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With this issue, March 2005, JMCP makes the transition to 9 publication dates
per year: separate issues for the months of March, April, May, June, September,
and October and combined issues for January/February, July/August, and
November/December. In 2004, JMCP made the transition to monthly supple-
ments with continuing education opportunities for readers.
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All articles and editorials in JMCP undergo blinded peer review. Letters may be peer reviewed to ensure accuracy. The fundamental departments for manuscript submission are:

- Original Research
- Subject Reviews
- Formulary Management
- Contemporary Subjects
- Editorials
- Letters

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**Original Research**

These are well-referenced articles based on original research that has not been published elsewhere and reflects use of the scientific method. The research is guided by explicit hypotheses that are stated clearly by the authors.

**Subject Reviews**

These are well-referenced, comprehensive reviews of subjects relevant to managed care pharmacy.

**Formulary Management**

These are well-referenced, comprehensive reviews of subjects relevant to formulary management methods or procedures in the conduct of pharmacy and therapeutics (P&T) committees and may include description and interpretation of clinical evidence.

**Contemporary Subjects**

These are well-referenced submissions that describe pilot projects or other subjects that are not intended to be comprehensive reviews of the subject.

**Editorials**

These submissions should be relevant to managed care pharmacy and address a topic of contemporary interest.

**Letters**

If the letter addresses a previously published article, an author response may be appropriate. (See “Letter to the Editor” instructions at www.amcp.org.)

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JMCP publishes peer-reviewed original research manuscripts, subject reviews, and other content intended to advance the use of the scientific method, including the interpretation of research findings in managed care pharmacy. JMCP is dedicated to improving the quality of care delivered to patients served by managed care pharmacy by providing its readers with the results of scientific investigation and evaluation of clinical, health, service, and economic outcomes of pharmacy services and pharmaceutical interventions, including formulary management. JMCP strives to engage and serve professionals in pharmacy, medicine, nursing, and related fields to optimize the value of pharmaceutical products and pharmacy services delivered to patients.

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Just what could the subjects of art and math possibly have in common? In the case of Dale Adcock’s artwork, the answer is: everything! His computer and mathematical formulas serve as his canvas and paints—Adcock creates his fantastic artwork not with a computer drawing application such as Adobe Illustrator but with a Macintosh-based program called “Fractal Domains.” When a mathematical formula known as a fractal is entered into the program, the resulting geometric lines and patterns form a graphic design. Adcock does use Photoshop to touch up many of the images he produces, but he said that he created this issue’s cover art, Fractal #29, solely with a fractal formula called “Julia,” named for French mathematician Gaston Julia (1893-1978).

Polish-born mathematician, Benoit Mandelbrot (1924-), Sterling Professor of Mathematical Sciences at Yale University and IBM Fellow Emeritus (physics) at the IBM T.J. Watson Research Center, is known as the founder of fractal geometry. He coined the word “fractal” from the Latin fractus, past principle of frangere, meaning to break or fragment. According to Wikipedia (the free encyclopedia Web site), “A fractal is a geometric object which can be divided into parts, each of which is similar to the original object. Fractals are said to possess infinite detail, and are generally self-similar and independent of scale. In many cases a fractal can be generated by a repeating pattern, typically a recursive or iterative process.”

“The Mandelbrot set, when programmed into a computer, will draw a pattern that is imitative of nature in the way it repeats shapes in a variety of ways,” Adcock explained. “There are many different fractal formulas now, but they all fit Mandelbrot’s original definition, and they all imitate nature’s growth patterns to one degree or another. Some scientists are using fractal formulas to predict natural phenomena and growth patterns. Snowflakes, ice crystals, cloud patterns, and weather patterns can all be imitated in fractal mathematics.”

Born and reared in Dearborn, Michigan, Adcock graduated from Michigan State University in 1974 with a BA in social work and a minor in sociology. He earned his BSN in 1993 from Wayne State University in Detroit. Aside from a few art appreciation courses in high school and college, he has had no formal art instruction.

Adcock believes that his avocation of creating fractal art helps to balance his life. He said, “During the day, I am a charge nurse in a psychiatric hospital. In the evening, I am a father, husband, and computer graphic artist. Although I have remained in the Dearborn area, my global outlook and love of artistic beauty are shaped by a larger world view. Sitting in my home studio, I am able to learn from people from all over the world via the World Wide Web. When not reading and writing, I explore new ways to express my creative energies on my computer.”

