETA medium dose 58%, ETA high dose 74% vs. placebo 14% (P<0.001 vs. placebo; NNT=2-4). At week 24: ETA low dose 58%, ETA medium dose 70%, ETA high dose 77%. % pts. clear/almost clear at week 12: ETA low dose 23%, ETA medium dose 34%, ETA high dose 49% vs. placebo 5% (P<0.001 vs. placebo; NNT=2-3). At week 24: ETA low dose 26%, ETA medium dose 39%, ETA high dose 55%. Pt.-oriented outcomes: % mean improvement in DLQI at week 12: ETA low dose 47%, ETA medium dose 51%, ETA high dose 61% vs. placebo 11% (P<0.001 vs. placebo; NNT=2-3). Improvements in PGA were significantly better in all ETA groups vs. placebo at week 12. Tolerability: ETA was well tolerated with similar incidence of AEs and infections across all groups. Eight ETA pts. had non-neutralizing ETA antibodies, with no difference in efficacy or safety noted. |

| Comments: Statistically significant improvements noted at 4 weeks in the ETA high dose and at 8 weeks in the ETA medium dose groups. Mean percentage improvements in QOL from baseline, as measured by PGA and DLQI, were statistically significant beginning at week 2. No significant increase in AEs noted with increasing doses of ETA. Data on follow-up period to evaluate duration of response not provided in this publication. |

| Gottlieb AB, Gordon KB et al., 2004 [poster]; Krueger GC, Lebwohl MG et al., 2004 [poster]; Leonardi CL, Elewski BE et al. 2004 [poster] |

| Study design: Follow-up extension of above study (of 652 pts.; 409 pts. were responders and entered withdrawal period). |

| Treatment(s): Active-treatment pts. were withdrawn from study drug after 24 weeks and followed for relapse. |

| OUTCOMES: Median time to relapse (loss of 50% of PASI improvement): ETA 25 mg once weekly 70 days, 25 mg twice weekly 85 days, 50 mg twice weekly 91 days. No reports of flare or rebound, with duration of response of approximately 3 months. Additional analysis (Krueger et al, 2004) showed for pts. not responding at 24 weeks, additional pts. (27%, 622 pts.) responded at 60 weeks with the 25 mg twice weekly and 6% (1/18 pts.) with the 50 mg twice weekly doses. Further analysis of re-TX pts. showed that pts. treated with etanercept after relapse had similar response to TX as observed with original TX (Leonardi, 2004). Pts. who were responders at week 24, showed similar response (PASI75 scores) upon re-TX with etanercept across all doses. |

| Comments: Poster presentations; full studies not published. |

AEs = adverse events; ALE = alefacept; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSA = body surface area; DB = double-blind; DLQI = Dermatology Life Quality Index; EFA = efalizumab; ETA = etanercept; IM = intramuscular; INF = infusion; IV = intravenous; MC = multicenter; NNT = numbers needed to treat; OL = open label; PASI = Psoriasis Area Severity Index; PC = placebo-controlled; PGA = Physician Global Assessment; Pts. = patients; QOL = quality of life; R = randomized; SC = subcutaneous; TX = treatment; ULN = upper limit of normal; VAS = Visual Analog Scale.

(Continued on next page)
TABLE 7  Placebo-Controlled Trials of Biologic Agents for the Treatment of Psoriasis

Langley et al., 2004*[9] [poster]

| Study design: | Pooled analysis of data from 2 phase 3 trials (n = 1,235). |
| Treatment(s): | ETA 50 mg twice weekly, ETA 25 mg twice weekly, 25 mg once weekly for 24 weeks or placebo for 12 weeks followed by ETA 25 mg twice weekly for 24 weeks. |

**OUTCOMES: End point—% pts. that were nonresponders at week 4 that went on to become responders with continued treatment. Of pts. who were not responders at week 4: 33% of 25 mg twice-weekly and 53% of 50 mg twice weekly pts. achieved PASI50 by week 8. Of pts. who were not responders at 4 weeks: those that became responders at 12 weeks were 51% for 25 mg twice weekly and 67% for 50 mg twice weekly. |

**Comments:** Improvements have been reported beginning at 2 weeks; however, these data indicate response can increase in nonresponders following 3 months of therapy. **Limitation:** Poster presentation, statistical significance not stated, full study not published.

Gottlieb et al., 2002**[9] [poster]

| Study design: | R, DB, PC, MC trial in pts. with stable plaque psoriasis (BSA >10%, trial of at least 1 systemic therapy) (n=112). |
| Treatment(s): | ETA 25 mg SC twice weekly or placebo. |

**OUTCOMES: Primary efficacy measure: % pts. achieving PASI75 at week 12: ETA 50 mg twice weekly 49%, ETA 25 mg twice weekly 34%, placebo 3% (P<0.001; NNT=4) and at week 24: ETA 50 mg twice weekly 52%, ETA 25 mg twice weekly 35%, placebo 2% (P<0.001; NNT=2). **Tolerability:** AEs were similar, except injection site reactions were higher with ETA. Rates of AEs overall were similar, except the rate per pt. year of any infection was significantly higher with ETA. |

**Comments:** Statistically significant improvements in PASI began at week 8, PGA at week 4, and Patient Global Score at week 2.

Elewski et al., 2004**[9] [poster]

| Study design: | MC, DB, R trial in pts. with stable plaque psoriasis (BSA >10%, trial of at least one systemic therapy or a candidate for systemic therapy) (n=583). |
| Treatment(s): | ETA 50 mg twice weekly for 12 weeks then 25 mg twice weekly (step-down) for 12 weeks, ETA 25 mg twice weekly for 24 weeks, or placebo for 12 weeks followed by ETA 25 mg twice weekly for 12 weeks. |

**OUTCOMES: Primary efficacy measure: % pts. achieving PASI75 at week 12: ETA 50 mg twice weekly 49%, ETA 25 mg twice weekly 34%, placebo 3% (P<0.001; NNT=4) and at week 24: ETA 50 mg twice weekly 52%, ETA 25 mg twice weekly 35%, placebo 2% (P<0.001; NNT=2). **Tolerability:** AEs were similar, except injection site reactions were higher with ETA. Rates of AEs overall were similar, except the rate per pt. year of any infection was significantly higher with ETA. |

**Comments:** Step-down dosing showed similar efficacy to that observed in 50 mg twice weekly dosing in study by Leonardi et al., 2003. Additional one third of pts. not responding on 50 mg twice weekly did go on to respond even following step-down dosing to 25 mg twice weekly. P-values were not provided to determine statistical significance.

**EFALIZUMAB**

Lebwohl and Tying et al., 2003**[9]

| Study design: | R, DB, PC, MC trial in pts. with moderate-to-severe plaque psoriasis (PASI of ≥12, BSA>10%, candidate for systemic therapy) (n=597). |
| Additional TXs allowed: | Eucerin cream, tar or salicylic acid agents for scalp, limited application of low-potency corticosteroids, and oral antipruritic agents. |
| Treatment(s): | Phase 1 (n=397): ETA 1 mg/kg/wk SC, ETA 2 mg/kg/wk SC, or placebo for 12 weeks. Phase 2 (n=434): pts. achieving >PASI50 were rerandomized to ETA 2 mg/kg/wk SC once weekly, ETA 2 mg/kg/every other week SC, or placebo. Pts. achieving <PASI50 were rerandomized to ETA 4 mg/kg/wk or placebo. Pts. were then followed for an additional 12 weeks. |

**OUTCOMES: Week 12 results—% pts. achieving PASI75 or greater: ETA 2 mg/kg 28%, ETA 1 mg/kg 22% vs. placebo 5% (P<0.001; NNT=4-6). % pts. achieving PASI50 or greater: ETA 2 mg/kg 57%, ETA 1 mg/kg 52% vs. placebo 16% (P<0.001; NNT=2-3). **Tolerability:** AEs were similar, except injection site reactions were higher with ETA. Rates of AEs overall were similar, except the rate per pt. year of any infection was significantly higher with ETA. |

**Comments:** Additional TXs allowed: Eucerin cream, tar or salicylic acid agents for scalp, limited application of low-potency corticosteroids, and oral antipruritic agents. **Duration of response:** At week 36, 30% of pts. maintained PASI50. Time to loss of PASI50 after 24 weeks of TX was 84 days.

**OUTCOMES: Week 24 results following 12 additional weeks of TX:** Pts. with PASI75 or greater at week 12, % pts. achieving PASI50 or greater: ETA 2 mg/kg/wk 78%, ETA 1 mg/kg/every other week 77% vs. placebo 20% (P<0.001; NNT=2). Pts. with PASI50 or greater at week 12, % pts. achieving PASI75 or greater: ETA 2 mg/kg 53%, ETA 2 mg/kg/every other week 29% vs. placebo 4% (P<0.001; NNT=2). Pts. with <PASI50 at week 12, % pts. achieving PASI 75 or greater: ETA 4 mg/kg/wk 13% vs. 2% (P=0.2; NNT=9). **Tolerability:** Placement: ETA was well tolerated. Acute AEs (headache, chills, fever, nausea, myalgia) were most common following the first dose, were transient, and mild. AEs during the second phase were similar with fewer acute AEs noted. Antietsalizumab antibodies were found in 5% of pts., with no difference in AEs. **Limitation:** AEs were similar, except injection site reactions were higher with ETA. Rates of AEs overall were similar, except the rate per pt. year of any infection was significantly higher with ETA. **Comments:** Mean PASI at baseline was 20, mean duration of psoriasis was 19 years, 67% of pts. had received previous TX with systemic therapy. Significant difference in efficacy was noted at week 4 of TX with ETA vs. placebo. This study did not evaluate PGA of improvement. The 2 mg/kg/wk and 4 mg/kg/wk doses are higher than the FDA-recommended dose of 1 mg/kg/wk. There were no statistically significant differences in efficacy between the 1 mg/kg/wk and the 2 mg/kg/wk doses. Of pts. who achieved PASI50 with ETA during the initial 12 weeks and were then switched to placebo, only 20% maintained that improvement at week 24 vs. 77% of pts. who continued with ETA treatment. At week 24, relapse (50% or more loss in improvement) occurred in 8% of pts. who continued on ETA and in 67% of pts. who discontinued ETA therapy after 12 wks.

AEs=adverse events, AL=alkefact, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BSA=body surface area, DB=double-blind, DLQI=Dermatology Life Quality Index, ETA=efalizumab, ETN=etanercept, IM=intramuscular, INF=infusion, IV=intravenous, MC=multicenter, NNT=numbers needed to treat, OL=open label, PASI=Psoriasis Area Severity Index, PC=placebo-controlled, PGA=Physician Global Assessment, Pts.=patients, QOL=quality of life, R=randomized, SC=subcutaneous, TX=treatment, ULN=upper limit of normal, VAS=Visual Analog Scale.

(Continued on next page)
observed in patients who experienced a 50% or 75% improvement in PASI at 12 weeks compared with patients treated with placebo (P <.05). The general QOL survey (SF-36) was found to be less specific in determining QOL in these patients. Similar results were noted in 509 patients with moderate-to-severe chronic plaque psoriasis who were treated with alefacept 15 mg administered intramuscularly. At 12 weeks, patients treated with alefacept experienced statistically significant improvements in DLQI, DQOLS, and SF-36 compared with patients treated with placebo.

Efalizumab

Efalizumab was shown to improve DLQI scores in a pooled

<table>
<thead>
<tr>
<th>TABLE 7</th>
<th>Placebo-Controlled Trials of Biologic Agents for the Treatment of Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon et al., 2003[8]</td>
<td><strong>Study design:</strong> R, DB, PC, MC trial in pts. with moderate-to-severe plaque psoriasis (PASI of &gt;12, BSA&gt;10%, candidate for systemic therapy) (n=556) <strong>Additional TXs allowed:</strong> Emollients, tar or salicylic acid agents for scalp, limited application of low-potency corticosteroids for face, hands, feet, groin, and axillae. <strong>Treatments:</strong> INF 5 mg/kg 82%, INF 10 mg/kg 73% vs. placebo 18%. <strong>OUTCOMES: at week 12:</strong> % pts. achieving PASI73: INF 5 mg/kg 76%, INF 10 mg/kg 78% vs. placebo 18% (P&lt;0.001; NNT=2). % pts. achieving PASI100: INF 5 mg/kg 58%, INF 10 mg/kg 61% vs. placebo 7% (P&lt;0.001; NNT=4). <strong>Pt.-oriented outcomes:</strong> DLQI score was higher with INF vs. placebo (47% vs. 14%, P&lt;0.001) with greater improvement seen in pts. achieving PASI50. <strong>Improvement in itching VAS score:</strong> EFA 38% vs. placebo -0.2% (P&lt;0.001). <strong>Improvement in PSA scores:</strong> Frequency of symptoms—INF 48% vs. placebo 18% (P&lt;0.001), severity of symptoms—INF 47% vs. placebo 17% (P&lt;0.001). Greatest improvement was with itching and scaling. <strong>Tolerability:</strong> EFA was well tolerated, AEs were primarily mild flu-like symptoms observed with the first 2 injections. No significant difference in infections between groups. Antifalizumab antibodies were noted in 2% of pts. with no significant AEs. Worsening of psoriasis occurred in 28% of placebo pts. vs. 13% of EFA pts. <strong>Comments:</strong> Logistic regression analysis did not show a difference in efficacy based on baseline PASI score, age, sex, or history of prior systemic therapy. Onset of response occurred at 4 weeks, but duration of response was not measured in this study.</td>
</tr>
<tr>
<td>Papp et al., 2001[7]</td>
<td><strong>Study design:</strong> R, DB, PC, MC study in pts. with moderate-to-severe plaque psoriasis (n=145). <strong>Treatments:</strong> INF 5 mg/kg, INF 10 mg/kg, or placebo at weeks 10, 12, and 16, with follow-up through week 26. <strong>Additional TXs allowed:</strong> Nonmedicated emollients, tar, salicylic acid for scalp, limited application of low-potency corticosteroids for face, hands, feet, groin, and axillae. <strong>OUTCOMES:</strong> INF 5 mg/kg 82%, INF 10 mg/kg 91% vs. placebo 18% (P&lt;0.001). <strong>Pt.-oriented outcomes:</strong> DLQI score was higher with INF vs. placebo (47% vs. 14%, P&lt;0.001) with greater improvement seen in pts. achieving PASI50. <strong>Improvement in itching VAS score:</strong> EFA 38% vs. placebo -0.2% (P&lt;0.001). <strong>Improvement in PSA scores:</strong> Frequency of symptoms—INF 48% vs. placebo 18% (P&lt;0.001), severity of symptoms—INF 47% vs. placebo 17% (P&lt;0.001). Greatest improvement was with itching and scaling. <strong>Tolerability:</strong> EFA was well tolerated, AEs were primarily mild flu-like symptoms observed with the first 2 injections. No significant difference in infections between groups. Antifalizumab antibodies were noted in 2% of pts. with no significant AEs. Worsening of psoriasis occurred in 28% of placebo pts. vs. 13% of EFA pts. <strong>Comments:</strong> No significant difference in efficacy with the lower dose of EFA vs. placebo.</td>
</tr>
<tr>
<td>Chaudhari et al., 2001[6]</td>
<td><strong>Study design:</strong> R, DB, PC trial in pts. with moderate-to-severe plaque psoriasis (n=33) <strong>Treatments:</strong> INF 5 mg/kg, INF 10 mg/kg, or placebo at weeks 0, 2, and 6. <strong>Additional TXs allowed:</strong> Nonmedicated emollients, tar, salicylic acid. <strong>OUTCOMES:</strong> % pts. achieving a 50% or better PGA at 8 weeks: INF 0.3 mg/kg/wk 48% vs. placebo 15% (P=0.002). INF 0.7 mg/kg/wk 48% vs. placebo 15% (P=0.002). INF 1 mg/kg/wk 19% (P&lt;0.001). <strong>Tolerability:</strong> INF was well tolerated, with only headaches reported more commonly with INF vs. placebo. <strong>Comments:</strong> Significant improvements in PASI scores were noted beginning at week 2, with a median response of 4 weeks. <strong>Limitation:</strong> Small study size.</td>
</tr>
<tr>
<td>Gottlieb and Chaudari et al., 2003[72] (open-label extension trial of Chaudhari et al., 2001)</td>
<td><strong>Study design:</strong> OL, extension trial of a previously listed trial (n=30). R, DB, PC trial in pts. with moderate-to-severe plaque psoriasis (BSA&gt;5%; failure to respond to topical corticosteroids) (n=33) <strong>Treatments:</strong> INF 5 mg/kg, INF 10 mg/kg, or placebo at weeks 10, 12, and 16, with follow-up through week 26. <strong>Additional TXs allowed:</strong> Nonmedicated emollients, tar, salicylic acid. <strong>OUTCOMES:</strong> % pts. maintaining PASI75 at week 26: INF 5 mg/kg 33%, INF 10 mg/kg 67%. <strong>Tolerability:</strong> INF was well tolerated, with only headaches reported more commonly with INF vs. placebo. <strong>Comments:</strong> Limitation: Small study size.</td>
</tr>
</tbody>
</table>

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**Notes:**
- AEs = adverse events; ALE = alefacept; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSA = body surface area; DB = double-blind; DLQI = Dermatology Life Quality Index; EFA = efalizumab; ETA = etanercept; IM = intramuscular; INF = infusion; IV = intravenous; MC = multicenter; NNT = numbers needed to treat; OL = open label; PASI = Psoriasis Area Severity Index; PC = placebo-controlled; PGA = Physician Global Assessment; Pts. = patients; QOL = quality of life; R = randomized; SC = subcutaneous; TX = treatment; ULN = upper limit of normal; VAS = Visual Analog Scale.
analysis of 2 phase III studies. QOL was assessed in 1,095 patients with moderate-to-severe psoriasis treated with efalizumab or placebo. DLQI scores decreased from 12 to 6 with efalizumab 1-2 mg/kg/wk compared with an improvement from 12 to 10 with placebo. Similar results were shown in a phase III trial in 556 patients with moderate-to-severe psoriasis. Significantly greater improvements were reported with efalizumab-treatment compared with placebo treatment at 12 weeks (47% versus 14%; P<.001). Significant improvements were noted in the efalizumab-treated patients beginning at week 4 and were consistent across all DLQI components, with the greatest improvements in the symptoms and feelings sections. Additional analyses showed the greatest improvements in DLQI were observed in patients achieving a PASI50.

**Etanercept**

In a follow-up to the study by Mease et al., which evaluated the efficacy of etanercept in treating 205 patients with active psoriatic arthritis, etanercept was shown to result in significant improvements in HRQOL compared with treatment with placebo at 24 weeks. Patients receiving etanercept experienced significantly greater improvements in Health Assessment

### TABLE 8 Combination Therapy Trials of Biologic Agents for the Treatment of Psoriatic Arthritis With or Without Psoriasis

<table>
<thead>
<tr>
<th>Biologic Agent</th>
<th>Study Design</th>
<th>Treatment(s)</th>
<th>OUTCOMES</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ETANERCEPT</strong></td>
<td>Case control series in pts. with severe recalcitrant psoriasis (n=6)</td>
<td>ETA 25 mg SC twice weekly, Additional TXs: oral MTX (2 pts.), oral cyclosporine (1 pt.), acitretin/hydroxyurea on alternate days (1 pt.), acitretin/UVB on alternate days (1 pt.), or topical calcipotriene (1 pt.)</td>
<td>PASI scores improved by approximately 50% in all pts. Pts. with psoriatic arthritis experienced a moderate-to-major improvement in arthritis. Combination therapy was well tolerated with no significant AEs reported.</td>
<td>Uncontrolled case-series study. Time frame for response not stated in all pts., 2 pts. showed improvements within 5-8 weeks.</td>
</tr>
<tr>
<td><strong>INFliximAB</strong></td>
<td>OL trial in pts. with severe psoriatic arthritis failing MTX therapy (n=6). Additional TX allowed: NSAIDs, MTX, steroids</td>
<td>INF 5 mg/kg on week 0, 2, 6</td>
<td>100% pts. achieved ACR50 at week 10, 83% of patients achieved ACR70 at week 10. HAQ improved by 78%, PASI decreased from 5.3 to 2.6 by week 10.</td>
<td>Case series provides low evidence, due to small size and lack of controls.</td>
</tr>
<tr>
<td><strong>DECHANT</strong></td>
<td>Case series of pts. with severe psoriatic arthritis (n=10)</td>
<td>INF 5 mg/kg on week 0, 2, 6, and concomitant MTX (7 patients), sulfasalazine (1 patient), no other DMARD (2 patients), then TX was adapted to pt. need and pts. were followed for up to 1 year.</td>
<td>1 pt. with ACR70 at week 10 stopped therapy and was in remission for 5 months. Four pts. with ACR70 and 1 pt. with ACR 50 at week 10 received INF 3-4 mg/kg Q 8 weeks. For 3 cases, pts. stopped therapy after 5-6 months due to remission. At 1 year, all 5 pts. maintained ACR70. Remaining 4 pts. TX with INF 3-4 mg/kg every 8 weeks, 3 had ACR50 at 1 year. One pt. had a flare that responded to increased dose and frequency of INF.</td>
<td>Case series provides low evidence, due to small size and lack of controls.</td>
</tr>
<tr>
<td><strong>ANTONI</strong></td>
<td>OI trial in pts. with severe psoriatic arthritis and psoriatic skin lesions (n = 6).</td>
<td>INF 5 mg/kg on week 0, 2, 6, and no other DMARD therapy.</td>
<td>100% pts. achieved ACR50 at week 10, 83% of patients achieved ACR70 at week 10. HAQ improved by 78%, PASI decreased from 5.3 to 2.6 by week 10.</td>
<td>Case series provides low evidence, due to small size and lack of controls.</td>
</tr>
<tr>
<td><strong>Ogilvie et al., 2001</strong></td>
<td>Case series in pts. with psoriatic arthritis resistant to DMARD therapy (n = 3).</td>
<td>INF 3 mg/kg on weeks 0, 2, 6, and 3 mg/kg every 8 weeks. Additional TXs: MTX or sulfasalazine.</td>
<td>All pts. experienced reduced symptoms of psoriatic arthritis. One pt. experienced recurrent flares in arthritis, thus requiring INF every 4 weeks, with successful response.</td>
<td>Case series provides low evidence, due to small size and lack of controls.</td>
</tr>
<tr>
<td><strong>Bray et al., 2001</strong></td>
<td>Case series in pts. with psoriatic arthritis resistant to DMARD therapy (n = 3).</td>
<td>INF 5 mg/kg on week 0, 2, 6, and no other DMARD therapy.</td>
<td>100% pts. achieved ACR50 at week 10, 83% of patients achieved ACR70 at week 10. HAQ improved by 78%, PASI decreased from 5.3 to 2.6 by week 10.</td>
<td>Case series provides low evidence, due to small size and lack of controls.</td>
</tr>
</tbody>
</table>

ACR = American College of Rheumatology score; AEs = adverse events; DMARDs = disease-modifying anti-rheumatic drugs; ETA = etanercept; HAQ = Health Assessment Questionnaire; INF = infusion; MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs; PASI = Psoriasis Area Severity Index; Pts. = patients; SC = subcutaneous; TX = treatment; UVB = ultraviolet B.
Questionnaire scores, with an improvement of 0.6 units compared with a 0.1 unit improvement with placebo (54% versus 7%; \(P < .001\)). An improvement of 0.22 units is considered clinically significant. Similarly, a significant improvement in the Medical Outcomes Study SF-36 scores was observed with etanercept compared with placebo (mean change of 9.3 versus 0.7 with placebo; \(P < .001\)). This was primarily attributed to improvements in the Physical Component Summary with a trend toward improvement in the Mental Component Summary, which did not reach statistical significance. A significant improvement in the EuroQOL Feeling Thermometer, which is a multidimensional measure of HRQOL, was reported with etanercept compared with placebo (mean improvement of 14.3 units versus 2.1 units; \(P < .001\)).