Adcock also said, “Fractal art is a medium that has limitations, just like any other art medium—maybe more so. It is inherently a medium of abstract art. I find an image by playing with the [computer] program’s controls, much like driving around sightseeing in a colorful math world. Then when I get somewhere interesting, I tweak it, mold it, reshape it, and fuss with it, until it looks beautiful to me.” He continued, “The program lets me concentrate on the variables that give me control over how the image is drawn. I determine the resolution of depth in the 3-dimensional plane, and the coordinates of the complex plane center. I also manage the iteration, escape radius, and dwell-limit method. Finally, and most importantly, is the determination of the color scheme. The right set of values can please the eye and stir the imagination, but the wrong set of values can create an ugly mess.”

His MegArt Web site, www.megart.com, provides an opportunity for Adcock to exhibit and sell his fractal art online. Each fractal image has a link to zoom in for a close-up view, which is particularly helpful in seeing the details of Fractal #29. This 3-dimensional image resembles a group of Chinese dragons swirling outward from a mysterious source. Two of the dragons seem to pause and stare intently, while the other pair disappears from the page to explore their artificial universe.

Adcock feels that his art is emotional rather than cerebral, saying, “I believe bright color lifts up the spirits of the observer. If the sensation of beauty hits you at an emotional level, then I have succeeded. I attempt to create an atmosphere of brightness and light and a landscape of organic orderliness that says life is full of wonder and surprising structure. I also try to convey the message that life and art are not only about the overview but about the details, too.”

Sheila Macho
JMCP Cover Editor

COVER CREDIT

SOURCES
Interview with the artist.
www.megart.com
http://en.wikipedia.org/wiki/Fractal
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common types of references below:
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3. Journal paginated by issue
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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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- Manuscript: prepared in 12-point type, 1.5 line spacing, including:
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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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• briefly describes the importance and scope of the manuscript,
• 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
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  - keywords: follows the abstract
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- 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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An abstract is required in the format of:
• Objective
• Results
• Keywords

Subject Reviews
An abstract is required, generally in the format of:
• Objective
• Conclusion

Formulary Management
An abstract is required in the format of Original Research or Subject Reviews, depending upon the subject matter.

Contemporary Subjects
An abstract is required in the format of Original Research or Subject Reviews, depending upon the subject matter.

Editorials
These submissions require no abstract but should include references.

Letters
These submissions require no abstract or title page.

Please note:
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• Most articles published in JMCP, particularly Subject Reviews, should incorporate or at least acknowledge the relevant work of others published previously in JMCP (see “Article Index by Subject Category” at www.amcp.org).
• For articles in Original Research, a figure is recommended for making the effects of the inclusion and exclusion criteria clear to readers (see JMCP examples in 2003;9(4):320 [Figure 1] or 2003;9(3):258 [Table 1]).
• Product trade names may be used only once, for the purpose of providing clarity for readers, generally at the first citation of the generic name but not in the Abstract.

Reference Style

References should be prepared following modified AMA style. All reference number in manuscript should be superscript (e.g., 1). See examples of
Prevalence and Burden of Illness of Migraine in Managed Care Patients

KENNETH A. KOBAK, PhD; DAVID J. KATZELNICK, MD; GEORGE SANDS, MD; MONICA KING, MS; JOHN H. GREIST, MD; and MARY DOMINSKI, MD

ABSTRACT

OBJECTIVE: To determine the 3-month prevalence rate of migraine in a health maintenance organization (HMO) population, using a 2-stage screening process and neurologist exam, and to examine the burden of illness associated with both previously diagnosed and previously undiagnosed migraine in this population.

METHODS: A migraine assessment was sent to a random sample of 1,000 HMO patients between April 1999 and January 2000. Those screening positive and a random sample of those screening negative for migraine were evaluated by neurologists using a structured diagnostic assessment. Then, those diagnosed to have migraines by the study’s neurologists completed a battery of 3 questionnaires, evaluating severity, distress, and impairment.

RESULTS: Of 1,000 questionnaires sent, 753 (75.3%) were returned. The estimate of prevalence of migraine in this population ranged from 21.4% (adjusted for response bias) to 27.8% (unadjusted for selection bias). Only 48% of respondents had been previously diagnosed with migraine. The typical migraine caused moderate-to-severe distress in 69%, and 66% had definite or extreme interference in their social or occupational functioning. The average migraineur missed 7.6 hours of work due to migraine in the past 3 months. Previously undiagnosed migraine was associated with substantial impairment, with 58% of responders reporting interference with daily activities and 54% reporting moderate or greater distress. There was no significant difference between previously diagnosed and undiagnosed migraineurs on 3 outcome measures: pain, interference, or days of missed work. A higher proportion of previously diagnosed migraineurs (84%) reported moderate or greater distress compared with undiagnosed migraineurs (54%, \( P=0.002 \)).

CONCLUSIONS: Using a neurologist exam, the researchers found that the prevalence of migraine headaches was higher than previously reported. About one half of migraineurs had been previously undiagnosed. Undiagnosed migraine is associated with significant pain, distress, and dysfunction and is similar in these respects to diagnosed migraine. Increased public education and physician education on migraine are warranted.

KEYWORDS: Migraine, Quality of life, Disability, Managed care, Epidemiology

J Manag Care Pharm. 2005;11(2):124-36

Methods

Subjects

Subjects were enrollees in one of the 13 separate clinics of the Dean Health Plan, a 175,000-member organization based in Madison, Wisconsin. The population of the chosen clinic (Middleton Clinic, a sample of convenience) was approximately
4,164. Subjects were considered eligible if they met the following criteria:
1. they were between 18 and 63 years old;
2. they did not have a diagnosis of a life-threatening illness or neurological condition (e.g., Huntington’s, Parkinson’s, or multiple sclerosis) that would exclude them from participation;
3. they did not have point-of-service coverage; and
4. they had been continuously enrolled in the HMO for at least 1 year.

Study Procedures
A total of 3,286 patients from the participating study clinic were identified as meeting the study eligibility requirements from April 1999 to January 2000 by examining the Dean Health Plan claims database from the previous 12 months. Of these patients, a random sample of 1,000 patients was selected. These 1,000 patients were then sent a health assessment questionnaire and a letter from the principal investigator inviting them to participate in a study on the effect of illness on quality of life. Subjects were informed that they may be invited to participate in the second step of the study based on their answers to the assessment packet and were asked to indicate if they were willing to be contacted for this study. A $5 bill was enclosed with the letter as an incentive and a goodwill gesture for their time. Subjects who did not return the assessment packet within 2 weeks were mailed a second letter and assessment packet.

The health assessment questionnaire consisted of 14 yes or no questions of which 9 screened for migraine (Table 1). The questionnaire was developed specifically for this study since no similar validated public domain migraine screener was available at the time of the study. A positive screen for migraine was defined as affirmation of at least 2 of the 8 migraine symptoms mentioned in the questionnaire, whereas a negative screen was defined as no symptoms or 1 symptom. Individuals who screened positive for migraine were contacted and invited to participate in the next step of the study, as was a random sample of the respondents with negative screens. Because we took only a random sample of those screens consenting to be contacted, all data were weighted to reflect this sampling design (Figure 1).

The next step in the study consisted of an in-person neurological examination by board-certified neurologists (4 independent physicians not affiliated with the study) with expertise in the diagnosis and treatment of migraine. The neurologist examination served as the standard for the diagnosis of migraine and ruled out other diagnoses that could have accounted for patient symptoms. The examination was conducted with the use of a semistructured interview guide to ensure reliability among the 4 neurologists who conducted the examinations. In addition, study neurologists attended inter-rater reliability training on the administration of the semistructured interview, which included viewing a video and practice administration of the interview. Examination results were reviewed by an expert consultant (author M. Dominski) and any questions were discussed and clarified.

All subjects who were diagnosed with migraine by the neurologist also completed a battery of 3 questionnaires evaluating migraine severity, distress, and impairment. All subjects signed informed-consent documents, reviewed and approved by the Dean Foundation Institutional Review Board.