### VI. Pharmacoeconomics

In an economic study published by Feldman et al., methotrexate was the least costly treatment at $1,600 annually, followed by phototherapy $3,600, PUVA $4,600, acitretin $5,200, cyclosporine $6,500 to $10,000 (3 - 5 mg/kg/day), alefacept $16,000 to $20,000 (1.5 courses/year—assumes intravenous [IV] administration, labs tests and office visits), and etanercept $16,900 to $33,000 (25 mg twice weekly - 50 mg twice weekly). Assumptions included costs of laboratory tests, office visits, and drug acquisition costs (average wholesale price) but did not include costs associated with rare adverse events. The analysis also included assessment of the cost per treatment success based on efficacy from published studies but not from head-to-head comparisons. Methotrexate remained the least costly therapy at $5,400; both UVB and PUVA had similar costs per treatment at $5,100 to $5,700, while costs per treatment were somewhat higher for cyclosporine (5 mg/kg/day) at $14,200 and acitretin monotherapy at $17,300. However, costs per treatment with the biologic agents were higher than the traditional therapies at $35,900-$40,600 annually for etanercept (25 mg twice weekly - 50 mg twice weekly). Infliximab costs per treatment were lower at $22,500 for 5 mg/kg (6 infusions) but were based on a high efficacy rate of 80% noted in a single trial.

In a decision-analytic model by Chiou et al., the cost-efficacy of biologics was compared in treating psoriasis. Data were based on package insert information and published clinical trial data that were then reviewed by an expert panel of dermatologists. The analysis was conducted from a managed care perspective and was evaluated over a 6-month period, based on efficacy at 12 to 14 weeks that was assumed to be maintained at 6 months. Costs included drug costs, laboratory monitoring, and costs of treating moderate-to-severe adverse events. Costs of therapy over 6 months were $11,295 for alefacept (dosed for 12 weeks); $11,295 for efalizumab; $9,781 for etanercept (25 mg twice weekly); $14,273 for etanercept step-down dosing (50 mg twice weekly for 12 weeks, then 25 mg twice weekly for 12 weeks); and $18,600 for etanercept 50 mg twice weekly. However, additional analyses of incremental cost-efficacy showed etanercept to be the most cost-effective agent because of higher efficacy rates. Limitations included lack of head-to-head data and use of expert opinion to classify adverse events. It should be noted that the study was supported by a grant from Immunex/Amgen, the manufacturer of Enbrel (etanercept).

Additional useful measures of the costs associated with use of biologic agents would be to calculate cost per day of response to therapy or the cost of treatment failure compared with conventional therapies or other biologic agents. See Table 9 for sample annual costs for 1 year of treatment for psoriasis or psoriatic arthritis.

### VII. Adverse Effects

Many of the systemic agents used in treating psoriasis and psoriatic arthritis work by affecting the immune system, thus causing concern over their long-term use and the potential for an increased risk of infection. The commonly reported adverse effects associated with conventional systemic therapies for psoriasis are provided in Table 10. These data highlight the safety and toxicity issues associated with these therapies that have led to development and increased utilization of biologic agents.

#### Alefacept

The most common adverse effects reported with alefacept were chills, dizziness, nausea, increased cough, and injection site pain. Serious adverse effects were uncommon but included lymphopenia (dose-dependent reductions in CD4+ and CD8+ counts), which accounted for 4% of patients receiving intra-
Adverse Effects of Conventional Systemic Therapies for Psoriasis/Psoriatic Arthritis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>hepatoxicity, gastrointestinal malaise, headache, reactivation of phototoxic reactions, ulcerative stomatitis, myelosuppression, anemia, pulmonary fibrosis, induction of lymphomas</td>
</tr>
<tr>
<td>Acitretin</td>
<td>black box warning regarding teratogenicity and hepatotoxicity, hyperlipidemia, mucocutaneous skin reactions, alopecia, gastrointestinal effects, arthralgias and myalgias, pseudotumor cerebri, hyperostosis; may worsen psoriasis initially</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>renal toxicity, hypertension, gastrointestinal effects, flu-like symptoms, hypertrichosis, gingival hypertrophy, skin malignancies with PUVA</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>myelosuppression, gastrointestinal effects, hyperpigmentation, renal dysfunction, oral and leg ulcers, dermatomyositis-like skin changes</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>block box warning regarding increased risk of neoplasia with chronic use, gastrointestinal hypersensitivity, hematologic toxicities</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>gastrointestinal effects, headache, rash, fever, dizziness, stomatitis, pruritus, abnormal liver function tests, leukopenia, thrombocytopenia, rare immunoglobulin suppression (serum-like sickness), hypersensitivity reactions</td>
</tr>
<tr>
<td>Auranofin</td>
<td>gastrointestinal effects, rash, pruritus, stomatitis, conjunctivitis, abnormal liver function tests, proteinuria</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>allergic reactions, generalized purities/rashes/drug eruptions, gastrointestinal effects, leukopenia, thrombocytopenia, renal dysfunction, abnormal liver function tests</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>long-term, high-dose therapy can result in ocular dysfunction, seizures, auditory dysfunction, gastrointestinal effects, skin eruptions/rash/pruritus, headache, rarely hypotension</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>headache, dizziness, gastrointestinal effects</td>
</tr>
</tbody>
</table>

TABLE 10 Adverse Effects of Conventional Systemic Therapies for Psoriasis/Psoriatic Arthritis

Methotrexate: hepatotoxicity, gastrointestinal malaise, headache, reactivation of phototoxic reactions, ulcerative stomatitis, myelosuppression, anemia, pulmonary fibrosis, induction of lymphomas

Acitretin: black box warning regarding teratogenicity and hepatotoxicity, hyperlipidemia, mucocutaneous skin reactions, alopecia, gastrointestinal effects, arthralgias and myalgias, pseudotumor cerebri, hyperostosis; may worsen psoriasis initially

Cyclosporine: renal toxicity, hypertension, gastrointestinal effects, flu-like symptoms, hypertrichosis, gingival hypertrophy, skin malignancies with PUVA

Hydroxyurea: myelosuppression, gastrointestinal effects, hyperpigmentation, renal dysfunction, oral and leg ulcers, dermatomyositis-like skin changes

Penicillamine: allergic reactions, generalized purities/rashes/drug eruptions, gastrointestinal effects, leukopenia, thrombocytopenia, renal dysfunction, abnormal liver function tests

Chloroquine: long-term, high-dose therapy can result in ocular dysfunction, seizures, auditory dysfunction, gastrointestinal effects, skin eruptions/rash/pruritus, headache, rarely hypotension

Hydroxychloroquine: headache, dizziness, gastrointestinal effects

PUVA = psoralen plus ultraviolet A light

muscular injections to temporarily discontinue therapy. Subsequent courses resulted in a higher portion of patients experiencing below-normal counts.86 Data also showed a higher incidence of serious infections requiring hospitalization compared with placebo (0.9% versus 0.2%), which increased with subsequent courses (1%). Maximum effects on lymphocyte counts were observed at 6 to 8 weeks after initiation of therapy. The incidence of malignancy was also slightly higher with alefacept, with 1.3% of patients diagnosed compared with 0.5% of patients in the placebo group. The majority of cases were basal or squamous cell cancers, but 3 cases of lymphoma were reported. There were rare reports of increased transaminase levels 5 to 10 times the upper limit of normal (9 patients) during clinical trials.10

Efalizumab

Serious infections occurred in 0.4% of efalizumab-treated patients and 0.1% of placebo-treated patients during the initial 12 weeks of therapy.12 The risk of malignancy with efalizumab is not known, but because it is an immunosuppressive therapy, patients should be monitored for malignancy or the drug discontinued in patients diagnosed with a malignancy. Severe thrombocytopenia occurred in patients during clinical trials, with 0.3% of efalizumab-patients experiencing thrombocytopenia (platelet counts below 52,000 cell/ml.) compared with no cases reported with placebo. In 3 of the 8 patients experiencing severe thrombocytopenia, all cases were consistent with an immune-mediated reaction. Worsening of psoriasis occurred in 0.7% (19 patients) of efalizumab-treated patients, with most cases occurring after discontinuation of therapy. Some cases were severe and required hospitalization (17 of 19 patients) or alternative psoriasis therapy, with conversion to psoriatic erythroderma and pustular psoriasis reported in some patients. The rate of psoriasis adverse events, including both nonserious and serious cases, observed during placebo-controlled trials was 3.2% (52 of 1,620) with efalizumab compared with 1.4% (10 of 715) with placebo.11

Recent analysis of safety data from 13 clinical trials in 2,762 patients showed 13.8% of efalizumab-treated patients experienced psoriasis that returned to worse than baseline with discontinuation of therapy compared with 11.1% of patients.87 First-dose reactions of headache, fever, nausea, and vomiting occur with efalizumab, which are dose-related; thus, an initial lower conditioning dose is recommended. Hypersensitivity reactions were uncommon but occurred more commonly with efalizumab compared with placebo (1% versus 0.4%). Inflammatory/immune-mediated reactions occurred in 0.5% of patients treated with efalizumab, including 2 cases of interstitial pneumonitis. Elevations in alkaline phosphatase occurred more frequently with efalizumab compared with placebo (4% versus 0.6%), and the percentage of patients with above-normal liver function tests was also higher with efalizumab compared with placebo (3.1% versus 1.5%). Long-term immunogenicity of efalizumab is not known; however, 6.3% of patients developed antibodies to efalizumab.

Etanercept

The most frequent adverse event is injection site reactions (37%).13 Injection site reactions tend to decrease in severity over time. Recently published data analyzing safety from 1 phase II and 2 phase III trials showed the incidence of injection site reactions was lower than observed in rheumatoid arthritis trials.88 The incidence of infections overall was low, at less than 1% with no reports of conversion of psoriasis to other types. Etanercept has been associated with rare postmarketing reports of pancytopenia, including aplastic anemia, although a causal relationship has not been established.11 Caution is advised for use in patients with a history of significant hematologic abnormalities. Treatment with etanercept and other agents with similar mechanisms of action have been associated with rare reports of new onset of demyelinating disease such as multiple
sclerosis, and exacerbations of preexisting disease. Caution is advised when prescribing etanercept in patients with preexisting disease. Adverse events with etanercept treatment in pediatric patients are similar in frequency and type as those seen in adult patients. Non-neutralizing antibodies to etanercept have been reported in clinical studies, but no correlation to clinical response or adverse events was noted. Analysis of clinical trials in psoriasis patients showed a 6% incidence of antietanercept antibodies, although titers were low and antibodies were non-neutralizing with no apparent effects on safety or efficacy.98

**Infliximab**

Safety of infliximab is based on data from clinical trials in rheumatoid arthritis. Safety data for treatment of psoriasis have not been fully elucidated in large well-controlled trials. Similar to etanercept, demyelinating syndromes have been associated with infliximab. Use should be avoided in patients with preexisting multiple sclerosis.11 Efficacy with infliximab is more durably sustained when combined with methotrexate in treating rheumatoid arthritis. Data are not available to clarify if infliximab should be administered only in combination with methotrexate for psoriasis and psoriatic arthritis, but in preliminary studies, it was often used in combination with other agents, including methotrexate.

**Congestive Heart Failure With Infliximab or Etanercept**

During clinical trials evaluating the efficacy of etanercept and infliximab in patients with congestive heart failure (CHF), it was determined that these agents may not improve CHF and could decrease survival.89,90 Two phase II studies with etanercept (RENAISSANCE and RECOVER) were stopped early due to lack of efficacy and an increased incidence of worse outcomes in patients in one study. During the postmarketing period, cases of worsening heart failure have been reported in patients treated with etanercept in both patients with and without precipitating factors.11 In the ATTACH trial, infliximab was shown to increase the risk of mortality or worsen CHF; thus, this agent is contraindicated in patients with CHF. For CHF patients already on infliximab therapy, infliximab should be discontinued in patients whose CHF is worsening, and discontinuation should be considered in patients with stable concomitant CHF Current labeling contraindicates use of infliximab in patients with moderate-to-severe CHF and cautions use of etanercept in patients with CHF. The FDA and manufacturers of these products are conducting ongoing surveillance of the risk of CHF with these agents.91

### VIII. Drug/Food Interaction

Formal drug/food interaction studies have not been conducted with the biologic response modifiers. However, drug interactions are minimal compared with conventional therapies.

### TABLE 11 Drug/Food Interactions95

<table>
<thead>
<tr>
<th>Drug/Food Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alefacept:</strong> no formal studies—caution concomitant use with other immunosuppressive agents or phototherapy</td>
</tr>
<tr>
<td><strong>Efalizumab:</strong> no formal studies—caution concomitant use with other immunosuppressive agents or phototherapy; do not administer with acellular, live, or live-attenuated vaccines</td>
</tr>
<tr>
<td><strong>Etanercept:</strong> no formal studies—caution use with anakinra; do not administer with live vaccines</td>
</tr>
<tr>
<td><strong>Infliximab:</strong> no formal studies—do not administer with live vaccines</td>
</tr>
<tr>
<td><strong>Methotrexate:</strong> aminoglycosides, chloramphenicol, folic acid, NSAIDs, penicillins, salicylates, sulfonamides, tetracyclines, trimethoprim, digoxin, phenytoin, theophylline, thiopurines, food delays absorption</td>
</tr>
<tr>
<td><strong>Cyclosporine:</strong> drugs that affect cytochrome P450, nephrotoxic drugs</td>
</tr>
<tr>
<td><strong>Acitretin:</strong> ethanol, glibenclamide, progestin-only contraceptives, methotrexate, phenytoin, tetracyclines, vitamin A, or oral retinoids</td>
</tr>
<tr>
<td><strong>Hydroxyurea:</strong> no formal studies conducted</td>
</tr>
<tr>
<td><strong>Azathioprine:</strong> ACE inhibitors, allopurinol, methotrexate, anticoagulants, cyclosporine, nondepoloizing neuromuscular blockers</td>
</tr>
<tr>
<td><strong>Sulfasalazine:</strong> digoxin, folic acid, sulfonylureas</td>
</tr>
<tr>
<td><strong>Auranofin:</strong> phenytoin</td>
</tr>
<tr>
<td><strong>Penicillamine:</strong> gold therapy, antimalarial, cytotoxic drugs, iron salts, antacids, digoxin</td>
</tr>
<tr>
<td><strong>Chloroquine:</strong> hepatotoxic drugs</td>
</tr>
<tr>
<td><strong>Hydroxychloroquine:</strong> digoxin</td>
</tr>
</tbody>
</table>

**NSAIDs = nonsteroidal anti-inflammatory drugs.**

A summary of food/drug interactions with systemic therapies is presented in Table 11.

No formal drug interaction studies have been performed with alefacept, and the optimal time period between initiating other therapies following use of alefacept is not known.10 The safety and efficacy of administering live or live-attenuated vaccines with alefacept have not been fully evaluated. However, the effects of alefacept on the immune response were specifically evaluated in a randomized, controlled, open-label trial in 46 patients with chronic plaque psoriasis.94 Patients were randomized to treatment with alefacept 7.5 mg IV once weekly for 12 weeks or to a control group. Patients were then exposed to an antigen as well as to a recall antigen (tetanus toxic) to determine if there was a significant difference in the immune response between patients treated with alefacept or who were in the control group. Results showed similar mean antibody titers to both the antigen and tetanus toxic, thus suggesting that alefacept selectively inhibits T cells, allowing patients to retain a significant immune response to fight infection or to be able to respond appropriately to vaccinations. Conversely, although
IX. Indications/Monitoring/Precautions

A summary of indications, monitoring recommendations, and precautions with systemic therapies is presented in Table 12. FDA-approved dosing recommendations and a summary of patent information are presented in Table 13.

X. Conclusions

Psoriasis is a chronic skin condition that varies in extent and severity. The majority of patients have mild-to-moderate disease with approximately 30% of patients progressing to moderate-to-severe psoriasis. In general, the disease is not life-threatening, but for patients with more severe disease, it can greatly impact QOL. The goal in treating plaque psoriasis is to obtain rapid control and maintain such, which includes drug therapy with minimal adverse effects as well as a planned approach to address psychosocial implications of the disease. The approach to treatment is variable and dependent on the type of psoriasis, the extent of the disease, and the areas of involvement. The mainstay of therapy for localized disease is topical corticosteroids, calcipotriene, coal tar, tazarotene, and anthralin, while systemic therapy is usually reserved for generalized and more severe disease. For patients with progressive disease despite the aforementioned topical therapies, phototherapy (PUVA) can be used with or without a topical agent. Adjunctive therapy with emollients free of lactic acid or alpha-hydroxy acids can hasten lesion resolution with any of the treatments and should be encouraged. Systemic therapy—acitretin, methotrexate, cyclosporine, infiximab, efalizumab, alefacept, etanercept—should be reserved for patients with moderate-to-severe generalized disease. Furthermore, because of the potentially serious adverse effects associated with some of these agents, rotational therapy may be needed.

The American Academy of Dermatology is in the process of updating the evidence-based guidelines on the treatment of psoriasis published in 1991 and recently published a consensus statement on treatment to provide guidance in the interim. The statement suggests that selection of therapy include the following considerations: type of psoriasis; location of lesions; severity of the lesions, specifically thickness, redness, scaling; extent of the disease based on BSA or PASI score; age of the patient; symptoms, including pain and pruritus; response to previous therapies; accessibility to a dermatologist or ultraviolet light facility; physician preferences; economic factors; cost/benefit ratios; quality of life, specifically the ability to perform daily activities; employability; and interpersonal relationships. Additional considerations are comorbid diseases that may limit or affect treatment options, such as liver disease, hepatitis C, HIV infection, hypertension, and alcohol intake. Consideration must also be given to child-bearing potential, pregnancy, desire to become pregnant, and desire to impregnate.

Mild disease includes patients with limited BSA involvement and, with selection based on severity and location of lesions, is generally responsive to topical therapies such as topical corticosteroids, tazarotene, calcipotriene, anthralin, tar preparations, salicylic acid, lactic acid, urea, lubrication products, or combinations of these agents.

Moderate-to-severe disease generally includes patients with BSA > 10%, but patients with lower BSA involvement may be classified as moderate-to-severe if the palms, soles, head and neck, or genitalia are involved. These patients usually have more generalized or severe disease that is unresponsive to topical agents alone, thus prompting use of systemic therapies.

Phototherapy (UVB with or without topicals) or phototherapy (PUVA) with or without oral retinoids may be a first option for systemic therapy, depending on the availability of light facilities. Methotrexate and cyclosporine have similar efficacy and are alternative choices; often these agents are used in a rotational or sequential method to avoid toxicities observed with long-term use. For more chronic use, methotrexate may be preferred over cyclosporine since chronic use of this agent is typically limited to 1 year in duration. Acitretin, an oral retinoid, can be used alone, but it is also used in combination with phototherapy or photochemotherapy to reduce the doses required and decrease toxicity of light therapy.

The newer biologic agents, efalizumab and alefacept, are potential options, as is infliximab, which has shown some efficacy in psoriasis, although published data are currently limited. Etanercept was recently approved for psoriasis and has published data to support efficacy and safety. Notably, dosing is higher with etanercept for treating psoriasis than for the other approved indications. Thus, cost will be higher with the initially higher dose, but will be comparable with other biologics when the dose is reduced to the typical dose after the first 3 months of therapy. One economic analysis showed that step-down dosing with etanercept, which is the approved dose, was higher than efalizumab and alefacept at 6 months. However, based on a higher efficacy rate, it was deemed the most cost-effective agent, although this was not based on head-to-head trials.