Outcomes Measures
The following 3 instruments were administered (each was developed specifically for use in this study since no similar instruments were available at the time of the study):

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Migraine Screener</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health Status Questionnaire</strong></td>
<td></td>
</tr>
<tr>
<td>Instructions: For each question, check the one box that best describes your answer. Mark only one box for each question, and be sure to answer all items.</td>
<td></td>
</tr>
<tr>
<td>1. In the past three months, have you had any moderate or severe headaches? If you marked YES to #1, please answer #2. If you marked NO to #1, please skip to #3.</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Have any of these headaches been associated with the following?</td>
<td></td>
</tr>
<tr>
<td>a. Pain starting on one side</td>
<td>Yes</td>
</tr>
<tr>
<td>b. Throbbing or pulsating feeling in the head</td>
<td>Yes</td>
</tr>
<tr>
<td>c. Nausea or vomiting</td>
<td>Yes</td>
</tr>
<tr>
<td>d. Light being more bothersome than when you are without a headache</td>
<td>Yes</td>
</tr>
<tr>
<td>e. Sound being more bothersome than when you are without a headache</td>
<td>Yes</td>
</tr>
<tr>
<td>f. Changes in vision or seeing sparkling lights or jagged lines before or during the headache</td>
<td>Yes</td>
</tr>
<tr>
<td>g. Numbness or tingling of hand, arm, or face during the headache</td>
<td>Yes</td>
</tr>
<tr>
<td>h. Headaches made worse by routine physical activity, such as walking up stairs</td>
<td>Yes</td>
</tr>
<tr>
<td>3. In the past three months, have you had moderate or severe heartburn?</td>
<td>Yes</td>
</tr>
<tr>
<td>4. In the past three months, have you had moderate or severe arthritis?</td>
<td>Yes</td>
</tr>
<tr>
<td>5. In the past three months, have you had moderate or severe back or joint pain?</td>
<td>Yes</td>
</tr>
<tr>
<td>6. In the past three months, have you had moderate or severe allergies?</td>
<td>Yes</td>
</tr>
<tr>
<td>7. In the past three months, have you had any coughing up of blood?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
1. Sands-Taylor (ST) Migraine Questionnaire (George Sands and Kirk Taylor [a neurologist employed by Pfizer, Inc.], unpublished test) (Appendix A). The ST Questionnaire evaluated symptoms associated with headaches with mild, moderate, and severe head pain. Embedded within the ST are 3 questions from the Work Productivity and Activity Impairment Inventory, adapted for use with migraine patients. These questions evaluate the number of missed work days in the past 3 months, degree of reduction in work productivity, and degree of impairment in regular daily activities due to migraine.

2. Migraine Severity Scale (MSS; John H. Greist, Kenneth A. Kobak, and David J. Katzelnick) unpublished test) (Appendix B). The MSS is modeled on the Yale-Brown Obsessive-Compulsive Scale and evaluates the number and duration of migraines, as well as impairment, distress, and degree of control over migraines.

3. Headache Specialist Diagnostic Patient Interview (HSDPI; George Sands and Kirk Taylor, unpublished interview) (Appendix C). The HSDPI is a semistructured diagnostic interview developed for the current study that provides a migraine diagnosis based on International Headache Society criteria. Embedded within the HSDPI is a rating of average headache severity on a Likert scale ranging from 0 (no headache) to 10 (most severe headache). Scale ratings are subsequently translated into categories of mild (0-3), moderate (4-7), and severe (8-10).

### Results

#### Participants

Of the 1,000 subjects sent an assessment packet and invitation to participate in the study, a total of 753 (75.3%) returned the packet (mean age: 41.27 years; SD = ±10.87; female: 59%), and 570 (57%) of these patients consented to be contacted for further participation (228 of 288 [79%] positive screens and 342 of 465 [74%] negative screens). Of the 228 positive screens, 223 (98%) were contacted and invited to participate in the next step of the study, as was a random sample (53%) of the 342 negative screens (n = 182). A total of 237 subjects agreed to and completed the neurologist examination (136 positive screens and 101 negative screens). Of these 237, 68% were female, and the mean age was 41.3 years.

The weighted number of subjects completing the neurological exam was 336, of which 94 were migraine-positive. Of the 94 migraine-positive subjects, 79% were female and 21% were male. The mean age was 42.03 years (SD = ±8.84; range: 19-59).

#### Disease Prevalence

The prevalence of migraine in this population (unadjusted for selection bias, i.e., only a random sample of negative screens was contacted) was greater than 20% (mean: 27.8%; 95% confidence interval, .26-.28, with a prevalence of 19% in males and 34% in females. Only 48% of subjects with a diagnosis of migraine on the neurological exam reported having been previously diagnosed with migraine by a health care professional.