In addition to this guidance, additional considerations are that long-term data are not available with the biologic response modifiers. Exceptions are that long-term data are available with etanercept and infliximab in treating other conditions. Biologic agents do appear less efficacious compared with methotrexate and cyclosporine, but they may be less toxic in the long-term. Other differences in systemic therapies that must be compared include onset of action and ease of administration. Alefacept has

Safety and efficacy of acellular, live, and live-attenuated vaccines have not been studied, a similar study with efalizumab showed secondary immune responses were ablated. Thus, administration of vaccines with efalizumab is not recommended. Similar to alefacept, etanercept is not recommended for administration with live vaccines. Use of etanercept is also cautioned with anakinra due to an increased incidence of neutropenia and serious infections.
**TABLE 12** Indications for Agents for Psoriasis/Psoriatic Arthritis

<table>
<thead>
<tr>
<th>Agent</th>
<th>FDA-approved indications</th>
<th>Investigational uses</th>
<th>Routine monitoring</th>
<th>Special considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALEFACEPT</td>
<td>TX of moderate-to-severe chronic plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.</td>
<td>Psoriatic arthritis.</td>
<td>CD4+ T-cell lymphocyte counts weekly during 12-week regimen, hold dose if count &lt; 250 cells/ml.</td>
<td>Do not initiate in pts. with normal CD4+ counts. Caution use if at high risk for malignancy. Discontinue use if malignancy develops.</td>
</tr>
<tr>
<td>EFALIZUMAB</td>
<td>Treatment of moderate-to-severe chronic plaque psoriasis in adults (age 18 years and older) who are candidates for systemic therapy or phototherapy.</td>
<td>Psoriatic arthritis.</td>
<td>Monthly platelet counts upon initiation, then every 3 months with continued therapy.</td>
<td>Do not initiate in pts. with signs or symptoms of new or worsening heart failure. Ascertain TB risk before starting TX.</td>
</tr>
<tr>
<td>ETANERCEPT</td>
<td>Treatment of adult pts. (age 18 years and older) with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.</td>
<td>Moderate-to-severely active RA.</td>
<td>CBC, LFTs every 2 weeks for 4-8 weeks.</td>
<td>Do not use in pts. with CHF, reevaluate CHF in patients who are currently receiving infliximab.</td>
</tr>
<tr>
<td>INFLIXIMAB</td>
<td>Moderate-to-severely active Crohn's disease, enterocutaneous fistulae.</td>
<td>Juvenile RA, spondyloarthropathy.</td>
<td>CBC with platelets, hepatic enzymes, renal/hepatic function monthly.</td>
<td>Do not use in pts. with CHF, reevaluate CHF in patients who are currently receiving infliximab.</td>
</tr>
<tr>
<td>METHOTREXATE</td>
<td>Symptomatic control of severe calcinosis.</td>
<td>Juvenile RA, spondyloarthropathy.</td>
<td>Monthly platelet counts upon initiation, then at total cumulative dose of 1.5 grams and after each additional 1-1.5 grams.</td>
<td>Do not use in pts. with CHF, reevaluate CHF in patients who are currently receiving infliximab.</td>
</tr>
<tr>
<td>ACITRETIN</td>
<td>TX of severe psoriasis.</td>
<td>Psoriatic arthritis.</td>
<td>CBC with platelet count and renal function tests, LFTs.</td>
<td>Do not use in pts. with CHF, reevaluate CHF in patients who are currently receiving infliximab.</td>
</tr>
<tr>
<td>CYCLOSPORINE</td>
<td>TX of adult, nonimmunocompromised pts. with severe calcinosis, plaque psoriasis who have failed at least one other systemic therapy.</td>
<td>Psoriatic arthritis, various cancers.</td>
<td>CBC with platelet count and renal function tests, LFTs.</td>
<td>Do not use in pts. with CHF, reevaluate CHF in patients who are currently receiving infliximab.</td>
</tr>
<tr>
<td>AZATHIOPRINE</td>
<td>For management of severe RA, unresponsive to NSAIDs or DMARDs.</td>
<td>Psoriatic arthritis, rejection in organ transplantation patients, ankylosing spondylitis.</td>
<td>CBC and platelet count, renal function tests, LFTs.</td>
<td>Do not use in pts. with CHF, reevaluate CHF in patients who are currently receiving infliximab.</td>
</tr>
<tr>
<td>HYDROXYUREA</td>
<td>TX of tumors (melanoma, CML, ovarian, squamous cell carcinoma), sickle cell anemia.</td>
<td>Psoriasis, various malignancies.</td>
<td>CBC and platelet count, renal function tests, LFTs.</td>
<td>Do not use in pts. with CHF, reevaluate CHF in patients who are currently receiving infliximab.</td>
</tr>
<tr>
<td>SULFASALAZINE</td>
<td>Ulcereative colitis.</td>
<td>Psoriatic arthritis and psoriasis, ankylosing spondylitis.</td>
<td>CBC, LFTs every 2 weeks for 3 months, then periodic, renal function tests.</td>
<td>Do not use in pts. with CHF, reevaluate CHF in patients who are currently receiving infliximab.</td>
</tr>
<tr>
<td>AURANOBOIN</td>
<td>Treatment of RA unresponsive to NSAIDs.</td>
<td>Psoriatic arthritis, psoriasis.</td>
<td>CBC with platelet count and urinalysis monthly.</td>
<td>Do not use in pts. with CHF, reevaluate CHF in patients who are currently receiving infliximab.</td>
</tr>
<tr>
<td>PENICILLAMINE</td>
<td>Severe active RA, unresponsive to conventional therapies.</td>
<td>Psoriatic arthritis, acetaminophen poisoning.</td>
<td>CBC and platelet count, renal function tests, LFTs.</td>
<td>Do not use in pts. with CHF, reevaluate CHF in patients who are currently receiving infliximab.</td>
</tr>
</tbody>
</table>

(Continued on next page)
Clinical Monograph for Drug Formulary Review: Systemic Agents for Psoriasis/Psoriatic Arthritis

**TABLE 12** Indications/Monitoring/Precautions for Agents for Psoriasis/Psoriatic Arthritis

**ROUTINE MONITORING:** CBC with platelet counts, urinalysis, and body temperature every 2 weeks for 6 months. LFT every 6 months.

**Special consideration:** Pregnancy category D.

**CHLOROQUINE:** FDA-approved indications: Amebiasis, extraintestinal amebiasis, malaria-suppression and TX. **Investigational uses:** Psoriatic arthritis, cholestasis, lupus erythematosus, pneumonia, rheumatoid arthritis, sarcoidosis, ulcerative colitis. **Routine monitoring:** Eye function tests initially and then periodically thereafter. **Special consideration:** Pregnancy category C.

**HYDROXYCHLOROQUINE:** FDA-approved indications: Malaria-suppression and TX, discoid and systemic lupus erythematosus, RA. **Investigational uses:** Psoriatic arthritis, Alzheimer's disease, asthma, atopic dermatitis, hypercalcemia, lyme disease arthritis, pulmonary embolism, Sjogren's syndrome, deep vein thrombosis. **Routine monitoring:** Baseline and periodic ocular exams, neuromuscular function. **Special consideration:** Pregnancy category C.

**TABLE 13** Adult Dosing/Patent Issues

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
<th>Monitoring/Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Alefacept</em></td>
<td>Administered under the supervision of a physician—15 mg IM or 7.5 mg IV bolus administered once weekly for 12 weeks. Following 12 weeks off treatment, another course can be administered if CD+ counts are within normal range. Data on courses beyond 2 are limited.</td>
<td><strong>Note:</strong> Based on study data, it is estimated that most patients may require 1.5 treatments per year depending on the patient's duration of response.</td>
</tr>
<tr>
<td><em>Efalizumab</em></td>
<td>Initial conditioning dose of 0.7 mg/kg SC followed by 1 mg/kg/week (maximum 200 mg/dose).</td>
<td><strong>Note:</strong> typically given continuously to prevent rebound/flare</td>
</tr>
<tr>
<td><em>Etanercept</em></td>
<td>For <strong>psoriasis</strong>—50 mg twice weekly (administered 3 to 4 days apart) for 3 months, then the dose can be reduced to 50 mg once weekly. The 25 mg and 50 mg once-weekly doses were also found to be efficacious, but response rates were related to dose. For <strong>psoriatic arthritis</strong>—50 mg/week SC</td>
<td></td>
</tr>
<tr>
<td><em>Infliximab</em></td>
<td>Not FDA-approved for psoriasis or psoriatic arthritis</td>
<td></td>
</tr>
<tr>
<td><em>Methotrexate</em></td>
<td>For <strong>psoriasis</strong>—10 mg to 25 mg once weekly, can be titrated by 2.5 mg/week up to 30 mg/week</td>
<td></td>
</tr>
<tr>
<td><em>Acitretin</em></td>
<td>For <strong>psoriasis</strong>—25 mg to 50 mg/day as single dose with a main meal. Maintenance doses of 25 mg to 50 mg/day can be used based on response to initial therapy. Decrease dose of phototherapy if used in combination with acitretin.</td>
<td></td>
</tr>
<tr>
<td><em>Cyclosporine (modified)</em></td>
<td>2.5 mg/kg/day (as 2 divided doses 1.25 mg/kg) for 4 weeks, can be titrated to response (and as tolerated) as increase of 0.5 mg/kg/day every 2 weeks to maximum of 4 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td><em>Azathioprine</em></td>
<td>Not FDA-approved for psoriatic arthritis. Doses used in studies for psoriatic arthritis: 3 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td><em>Sulfasalazine</em></td>
<td>Not FDA-approved for psoriatic arthritis; doses used in studies for psoriatic arthritis: initiated at 500 mg/day then titrated up to 2 grams/day</td>
<td></td>
</tr>
<tr>
<td><strong>Patent issues:</strong></td>
<td>Because of the complexity of producing biologic proteins, the potential for immunogenicity, safety concerns, and the ability to produce therapeutically equivalent generic products, it is unclear when or if generic biologic agents will become available. The FDA is currently reviewing and trying to develop guidelines for approval and development of generic biologic agents.</td>
<td></td>
</tr>
</tbody>
</table>

It should be noted that the use of NSAIDs may exacerbate psoriasis. Patients with more severe disease who are unresponsive to NSAID therapy should be treated with disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, and cyclosporine. Intra-articular injections of corticosteroids may be a therapeutic option in patients with limited disease in only one or two joints, but systemic use of corticosteroids is not recommended. For patients unable to tolerate DMARDs, biologic agents, such as etanercept and infliximab, are efficacious and safe. For patients with psoriatic arthritis with spinal involvement such as spondylitis, biologic agents may be used more as a first-line therapy compared with other forms such as DIP, symmetric disease, or asymmetric disease, which primarily affects joints in the hands and feet.

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*a:* It should be noted that the use of NSAIDs may exacerbate psoriasis. Patients with more severe disease who are unresponsive to NSAID therapy should be treated with disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, and cyclosporine. Intra-articular injections of corticosteroids may be a therapeutic option in patients with limited disease in only one or two joints, but systemic use of corticosteroids is not recommended. For patients unable to tolerate DMARDs, biologic agents, such as etanercept and infliximab, are efficacious and safe. For patients with psoriatic arthritis with spinal involvement such as spondylitis, biologic agents may be used more as a first-line therapy compared with other forms such as DIP, symmetric disease, or asymmetric disease, which primarily affects joints in the hands and feet.
However, safety and efficacy of the biologic agents in the long-term treatment of psoriatic arthritis are not available.

**Author’s Note:** As part of the formulary review process, we provide P&T committee members with a summary of available data on the agents under review (see Table 15, page 52) in addition to the full clinical monograph. This table is designed to highlight key points pertinent to the decision criteria the committee uses to decide product formulary status, including effectiveness and efficacy outcomes, safety, and clinical attributes. Cost is considered only if all other decision criteria are similar and it provides a differentiation point in determining the value of the products under review.

**ACKNOWLEDGMENTS**

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**DISCLOSURES**

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**REFERENCES**


(Continued on page 53)
TABLE 15 Summary of Available Data

<table>
<thead>
<tr>
<th>Decision Criteria</th>
<th>Alefacept (Amevive)</th>
<th>Efalizumab (Raptiva)</th>
<th>Etanercept (Enbrel)</th>
<th>Other Systemic Therapies: Methotrexate, Soriatane (Acitretin), Cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness outcomes</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
<td>Yes—Methotrexate (MTX)—psoriasis: (PASI90 by 40% of pts., PASI75 by 60% of pts.), similar to cyclosporine, better than biologics; psoriatic arthritis: significant improvements in disease activity, and patient and physician assessments of disease.</td>
</tr>
<tr>
<td>Efficacy outcomes</td>
<td>Delayed onset of effects with full effects not seen until 8 weeks after treatment period; slightly lower efficacy than Raptiva</td>
<td>Rapid onset of effects compared with Amevive; slightly higher efficacy than Amevive</td>
<td>Duration of response is shorter than Amevive (9-10 weeks vs. 7 months); requires continuous dosing to maintain effects</td>
<td>Psoriatic arthritis—Efficacy as monotherapy: DOE—(ACR20, ACR50 NNT = 2) improves QOL. POE—decreases signs and symptoms of disease as measured by ACR response rates and improvement in QOL measures.</td>
</tr>
<tr>
<td></td>
<td>DOE—21% pts. achieved PASI75 at 14 weeks (NNT = 6)</td>
<td>DOE—27% pts. achieved PASI75 at 12 weeks (NNT = 4)</td>
<td>DOE—PASI75, PASI50; (NNT = 4-5)</td>
<td>Psoriasis—At 50 mg, twice-weekly or step-down dosing, appears more efficacious than Amevive or Raptiva.</td>
</tr>
<tr>
<td></td>
<td>POE—significant improvements in DLQI and DQOLs noted starting at 12 weeks</td>
<td>POE—significant improvements in DLQI starting at 4 weeks</td>
<td>POE—significant improvements in QOL at 24 weeks</td>
<td>At 25 mg, twice-weekly dosing, efficacy similar to Raptiva.</td>
</tr>
<tr>
<td></td>
<td>Safety</td>
<td>No rebound or flare noted after discontinuation (ARI=2.7% vs. placebo; NNH=37); must give continuously to maintain efficacy.</td>
<td>Monitor for thrombocytopenia monthly</td>
<td>Cyclosporine—psoriasis: (PASI90 by 33% of pts., PASI75 by 71% of pts.) similar to MTX, better than biologics; slow onset of effects (discontinue if satisfactory response not observed by 6 weeks at dose of 4 mg/kg/day); psoriatic arthritis: significant improvements in disease activity, and patient and physician assessments of disease, better than sulfasalazine.</td>
</tr>
<tr>
<td></td>
<td>Safety data</td>
<td>Safety data</td>
<td>Safety data up to 5 years</td>
<td>Sulfasalazine and azathioprine—psoriatic arthritis: some data from small trials show positive results, but systematic reviews show efficacy of both agents compared with placebo; slow onset of effects; psoriasis: azathioprine has not been extensively studied in psoriasis and sulfasalazine is not used for this indication.</td>
</tr>
<tr>
<td></td>
<td>Monitoring CD4 counts weekly during therapy</td>
<td>Severe rebound or flare noted with discontinuation (ARI=2.7% vs. placebo; NNH=37); must give continuously to maintain efficacy.</td>
<td>No rebound or flare noted after discontinuation, in preliminary studies</td>
<td>No—Penicillamine (psoriatic arthritis—very limited data), chloroquine/hydroxychloroquine (limited to small studies in psoriatic arthritis [&lt;30 pts.]), hydroxyurea (psoriasis—small studies), auranofin (limited data with some data from small studies showing efficacy for psoriatic arthritis), infliximab (psoriasis/psoriatic arthritis, limited studies published to fully evaluate).</td>
</tr>
<tr>
<td></td>
<td>Pregnancy category B</td>
<td>Must monitor CD4 counts weekly during therapy</td>
<td>Primarily injection site reactions, bold warning on serious infection and TB risk</td>
<td>Many years of use, thus most toxicities and monitoring requirements are known for these agents. Long-term toxicities are associated with these agents, thus they are usually used in a rotational/sequential or intermittent method to avoid long-term toxicities.</td>
</tr>
<tr>
<td></td>
<td>No rebound/flare reported with discontinuation, similar efficacy achieved after readministration</td>
<td>Severe rebound or flare noted after discontinuation (ARI=2.7% vs. placebo; NNH=37); must give continuously to maintain efficacy.</td>
<td>Demyelinating effects possible; increased risk of lymphoma may exist with all TNF inhibitors. May worsen CHF, caution; patients must dilute multidose vial, which contains 2 doses and is stable for 14 days</td>
<td>MTX—hepatotoxicity (liver biopsy every 1.5 to 3 years with continued long-term use), requires monitoring, often used in rotation/sequential pattern (low-dose intermittent therapy) alternating with other agents to avoid cumulative toxicities. Highly teratogenic.</td>
</tr>
<tr>
<td></td>
<td>Pregnancy category C</td>
<td>Monitor for thrombocytopenia monthly</td>
<td>Pregnancy category C</td>
<td>Cyclosporine—duration of response is about 6 weeks, rebound/flare has rarely been observed. Continued use beyond 1 year not recommended. Hypertension, renal toxicity. Rotation with other agents used to decrease cumulative toxicity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Safety at 50 mg twice weekly, used in psoriasis, not fully studied</td>
<td>Acitretin—may worsen psoriasis initially, mucocutaneous reactions, hepatotoxic, increases lipids. Monitor lipids and liver function tests every 2 weeks for 6-8 weeks.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Azathioprine—black box warning regarding increased risk of neoplasia with long-term use. Monitor CBC and platelets weekly for first month, then twice monthly for 2 months, then monthly. Most agents can cause hematologic and hepatotoxic abnormalities and require regular monitoring. Sulfasalazine is pregnancy category B, all others are C-X.</td>
</tr>
</tbody>
</table>

(Continued on next page)
TABLE 15 Summary of Available Data

<table>
<thead>
<tr>
<th>Decision Criteria</th>
<th>Alefacept (Amevive)</th>
<th>Efalizumab (Raptiva)</th>
<th>Etanercept (Enbrel)</th>
<th>Other Systemic Therapies: Methotrexate, Soriatane (Acitretin), Cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical attributes</td>
<td><strong>Psoriasis</strong>—long remission rates of approximately 7 months noted, higher following 2 courses of therapy Administered IM, but not patient-administered Administered once weekly for 12 weeks, then off for 12 weeks</td>
<td><strong>Psoriasis</strong>—rapid onset of effects Administered SC by patient; distributed through specialty pharmacies only</td>
<td><strong>Psoriasis</strong>— Administered SC by the patient <strong>Psoriatic arthritis</strong>— Administered SC by the patient, requires once-weekly dosing; new once-weekly 50 mg dosage formulation available; only biologic FDA-approved for psoriatic arthritis Other indications for RA, juvenile RA, ankylosing spondylitis, seeking psoriasis indication</td>
<td>MTX, cyclosporine, and acitretin are FDA-approved for the treatment of severe psoriasis. MTX can be used alone or in combination with topicals (decreased dose needed). All are administered orally and can be administered in sequential or rotational pattern for maintenance and to decrease toxicities. All agents, except acitretin, are approved and primarily used for other indications/disease states.</td>
</tr>
<tr>
<td>Cost</td>
<td>More than traditional agents, similar to Raptiva</td>
<td>More than traditional agents, similar to Amevive</td>
<td>More than NSAIDs and DMARDs for psoriatic arthritis; less than Amevive and Raptiva at traditional doses (50 mg once weekly), but higher, if administered at higher doses (50 mg BIW or step-down dose); the step-down dose is the approved dose for psoriasis</td>
<td>Less than biologics; generics least expensive</td>
</tr>
</tbody>
</table>

CBC = complete blood count; CHF = congestive heart failure; DLQI = Dermatology Life Quality Index; DMARDs = disease-modifying antirheumatic drugs; DOE = disease-oriented evidence; DQOL = dermatology quality of life; FDA = U.S. Food and Drug Administration; IM = intramuscular; MTX = methotrexate; NNH = number needed to harm; NNT = number needed to treat; NSAIDs = nonsteroidal anti-inflammatory drugs; PASI = Psoriasis Area Severity Index; POE = patient-oriented evidence; Pts. = patients; PUVA = psoralen plus ultraviolet A light; QOL = quality of life; RA = rheumatoid arthritis; SC = subcutaneous; TB = tuberculosis; TNF = tumor necrosis factor.


83. Finlay AY, Salek MS, Haney J, for the Alefacept Clinical Study Group.


Formulary Review of Therapeutic Alternatives for Atopic Dermatitis: Focus on Pimecrolimus

JEFFREY M. WEINBERG, MD

ABSTRACT

OBJECTIVE: Atopic dermatitis (AD), often called eczema, is characterized by intense pruritus, erythema, dry skin, and inflammation. The condition is chronic and relapsing, and often occurs in patients with a family history of the atopic triad (asthma, allergic rhinitis, and AD). Use of topical steroids has been the mainstay of medical treatment for AD. Steroid-free treatments for AD, with a more favorable safety profile, have become available within the past 2 years. Tacrolimus ointment, a topical immunomodulator, became available in early 2001 and is indicated for moderate-to-severe AD. A similar but highly skin-selective cytokine inhibitor, pimecrolimus cream 1%, became available in March 2002. Pimecrolimus is indicated for mild-to-moderate AD. The objective of this article is to review the key characteristics that differentiate pimecrolimus from steroids and tacrolimus in the treatment of AD.

METHODS: Using secondary resources, the clinical aspects and conventional treatment strategies for AD are reviewed as are the pivotal clinical studies with pimecrolimus and literature on quality of life and economic burden of disease for AD patients and families.

SUMMARY: Pimecrolimus is an effective, steroid-sparing therapy for mild-to-moderate AD. Early treatment prevents flares, the agent works quickly to reduce signs and symptoms of more advanced AD, and it is safe and appropriate for intermittent long-term therapy. Pimecrolimus has fewer side effects than topical steroids and a better side-effect profile than tacrolimus. It can also be used as a first-line therapy. In studies with patients aged 2 to 17 years, it has been shown to be particularly effective in improving eczema of the face and neck, and its use may improve quality of life for many patients, especially children. A single-strength dose (1%) is safe and medically beneficial for pediatric, adolescent, and adult patients. The direct drug cost of pimecrolimus compares favorably with tacrolimus, but it is significantly more expensive than generic topical steroid creams.

KEYWORDS: Atopic dermatitis, Nonsteroid, Cytokine inhibitor, Topical immunomodulator

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Societal and Patient Costs

Approximately 49% to 70% of childhood AD cases occur by 6 months of age, while 80% to 90% present by age 5. Males and females are affected in equal proportion, and no differences have been found between children of different racial and ethnic backgrounds. Psychological problems are a concern in treating children with AD, and an Australian cross-sectional survey found that childhood AD has a profound impact on families.

AD presents an economic burden to families, society, and the health care system. U.S. data indicate that direct medical costs, consisting of emergency room visits, outpatient treatment, physician office visits, and prescriptions for AD patients younger than 25 years totaled $364 million in 1990. Another study, using 1997 and 1998 claims data from a private insurer and state Medicaid program, examined the third-party payer costs for AD and eczema, finding that costs ranged from $0.9 billion to $3.8 billion when projected across the total number of persons younger than 65 years. The authors concluded that the cost of AD is similar to diseases such as emphysema, psoriasis, and epilepsy.

Families bear a substantial portion of the health care costs for AD. Two studies done in large managed health care organizations using claims data and patient/parent surveys came to similar conclusions: In the first, 962 AD patients were identified, of which almost half were children younger than 17 years. Mean per-patient annual costs totaled $609, with the third-party payer covering only 24%, or $167 per patient. Third-party payer costs were almost entirely due to costs of office visits and prescription medications. About 50% of the total burden of illness was related to lost productivity; the remainder was paid directly by the patient or parent for treatments not covered by insurance.
focused exclusively on pediatric and adolescent patients, estimated that direct medical costs paid by the insurer accounted for 30% of the total financial burden for that organization’s AD patients younger than 18 years. The parental financial burden (which also included estimated costs of lost productivity) averaged $439 per year. These authors projected their data to estimate national costs. Assuming an AD prevalence of 12% to 16% of U.S. school-aged children, total costs for treatment of pediatric AD in the United States could range from $4.9 billion to $6.5 billion per year.

**Novel, Steroid-free Agents**

Although topical steroids can be effective in AD treatment, their use is limited due to the potential for side effects, both local and systemic (Table 1). Several factors have driven the development of more effective, steroid-free therapies to treat AD. First, the evolving understanding of the pathogenesis of AD has allowed researchers to target specific steps in the inflammatory cascade. Second, the limitations of topical corticosteroids are well known. The third driver is related to the second: patients and parents may be phobic about using steroids and, therefore, be noncompliant.

Two effective, steroid-free treatments for AD have become available within the past 2 years. Tacrolimus ointment (Protopic 0.03% and 0.1%), a topical immunomodulator, became available in early 2001. A similar but highly skin-selective cytokine inhibitor, pimecrolimus cream (Elidel 1%), became available in March 2002.

**Indications**

Pimecrolimus is approved for mild-to-moderate AD, while tacrolimus is indicated for moderate-to-severe AD. Pimecrolimus cream 1% is indicated for all patients aged 2 years and older. The 0.03% strength tacrolimus ointment is recommended for children aged 2 to 15 years, and the 0.1% strength is recommended for adults. Both agents are indicated for the short-term and intermittent, long-term management of AD (eczema) in nonimmunocompromised patients, in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to, or are intolerant of, alternative, conventional therapies.

**Pharmacology**

The full mechanism of action of pimecrolimus has not been completely elucidated. However, inhibition of the calcium-dependent phosphatase, calcineurin, has been observed. Consequently, the drug inhibits T-cell activation by blocking the transcription of early cytokines. In addition, pimecrolimus inhibits the release of inflammatory cytokines and mediators from mast cells and basophils in vitro after stimulation by antigen/Ig (immunoglobulin) E. Pimecrolimus has no effect on keratinocytes, fibroblasts, endothelial cells, Langerhans cells, the hypothalamus, or the adrenal gland.

The mechanism of action and pharmacological profile of pimecrolimus differ markedly from corticosteroids. Figure 1 shows the mechanism of action of pimecrolimus versus corticosteroids. Pimecrolimus interferes with the inflammatory process by preventing release of cytokines without affecting other skin systems.

**Pharmacokinetics**

Preclinical pharmacokinetic studies indicated that pimecrolimus is highly absorbed into the skin but has little or no absorption into systemic circulation. In 12 adults with extensive AD, 78% of 444 blood samples had pimecrolimus concentrations below the limit of quantification (0.5 ng/ml). This skin-selective property makes pimecrolimus different from tacrolimus. Billich et al. compared...
pared the in vitro skin penetration and permeation of pimecrolimus and tacrolimus and 3 representative corticosteroids (betamethasone-17-valerate, clobetasol-17-propionate, and diflucortolol-21-valerate). Drug concentrations of pimecrolimus and corticosteroids in human skin were found to be in the same order of magnitude. Permeation of pimecrolimus through human skin was, however, lower by factors of 70 to 10 as compared with the steroids. When pimecrolimus was compared with tacrolimus in human, pig, or rat skin, similar concentrations of the 2 compounds were measured in the skin, whereas permeation of pimecrolimus through skin was consistently lower by factors of 9 to 10. Lipophilicity was found to be highest for pimecrolimus, its octanol-water distribution coefficient being higher by factors of 8 and 25 to 450 than that of tacrolimus and the corticosteroids, respectively. The authors postulated that the low permeation of pimecrolimus may be explained by its higher lipophilicity (compared with tacrolimus and the corticosteroids) and higher molecular weight (compared with steroids). They concluded that pimecrolimus appears to have a favorable skin penetration/permeation profile, featuring a low degree of percutaneous absorption. Work with animal models also indicated that pimecrolimus is less likely than tacrolimus to induce immunosuppression (as measured by graft/host rejection).

Pimecrolimus may have a high affinity for the skin because of its highly lipophilic nature. That hypothesis is anecdotally supported by a small, 4-week study performed with 16 healthy volunteer subjects. In the randomized, double-blind, controlled trial, pimecrolimus 1% was compared with corticosteroid cream to determine skin atrophy effects. Subjects applied the cream twice daily, 6 days a week, for 4 weeks. Skin thickness was evaluated by ultrasound, clinical signs of atrophy, and epidermis thickness. Topical steroid preparations caused a significant reduction in skin thickness, whereas the pimecrolimus and vehicle induced no skin thinning.

While corticosteroids are readily absorbed through the dermis and into the systemic circulation, pimecrolimus penetrates the dermis only minimally; therefore, systemic absorption of pimecrolimus cream is consistently low. Preclinical investigations found that blood concentrations were minimal in children and infants. In 26 pediatric AD patients, aged 2 to 14 years with 20% to 69% body surface area involvement, blood concentration with twice-daily application averaged <3 ng/mL. The majority of blood samples were below the limit of quantification (0.5 ng/mL). This result was consistent (ranging from 0.1 ng/mL to 2.6 ng/mL) even with application on up to 92% of body surface area in 22 infants aged 3 to 23 months.

## Comparative Efficacy

The pimecrolimus clinical research program has now gathered extensive data in short- and long-term studies of patients with AD. The program has focused primarily on children but has included infants and adults. Extensive pharmacokinetic profiling has been performed in patients down to 3 months of age.

### Short-term Studies

Pivotal data came from 3 short-term trials, the results from 2 trial groups (children and adolescents aged 2 to 17 years [n = 403], reported as pooled data by Eichenfield et al. in 2002) and a trial with infants aged 3 to 23 months (n = 186), reported by Ho et al. in 2003. These 3 study designs were identical, providing some justification for the use of pooled data to determine effects in children aged 2 to 17 years. The common study design consisted of 6 weeks of treatment in a randomized, placebo-controlled, double-blind phase, followed by an open-label extension of 20 weeks during which all patients received pimecrolimus treatment. In the double-blind phase, pimecrolimus was compared with a placebo vehicle; no corticosteroids were given. Six weeks of therapy in clinical practice is considered sufficient to obtain significant improvement in symptoms of AD. Without satisfactory response by 6 weeks, good practice indicates a need to reevaluate the patients. However, during trials with pimecrolimus, response was observed in a much shorter time frame.

At each visit, investigators assessed efficacy and safety using several measurements. Efficacy endpoints included the Investigator Global Assessment (IGA) score, the Eczema Area and Severity Index (EASI), severity of pruritus, and the subject's own assessment of disease control. (Dermatologists in clinical practice do not generally measure effectiveness through the use of instruments such as the IGA and EASI, but these are common clinical research tools.) The IGA score is based on a 5-point rating scale that rates severity of signs and symptoms of AD. A score of 2 or 3 indicates mild-to-moderate symptoms, e.g., mild erythema and papulation/infiltation, or 3, moderate erythema, papulation/infiltation. A rating of 5 is defined as very severe erythema, papulation/infiltation with oozing/crusting. The EASI measures body area affected by and the severity of 6 clinical signs of AD; the EASI is also expressed as a composite score of the 6 measures: edema, erythema, excoriation, lichenification, oozing, and scaling. Hanifin et al. performed an evaluation to validate the reliability of the EASI scoring system by assessing inter- and intraobserver consistency. Twenty adults and children with AD were evaluated: cohort 1 (10 patients aged ± 8 years) and cohort 2 (10 patients aged < 8 years). The EASI was utilized by 15 dermatologist evaluators to assess AD in cohort 1 and cohort 2 on 2 consecutive days.

The authors found that overall intraevaluator reliability of the EASI was in the fair-to-good range. Interevaluator reliability analyses indicated that the evaluators assessed the patients consistently across both study days. The authors concluded that the EASI can be learned quickly and utilized reliably in the assessment of severity and extent of AD and that these results support the use of the EASI in clinical trials of therapeutic effectiveness.
agents for AD. End points were expressed as percentage of change from baseline in IGA and EASI scores.

The pooled data study included 403 pediatric patients aged 2 to 17 years who had AD affecting at least 5% of total body surface area. Children had to have a baseline IGA score of 2 or 3, corresponding to mild-to-moderate disease. Significant improvement in primary and secondary efficacy measures occurred. For example, as measured by IGA scores at 6 weeks, 34.8% of those using pimecrolimus had ratings of 0 or 1, indicating that AD was clear or almost clear. The placebo group, on the other hand, reported 18.4% of 0 or 1 scores. As shown in Figure 2, the study medication had a rapid onset of action. By day 8 of treatment, a statistically significant difference was noted between the pimecrolimus and vehicle (placebo) groups ($P < 0.05$). Figure 2 also shows that similar results were derived from Ho’s study of infants aged 3 to 23 months, which was also randomized, double-blind, and placebo-controlled.

At 6 weeks, 55% of the pimecrolimus group versus 24% of the vehicle group were clear or almost clear of AD. Results were statistically significant during each week of the study.

In both the pediatric and infant clinical trials, patients reported significant pruritus relief in the first week of treatment. At the end of 6 weeks, 54% of children using pimecrolimus and 32.5% of those using the vehicle reported pruritus relief. Similar results were found in infants: at 6 weeks, 72% versus 33% of pimecrolimus- and vehicle-treated patients, respectively, reported pruritus relief ($P < 0.005$). EASI scores also improved significantly. Pediatric patients on pimecrolimus had a median improvement in EASI scores from baseline of 61% at 6 weeks.

After the placebo-controlled period, children receiving the vehicle were switched to pimecrolimus during a 20-week open-label continuation phase. Figure 3 shows that, beginning at 6 weeks, those in the vehicle arm who began treatment with pimecrolimus experienced a median improvement in EASI scores from 14% to 63% at day 71 and had a 79% improvement at 6 months.

Infants experienced even greater improvement in EASI scores. At the end of 6 weeks, infants’ EASI scores improved by 81.6% compared with 4% in the control group ($P < 0.001$). Beginning at 6 weeks, infants previously receiving the vehicle began pimecrolimus treatment. Between day 43 and day 71 (4 weeks of treatment), infants using pimecrolimus experienced an 81% improvement in EASI scores.

In young children, and especially in infants, facial involvement of AD is common. Steroids, however, can be used only sparingly on the face and neck because of side effects that include skin thinning. In the infant studies, investigators specifically looked at improvement of the EASI scores in the head and neck area. As shown in Figure 4, the median percentage improvement in overall EASI scores was significant at all postbaseline visits to vehicle ($P < 0.001$). The median percentage improvement in the head and neck area was substantial.

Kempers et al. evaluated pimecrolimus cream 1% and tacrolimus ointment 0.03% in pediatric patients with moderate AD. In this study, 141 patients (aged 2 to 17 years) were randomized to treatment with pimecrolimus cream 1% ($n = 71$) or tacrolimus ointment 0.03% ($n = 70$) twice daily for 6 weeks. At day 4, local, application-site reactions were less common and

![Figure 2](image-url)

**Figure 2** Short-term Studies in Infants and Children Percentage Rated Clear or Almost Clear by IGA Score (0 or 1)

<table>
<thead>
<tr>
<th>Subjects (%)</th>
<th>Baseline</th>
<th>8</th>
<th>15</th>
<th>22</th>
<th>29</th>
<th>43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>12</td>
<td>2.2</td>
<td>6.6</td>
<td>7.4</td>
<td>11.8</td>
<td>18.4*</td>
</tr>
<tr>
<td>Pimecrolimus</td>
<td>21</td>
<td>2.2</td>
<td>6.6</td>
<td>7.4</td>
<td>11.8</td>
<td>18.4*</td>
</tr>
<tr>
<td>Vehicle</td>
<td>27</td>
<td>2.2</td>
<td>6.6</td>
<td>7.4</td>
<td>11.8</td>
<td>18.4*</td>
</tr>
</tbody>
</table>

* $P < 0.05$, $P < 0.001$, $P < 0.001$. **Success: IGA (Investigator Global Assessment) score = 0 (clear) or 1 (almost clear).
of shorter duration with pimecrolimus than with tacrolimus. The incidence of erythema/irritation was 8% (6 of 71) with pimecrolimus, compared with 19% (13 of 70) with tacrolimus (P = 0.039). While the incidence of warmth, stinging, and burning was similar in both groups, reactions lasting >30 minutes were fewer with pimecrolimus (0%, 0 of 14) than with tacrolimus (67%, 8 of 12; P < 0.001). Efficacy was similar in both treatment groups at day 43. The authors concluded that pimecrolimus cream 1% had better formulation attributes and local tolerability than tacrolimus ointment 0.03% while providing similar efficacy and overall safety in pediatric patients with moderate AD.32 This head-to-head study was sponsored by the manufacturer of pimecrolimus.

Long-term Studies

Infants and Children/Adolescents: Results of long-term studies of pimecrolimus are equally encouraging. The objective of the long-term management studies was to evaluate the 6- and 12-month efficacy and safety of a pimecrolimus-based, long-term management strategy versus conventional treatment.28,29 All disease severities were allowed, and medium potency corticosteroids were used to control severe flares in both groups. Figure 5 illustrates the study design. All patients used emollients. At the first signs and symptoms of AD, pimecrolimus or the vehicle was applied to the affected areas. The primary efficacy end point was the number of flares at 6 months. Secondary measures included the number of flares at 12 months and the number of flares by disease severity at baseline. Efficacy was also measured by the reduction in corticosteroid use and the EASI score. Safety end points included number and type of adverse events, physical examination, and laboratory evaluations performed at screening, 6 months, and study end.

Significant improvement occurred with pimecrolimus versus conventional therapy. As shown in Figure 6, 68% of infants and 61% of children/adolescents treated with pimecrolimus reported no flares at 6 months. At 12 months, 57% of infants and 51% of children/adolescents had no flares.28,29 Long-term use of steroids among children/adolescents was significantly reduced by pimecrolimus treatment.29 At 6 months, 66% of pimecrolimus-treated patients reported 0 days of steroid therapy compared with 38% treated with conventional therapy. Figure 7 shows steroid use in children/adolescents at the end of 12 months. Fifty-seven percent of the pimecrolimus group had 0 days of corticosteroid therapy, whereas only 32% of the conventional treatment group had 0 days of steroids. In the pimecrolimus group, four fifths (83%) of patients required 14 days or fewer of corticosteroid therapy compared with 60% of those on conventional therapy.28

Adults: A 6-month, randomized, controlled trial assessed the efficacy and safety of pimecrolimus in adults with moderate-to-severe AD.31 A sample of 192 patients was randomized to either pimecrolimus or placebo cream. Pimecrolimus proved significantly more effective than placebo (P ≤ 0.001), as measured by percentage of days requiring second-line rescue therapy. Fifty-eight percent of pimecrolimus-treated versus 30% of placebo-treated patients reported 0 flares by study end.31
**Adverse Events**

The potential toxicity of pimecrolimus has been studied extensively. No evidence has been noted for reproductive toxicity or carcinogenicity in mice at relevant doses or for photocarcinogenicity and mutagenicity in mouse models.\(^{21,25}\) Label “warnings” include the results of rat dermal carcinogenicity studies using pimecrolimus in which there were statistically significant increases in the incidence of follicular cell adenoma of the thyroid, but the doses of pimecrolimus cream were 1.5 to hundreds of times the maximum recommended human dose based on area under the curve comparisons.\(^{33}\) Dermatotoxicity studies show no cumulative irritancy, sensitization potential, phototoxicty, photoallergy, or skin atrophy in mouse models.\(^{21,25}\)

Adverse event profiles from short-term clinical trials were comparable in children and infants.\(^{26,27}\) Most adverse events were mild or moderate and representative of typical childhood illnesses. No clinically relevant, drug-related systemic effects occurred. Upper respiratory tract infection was the most commonly reported adverse event (14.2% pimecrolimus versus 13.2% vehicle). The percentage of children and adolescents experiencing an adverse event of any kind was similar between those two groups. Application site reactions were less common in pediatric patients receiving pimecrolimus (10.4%) than those receiving the vehicle (12.5%).\(^{27}\) A warmth or burning sensation was mostly mild to moderate and transient. Pruritus occurred in 1.1% versus 1.5% of control-treated patients. In short-term pediatric trials of tacrolimus 0.03%, pruritus occurred in 41% versus 27% of control-treated patients.\(^{34}\) Patients in pimecrolimus infant studies showed a similar lack of significant difference in the incidence of adverse events between pimecrolimus and placebo as those in pediatric studies.\(^{26}\)

In long-term pediatric trials, no significant differences in adverse events were found between pimecrolimus and conventional therapy groups. Both groups had similar rates of application site reactions (10.5% versus 9.3%, pimecrolimus versus control), viral skin infections (12.4% versus 6.3%, pimecrolimus versus control), and bacterial skin infections (14.2% versus 30.9%, pimecrolimus versus control).\(^{28}\) Pruritus occurred in 1.8% versus 0% in the control group. In the infant studies, there was a similar lack of significant difference in incidence of adverse events between pimecrolimus and control groups.\(^{29}\)

In long-term studies of tacrolimus, 0.1%, bacterial skin infections occurred in 11% of both pediatric and adult patients; viral infections occurred in 14% of pediatric and 8% of adult patients. Pruritus occurred in 25% of both pediatric and adult patients.\(^{34}\)

The most common adverse effects in all trials were application site reactions, such as itching or a burning sensation. As shown above, with use of pimecrolimus, incidence of burning sensation was low and occurred almost equally in the pimecrolimus and control groups (10.5% versus 9.3%, respectively).\(^{28}\) During tacrolimus clinical trials, with use of a significantly lower-strength ointment (tacrolimus 0.03%), burning occurred in 43% and 46% of pediatric and adult patients, respectively.\(^{34,35}\) With use of the 0.1% strength tacrolimus ointment, burning occurred in 58% of adults.\(^{35}\) It is not considered good science to make cross-trial comparisons, but there are no head-to-head comparative trials to rigorously test the differences in the side-effect profiles of these two products.

**Drug Interactions**

Interactions between pimecrolimus and systemically administered medication are considered unlikely due to minimal absorption.
Neither pimecrolimus nor tacrolimus should be used concomitantly with topical anti-inflammatories, including steroids, or with other immunosuppressives. Caution should be used in concomitant administration with the known CYP3A family of inhibitor drugs, such as erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers, and cimetidine.

**Dosing and Administration**

Pimecrolimus can be used on all skin surfaces, including the head, neck, and interiginous areas. It is safe under clothing and washes off with soap and water. Moisturizers can be used after applying the medicated cream. There are no restrictions on the amount applied, the body surface area treated, or the duration of treatment.

A thin layer of pimecrolimus cream should be applied to the affected skin and rubbed in gently and completely. Pimecrolimus cream may be used twice daily as long as symptoms persist but should be discontinued if signs and symptoms of eczema disappear. If symptoms persist beyond 6 weeks, the patient should be reevaluated. Application of tacrolimus ointment is similar; however, treatment should be continued for 1 week after signs and symptoms clear. Neither product is approved for use under occlusive dressings.

Neither pimecrolimus nor tacrolimus should be used on areas of the skin affected by a viral or clinical infection. The infection should be cleared before beginning therapy. No controlled studies have been conducted with pregnant women; therefore, neither agent is recommended for use by pregnant or lactating females.

**Availability**

Pimecrolimus cream 0.1% is available by prescription only and is available in tubes of 30 grams, 60 grams, and 100 grams for patients 2 years and older. Tacrolimus ointment 0.03% and 0.1% are both available in tubes of 30 grams, 60 grams, and 100 grams. Only the 0.03% ointment is indicated for pediatric use and is limited to children 2 years and older. Both products should be stored at room temperature (59 to 86 degrees Fahrenheit).

**Costs of Therapy**

The costs of therapy are impacted by many factors. Pimecrolimus and tacrolimus are priced similarly when compared in terms of direct drug cost, but both have a much higher direct drug cost compared with the topical corticosteroids, most of which are available in generic form (Table 2). Hydrocortisone butyrate 0.1% is available over the counter (OTC; e.g., Florasone) and by prescription (e.g., Locoid), and both prices are included for comparative purposes. Desonide is similar in potency to hydrocortisone, is not available OTC, but is available in generic form. Clobetasol is higher in potency compared with desonide and hydrocortisone butyrate, is not available OTC, but is available in generic form. Clobetasol suppresses the hypothalamic-pituitary-adrenal axis at doses as low as 2 grams per day, and therefore may not be the best choice for children.36

**Quality-of-Life Assessments**

AD impairs quality of life for those affected and for their caregivers. For example, one study assessed 239 AD patients aged 4 to 70 years.37 Using various quality-of-life measures, researchers found that AD was associated with deficits in social functioning and psychological well-being. Greater health-related quality-of-life decrements were associated with more

---

### Figure 7

**Use of Corticosteroids in Children/Adolescents During 12 Months of Treatment: Pimecrolimus Versus Conventional Therapy**

- **Pimecrolimus**
  - 0 days: 17%
  - 1-14 days: 26%
  - ≥14 days: 57%

- **Conventional Therapy**
  - 0 days: 28%
  - 1-14 days: 32%
  - ≥14 days: 41%

*Conventional therapy: emollients for dry skin and moderately potent topical corticosteroids for flares of atopic dermatitis.

### Table 2

**Direct Drug Costs for Topical Therapeutic Alternatives for Atopic Dermatitis**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimecrolimus 1% 30 grams</td>
<td>$57.84</td>
</tr>
<tr>
<td>Pimecrolimus 1% 60 grams</td>
<td>$108.04</td>
</tr>
<tr>
<td>Tacrolimus 0.03% 30 grams</td>
<td>$59.53</td>
</tr>
<tr>
<td>Tacrolimus 0.1% 30 grams</td>
<td>$61.72</td>
</tr>
<tr>
<td>Tacrolimus 0.1% 60 grams</td>
<td>$124.57</td>
</tr>
<tr>
<td>Clobetasol propionate cream 0.05% 15 grams</td>
<td>$10.99</td>
</tr>
<tr>
<td>Clobetasol propionate cream 0.05% 30 grams</td>
<td>$15.53</td>
</tr>
<tr>
<td>Desonide cream 0.05% 15 grams</td>
<td>$10.99</td>
</tr>
<tr>
<td>Desonide cream 0.05% 60 grams</td>
<td>$17.99</td>
</tr>
<tr>
<td>Hydrocortisone butyrate 0.1% 15 grams (Locoid)</td>
<td>$35.10</td>
</tr>
<tr>
<td>Hydrocortisone butyrate 0.1% 45 grams (Locoid)</td>
<td>$72.89</td>
</tr>
<tr>
<td>Hydrocortisone butyrate 0.1% 30 grams (Florasone, OTC)</td>
<td>$5.73</td>
</tr>
</tbody>
</table>

severe disease. These researchers also found that patients with AD had poorer mental health scores than those with diabetes or hypertension. Another study found that AD patients rated their health at only 73% of perfect health. Quality of life improves with successful treatment of AD for pediatric patients and their parents. Parents reported that they were able to get more sleep, devote less time to treatments, and spend less time worrying. Because pimecrolimus effectively reduces flares and reduces the need for steroid use, it can be assumed that its use will also positively affect quality of life for patients and families.

**Summary**

Pimecrolimus is a cell-selective inhibitor of inflammatory cytokines. Because it has low absorption through the skin, it is not associated with the atrophogenic effects to the skin found with the corticosteroids and has low potential to impair the HPA. Pimecrolimus blood levels remain consistently low after repeated topical application, and no clinically relevant drug-related systemic effects have been reported among the 8,000 patients treated in clinical trials to date.

Pimecrolimus is a safe and effective steroid-free treatment for AD. Consistently positive results have been found with pimecrolimus treatment in infants, children, adolescents, and adults. Unlike tacrolimus, a single strength is recommended for use in all ages. Tacrolimus 0.03% is indicated for children 2 to 17 years and the 0.1% strength is indicated for adults. When used at the first signs and symptoms of AD, pimecrolimus reduces flares by preventing disease progression to flare. In clinical trials comparing pimecrolimus with placebo or topical corticosteroids, no significant differences between treatment groups were found in percentage or type of adverse events, infections, and application site reactions.