Because those with migraine may be more likely to return the mailed assessment packet, this prevalence may be inflated, with the low estimate of 21% being based on the assumption that all those who did not return the assessment packet were nonmigraineurs. An analysis of the HMO claims database found no significant difference between those who returned and those who did not return the assessment packet in the percentage of subjects with a claims diagnosis of migraine (4.7% versus 4.2%, \( P = 0.755 \)) or in the percentage of subjects using triptans (3.1% versus 2.5%, \( P = 0.657 \)), but there was a significant difference in mean age (38.8 versus 35.6 years, \( P = 0.001 \)) and percent female (58.8% versus 50.0%, \( P = 0.016 \)).

We also compared those consenting to be contacted with those who did not consent to be contacted in order to determine if those consenting to be contacted were more likely to have migraine and thus artificially inflate the prevalence estimates. An examination of the HMO claims database found that those who consented to be contacted had a significantly higher rate of migraine in the HMO claims database (5.8% versus 1.2%, \( P = 0.019 \)). We recalculated the prevalence using the most...
conservative approach (i.e., we assumed that all those who did not consent to be contacted were migraine-negative). Using this approach to adjust for apparent response bias, the prevalence of migraine in this population was 21.4%. Finally, among those consenting to be contacted, there was no significant difference between those completing and those not completing the neurological examination in terms of prevalence of migraine or percentage using triptans in the HMO database. However, a small but significant difference was found in the percentage of females (67.9% versus 57.7% respectively, \( P = 0.036 \)).

**Pain, Distress, and Dysfunction**

The average pain severity of the typical migraine rated by neurologists on the 0 to 10 HSDPI Likert scale was 7.21 (SD = 2.12; median: 8.0). When collapsed into 3 categories, 5% could be categorized as mild (0-3 on the HSDPI), 42% as moderate (4-7), and 53% as severe (8-10). On the self-report MSS, the typical migraine was rated as causing moderate distress by 43% of migraineurs, severe distress by 19%, and extreme distress by 7% (Table 2). Sixty-six percent said their migraines caused definite-to-extreme interference in their social or occupational functioning (Table 3). Only 46% reported they were “always” or “usually” successful in stopping their migraines once they felt one coming on (Table 4). The average migraineurs missed 7.6 hours of work due to migraine in the past 3 months (SD = ±13.4), and migraine patients were limited in their activities on an average of 2.4 days in the past 3 months (SD = ±3.3). Sixty-three percent reported having at least 3 migraines over the last 3 months, and 21% reported 7 or more. Eighty-nine percent reported having migraines for longer than 2 years (median: 14 years), and 66% had migraines for 10 years or longer. Seventy-two percent had a positive family history of migraine.

**Diagnosed Versus Undiagnosed Migraine**

Previously diagnosed migraineurs were 89% female, compared with 71% female in the previously undiagnosed migraine group; \( \chi^2(1) = 4.629, P = 0.031 \). Mean age was 42.20 years (SD = 8.96; range: 20-56) for those previously diagnosed compared with 41.88 years (SD = ± 8.83; range: 19-59) for those previously undiagnosed, \( t(92) = 0.173, P = 0.863 \).

Undiagnosed migraine was associated with substantial distress and impairment and was similar in migraine intensity and impairment as reported by patients in whom migraine had been previously diagnosed. A comparison between migraineurs who reported having been previously diagnosed with migraine by a health care professional and those who had not been previously diagnosed is presented in Table 5 and Figures 2-4. There was no significant difference between diagnosed and undiagnosed migraineurs on the mean pain associated with their typical migraine as reported on the HSDPI (7.36 versus 7.09, respectively, \( t(92) = .607, P = 0.545 \)). Similarly, no signifi-

### Table 2

**Self-Reported Distress Caused by the Typical Migraine for Subjects Diagnosed With Migraine by Neurologist Exam (N = 94*) on the Migraine Severity Scale**

<table>
<thead>
<tr>
<th>Distress Level</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Mild, infrequent, and not too disturbing</td>
<td>20 (21%)</td>
</tr>
<tr>
<td>Moderate, frequent, and disturbing, but manageable</td>
<td>39 (43%)</td>
</tr>
<tr>
<td>Severe, very frequent, and very disturbing</td>
<td>17 (19%)</td>
</tr>
<tr>
<td>Extreme, near constant, and disabling distress</td>
<td>6 (7%)</td>
</tr>
</tbody>
</table>

* Data were not obtained on 3 patients.