Tacrolimus has demonstrated efficacy in more severe patients while pimecrolimus data support use for mild-to-moderate AD patients. Both offer alternative treatment to steroids. Pimecrolimus’s safety, efficacy, and positive impact on quality of life make it an important addition to the physician’s treatment options, and available clinical data show excellent results in infants and in use on the face and neck. Pimecrolimus should be regarded as an effective, steroid-sparing therapy for mild-to-moderate AD in patients of all ages. Although pimecrolimus and tacrolimus have U.S. Food and Drug Administration indications to treat children as young as 2 years old, pimecrolimus has published evidence that it is effective in infants as young as 3 months old. It is appropriate as a first-line agent as well as for long-term, intermittent therapy.

Recent case studies indicate that pimecrolimus may have many potential applications, by both topical and oral administration. In 2002, Crutchfield reported a case of effective topical treatment for facial seborrheic dermatitis with pimecrolimus. Topical treatment may also have a role in such diverse conditions as contact dermatitis, hand dermatitis, acne and steroid rosacea, inverse psoriasis, vitiligo, intertrigo, facial dermatitis, and blepharitis of various etiologies.

Also in 2002, Rappersberger et al. reported a phase I/II randomized, double-blind, placebo-controlled, multiple rising-dose, proof-of-concept study in which psoriasis patients were treated with oral pimecrolimus or placebo. Clear clinical efficacy occurred in patients receiving 20 mg or 30 mg of pimecrolimus twice daily. Psoriasis Area (PI) and Severity Index (SI) were reduced by 60% and 75%, respectively. No notable clinical, laboratory, kidney function, or immunologic side effects were reported.

Considering the economic burden of the disease, the relative and total costs associated with available treatment options are important to patients and their families as well as to insurers. The preliminary data, which were derived through studies of cost impact within managed care organizations, indicate that pimecrolimus use may have the potential to reduce overall costs of the disease. Although preliminary, these economic data are encouraging since they support the opinion that using new, more effective treatments for AD can lessen reliance on corticosteroids.

**DISCLOSURES**

The author reports no sources of funding for this manuscript. He is a member of the speakers’ bureau for Novartis, the manufacturer of pimecrolimus, and has received clinical research grants from Novartis and Fujisawa pharmaceutical companies.

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Health Plan Budget Impact Analysis for Pimecrolimus

JANE CHANG, MPH, and JENNIFER SUNG, PharmD, MS

ABSTRACT

OBJECTIVE: Budget impact models are useful tools for managed care organizations to make drug formulary decisions. The objective of this study was to estimate the incremental budgetary change in per-member-per-month (PMPM) medical and pharmacy costs for atopic dermatitis (AD) or eczema after the introduction of pimecrolimus cream 1%, a topical calcineurin inhibitor.

METHODS: Estimates of the percentage of patients seeking care, treatment patterns, and quantities of medications dispensed for AD were measured using 2001 and 2002 medical and pharmacy records in a proprietary database for health plans distributed throughout the United States. Approximately 2.5 million health plan members had continuous health insurance coverage during the study period. Costs for medications were assigned using the 2003 wholesale acquisition cost, and costs for physician visits were based on average 2003 Medicare reimbursement rates. Efficacy data from clinical trials were used to model the impact of pimecrolimus on subsequent physician visits. Sensitivity analyses were performed to evaluate the impact of varying the percentage of patients seeking care, practice patterns, medication quantities, percentage of pimecrolimus users, and levels of patient cost sharing.

RESULTS: The estimated percentage of health plan members seeking care for AD in 2001 was 3.2%. The estimated total cost PMPM for AD treatment prior to introduction of pimecrolimus was $0.362 for all covered lives, assuming no patient cost sharing. In the year after its introduction, 5.2% of the AD population filled a prescription for pimecrolimus. The incremental increase in pharmacy benefit cost was $0.008 PMPM in 2003 dollars, but the total incremental medical and pharmacy cost was $0.002 PMPM after accounting for the projected reduction in physician visit costs, representing a 0.7% increase in all AD-related costs. Based on sensitivity analyses, the incremental total cost PMPM after the introduction of pimecrolimus ranged from -$0.004 to $0.026.

CONCLUSION: Using claims data for the medical treatment of AD in 2001-2002 and the utilization of pimecrolimus, the addition of pimecrolimus as a treatment option for AD had a minimal impact on PMPM costs for AD-related care in 2003 dollars. As with all pharmacoeconomic models, health plans should perform their own budget forecasting using assumptions derived from their own pharmacy and medical claims data.

KEYWORDS: Atopic dermatitis, Budget impact model, Elidel, Pimecrolimus, Treatment costs, Practice patterns


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Editor’s Note: This article, highlighting a budget impact analysis, is published coincident with an overview of atopic dermatitis that focuses on nonsteroidal topical therapies, particularly pimecrolimus. Budget impact forecasting is a component of pharmacoeconomic analyses recommended in the AMCP Format (dossier) process.

A topic dermatitis (AD) is a chronic disease of the skin characterized by itching, redness, and swelling. Primarily affecting infants and children, it is estimated that 20% of infants and young children are affected by AD, while 60% of these children continue to experience symptoms into adulthood. Overall, a 2- to 3-fold increase in AD has been observed over the past 30 years, and it is currently believed to affect 10% to 15% of the population at some point in childhood. The prevalence of AD has risen along with asthma and other atopic diseases. This epidemiological change is attributed to environmental factors (such as allergens and pollutions) and lifestyle factors (such as diet and stress).

Fifteen percent to 30% of AD patients are estimated to have coexistent asthma, and nearly 80% of children with AD will subsequently develop allergic airway disease, such as asthma or allergic rhinitis. As such, AD has been suggested as an “entry point” for subsequent allergic disease. Researchers have hypothesized that AD and asthma share common pathophysiologic mechanisms related to early immunoglobulin (Ig) E production and consequent allergen/IgE reactivity. 3 of the AD linkages have been found to correspond with known asthma loci, indicating that AD shares genetic determinants with asthma.

In 1997, the direct medical cost of AD in the United States for patients aged <65 years was estimated to range from $1 billion to $4 billion depending on the extent to which costs for comorbid conditions were considered. However, these estimates do not include costs for items or services not paid by third-party payers such as patient copayments for office visits and prescription medications as well as for over-the-counter (OTC) products. A study conducted in a large managed care organization calculated that the total burden of AD, including direct medical costs, out-of-pocket expenses, and lost productivity, amounted to an annual cost of $609 per patient, with 27% attributed to direct medical costs. Outpatient visits and prescription medications accounted for 63% and 30% of the direct medical costs, respectively. Productivity loss accounted for almost 30% of the total burden, and the impact was significantly higher for individuals with severe disease.

Traditionally, treatment has primarily involved the use of emollients to ameliorate dry skin and short-term use of topical
corticosteroids to treat acute disease flares. Although treatment with topical corticosteroids is efficacious, long-term use of these agents can cause skin atrophy and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. These adverse events have led patients and practitioners to express the need for alternative therapeutic options for the treatment of AD. The introduction of pimecrolimus (Elidel) cream 1% in January 2002 provided practitioners with a nonsteroidal, topical treatment option that has been shown to be effective in AD management. In addition, early use of pimecrolimus has been shown to reduce or eliminate the need for topical corticosteroids.

A budget impact model was developed to estimate the annual direct medical cost of treatment for AD and to estimate the incremental budgetary impact of the introduction of pimecrolimus as a treatment option for AD or eczema.

Methods

A retrospective pre-post study design was implemented to estimate treatment cost of AD prior to and after the market introduction of pimecrolimus in January 2002. The calculation was replicated in a Microsoft Excel-based spreadsheet model, which serves as a flexible analytic tool to examine the budgetary impact of the introduction of pimecrolimus from both a societal and a managed care organization perspective. The analysis included AD costs from outpatient physician visits and medications. Hospital costs were not included because inpatient care for this condition is extremely rare.

Claims data from MarketScan (MedStat, Ann Arbor, Michigan) served as the primary data source for estimates of resource utilization. This database provided integrated pharmacy and medical claims from various health plans in the United States. The analysis cohort consisted of individuals who were continuously enrolled in a health plan in 2001 and 2002 and who had a claim for at least one office visit with a diagnosis code indicating atopic dermatitis or eczema (ICD-9-CM: 691.8, “other atopic dermatitis”; ICD-9-CM: 692.9, “dermatitis not otherwise specified”) in either year. Based on the structure of the claims database, 5 diagnosis-related code fields were reviewed for these AD diagnoses. Most office visits (92.8%) captured in the model were identified based on the primary diagnosis code, separately for generalist and specialist physicians. Hospital costs were not included because inpatient care for this condition is extremely rare.

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Annual rates of physician visits for AD were estimated separately for generalist and specialist physicians. Generalist physicians consisted of internists, family practitioners, and pediatricians. Specialist physicians represented practitioners of various therapeutic areas, primarily dermatology.

To estimate annual costs for medications, the model was designed to multiply the proportion of patients with AD who were treated with different types of medications for AD by the average number of each type of medication used each year. Medications were categorized as brand prescription corticosteroids, generic prescription corticosteroids, OTC corticosteroids, tacrolimus (Protopic), or pimecrolimus. The wholesale acquisition cost (WAC) was used to estimate medication costs based on 30 gram tubes for all medications considered (the WAC cost for 30 gram tube pimecrolimus 1% was effective on January 7, 2003). Because OTC treatments are not captured in the MarketScan data, published data were used to estimate the utilization of OTC topical corticosteroids for AD. The proportions of patients taking each type of prescription medication were based on utilization patterns in the MarketScan data. To simplify the model, when patients had claims for more than one type of medication (6.4% of patients), treatment classification was based on the most frequently prescribed medication. However, after the introduction of pimecrolimus, “cotreatment” with pimecrolimus and corticosteroids was accounted for in the model. Unit costs assigned to physician visits and medications are reported in Table 1.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Unit Costs Applied in Base-Case Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resource</strong></td>
<td><strong>Cost (2003 $)</strong></td>
</tr>
<tr>
<td><strong>Office Visits</strong></td>
<td></td>
</tr>
<tr>
<td>Generalists</td>
<td>51.15</td>
</tr>
<tr>
<td>Specialists</td>
<td>116.49</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
</tr>
<tr>
<td>Brand corticosteroid*</td>
<td>28.29</td>
</tr>
<tr>
<td>Generic corticosteroid†</td>
<td>2.90</td>
</tr>
<tr>
<td>OTC corticosteroid‡</td>
<td>1.80</td>
</tr>
<tr>
<td>Tacrolimus§</td>
<td>47.96</td>
</tr>
<tr>
<td>Pimecrolimus</td>
<td></td>
</tr>
</tbody>
</table>

* Cutsivate (fluticasone propionate) cream 0.05%, 30 grams.
† Triamcinolone acetonide cream 0.1%, 30 grams.
‡ Hydrocortisone cream 1%, 30 grams.
§ Tacrolimus ointment 0.03%, 30 grams.
|| Pimecrolimus cream 1%, 30 grams.

WAC = wholesale acquisition cost; OTC = over the counter.
number of flares observed among patients using pimecrolimus in the trial as a proxy for a reduction in physician visits, assuming that fewer flares led to fewer physician visits.

Benefit Design
The budget impact model was designed to incorporate patient cost sharing. For prescription medications, 1-, 2-, or 3-tier copayment or coinsurance designs could be applied. Also, copayments for office visits to generalists and specialists could be applied separately. However, unless specified, patient cost sharing was not considered as all patient copayments (or coinsurance rates) were set to $0 (or 0%).

Cost Metrics
The resulting estimates were reported in 2003 U.S. dollars in 2 ways: (1) aggregate costs based on 1 million hypothetical enrollees and (2) cost per member per month (PMPM).

Sensitivity Analysis
One-way sensitivity analyses were carried out to evaluate the impact of varying model parameters without patient cost sharing. Key parameters included were the cost of medications, percentage of patients seeking care for AD, treatment patterns, and treatment efficacy. Sensitivity analyses of prescription medication costs considered a relative change of ± 50% in WAC and an alternative pricing scenario based on average wholesale pricing (AWP). Other sensitivity analyses evaluated estimates of the percentage of patients seeking care, percentage of pimecrolimus users, average number of pimecrolimus prescriptions, and the impact of pimecrolimus on corticosteroid use and subsequent physician visits for AD by a relative change of ±50%.

To evaluate a worst-case (highest annual cost and incremental cost) scenario, the following estimates were jointly increased or decreased by 50% relative to the estimates used in the base-case analysis:

**Worst-case Scenario**
- Cost of pimecrolimus (+50%)
- Percentage of pimecrolimus users (+50%)
- Average number of pimecrolimus prescriptions (+50%)
- Reduction in the proportion of pimecrolimus-treated patients requiring cotreatment with prescription corticosteroids (-50%)
- Reduction in the number of AD-related physician visits for patients treated with pimecrolimus (-50%)

To evaluate a best-case (lowest annual cost and incremental cost) scenario, the following estimates were jointly increased or decreased by 50% from the estimates used in the base-case analysis:

**Best-case Scenario**
- Cost of pimecrolimus (-50%)
- Percentage of pimecrolimus users (-50%)
- Average number of pimecrolimus prescriptions (-50%)
- Reduction in the proportion of pimecrolimus-treated patients requiring cotreatment with prescription corticosteroids (+50%)
- Reduction in the number of AD-related physician visits for patients treated with pimecrolimus (+50%)

From the payers’ perspective, the budgetary impact of imposed patient cost sharing was evaluated in the model by incorporating patient copayments for office visits and medications into the base case. Office visits to generalists required a $10 copayment while visits to specialists assumed a $20 copayment. For medications, brand-name corticosteroids, tacrolimus, and pimecrolimus were assumed to have a $20 copayment while generic corticosteroids had a $10 copayment or were equal to the cost of the medication, whichever was less. OTC corticosteroids were also assumed to be paid entirely by the patient.

Lastly, the 2003 pimecrolimus utilization data derived from MarketScan were also utilized along with 2004 pricing data for physician visit and drug costs, assuming no patient cost sharing.

### Results

#### Base-Case Analysis
Approximately 2.5 million individuals who had continuous health insurance coverage throughout 2001 and 2002 were included. Among these individuals, a total of 80,119 patients (3.2%) had a diagnosis of AD (or eczema) in 2001. An assessment of their resource utilization indicated that these...
patients made an average of 1.17 visits per year to generalist physicians and 0.57 visits per year to specialists for the treatment of AD. Among the AD patients identified in the 2001 dataset, 13.7% received brand corticosteroids, 17.9% received generic corticosteroids, and 1.4% received tacrolimus. On average in 2001, patients filled a total of 1.6 prescriptions for brand corticosteroids, 1.6 prescriptions for generic corticosteroids, and 2.2 prescriptions for tacrolimus. The model results showed that physician visit costs comprised 93.0% of the total cost in the management of AD before the introduction of pimecrolimus.

Based on a hypothetical health care plan with 1 million enrollees with no patient cost sharing, annual medication costs for AD were estimated at $304,796, and annual physician visit costs were estimated at $4,039,380 (Table 2). When combining costs for medications and physician visits, the total cost PMPM was approximately $0.362.

After the introduction of pimecrolimus, 4.6% of patients previously prescribed brand corticosteroids, 4.7% of patients previously prescribed generic corticosteroids, and 5.2% of patients using OTC corticosteroids or no corticosteroids (including patients with their first diagnosis of AD in 2002) migrated to treatment with pimecrolimus. In addition, 20.2% of patients who were previously prescribed tacrolimus in 2001 switched to treatment with pimecrolimus in 2002. Overall, it was estimated that 5.2% of patients with AD received a prescription for pimecrolimus, and these patients filled an average of 1.5 prescriptions in 2002. Assuming no patient cost sharing, aggregate medication costs for AD increased by 31.5% to $399,338 for the year prior to the introduction of pimecrolimus and $519,028 in the year after its introduction to the marketplace, representing differences of approximately ±$0.005 PMPM relative to the base case of $0.364 PMPM.

Sensitivity Analysis

Figure 1 summarizes the findings from 1-way sensitivity analyses assuming no patient cost sharing. The 3 primary cost drivers in the model were the cost of pimecrolimus, the annual number of pimecrolimus prescriptions, and the reduction in physician visits for patients using pimecrolimus. Since these cost drivers affect only the AD treatment costs after pimecrolimus introduction, treatment costs prior to the introduction in these 3 analyses and the base case are the same. When either the cost of pimecrolimus or the annual number of tubes of the medication dispensed was decreased by 50%, medication costs only increased by 13.5% and total cost decreased by 0.6% (or by $0.002 PMPM) after the introduction of pimecrolimus to the marketplace as compared with the previous year without pimecrolimus. When increasing the cost of pimecrolimus or the number of tubes of pimecrolimus dispensed by 50%, medication costs increased by 49.5% and total cost increased by 1.9% (or by $0.007 PMPM). When the reduction in physician visits resulting from pimecrolimus was reduced to 15.7%, physician visit costs decreased by 0.8% and total costs increased by 1.5% (or by $0.005 PMPM). Across the 3 sets of sensitivity analyses, total cost PMPM after the introduction of pimecrolimus ranged from $0.360 to $0.369.
an increase of 30.0% in medication costs; total cost PMPM increased by 1.2% (or by $0.004 PMPM).

Varying the percentage of patients seeking care for AD did not affect the percentage change in costs after the introduction of pimecrolimus but had a significant impact on the magnitude of the cost estimates. For each 1% absolute increase, medication costs after the introduction of pimecrolimus increased by $125,267 ($0.010 PMPM); total costs also increased by $1,366,785 ($0.114 PMPM) per percentage point (Figure 2).

In the sensitivity analysis where the percentage of pimecrolimus users was increased, for each 1% absolute increase, medication costs increased by approximately $22,322 ($0.002 PMPM), and total costs increased by approximately $9,669 ($0.001 PMPM) after the introduction of pimecrolimus (Figure 3). The relative change of ±50% in the reduction on corticosteroid use among pimecrolimus users only had a minimal impact of approximately ±$0.001 PMPM relative to the base case.

Figure 4 summarizes the worst- and best-case scenarios. Variations in model parameters affected only the AD treatment costs after the introduction of pimecrolimus so treatment costs prior to pimecrolimus introduction in these scenarios and in the base-case scenario are the same. In the worst-case scenario, using estimates and assumptions resulting in the highest costs to the health care system including no patient cost sharing, medication costs increased by 117.3% to $662,217, physician visit costs decreased by 1.2% to $3,989,488, and the total cost increased by 7.1% to $4,651,704 after the introduction of pimecrolimus. Using the PMPM metric, medication costs increased from $0.025 to $0.055, physician visit costs decreased from $0.337 to $0.333, and total costs increased from $0.362 to $0.388.

In the best-case scenario, using estimates and assumptions resulting in the lowest costs and assuming no patient cost sharing, medication costs increased by 1.4% to $309,115, physician visit costs decreased by 1.2% to $3,989,488, and the total cost decreased by 1.0% to $4,298,602 after the introduction of pimecrolimus. Using the PMPM metric, medication costs increased by <$0.001, physician visit costs decreased from $0.337 to $0.333, and total costs decreased from $0.362 to $0.358. The impact of decreasing the percentage of pimecrolimus users and increasing the impact of pimecrolimus on subsequent physician visits in the best-case scenario had the same impact as increasing the percentage of pimecrolimus users and decreasing the impact on subsequent physician visits in the worst-case scenario. Thus, the impact on costs for outpatient physician visits was the same in both scenarios.

From the perspectives of payers and patients, the impact of imposing patient cost sharing was considerable. Prior to the introduction of pimecrolimus, for a hypothetical population of 1 million enrollees, total annual costs to the payer were estimated at $3,383,165 ($0.282 PMPM) and total annual costs for patients were estimated at $961,011 ($0.080 PMPM). After its introduction, total annual costs to the payer actually decreased slightly to $3,379,504 ($0.282 PMPM) and increased to $994,209 ($0.082 PMPM) for the patients. Thus, after imposing patient cost sharing, the managed care organizations accrued a 0.1% savings in total costs in the year following the introduction of pimecrolimus while total cost for patients increased by 3.5%.

An analysis update using 2003 MarketScan data indicated that the estimated percentage of AD patients seeking care was...
2.9%. Among these AD patients, 8.4% were prescribed pimecrolimus and used approximately 75 grams per year. If a health plan were to place pimecrolimus on their formulary with 2004 pricing and without patient cost sharing, medication costs would be $572,122 ($0.048 PMPM) and physician costs would be $3,718,082 ($0.310 PMPM), resulting in a total cost PMPM of $0.358, an increment of $0.015 from before formulary placement.

**Discussion**

AD is a prevalent disease and imposes great financial burden on the health care system and even more so on individuals when considering out-of-pocket medical expenses and indirect costs due to loss of productivity. The evidence of AD being a risk factor for childhood asthma is convincing. Although it remains to be proven that the appropriate management of AD is effective in preventing other allergic diseases, future disease prevention is an important focus in developing treatment guidelines in light of the medical and economic impact of the increasing prevalence of allergic diseases. Budget impact models provide a valuable tool to health plans in making formulary decisions. Such models allow managers to gauge the potential economic impact resulting from the introduction of a new pharmacological treatment on medical and pharmacy budgets. This budget impact model quantifies both the pharmacy and medical costs for patients with AD using actual treatment patterns as measured in a claims database.

Given pimecrolimus usage in the insured marketplace after its introduction, it appears that overall health care budgets for AD-related care will be modestly affected—by approximately 0.7%. Our analysis also showed that medication costs for AD prior to pimecrolimus introduction are relatively low at approximately $0.025 PMPM, even in consideration of patients' out-of-pocket expenses for prescription copayments and OTC medications. The introduction of pimecrolimus was estimated to increase medication costs by about $0.008 PMPM, or approximately $96,000 annually for a health plan with 1 million beneficiaries. This increase in medication costs was offset by a reduction in estimated costs for outpatient physician visits of approximately $66,500, or $0.006 PMPM. The net increase in total cost was estimated at approximately $29,500, or $0.002 PMPM.

Sensitivity analysis was conducted to provide a range of estimates a health plan might expect to see when varying assumptions regarding treatment patterns. In a hypothetical cohort of 1 million health plan members, total costs after the introduction of pimecrolimus to the marketplace ranged from $4,298,602 to $4,651,704. The total cost PMPM ranged from $0.358 to $0.388, representing an incremental PMPM from -$0.004 to -$0.026. Given that most health plans provide medication benefits at $25 to $35 PMPM, the relative impact of the addition of pimecrolimus in the first year after its introduction was relatively minimal, even in the worst-case scenario.

**FIGURE 4**

Sensitivity Analysis: Case Scenarios of PMPM Costs Prior to and After the Introduction of Pimecrolimus*

<table>
<thead>
<tr>
<th>Incremental Costs PMPM ($)</th>
<th>Worst Case</th>
<th>Base Case</th>
<th>Best Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Costs</td>
<td>-$0.004</td>
<td>$0.002</td>
<td>$0.026</td>
</tr>
<tr>
<td>Physician Visit Cost</td>
<td>-$0.004</td>
<td>-$0.006</td>
<td>-$0.004</td>
</tr>
<tr>
<td>Drug Cost</td>
<td>$0.000</td>
<td>$0.008</td>
<td>$0.030</td>
</tr>
</tbody>
</table>

* Costs are presented in 2003 U.S. dollars. PMPM = per member per month.

**Limitations**

One limitation of this study is that the proportion of patients switching from other therapies to pimecrolimus was based on data from the first year after the market introduction of pimecrolimus. This proportion may or may not pertain to subsequent years, and the use of pimecrolimus would be expected to increase over time. Health plans should perform their own budget forecast modeling using assumptions derived from their own pharmacy and medical claims data.

Our findings may not be generalizable to plans with other cost-sharing arrangements; for example, migration rates to pimecrolimus in a given health plan may differ from the data found in this proprietary database due to different formulary structures and copayment requirements. Nevertheless, this model is intended to assist managed care organizations to estimate potential budgetary impact upon the addition of pimecrolimus to the formulary. Even though our base-case estimate of percentage of pimecrolimus users may not accurately reflect generalizable migration rates, by varying this variable in a sensitivity analysis, the total cost PMPM was found to increase approximately $0.001 for each 1% increase in pimecrolimus users. In addition, by using recent utilization data along with updated pricing to increase the relevance of this analysis to health plans today, the total cost PMPM was $0.358, an increment of $0.015 from before formulary placement, demonstrating a small budget impact.

Another potential study limitation pertains to our assumption that flare reduction in a clinical trial is directly reflected in reductions in physician visits in real-world practice. If routine follow-up appointments are made, there will be no cost offset from a reduction in the costs of physician office visits. It is also possible that the number of physician visits may have been...
Health Plan Budget Impact Analysis for Pimecrolimus

underestimated if more patients begin seeking medical care for treatment of AD when an alternative to topical steroid therapy becomes available. In this budget impact model, attempts were made to address this limitation by including patients with their first diagnosis of AD in 2002 and who were prescribed pimecrolimus. In addition, when examining only the pharmacy impact, assuming no reduction in physician visits, PMPM increased minimally by $0.008.

Further, an assessment of the patient’s disease severity was not possible in this pharmacy and medical claims database analysis, and costs associated with adverse events caused by treatments were not considered. Ninety percent of AD patients suffer from mild-to-moderate disease, which accounts for 90% of AD visits to dermatologists. Before the introduction of pimecrolimus, topical corticosteroids were the mainstay of pharmacological management for AD. However, duration and intensity of corticosteroid therapy is generally restricted for children because of potential treatment side effects. By managing the mild-to-moderate AD patients more effectively using medications with better side-effect profiles, a reduction in physician visits due to better control of AD and avoidance of potential adverse events may occur. These factors will change the budgetary impact and should be taken into consideration. The conduct of sensitivity analysis on several variables helps to address some of the limitations in the model assumptions.

Conclusion

Given the estimated percentage of patients seeking care for AD (3.2%) from this pharmacy and medical claims database analysis, this budget impact model demonstrates that a relatively minimal incremental budget impact of pimecrolimus would be expected. The estimated incremental increase in pharmacy benefit cost in 2003 dollars was $0.008 PMPM, but the incremental total combined medical and pharmacy cost was reduced to $0.002 PMPM after accounting for the projected reduction in physician visit costs. Incremental total costs of $0.002 PMPM represented a 0.7% increase in all AD-related costs. Health plans should perform their own budget forecast modeling using assumptions derived from their own pharmacy and medical claims data for pimecrolimus and the treatment of AD.

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DISCLOSURES

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REFERENCES


CONTEMPORARY SUBJECT

Older Adults’ Drug Benefit Beliefs: A Focus Group Study

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ABSTRACT

OBJECTIVES: The Medicare Prescription Drug Improvement and Modernization Act will provide drug benefits for a large proportion of persons aged 65 years and older in the United States. Few studies have examined the beliefs and attitudes of older adults with respect to prescription drug insurance programs. The objective of this study was to better understand the nature and range of older adults’ beliefs regarding prescription drug benefits.

METHODS: This study employed a qualitative, focus group design. Three focus groups with a total of 19 community dwelling adults aged 65 years and older were conducted in June 2003. The participants were members of the Minnesota Seniors Federation and included persons with and without prescription drug insurance. Discussions were structured and guided by an interview schedule developed a priori. The focus groups were audiotaped and transcribed verbatim. Thematic textual analysis was used to identify codes and categories from the language and ideas of the group participants.

RESULTS: Study participants identified a variety of important drug benefit facets. The common themes identified from the 3 groups were: (1) prescription drug access, (2) drug benefit comprehensibility, (3) powerful others, (4) affordability, and (5) equity.

CONCLUSION: Older adults view drug benefits as complex entities composed of at least 5 dimensions. In addition to more commonly discussed issues such as access and affordability, seniors evaluate several other aspects of drug insurance programs such as fairness, the ease with which plan terms can be understood, and the degree to which outside actors influence plan policies.

KEYWORDS: Prescription drug benefits, Medicare, Older adults, Focus groups

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MEDICATIONS are an essential part of medical treatment, and this is especially true for older adults (aged 65 years and older). On average, older Americans obtain 22.6 prescriptions annually, more than twice the U.S. average for all age groups.1 It is estimated that drug spending among these individuals will grow at more than 10% per year from $95 billion in 2003 to $284 billion in 2013.2 Older adults account for only 15% of the population, but they account for nearly 40% of medication expenditures.3

Although older adults use many medications to maintain and improve their health, insurance coverage for prescription drugs is often absent, inadequate, or unstable.45 Past research suggests that when older adults lack drug benefit coverage, there are serious impacts on their access to prescription medicines.67 For example, Safran et al. found that seniors lacking drug coverage were 2 to 3 times more likely to not have a prescription dispensed.8 Tseng et al. reported that seniors who had exceeded prescription coverage payment caps were more likely than those who had not to use less than the prescribed amount of medicines for chronic health conditions.7

Estimates such as these prompted passage of the Medicare Prescription Drug, Improvement and Modernization Act (MMA) of 2003.4 MMA is the most sweeping revision of the Medicare program to date and has as one of its primary aims the reduction of financial barriers that may prevent beneficiaries from obtaining needed drugs.9 From June 2004 until January 2006, beneficiaries can receive Medicare Prescription Drug discount cards. After this, participants can receive benefits from managed care plans or from stand-alone prescription drug plans if they choose to remain in the traditional Medicare fee-for-service program.10

The various provisions of MMA were negotiated with little direct input from older adults. However, developing a more complete understanding of older adults’ beliefs regarding drug benefits is important for several reasons. First, the Medicare program is a large social insurance program, providing health care coverage for roughly 40 million Americans, the vast majority of whom are older adults. To the extent that government is an instrument of the people, social programs should reflect their preferences and values. Second, insight into program participants’ beliefs, values, and preferences regarding drug benefits will provide information that can be useful in designing benefit descriptions under MMA. Third, Medicare beneficiaries’ beliefs regarding various aspects of drug benefits may impact their choices and influence satisfaction and other humanistic outcomes associated with the delivery of prescription drug benefits under MMA.

Previous Research

Two streams of research are relevant to the current study. The first of these involves the use of hypothetical choice
Older Adults’ Drug Benefit Beliefs: A Focus Group Study

experiments to investigate preferences for various drug benefit attributes. For example, Holdford and Carroll used conjoint analysis to study the effects of varying 3 drug plan attributes (copayment amount, freedom to choose one’s pharmacy, and use of a restrictive formulary) on likelihood of prescription benefit plan choice. In a second study, Cline and Mott used discrete choice modeling to study hypothetical drug benefit plan choices in a survey of 1,086 older adults. Respondents were asked to choose a plan that would best meet their needs from a menu of 4 drug benefit plans. These plans varied with regard to attributes (copayment amount, monthly premium, use of a restrictive formulary, and required use of a mail-service pharmacy). Together, the results of these studies suggest that financial components of drug plans, such as lower copayments and lower premiums, are related positively to choices while access components, such as the inability to choose one’s pharmacy and the use of a restrictive formulary, are associated negatively with plan choices.

A second area of research related to the current investigation is the study of drug benefit plan satisfaction. Desselle studied drug plan satisfaction using in-person surveys of 504 community pharmacy patrons. The survey utilized a scale designed to account for several facets of drug benefits, including the use of restrictive formularies, out-of-pocket costs, and the ability to choose one’s pharmacy. Mohteral and Heinele examined the correlates of drug benefit plan satisfaction using mail survey responses of 3,819 individuals enrolled in a large pharmacy benefit management plan. The findings of these 2 studies are consistent with those of plan choice studies; individuals who believed that their plan had no coverage limitations were more satisfied, as were those free to patronize a pharmacy of their choice. Lower out-of-pocket costs (e.g., copayments, coinsurance amounts, and premiums) also were associated with higher member satisfaction levels.

These studies have contributed to our understanding of the facets of prescription drug programs that consumers deem important. Specifically, they have identified the importance of drug plan attributes impacting access (e.g., formularies, restrictive pharmacy networks) and affordability (e.g., premiums, copayments). However, these studies suffer from 2 shortcomings. First, with one exception, these investigations were conducted among working age adults receiving drug benefits through private insurers. Second, these studies employed preconceived conceptual frameworks that limited the drug benefit attributes studied. The goal of this study was to extend the findings of prior research and better understand the nature and range of older adults’ views on prescription drug benefits in general and as part of the Medicare program.

Methods

Design and Data Collection

The current study was a qualitative investigation employing focus groups for data collection. The method allows the researcher to capitalize on communication between research participants to generate pertinent information. The focus group method was chosen because of its speed of completion, high internal validity, and flexibility to explore unanticipated issues. Approval was obtained from the Institutional Review Board at the University of Minnesota before data collection began. A purposive sample of older adults belonging to the Minnesota Seniors Federation (MSF) metro chapter was employed to meet the objectives of the study because they had certain characteristics in common that relate to the topic of this study. The MSF is a statewide, nonprofit organization open to Minnesota seniors aged 55 years and older and is similar to AARP in its advocacy efforts.

The participants chosen for the study included seniors with and without drug insurance who were aged 65 years and older. Seventy-four potential participants responded to a recruitment advertisement in a monthly publication of the MSF. They were telephoned by the authors and invited to attend 1 of 3 focus groups. Nineteen participants agreed to participate. Three groups, composed of 6 or 7 persons each, were used to achieve saturation (the point at which the participants provided no new information to the researchers). No individual participated in more than 1 group.

The Focus Group Discussion

The focus group interviews were conducted in June 2003 at the MSF offices. Before beginning each session, study volunteers completed informed-consent forms and a short demographic questionnaire. The aims and methods to be used were first reviewed with the participants by the moderator and then by a research assistant. At the beginning of the focus group session, the moderator attempted to create a thoughtful, nonthreatening atmosphere and set the tone for the discussion. For example, the researchers dressed casually, introduced themselves to each participant upon arrival, and served light refreshments before and throughout the sessions. The route of questioning in these groups centered on (a) the attributes of prescription drug plans most salient to the participants, (b) the participants’ understanding of these attributes and their functions, and (c) the language used by the participants to describe and talk about drug plan attributes. The participants were encouraged to respond to all the issues raised by the moderator but were informed that they had the right not to respond to any issue. Each group was audiotaped and field notes also were taken. Each session was approximately 2 hours in length. Each study participant received a $20 honorarium.

Every effort was made to maintain control and create an environment that encouraged shy individuals to participate fully in the discussion. In order to overcome interviewer bias, the moderator made minimal interventions and maintained a neutral position by not presenting his own views during data
Results

Analysis of Text

Analysis of the sessions was performed according to steps outlined by Krueger and Casey and Morgan. The tapes were transcribed verbatim on a word-processing file, and the resulting text was analyzed in a descriptive and interpretive manner. In addition, group-to-group validation was carried out to identify themes consistently across groups. The transcripts and field notes were read several times by each of the 4 study investigators independently, and the main themes were extracted.

Theme extraction was based on convergence and external divergence; that is, identified themes were internally consistent but distinct from one another. The participant statements referring to a particular theme were grouped together under each theme after examining them further for convergence as well as comparing them with initial concepts and categories. Once the primary analysis was completed, the interpretations were discussed among the 4 study investigators. Agreement was negotiated as a valid interpretation of the text, and this discussion was driven by the study objectives as well as consistency among the emergent themes. When the final set of analyses was finished, all investigators agreed upon major themes.

To ensure quality and credibility of analysis, researchers identified negative cases for some themes. These included comments from participants that did not fit into the pattern or themes. These cases were few enough to be considered exceptions to the rule; hence, to an extent, they proved the rule or theme. Triangulation done by using multiple analysts also provided a quality check on selective perception and blind interpretive bias that could occur through a single person doing all of the analysis.

Results

The 3 focus groups were composed of a total of 12 females and 7 males. Approximately 53% of the participants were between 75 and 84 years of age, and the remainder were within 65 and 74 years. A large proportion of the participants were highly educated, with 8 (42%) holding a master’s, PhD, or other professional degree. Not surprisingly, all participants used one or more prescriptions, with more than half (52.6%) using 3 or more prescriptions on a daily basis. A slight majority of the participants (52.6%) reported their physical health as “very good” or “excellent,” and none of the participants reported it as “poor.”

Thematic analysis of the focus group transcripts identified 5 common themes: (1) prescription drug access, (2) drug benefit comprehensibility, (3) powerful others (4) affordability, and (5) equity. The next 5 sections describe these themes in detail, with both researcher interpretation and verbatim examples of participants’ comments and discussion.
benefit management services. Growth in the number of prescriptions dispensed by mail-order pharmacies has been rapid. Among those aged 65 years and older, the proportion using mail-order pharmacies rose significantly—from 17% to 27%—between 1998 and 2001. Some representative comments from study participants included:

*I like the mail-order service where you can get 3 months of service on time. This month thing drives me nuts because I am away from home a lot, and to have it renewed every month is terrible.* (P8)

*I like the ease of ordering. I can do it by phone as long as I have got the prescription. I can get a 90-day supply, and I don’t have to run to some place to pick it up, anyway.* (P7)

Each of the 3 focus groups included discussions regarding reimportation of drugs from Canada. Among the reasons discussed for reimportation, cost appeared to be the primary impetus for this decision. However, more relevant to the theme of access, many study volunteers talked about easy access to medications as well as being pleased with the quality of service and products when using Canadian pharmacies.

*You can understand that a lot of people are going to Canada for their drugs; you go to Canada, and they will give you a 90-day supply just like that.* (P3)

*I get my orders in about 10-15 days from the time I fax the order up to Canada. They have never made a mistake. And one of the things I really like is all my drugs come in the original sealed containers from the manufacturers, nobody counting pills. So you don’t have to worry about somebody making a mistake or tampering with the containers. You’re getting the original drugs.* (P16)

### 2. Drug Benefit Comprehensibility

Like most insurance policies, drug benefits typically contain a great many provisions, defining who is covered, where they are covered, what medications are paid for, and how they are paid for. Drug benefit comprehensibility is the ease with which the drug plan’s provisions can be understood. Focus group participants often expressed confusion about the terms and cost containment policies used by pharmacy benefit plans as well as health insurance policies in general. Seniors discussed the fact that they could not easily comprehend the reasons underlying various features.

*It’s very difficult to understand the insurance company; but then, insurance has never really made sense, though.* (P7)

*I tried to get from BlueCross 3 months supply because I go down south often. They wouldn’t give it to me. It’s so unreasonable that you are the same patient, it’s the same doctor, the same order, and you just want a larger quantity because you are on the drug for a whole year. I don’t know why BlueCross wouldn’t do it.* (P3)

*My husband, one time, when he lived, had a double hernia surgery. Medicare would pay for one side and not another. They told us if he had gone to the hospital and had one side done, gone home, and then gone back in then... Think of the waste, you know?* (P4)

Although many participants were not even aware of the existence of formularies as a tool to contain costs, a small proportion of patients had experiences with formularies that caused a great deal of confusion and inconvenience. These study volunteers suggested that formularies are not very popular from the perspective of the elderly population.

*You go to the doctor, you get diagnosed, and he prescribes the medicine, and you take it to the pharmacy and the pharmacist comes and says, “Sorry, it’s a formulary problem.”* (P13)

*I was really sick. I couldn’t wait to go to the doctor to get the medicine, and the word was even foreign to me, like the “formulary”?* (P10)

An aversion to insurance benefit complexity also was apparent when participants discussed the drug discount card program being discussed at the time for possible inclusion in the Medicare drug benefit. These older adults expressed concern that they might have to purchase more than one discount card plan to cover all of their medications.

*I know what I don’t want. I don’t want discount cards from every separate pharmaceutical company. Who wants to mess around with a whole pocket full of cards, and half the time you wouldn’t know which company made this drug anyway?* (P12)

### 3. Powerful Others

The participants were cognizant of social, political, and economic forces outside their control that impact the costs and use of medicines. To describe this notion, we used the theme “powerful others,” which is similar to the external locus of control construct found in the health behavior literature. The outside forces included the actions of pharmaceutical companies and legislators. Many study participants believed that direct-to-consumer advertising (DTCA) contributes to the high prices and unnecessary use of pharmaceuticals.

*I think advertising for prescription drugs should be done away with. This would prevent or would help to prevent people from wanting drugs that they don’t really need. Doctors prescribe it because they are asked.* (P6)

*The patients demand the physician to prescribe the stuff. They ask for it, and when they don’t get it, they go to another physician.* (P19)
The pharmaceutical companies don’t want to have price controls, but they make a huge margin. The price is going up and you know the other share is the advertising cost. They spend more on promoting their drugs than they do on research. (P18)

Participants also identified the lobbying efforts of pharmaceutical manufacturers as forces influencing the formation of drug benefit policies and reimbursement decisions by lawmakers. I would like to tell my congressman, “Please, if you take any money under the table from the pharmaceutical companies, don’t let it influence your decisions to help us.” (P8)

To have some agency controlling the cost of drugs would be a good thing. But again, you would have to fight all the pharmaceutical companies to have it done. (P9)

4. Affordability

Affordability refers to the effective out-of-pocket costs of prescription medications relative to the individual’s income. We used the term “affordability” to describe this theme since the study participants defined the issues related to the costs of prescription drugs by comparing the costs of other necessities with that of prescription drugs. Many participants expressed varying degrees of outrage at the high costs of their prescription drugs. Many had powerful stories to relate reflecting the economic barriers associated with paying for prescription drugs.

But do you realize that I have very small earnings, haven’t worked much in my married life, and I get a very small Social Security check. It would take all but $11; my Social Security check is $496 and this would be $487. So I didn’t have much of anything else. No one else to support me, but God! There goes the whole thing. That is really discouraging. . . . (P8)

I can’t have food or I can’t have the drugs. Well, I would like to spend money on other things, too. (P5)

We used to pay like $24 for a 90-day supply of Fosamax. And now it says $40. Just recently went up, which was discouraging. That’s something congressmen should realize.

People can’t afford to buy the drug and they get sick. (P3)

Many volunteers believed that they could not afford their medicines because drug companies spend more on advertising and promotion than research, thus contributing to the increase in prescription costs.

The drug companies spend about 36% of the budget on advertising; they make about 18% profits a year whether the economy goes up or down. And we all have to pay the cost. (P3) 36% of the pharmaceutical companies’ budget in advertising! Terrible. . . . Terrible. . . . It can reduce the price of drugs. (P1)

The MSF offers the Canadian Prescription Drug Importation Program through which they provide members with medications at discount prices negotiated by the Canadian government with many pharmaceutical companies.45 The program also lowers medication costs by charging in Canadian dollars, which historically trade at a substantial discount to the U.S. dollar. The overwhelming response of the members regarding drug importation from Canada reinforced the observation that, to cope with inadequate prescription drug coverage and rising costs, seniors are buying medicines from Canada, despite the fact that they would prefer to purchase their medications in the United States.

I wrote a note to the doctor saying that, in order to be able to afford my drugs, we really want to do this. “Would you please cooperate?” and I needed a prescription sent for this drug up to Canada and gave him the form; I had filled it all out. (P13)

Because I weighed it all, and I can do better buying 2 drugs through Canada and 1 drug here, and I cut my premiums in half. (P10)

Now, I would by far prefer to buy all of my drugs in the United States at 1 place. So they know everything that I am taking. I am going for it because of the cost. (P12)

Not surprisingly, group participants placed much emphasis on the out-of-pocket costs associated with drug benefits.

I had a copay, which kept going up every year. But I am fortunate. I had experiences with many people whose copayments are very costly. (P17)

I would like a plan with a low copay. (P4)

Other group members felt fortunate for having prescription drug insurance, which made it possible for them to afford drugs.

I think I am fortunate because my insurance pays 80% of my prescriptions. But there was a time when we had to pay for our prescription and send all the receipts in to get paid. One month, in between, my husband and I had to pay $749. My husband had lung cancer, so there were a lot of medications. But I am very fortunate now that I go to the drugstore, and they just fill Pravachol, which is $90 or something; I get it for $15. It would cost $275 a month for my prescription drugs, while actually I pay $47, and you can’t beat that, I know. (P9)

I became aware of how important prescription coverage was when we were raising our family. Our kids were fairly healthy—they get sick once in a while—and it was kind of an acute thing. I developed chronic asthma and started taking some drugs, and month after month, it dragged us down. If we hadn’t had coverage, it would have been much
harder for us. So I was introduced to this chronic thing pretty young, and as I got older, some other things have cropped in, too. So it’s no relief for months . . . and insurance coverage is really important to me. (P13)

5. Equity

Study volunteers in all 3 groups repeatedly raised the issue of fairness in prescription drug payment plans. The participants believed that a Medicare drug benefit should be uniform with respect to both premiums and benefits and should be uniform across the United States.