### Table 3

**Amount of Self-Reported Interference With Everyday Activities Caused by Typical Migraine for Subjects Diagnosed With Migraine by Neurologist Exam (N = 94*) on the Migraine Severity Scale**

<table>
<thead>
<tr>
<th>Distress Level</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Slight</td>
<td>23 (25%)</td>
</tr>
<tr>
<td>Definite, but manageable</td>
<td>28 (31%)</td>
</tr>
<tr>
<td>Substantial</td>
<td>20 (22%)</td>
</tr>
<tr>
<td>Extreme, incapacitating</td>
<td>12 (13%)</td>
</tr>
</tbody>
</table>

* Data were not obtained on 3 patients.

### Table 4

**How Often Migraineurs Are Successful in Stopping Migraines Once They Feel One Coming On (N = 94*)**

<table>
<thead>
<tr>
<th>Success Level</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always</td>
<td>15 (16%)</td>
</tr>
<tr>
<td>Usually</td>
<td>27 (29%)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>25 (27%)</td>
</tr>
<tr>
<td>Rarely</td>
<td>20 (22%)</td>
</tr>
<tr>
<td>Never</td>
<td>5 (6%)</td>
</tr>
</tbody>
</table>

* Data were missing on 2 patients.

**Note:** The question was worded “How much control do you have over your migraine headaches? How successful are you in stopping them once you feel one coming on, for example, with medication, bed rest, relaxation, or other action?”

### Table 5

**Age, Gender, and Severity of Migraine Pain Between Neurologist-Diagnosed Migraine Subjects Who Have Been Previously Diagnosed (n = 43) Versus Those Not Previously Diagnosed (n = 51) on the Headache Specialist Diagnostic Patient Interview (HSDPI) Severity Scale**

<table>
<thead>
<tr>
<th>Severity Level</th>
<th>Previous Diagnosis</th>
<th>No Previous Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>42.20</td>
<td>41.88</td>
</tr>
<tr>
<td>% female</td>
<td>89%</td>
<td>71%</td>
</tr>
<tr>
<td>Mild (0-3)</td>
<td>0 (0%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Moderate (4-7)</td>
<td>20 (47%)</td>
<td>19 (38%)</td>
</tr>
<tr>
<td>Severe (8-10)</td>
<td>23 (53%)</td>
<td>27 (53%)</td>
</tr>
</tbody>
</table>

* HSDPI rates headaches on a 0-10 scale, with 0 indicating no headache pain and 10 indicating most severe headache pain.

* Data were not obtained on 3 patients.
A significant difference was found between diagnosed and undiagnosed migraineurs in the percentage of headaches with head pain categorized as mild (0-3), moderate (4-7), and severe (8-10), $\chi^2(2) = 4.70, P = 0.095$.

No significant difference was found between diagnosed and undiagnosed migraineurs in the amount of interference the typical migraine caused with daily activities, $\chi^2(4) = 5.09, P = 0.278$ (Figure 2). Fifty-nine percent of undiagnosed subjects reported definite, substantial, or extreme interference with daily activities compared with 75% for those previously diagnosed, $\chi^2(1) = 2.76, P = 0.096$.

There was a significant difference between diagnosed and undiagnosed migraineurs in the amount of distress reported, $\chi^2(4) = 13.72, P = 0.008$: 53.6% of undiagnosed subjects reported moderate or greater distress associated with their migraines compared with 83.9% of those previously diagnosed, $\chi^2(1) = 9.34, P = 0.002$ (Figure 3).

No significant difference was found between diagnosed and undiagnosed migraineurs in hours of missed work due to migraine (Figure 4). Subjects with undiagnosed migraine missed an average of 8 hours of work in the past 3 months due to migraine compared with 7.2 hours for patients who had been previously diagnosed, $t(87) = 0.3, P = 0.76$.