I just wanted to repeat what we said; you know, we want something that is affordable and fair to everybody. And I think in the long run, we save; the country saves because people who don’t get or take their medications because they can’t afford to buy them become ill and end up in the hospital. And Medicare ends up paying for the health care because the person didn’t take drugs. And it is very important that we understand that. (P7)

. . . there shouldn’t be some states that give a copay and others that don’t give it. We all pay into the same system, so we should be treated all equal. (P5)

Well I think what’s important is everybody should be covered to the same extent, and one thing that I would like to tell my senators is, “Give us the same plan as what you senators and representatives have.” We all need equal. (P2)

Participants also discussed geographic differentials in payments to managed care organizations participating in the Medicare + Choice program that have resulted in inequities in the benefits offered by these plans.25

They don’t reimburse every state and every county the same although we all pay into the system in the same way from our paychecks. Why are these people from other states getting higher reimbursements for Medicare? (P3)

It’s not going to be fair unless they equalize the rate for Medicare. (P3)

I think they should have the same thing all over; Medicare should be the same all over the United States. (P10)

Discussion

The purpose of this study was to build on the results of past research and explore the nature and range of older adults’ beliefs about prescription drug insurance in general and as part of the Medicare program. Textual analysis of transcripts from 3 focus groups revealed 5 distinct themes that were consistent across the groups utilized in this study: (1) prescription drug access, (2) drug benefit comprehensibility, (3) powerful others, (4) affordability, and (5) equity. Consistent with previous research, 2 of the themes (access and affordability) related to individuals’ ability to purchase medications required for maintaining or improving their health.11-14 The other 3 themes we uncovered are less prominent in the literature. In the next paragraphs, we will discuss the 5 themes and suggest a framework and ideas for future research in each area.

Factors that impact older adults’ access to prescription drugs often were discussed during these focus groups. One of these factors was the portability of insurance benefits. This likely is important to many seniors because many individuals who live in cooler climates enjoy spending winter months in Sunbelt states. This raises an important issue for the Medicare prescription drug benefit because many of the private insurers expected to offer plans under this program will be regionally based and may not have contracts with pharmacies outside the beneficiary’s home area. A second factor affecting medication access often mentioned during these groups was the use of mail-order pharmacies. Participants liked the convenience of home delivery and of being able to receive a 90-day supply for many medicines. These findings are in accordance with findings from Cline and Mott’s study of hypothetical drug plan choices.12

Those authors reported that individuals currently using mail-order pharmacies were more likely than those using other types of pharmacies to choose a plan requiring mail-order use.

Although no studies known to the authors have investigated drug plan comprehensibility per se, health plan understanding, especially with regard to the Medicare program, has been studied.26,27 For example, Bann et al. studied Medicare beneficiaries’ knowledge of 7 program policies using a short quiz administered as part of the 1997 and 1998 Medicare Beneficiary Surveys.26 They found that a majority (78%) understood that Medicare did not cover all health care expenses but that far fewer understood that Medicare health maintenance organizations (HMOs) typically cover more services than the traditional Medicare fee-for-service program (37%) or that one could disenroll from an HMO and still be covered by Medicare (46%). In our study, the participants described similar issues, especially with regard to discount cards and formularies. In a recent survey of Medicare beneficiaries, more than half (56%) reported that they did not understand the new Medicare drug benefit well.28 Given that MMA relies upon markets (which require a reasonable degree of information and understanding on the part of purchasers) to deliver cost containment and quality improvements, comprehensibility may be key to the success or failure of the Act.

Participants in these focus groups recognized the influence that actors external to the medication use process, such as pharmaceutical manufacturers, exert on the demand for and cost of medications, a theory that has received some empirical support.29 Respondents also implied that this was a source of concern for them. Comments suggested that DTCA was perceived as persuasion, as opposed to information. It also
was apparent that some of these older adults believed that DTCA represents a harmful intrusion into the doctor-patient relationship. Some study participants understood and discussed the lobbying efforts of the pharmaceutical industry and their potential impact on the provisions of the Medicare drug benefit. Together, this evidence suggests that it may be worthwhile to include the concept of powerful others in future studies examining older adults’ drug benefit beliefs.

A great deal of study has been devoted to the effects of insurance coverage for prescription drugs on various aspects of affordability among older adults. Researchers have found that more generous drug benefits are associated with a lower likelihood of not receiving needed medications and cutting back on necessities such as food. Participants in our study confirmed that drug benefits were instrumental to their receiving necessary medicines, in addition to being an important component of household financial well-being. Among working-age adults, drug insurance satisfaction studies show that higher out-of-pocket expenses are associated with significantly lower satisfaction ratings. Our results imply that the cost-sharing provisions of a drug benefit are recognized and are likely to figure prominently in choices among and evaluations of drug benefit plans.

Equity was the fifth and final theme that we uncovered in our study. There was a clear sense that study subjects desired fairness for everyone in prescription drug payment plans. Not only did they desire uniformity with respect to premium and benefits but they also expressed the feeling that, since they did their duty by paying taxes their whole life, they now deserve coverage for their prescription drugs. There was a sense that drug manufacturers were taking advantage of the U.S. senior citizen population through charging high prices for drugs, and study participants were upset that the government wasn’t doing enough about it.

Such a reaction to prescription drug payment and procurement is consistent with the influences that shaped this generation. Our study subjects, aged 65 years and older, were either entering childhood or young adulthood during the New Deal and World War II. These influences shaped this generation as they watched older people making great sacrifices on their behalf. Reaching maturity in an era of conformism, they avoided risking their reputations while making early and unconditional commitments to family and career. As adults in the 1960s, they were further influenced as the government expanded its role as a protector via Medicare and Medicaid legislation. Now, as senior citizens, this generation of individuals wants to participate, to listen, to be seen as “hip,” often volunteering as teachers’ aides, museum docents, organizers of “grandtravel” trips, and as activists for causes they believe in.

Our findings related to equity and fairness as one of the five themes related to drug benefit beliefs is consistent with this generation’s characteristics. What is not known is how the next generations set to reach older adulthood (Baby Boomers, followed by Generation X) will view prescription drug benefits. There is some evidence to suggest that these generations may not value equity and fairness as much as they would value maximizing their personal utilities. Further inquiry into and tracking of older adults’ drug benefit beliefs would be prudent in this area.

Older Adults’ Drug Benefit Beliefs: A Preliminary Framework

A primary building block of any scientific theory is the concept. A concept refers to some portion of reality. Using focus groups and thematic analysis, we elucidated 5 recurrent concepts derived from our analysis, we suggest a preliminary framework of older adults’ drug benefit beliefs. We have attempted to define, both abstractly and concretely, these 5 concepts. For example, at an abstract level, “access” was defined as “factors that facilitate or inhibit one's acquisition of prescription medicines.” A concrete, or operational, definition can be derived directly from the comments of focus group participants (e.g., the presence or absence of drug benefit portability problems, etc.)

Taxonomies are frameworks composed of multiple theoretical concepts that are useful for organizing multiple variables associated with a given phenomenon. Using the 5 themes or concepts derived from our analysis, we suggest a preliminary taxonomy of older adults’ drug benefit beliefs (Figure 2). Our proposed taxonomy provides a simplified description of the complex phenomenon of beliefs regarding prescription drug.
insurance. The taxonomy comprises 5 overlapping circles that signify the manner in which the 5 themes intermingle when seniors evaluate prescription drug plans. The analogy of overlapping circles is used to signify the fact that some subthemes are multidimensional and appear under more than one concept. For example, “Reimportation” appears under “Prescription Drug Access” and also under “Affordability.” This is a preliminary framework, offered as a possible guide for future empirical and conceptual work in areas of inquiry surrounding drug benefits.

Implications for Managed Care

A taxonomy such as that proposed here may prove useful to managed care practitioners and administrators. Offering stand-alone prescription drug plans to Medicare beneficiaries is a new business venture for most pharmacy benefit managers. The proposed framework provides some insight into the dimensions along which Medicare recipients might evaluate various drug plan offerings in their areas and, as such, may guide benefit administrators in the rational design of such products. Although the trade-offs between access and affordability are widely recognized, understanding that customers value ease of comprehensibility and perceived equity may help a pharmacy benefit manager gain a competitive advantage in this market segment. The taxonomy may also be valuable in the design of satisfaction measurement instruments in this population.

Future Research

Results of this study suggest several paths that future researchers might follow. Replicating this study among various groups of older adults could serve to confirm or disconfirm the results reported here and may suggest other themes not identified in this study. Future studies might examine each theme in detail, e.g., the various aspects of affordability, providing a more complete conceptualization of each. Investigators also might seek to develop quantitative measures of the beliefs identified in this study. These measures could be used to develop a ranking of the relative importance of each theme. Such measures might also be useful for profiling differences in beliefs that may exist among various geographic, demographic, and political subgroups. Although preliminary in nature, the proposed framework could help guide this future research.

Limitations

The results of this study should be interpreted in light of several limitations. First, all participants volunteered for this study and, therefore, may have been more knowledgeable than the typical older adult with respect to the topic of drug benefits. However, the emphasis in focus group research is to select people who are conversant with a given phenomenon so this is not necessarily a bias. Second, there may have been some interviewer bias.

However, every effort was made to control this by maintaining a neutral position and intervening only to facilitate smooth discussion. Third, statements could be categorized in more than one way. Hence, identified themes cannot be regarded as exclusive or exhaustive. Fourth, the present study sample was drawn from a select geographic area. Seniors from different regions may not share the perceptions and views identified here. Finally, this study included only 3 focus groups. A more extensive study with more groups of older adults may reveal more significant themes not discovered in this analysis.

The findings of this largely exploratory investigation indicate that many older adults may have preferences for a Medicare drug benefit not like that introduced under MMA. For example, study volunteers often discussed the impact of high out-of-pocket expenses, a feature that many beneficiaries will encounter under the new Medicare drug benefit. Similarly, many participants mentioned ease of comprehensibility, while MMA introduces a complex benefit design requiring program participants to make a variety of choices that were not hitherto necessary. Further research will be necessary to better understand the impact of drug benefit beliefs on program performance and beneficiary outcomes.

Conclusion

The goal of this study was to develop a better understanding of the nature and range of older adults’ beliefs and attitudes with regard to drug benefits in general and as part of the Medicare program. Participants conceptualized prescription drug insurance as a complex, multidimensional phenomenon. As in past research, we found that factors impacting access and affordability were quite important to members of this group. In addition to these attributes, our results suggest that at least 3 other facets of prescription drug insurance plans are meaningful to seniors: drug benefit comprehensibility, powerful others, and equity.

DISCLOSURES

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Cline served as principal author of the study and was responsible for study concept and design. Analysis and interpretation of data and drafting of the manuscript were the work of Cline and authors Kiran Gupta, Reshmi L. Singh, and Jon C. Schommer, critical revision of the manuscript was the work of Cline, Singh, and Schommer.

REFERENCES


Older Adults' Drug Benefit Beliefs: A Focus Group Study


Each of the following Peer Reviewers contributed one or more reviews of manuscripts submitted to the Journal of Managed Care Pharmacy in calendar year 2004. We are indebted to these professionals for their assistance in continuous quality improvement of the content of JMCP.

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**Correction**

In the article entitled “Effects on the Cost and Utilization of Proton Pump Inhibitors From Adding Over-the-Counter Omeprazole to Drug Benefit Coverage in a State Employee Health Plan,” published in the September/October 2004 issue of the *Journal [2004;10(5):449-55]*, Table 1 contained a misspelling. The correct table is shown below.

| TABLE 1 Benefit Design and Pharmacy Reimbursement Changes for Proton Pump Inhibitors (PPIs) |
|---------------------------------|-----------------|-----------------|
| **Copayment**                   | **Prepolicy**   | **Postpolicy**  |
| OTC omeprazole                  | Not covered by plan | $5 (new OTC tier) |
| Rx omeprazole                   | $10             | $10 mg cap only: $25 |
| Rx (brand) omeprazole           | $25             | Not covered |
| Rabeprazole                     | $25             | $50             |
| Esomeprazole                    | $25             | $50             |
| Lansoprazole                    | $50             | $50             |
| Pantoprazole                    | $50             | $50             |
| **Dispensing fee**              | **Ingredient cost** |
| OTC                             | Not covered | AWP - 13% |
| Rx                              | $2.50          | AWP - 13%      |
| **Days-supply limit**           | **Rx**          |
| OTC                             | Not covered   | 42-day supply  |
| Rx                              | 30-day supply  | 30-day supply  |

*Days supply limit; there is not a quantity limit on any PPI. OTC = over the counter; Rx = prescription; AWP = average wholesale price.*
Bipolar Disorder Pills in Perspective: Questions From Peer Review

I recently performed a peer review of a manuscript submitted for consideration for publication in the *Journal of Managed Care Pharmacy (JMCP)* on the subject of the total costs of care for patients with bipolar disorder treated with divalproex versus one of 3 atypical antipsychotics; 2 different classes of medications were involved. In this regard, a point arose that divalproex treats mania but not depression in the condition singularly labeled as “bipolar disorder.” So, pitting the 2 classes against one another may not be appropriate unless one can argue that both classes treat the same problem.

To a neurologist, the question is: What is the actual defect? The 2 “poles” of bipolar disorder are the varied symptoms; however, the hypothesis of bipolar disorder is that these are 2 symptoms of the same illness. The hypothesis is: there is 1 problem.

Certainly, in many conditions, we recognize that we may treat the symptoms in addition to (or rather than) the disease. For example, in an infection, we may give medications to treat fever. Treatment of the fever has no benefit in eradicating the actual illness, but it alleviates symptoms. Both antibiotics and antipyretics could be useful; but, in an analysis for cost-effective therapy, one would not pit an antipyretic against an antibiotic.

The manuscript that I reviewed discussed the costs of treatment of a condition: bipolar disorder. The authors approached the issue under the examination of “treatment worthiness” as manifest in cost. In the manuscript, it was presumed that outcome was the same (or else the comparison of cost may be spurious). The manuscript did not, itself, examine outcome for the patients except to the extent of the presumption that lower subsequent overall cost would imply better outcome (which may or may not be true from a broader perspective).

In any event, the manuscript compared 2 types of medications: one from a class originally for seizures and others from a class for psychoses. Yet, the presumption was that these can be compared—with advocacy of which is the “best” treatment based simply on cost. Indeed, the presumption might be true. The original use of a class of medications may lead to an identifying label for the class (such as “anticonvulsants”), but this is only a reference to an original use. So, in the depths of brain physiology, it may be that the genesis of bipolar disorder, seizures, and psychosis have similar etiologies, and a single class of medications may address this etiology even though the class is named only for one use. Yet, we must understand our tenuous footing when we accept—without examination—the concept that treating the symptom is sufficient duty. “Bipolar disorder” is a label for a symptom complex. It is not a label for a specific pathophysiology. I would not place upon the pharmacological community the burden to understand why we could think of treating bipolar disorder with either an anticonvulsant or a neuroleptic. What is (Continued on page 89)
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the linkage between these? Perhaps bipolar disorder, seizures, and psychoses are all disorders of cell crosstalk regulation (the “kindling” notion). Perhaps there is some better understanding. It does not fall to the pharmacological community to decipher the problem. However, it does fall to the pharmacological community to know the difference between chasing symptoms and treating specific etiologies.

So, in the peer review of a manuscript that compares total costs of care for divalproex versus 3 atypical antipsychotics, it is necessary to pause to ask: Is there a fundamental difference between anticonvulsants and neuroleptics in the treatment of bipolar disorder that supersedes cost comparison? Does the comparison proceed erroneously?

Managed care pharmacy and JMCP are interested in measuring costs and identifying value in the use of pharmaceuticals. However, this interest must be examined in the broader context. The pharmacist is no longer simply a dispenser of pills, acting in response to doctor’s orders. The pharmacist’s role involves more than simply helping to choose among “equivalent” medications. The issues of the pharmacist have grown to be the issues of pharmacology itself. The pharmacist is the pharmacological intermediary—standing between the patients’ needs and the results of medical evaluation. The pharmacist of today is interested in the action of specific chemicals in biological processes. Ideally, for both pharmacologists and physicians our insight has grown beyond a focus on symptoms.

Therefore, a manuscript that compares the total costs of care in bipolar disorder patients who received divalproex or one of 3 atypical antipsychotics contains a hidden flaw of thinking—the flawed presumption that pharmacological choice can relegate itself to chasing after symptoms with the cheapest pill. Before we can consider this, we must ask if the comparison of costs is even appropriate. Do anticonvulsants and neuroleptics do the same thing in the treatment of bipolar disorder? And, if they do, what is that “thing”? If they don’t, then is cost an adequate assessment of treatment effectiveness? For example, in the 2 treatment groups, did one group show a higher likelihood of returning the patient to the workforce? In the total perspective of costs, this could outweigh other issues. So, before we can compare costs, we need to know that we are truly comparing equivalent alternatives.

JMCP can help the pharmacological community to rise to its full potential, and so we need to demand more. In a manuscript that compares the total costs of care for bipolar patients treated with divalproex to bipolar patients treated with one of 3 atypical antipsychotics, I would like to see the following foundations given at least passing acknowledgment. First, we must acknowledge that the specific biological defect of bipolar disorder is not known, and so specific etiologic treatment cannot be rendered. Therefore, treatment of this condition is focused on symptoms. Second, in the management of bipolar disorder symptoms, a comparison of anticonvulsant versus neuroleptic treatment cost would imply that these strategies have been found to be therapeutically equivalent. If the authors could not accept these preambles, then the study is specious. On the other hand, if the authors can accept these preambles, then JMCP and the pharmacological community should be interested in why anticonvulsants and neuroleptics are equivalent.

My medical practice was never about chasing symptoms. It was always about the attempt to remedy the defect that caused the illness. Concurrent to this pursuit, I would manage symptoms. Certainly, in many cases I needed to accept that the specific cause of the illness was not known, so treatment of symptoms was all that was possible. However, I never confused the two issues. JMCP also should not.

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According to a November 2004 report from the American Lung Association, nearly two thirds (64%) of smokers are not concerned about developing chronic obstructive pulmonary disease (COPD), America’s fourth ranking cause of death, despite the fact that more than half of them (55%) experience at least one of the symptoms of COPD a minimum of once each week.1 This is a mind-numbing finding that provides some insight into the nature of the societal burden created by what appears to nonsmokers as a largely self-inflicted disease. Norman Edelman, a medical consultant for the American Lung Association, found that smoking is the most common cause of COPD, responsible for 80% to 90% of all COPD deaths, and that the majority of smokers who could have COPD are ignoring the signs. COPD claims the lives of more than 120,000 Americans each year.

Denial or ignorance of the association between smoking and disability and death from COPD does not surprise those who have worked in clinical practice. Few clinicians, particularly those who are nonsmokers, will forget their first encounter in an intensive care unit (ICU) or coronary care unit (CCU) in which the patient is near death from a cardiovascular event and requests a cigarette. The point is further driven home when a close relative—a son, daughter, or spouse—lights up outside the waiting room (in the “old” days) adjacent to the ICU or CCU.

COPD is a term referring to a large group of lung diseases, principally emphysema and chronic bronchitis, characterized by obstruction to airflow that interferes with normal breathing;2 COPD patients typically describe the feeling as hungry for air, like trying to breathe through a straw. The American Lung Association estimates that COPD will be the third largest cause of death worldwide by 2020, rising from its present rank as the fourth leading cause of death. According to estimates by the National Heart, Lung, and Blood Institute, chronic bronchitis and emphysema take a heavy toll on the economy. In 2004, the annual cost of COPD in the United States was $37.2 billion. This included $20.9 billion (56%) in direct health care expenditures, $7.4 (20%) billion in indirect morbidity costs, and $8.9 (24%) billion in indirect mortality costs.1

In this issue of the Journal, Tinkelman, Nordyke, Isonaka, et al. examine the definitions of disability associated with COPD and estimate the economic burden of COPD on long-term disability.3 The conclusion from this research is that better methods are necessary to define disability associated with COPD and that the economic burden of COPD is apparently underestimated. On the former point, research has shown that a composite measure of COPD is a better predictor of the risk of death compared with forced expiratory volume (FEV1) alone. Evaluation of 207 patients with COPD found that 4 factors predicted the risk of death in this cohort: (a) the body-mass index [B], (b) the degree of airflow obstruction [O], (c) dyspnea [D], and (d) exercise capacity [E], measured by the 6-minute walk test. The 4 variables were used to construct the BODE index, a multidimensional 10-point scale in which higher scores indicate a higher risk of death. The hazard ratio for death from any cause per 1-point increase in the BODE score was 1.34 (95% CI, 1.26-1.42; P<0.001), and the hazard ratio for death from respiratory causes was 1.62 (95% CI, 1.48-1.77; P<0.001).4

For the latter point, highlighted by Tinkelman et al., COPD is the only chronic illness where the morbidity and mortality rates are going up, as are the direct and indirect costs of the disease. COPD has been identified by the Centers for Medicare and Medicaid Services (CMS) as one of 3 high expenditure chronic disease conditions (the other 2 are congestive heart failure and complex diabetes) to be targeted for disease management in the Chronic Care Improvement Program (CCIP) under the Medicare Modernization Act of 2003.2 Permanent disability accounts for about 14% of persons eligible for Social Security benefits in the United States, 6.5 million of 46.4 million beneficiaries, and about 14% (5.8 of 40.5 million) of Medicare beneficiaries.6 Data prepared for the CCIP showed 1,738,691 Medicare beneficiaries with COPD in 2002, 30.0% of the Medicare disabled population and 4.2% of all Medicare beneficiaries. The Medicare beneficiary with COPD accounts for mean annual Medicare expenditures that are about 2.4 times the average for all Medicare beneficiaries.7

What can be done to reduce this huge economic burden in the United States and the world? Most of COPD (80%-90%) is caused by smoking, and a smoker is 10 times more likely than a nonsmoker to die of COPD.9 Most of the burden of COPD is therefore preventable. Education would seemingly play a large role in any strategy to reduce the burden of COPD. An amazing statistic from the American Lung Association is that 51% of smokers are unaware of the disease, despite the fact that COPD deaths have increased in the United States over the past 3 decades. There is also a larger than expected incidence of COPD-related deaths in women—61,422 females in the United States died from COPD in 2002 compared with 59,133 males. Even passive exposure to cigarette smoke is associated with an increased risk of coronary heart disease (CHD), a relative risk of CHD of 1.23 for nonsmokers exposed to the smoke of 1 to 19 cigarettes per day and a relative risk of CHD of 1.31 for non-smokers exposed to the smoke of 20 or more cigarettes per day, compared with nonsmokers not exposed to smoke.10

There are at least 3 opportunities for managed care organizations (MCOs): (1) efficient treatment of COPD, (2) education campaigns to increase awareness of the direct association between smoking and COPD, and (3) prevention of the disease and its progression through smoking cessation interventions. For treatment, the evidence for safety and effectiveness is constantly changing, enough so that there were 3 major evidence-based clinical practice guidelines for disease...
management of COPD released in less than 2 years, in 2003-2004. Improved functional status and improved quality of life are elusive outcomes of care in COPD, and a randomized controlled trial (RCT) of lung-volume reduction surgery versus medical management did not favor either treatment. Greater public awareness of COPD and its causes has created some momentum at the national and international level, including designation of November 17, 2004, as World COPD Day, and the 2004 theme, “Don’t Ignore COPD.”

While there appears to be an ominous lack of awareness in the populace about the direct relationship between cigarette smoking and COPD, disability, and death, there are, at the same time, encouraging signals from employers. The direct medical economic burden of COPD is of course reflected in part in health care premiums and direct health costs for self-insured employers. Some employers are screening job applicants to prevent hiring persons who smoke, and some employers are forcing current employees who do not quit smoking to leave their jobs. Other employers require smokers to pay more for their health care coverage—in July 2005, Navistar International Corporation (Warrenville, Illinois), a large truck manufacturer, will begin charging employees who smoke, $50 more per month for their health care coverage.

Since cigarette smoking is the most important causative factor in COPD, smoking cessation is the mainstay of COPD therapy. It was therefore fitting and overdue for U.S. Health and Human Services (HHS) Secretary Tommy G. Thompson to announce on December 23, 2004, that CMS intended to provide new coverage allowing certain Medicare beneficiaries who smoke to receive counseling services that will help them to quit smoking. Secretary Thompson said, “This new benefit, focused on treating seniors’ smoking-related diseases, will go a long way toward reducing their risk of dying prematurely. The combination of lives lost, unnecessarily, and the cost of treating smoking-related diseases makes our investment in smoking cessation benefits all that more important. It’s never too late to benefit from quitting smoking.” Data released by CMS coincident with the announcement revealed that (a) about 9.3% of those aged 65 years and older smoke cigarettes; (b) about 440,000 people die annually from smoking-related disease, with 300,000 of those deaths (68%) in those aged 65 years or older; (c) the Centers for Disease Control and Prevention (CDC) estimated in 2002 that 57% of smokers aged 65 years and older reported a desire to quit; and (d) about 10% of elderly smokers quit each year, with 1% relapsing. CMS Administrator Mark McClellan, MD, PhD, said “The evidence available fully supports the hope that seniors at risk of the diseases caused by smoking can quit, given the right assistance. . . . As we add the ‘Welcome to Medicare’ exam and other preventive benefits and drug coverage, this is another step in using the medical evidence to turn Medicare into a prevention-oriented program.”

The proposal for Medicare to cover smoking cessation counseling resulted in part from a request from the Partnership for Prevention (PFP) in June 2004. The PFP requested that CMS open a national coverage decision to consider coverage of tobacco cessation counseling as detailed in the HHS Public Health Service 2000 Clinical Practice Guideline (CPG), “Treating Tobacco Use and Dependence.” The CPG has been endorsed by many health care and professional organizations, and CMS proposed to extend smoking cessation coverage to beneficiaries who smoke and have been diagnosed with a smoking-related disease or are taking certain drugs whose metabolism is affected by tobacco use. The announcement by CMS at year-end 2004 followed a series of HHS initiatives designed to help Americans quit smoking, including the opening of a new national quitline (1-800-QUITNOW) and designating all HHS campuses tobacco-free. The federal government apparently decided that it is never too late to quit smoking and that smoking cessation in the elderly is important to mitigating risk Medicare costs, even in those who have smoked for years. CMS noted that the Medicare drug benefit program that becomes effective on January 1, 2006, will cover smoking cessation treatments that are prescribed by a physician.

The recent increased federal emphasis on smoking cessation and the relationship of smoking to COPD would be better described as evolutionary than revolutionary. A U.S. Internal Revenue Service (IRS) ruling (99-28) in June 1999 revoked a 20-year-old ruling that said the costs of smoking cessation programs were tax-deductible medical expenses only for those employees with specific ailments or diseases such as emphysema. The new ruling made the costs of smoking cessation programs, including prescription drugs, tax deductible even if the individual employee does not have a specific smoking-related disease. These health benefits are tax deductible and can be funded through pretax contributions to flexible spending accounts. The IRS ruling in June 1999 was apparently influenced by the growing evidence at the time that smoking was a clear and direct threat to health—the ruling said “Scientific evidence has . . . established that nicotine is addictive and that smoking is detrimental to the health of the smoker.” On July 23, 2004, the U.S. Treasury Department defined smoking cessation drugs along with statins, angiotensin-converting enzyme inhibitors, and weight-loss drugs as exempt from the $1,000 annual deductible in the new health savings accounts established under the Medicare Modernization Act of 2003, “Drugs or medications are preventive care when taken by a person who has developed risk factors for a disease that has not yet manifested itself or not yet become clinically apparent . . . or to prevent the reoccurrence of a disease from which a person has recovered.”

In drug benefit plans, smoking cessation drugs have historically been more likely to be excluded from coverage. Over the 3-year period from 1997 through 1999, about two thirds of employer-sponsored drug benefit plans excluded
coverage for smoking cessation drugs.\textsuperscript{19} Since the nicotine replacement gum and transdermal patches are available over the counter, OTC coverage in drug benefit plans is key to health plan support of smoking cessation by this method, yet OTC coverage by health maintenance organizations appears to be little changed, at 31.5% of HMOs in 2003 compared with 32.1% in 2002 and 32.4% in 2001.\textsuperscript{20}

The results of MCO interventions in smoking cessation are mixed. Measures used by the National Committee for Quality Assurance (NCQA) in the Health Plan Employer Data and Information Set (HEDIS) Medical Assistance with Smoking include 3 components: (1) the percentage of smokers or recent quitters who received advice to quit smoking from their practitioner, (2) the percentage of smokers with whom the practitioner discussed smoking cessation \textit{medications}, and (3) the percentage of smokers whose practitioner discussed smoking cessation \textit{strategies}.\textsuperscript{21} For the most recent data available, commercial MCOs reported that 68.6% of current smokers or recent quitters received advice from practitioners to quit smoking in 2003, with a slightly lower rate for Medicare MCOs (63.3%) and Medicaid MCOs, (65.8%). These rates have remained constant in the 4-year period from 2000 through 2003. Perhaps more important, only 37.6% of current smokers or recent quitters in commercial MCOs discussed smoking cessation medication with their practitioner in 2003, and only 36% discussed smoking cessation strategies. The 2004 NCQA report (for 2003 data) estimated the direct and indirect costs of smoking to exceed $157 billion, or $3,443 per smoker per year, (for 2003 data) estimated the direct and indirect costs of smoking to exceed $157 billion, or $3,443 per smoker per year, and current smokers were associated with 18% higher health care costs over an 18-month period compared with those who never smoked.

It is worth noting that the proposed expansion in Medicare coverage for smoking cessation pertains to \textit{counseling} services. It will be up to drug benefit plans to determine which pharmacologic agents for smoking cessation, if any, will be included in coverage under the Medicare prescription drug benefit. The U.S. CPG, “Treating Tobacco Use and Dependence,” published in June 2000 by HHS, cited only 2 “first-line” pharmacotherapies for smoking cessation: bupropion SR and nicotine (in the form of gum, inhaler, nasal spray, or patch).\textsuperscript{22} There were only 2 second-line pharmacotherapies cited for smoking cessation: clonidine and nortriptyline. This comprehensive report (196 pages) included evaluation of 6,000 articles in the medical literature. “On-your-own” quit smoking rates were found to be in the range of 10% to 12% at 6 months, and motivation and willingness to quit are the most important factors in success for smoking cessation.

A more recent RCT conducted after publication of the 2000 U.S. CPG reinforced the prior evidence of the marginal value of nortriptyline in combination with nicotine replacement therapy. The smokers of 10 or more cigarettes per day were randomized to either nortriptyline or placebo before (14 days) and after quit day (12 weeks), and transdermal nicotine (21 mg per day) was started on quit day and continued for 8 weeks. This was a 3-mode intervention since behavioral intervention was also provided, consisting of 12 brief, individual visits. The smoking cessation rates at 6 months were 23% for nortriptyline versus 10% for placebo plus nicotine and behavioral therapy (absolute difference, 13%; 95% confidence interval, 1.3%-24.5%; \(P = 0.052\)).\textsuperscript{23} In the world of RCTs of pharmacologic interventions for smoking cessation, this 13% effect is huge.

It is clear that most pharmacologic agents alone are not much more effective than placebo in smoking cessation as measured by smoke-free results at 6 or 12 months. The controversy surrounding the value of nicotine replacement therapy (NRT) in smoking cessation is particularly heated. A March 2003 meta-analysis of the 7 OTC patch and gum studies found an average placebo group 6-month quit-smoking rate of just 3%, permitting the 7% quit rate for NRT at 6 months to earn a 2-fold odds ratio (OR).\textsuperscript{24} In one of the 7 studies used to compute the March 2003 OTC meta-analysis rates for OTC NRT, fewer than 1 in 5 subjects in the placebo patch group believed that they had received the “Real McCoy,” and the authors admitted that “the effect of such a blinding failure would probably be a reduction of the placebo effect.”\textsuperscript{25} Experts in smoking cessation have criticized the manufacturers of NRT commercial products for sponsoring research that corrupts the “evidence” that is relied upon by the medical research community in assessing the value of NRT in smoking cessation.\textsuperscript{26} One thing is clear in all of the work that has been done in assessing the value of alternate interventions in smoking cessation—“modest” effect is a common term, underscoring the difficulty of achieving the desired outcome of smoking cessation.

So, why should an MCO make an investment in smoking cessation given the dismal likelihood of a positive return on investment? A study conducted at Group Health Cooperative of Puget Sound by Curry et al. found that the average cost of providing smoking cessation benefits ranged from $0.89 to $4.72 per member per year (in 1997 dollars), depending upon coverage and member cost share.\textsuperscript{31} Estimates of the annual rates of use of smoking cessation benefits ranged from 2.4% among smokers with reduced coverage to 10% among smokers with full coverage. The average health plan cost per user who quit was calculated to be $797 (in 1997 dollars) for the standard plan (50% coverage of the behavioral component and full coverage of NRT), $801 for reduced coverage (50% coverage of both behavioral therapy and NRT), $870 for “flipped” coverage (full coverage of the behavioral component and 50% coverage of NRT), and $1,171 for full coverage (100% coverage for both NRT and behavioral therapy). The study results supported full coverage of smoking cessation programs, finding an estimated average 2.8% of smokers who quit under full coverage, 1.7% with “flipped” coverage, 1.3% with standard coverage,
and 0.7% with reduced coverage.

This study at Group Health Cooperative of Puget Sound wraps up the answer to a difficult question, surrounded in a mountain of literature, in a nice, neat package—it costs money to save money, but it is worth the investment. For this disease, pharmacologic interventions are not enough.

P&T Committees—Black Boxes Versus AMCP Format, and What Is the True Cost and Value of Pimecrolimus

Evidence-based medicine is a concept much easier to say than do. An academic definition of evidence-based medicine is, “the conscientious, explicit, and judicious use of the best current evidence in making clinical decisions about the care of individual patients.” A more practical definition is, “when there is evidence of benefit and value, do it; when there is evidence of no benefit, harm, or poor value, don’t do it; when there is insufficient evidence to know for sure, be conservative.”

For Pharmacy and Therapeutics (P&T) committees, the challenge to support evidence-based medicine is great, the potential value large, and the consequences potentially devastating. How many P&T committees added COX-2 drugs to the drug formulary from 1999 to 2004 when the evidence did not support either a safety advantage or cost-effectiveness?

Now, P&T committees are faced with a barrage of data and information from many sources regarding the relative safety and benefit of the other COX-2 drugs still available in the United States: celecoxib and valdecoxib.

P&T committees need tools, and the AMCP Format for Formulary Submissions represents a deliberate attempt to standardize the presentation of data and information by pharmaceutical companies to drug formulary (P&T) committees. Over time, standardization in the presentation of data and information will most likely evolve to standardization in the evaluation process used by drug formulary committees. Perhaps the AMCP Format for Formulary Evaluation will be forthcoming. This, like the first generation of “The AMCP Format,” would be a good thing since the new format will presumably further support the replacement of expert opinion with evidence, mostly derived from randomized controlled trials (RCTs), for unpublished as well as published RCTs. This future format for formulary decision making may help standardize the P&T decision-making process by presenting a “grid” for evaluating alternative therapies.

The grid might provide a structure or framework for formulary decisions in which decision factors are weighted, a priori. Formulary committees would determine the relative weighting, but the list of factors would be considered in every decision, much like a checklist for operating a boat or aircraft. It would include factors such as safety, efficacy, effectiveness, relative number of affected beneficiaries, actual relative drug cost before rebate, actual relative drug cost after rebate, total health system cost (hospital, drug and other direct medical costs), and total community cost (direct medical and indirect costs that include workplace productivity and social costs). For example, the total cost of a drug would include the (1) actual acquisition cost, after all discounts and rebates; (2) medical costs for administration of the drug, if relevant; (3) adjunct therapy, if required; (4) laboratory or other monitoring costs including medical visits; (5) direct and indirect costs of side effects; and (6) direct and indirect costs of therapeutic failure.

To progress to this future level of standardized drug formulary evaluation, it is helpful to know where we are today. Fisher, in this issue of the Journal, provides a snapshot of the clinical and cost outcome data presented in a real-world P&T committee process for evaluation of the treatment alternatives and methods for psoriasis and psoriatic arthritis. For those readers who have not participated in decision making in a P&T process, this article provides a clear picture of the “evidence” that is considered in “evidence-based decision making.” For those who do have first-hand experience with the P&T decision-making process, the clinical monograph by Fisher should provide a useful, contemporary benchmark. Readers should note that this P&T committee examines actual cost and utilization data from its health plans and PBM operations for the most recent calendar quarter(s) available at the time of decision making.

Two other articles in this issue of the Journal provide examples of information that might be considered by P&T committees. Weinberg reviews the subject of atopic dermatitis (AD) and its therapeutic alternatives, particularly pimecrolimus, one of 2 topical immunomodulators that have been added to the pharmacotherapeutic arsenal to treat AD since the year 2000. Tarcrolimus ointment in strengths of 0.03% for children aged 2 to 15 years or adults and 0.1% for adults only, was approved by the U.S. Food and Drug Administration (FDA) on December 8, 2000. Tacrolimus ointment is indicated for short-term and intermittent long-term therapy in the treatment of patients with moderate-to-severe atopic dermatitis in whom the use of alternative, conventional therapies are deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies. Pimecrolimus cream 1% was approved by the FDA one year later, on December 31, 2001, for “short-term and intermittent long-term therapy in the treatment of mild-to-moderate atopic dermatitis in nonimmunocompromised patients 2 years of age or older in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies.

Chang and Sung present a budget impact analysis for pimecrolimus. Both articles, by Weinberg and by Chang and Sung, represent information that might be contained in a product dossier that is considered by a P&T committee.
A budget impact model is a part of the pharmacoeconomic analyses recommended by the AMCP Format for Formulary Submissions, Version 2.0, although a health system cost-effectiveness model is preferred. As with all information examined by P&T committees charged with making value decisions, the source of the information is relevant and should be disclosed and acknowledged. Weinberg reported no specific funding for his review of AD and pimecrolimus, but he disclosed the receipt of research funds and compensation for participation in the speakers’ bureau for Novartis Pharmaceuticals, manufacturer of pimecrolimus.

Chang and Sung are employees of Novartis Pharmaceuticals, the manufacturer of pimecrolimus. One might expect the assumptions in their budget impact model to be conservative, forecasting a small budget impact associated with pimecrolimus. It is up to P&T committees for health plans and pharmacy benefit managers (PBMs) to use their own data to formulate the assumptions in the budget impact model presented by Chang and Sung or to create their own budget impact model and projection. Fairman and Motheral earned the JMCP 2003 Award for Excellence for their article that employed actual health plan data to overturn the assumptions used in the earlier decision-analytic pharmacoeconomic models of cost-effective treatments for eradication of Helicobacter pylori.

Health plans are well advised by authors Chang and Sung to determine their own medical visit costs for treatment of AD and pharmacy costs for topical immunomodulators approved for use in AD. For example, data from a PBM pharmacy claims database show that there has been a much larger increase in expenditures for pimecrolimus than suggested by Chang and Sung. Pimecrolimus was ranked #134 in drug plan expenditures in 2004, accounting for 0.16% of total drug plan spending. Claims data from this PBM data warehouse showed that drug plan spending for pimecrolimus increased by 30% in 2004, from 0.12% of total drug plan spending in 2003. Over the 2-year period from 2002 to 2004, drug plan spending on pimecrolimus increased more than 3-fold, from 0.05% of total drug plan expenditures in 2002 (drug expenditure rank #305) to 0.12% in 2003 (drug expenditure rank #163) and 0.16% in 2004 (drug expenditure rank #134). Further examination of these real-world data shows that almost all of the 3-fold increase in the proportion of drug plan expenditures for pimecrolimus over this 2-year period was attributable to utilization. The average actual price per standardized 30-day supply of pimecrolimus was $127 in 2002, rising 13% to $142 in 2003 and rising by 9% to $155 in 2004.

Stated in other terms, the per-member-per-month (PMPM) cost of pimecrolimus was about $0.01 in 2002, $0.03 in 2003, and $0.05 in 2004. These data differ dramatically from that presented by Chang and Sung in the results of their pharmacoeconomic model. Their reported $0.008 PMPM drug cost for pimecrolimus in 2003 would appear to underestimate the actual cost experienced in this PBM database by about 75%.

### Prescription-Equivalent Over-the-Counter Drugs for Allergy, Heartburn, and Cholesterol Reduction

The first over-the-counter (OTC) statin in the world was introduced to the market in the United Kingdom in August 2004 as Zocor Heart-Pro. The 10 mg simvastatin was marketed by a joint venture of Merck and Johnson & Johnson. Whether or not the U.S. Food and Drug Administration (FDA) permits access to an OTC statin in 2005, it seems likely that a low-dose statin will ultimately be available OTC in the United States at some point. As with all conversions from prescription (Rx) to OTC status, savings can accrue from more than the direct cost of the drug. The largest source of cost savings may be derived from fewer physician office visits. From this perspective, organized medicine in general might be expected to oppose to Rx to OTC “switches.”

For consumers and payers, the savings from Rx to OTC conversions can be very large. Harris et al. showed in a previous issue of JMCP that a state health plan reduced spending on proton pump inhibitors (PPIs) by at least 50% through a benefit design change and increase in pharmacy reimbursement that favored OTC omeprazole (Prilosec OTC). Health plan members saved between 80% and 90% in copayments per Rx for OTC omeprazole and 17% in the average PPI claim. Similar but less dramatic savings for drug plan sponsors and drug plan members could be realized through drug benefit coverage of OTC loratadine in which the OTC version (e.g., Alavert) can be purchased for about $14 per 30-day supply, 80% less than the $69 charge for a 30-day supply of either desloratadine (Clarinex) or fexofenadine (Allegra).

In a previous issue of JMCP, Richards, Blumenfield, and Lyon found generally favorable but not universally favorable opinions among pharmacy and medical officers in managed care organizations (MCOs) and pharmacy benefit managers (PBMs) regarding the possible introduction of OTC lovastatin to the U.S. market. More curious in the findings was the reaction of PBMs and MCOs to the availability of generic lovastatin: no PBMs and only 28% of MCOs changed the formulary status of the other statins. In anticipation of an OTC statin, no PBM or MCO would cover the OTC statin, and only 50% of all respondents, including one of 4 PBMs, reported that they would encourage use of the OTC statin. This is befuddling and suggests that health plans in general and PBMs in particular will not realize the cost-savings potential of market introduction of OTCs in their administration of prescription drug benefits.

Additional context for the findings of Richards, Blumenfield, and Lyon can be found in the results of 2 surveys conducted during one week in January 2004. Nearly three
fourths of 200 family practice physicians and 200 internists believed that new approaches are needed to reach consumers at risk for heart disease who are currently not being treated. (The survey apparently did not ask explicitly if the physicians supported OTC status for statins.) A separate survey of 600 consumers aged 30 years or older found that 33% were currently being treated for high cholesterol. Not surprisingly, OTC statin was of more interest to persons who were already taking supplements, avoided smoking, engaged in exercise, ate a low-fat diet, or who were trying to lose weight either regularly or occasionally.

Lovastatin is not a second-class drug for the reduction of low-density lipoprotein cholesterol (LDL-C) and triglycerides and increase of high-density lipoprotein cholesterol (HDL-C). In 33,318 patients switched from simvastatin (Zocor) to generic lovastatin, Kaiser Permanente researchers found better clinical outcomes with lovastatin at much lower cost. These study results were presented by Kaiser researchers, David Campen and Eleanor Levin (chief of cardiology for Kaiser Permanente in northern California), at the Scientific Sessions of the American Heart Association during the week of November 7, 2004. Specifically, the 33,318 patients (45% women) were switched from simvastatin (average dose 25.6 mg per day), to lovastatin (average dose 51.1 mg per day). In the primary prevention group, average LDL-C fell from 119.4 on simvastatin to 116.6 on lovastatin (P<0.001), and average triglycerides decreased from 171.5 to 169.7 mg/dL (P<0.01); average HDL-C rose from 50.9 on simvastatin to 53.0 on lovastatin (P<0.001). For the secondary prevention group, LDL-C fell from 101.1 to 99.0 (P<0.001), and triglycerides fell from 170.7 to 169.5 mg/dL (P = 0.046); HDL-C rose from 45.7 to 48.1 (P<0.001). Elevated transaminase or creatine kinase levels were comparable during simvastatin and lovastatin treatment. The authors concluded that clinical outcomes were the same or better for lovastatin compared with simvastatin in patients switched to lovastatin, representing a large improvement in quality since generic lovastatin is much less expensive than simvastatin. Additional quality improvement from this intervention to switch patients from simvastatin to lovastatin might be derived from a smaller proportion of patients discontinuing statin therapy due to the (copayment) cost since a generic copayment is generally at least 50% lower than a brand-drug copayment. The authors also observed that the average 51.1 mg per day of lovastatin suggests additional room for dose increases since the maximum approved dose is 80 mg per day.

Now would seem to be a good time for P&T committees in both health plans and PBMs to anticipate the introduction to the U.S. market of an OTC lovastatin. The FDA advisory panel may consider an application from Merck to sell Mevacor (lovastatin) over the counter at its meeting on January 13 and 14, 2005, and Bristol-Myers Squibb announced in mid-December 2004 that it would seek FDA approval for OTC sale of Pravachol (pravastatin) in anticipation of generic competition in April 2006. The short-term value (clinical outcome divided by cost) opportunity may not be as large as that possible with coverage of OTC omeprazole, where savings are 50% or greater, but the long-term value opportunity could be large and certainly warrants attention by P&T committees.

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REFERENCES

Letters to the Editor

JMCP welcomes letters that serve to clarify subjects published in previous issues of the Journal or regarding subject matter of interest to managed care pharmacists. Letters in JMCP are not peer reviewed but are subject to editorial review. When a submitted letter refers to an article published in a previous issue of the Journal, the letter is sent to the authors of the subject article to allow their response to be published with the letter.

Each letter should be signed by no more than 3 authors. Submissions must include your title, affiliation, complete mailing address, telephone number, and e-mail address. Potential bias or conflicts of interest must be disclosed.

Letters should be prepared in a word processing program, preferably Microsoft Word, and submitted electronically at jmcp.msubmit.net.