**Discussion**

The prevalence of migraine based on International Headache Society criteria, as confirmed by structured neurological evaluation and examination in this managed care population (21.4% adjusted for selection bias, 27.8% unadjusted), is at least as high as, if not higher than, previous epidemiologic studies of community samples.¹⁴,¹⁵ Higher prevalence could be explained by several differences in methodology between the current study and previous studies.

First, this study excluded members younger than 18 and older than 65 years. Individuals in these age categories are less likely to be actively having migraine headaches,¹ but they may have been included in other study populations. Second, follow-up exams by neurologists resulted in a migraine diagnosis for some individuals who initially screened negative on the mailed assessment packet. Failing to identify this group would result in lower estimates of prevalence. Conversely, the inclusion of a structured headache interview administered by neurologists eliminated a diagnosis for participants who appeared to have migraine headaches but actually had other types of headaches.

Third, the higher rates of return of the mailed assessment packet by female members may have inflated the migraine prevalence. Finally, since this study was conducted in a single, fairly homogeneous clinic of a managed care organization, a replication study with a larger sample size and a more heterogeneous population is warranted to determine the generalizability of the results.
More than half of these individuals had never been told they had migraine headaches by a health care professional despite the fact that most reported having had migraine headaches for many years, having experienced real impairment, and having had health insurance coverage. This is cause for concern, and although this study was performed in 1999, under-recognition and under-diagnosis of migraine continue to be problems today.15

Increased public education and physician education about the symptoms and accurate diagnosis of migraine headache are urgently needed, as are simple and effective screening methods to identify patients with migraine in the family practice setting. Application of International Headache Society diagnostic criteria for migraine would be complex in this setting. However, diagnosis could be facilitated by simpler and more easily administered screening tools, such as the ones utilized in the current study. Other screens have also been reported to have good sensitivity and specificity.16-23

Limitations of this study include the fact that these data are now 5 years old, although it seems unlikely that the prevalence or burden of migraine in managed care members is less today than it was when these data were collected. We also did not measure costs and did not calculate the financial burden of migraine. We found that previously undiagnosed migraine patients reported pain, interference with activities of daily living, and hours of missed work in similar proportion to previously diagnosed migraine patients. This suggests a potential opportunity for diagnosis and treatment of undiagnosed patients; we did not, however, assess if this potential opportunity could be fulfilled in undiagnosed migraine patients. Use of a structured screening interview such as the one used in this study may increase the identification and treatment of previously undiagnosed patients. A study identifying and treating previously undiagnosed migraine and examining the impact of treatment on patient distress, disability, and financial burden would be instructive.

In this study, previously diagnosed migraineurs did not differ from previously undiagnosed migraineurs on 3 of 4 outcome measures but did have a higher proportion of patients reporting moderate or greater levels of distress. This finding may suggest that distress more than impairment drives migraineurs to seek help from the health care system. However, undiagnosed and diagnosed migraineurs had similar, elevated levels of severity, impairment, and missed work time. Therefore, the reasons for not seeking diagnosis or treatment must be more complex than milder symptoms or less impairment (though this similarity could be the result of previously diagnosed migraineurs’ having already received treatment).

The high levels of impairment and disease severity in diagnosed migraineurs also highlights undertreatment of migraine, which is still a relevant issue today. Evidence-based guidelines for the prevention and management of migraine have been published by the American Academy of Neurology (AAN) and others to assist family practitioners in generating algorithms that are appropriate for their practices.24-25 Current treatment algorithms recommend triptans for those with moderate-to-severe migraines or poor responses to nonsteroidal anti-inflammatory drugs.6,24-26 and triptan use reduces functional disability27-32 and is cost effective.33,34 Preventative therapies identified by AAN as having the highest level of evidence-based efficacy and safety include antiepileptics (divalproex sodium/sodium valproate), antidepressants (amitriptyline), and beta-blockers (propranolol or timolol). Cognitive and behavioral treatments such as relaxation training, biofeedback, and cognitive behavior therapy are also recommended by AAN as possible preventative strategies.

Conclusions
The prevalence of migraine was high in this managed care population (34% of women and 19% of men, when unadjusted for selection bias, and 30% of women and 12% for men, when adjusted for probable response bias) compared with published population studies (18% of women and 6% of men). These values are very relevant to the family practice setting, perhaps even more relevant than those of general population studies since our study population comprised individuals who use the health care system. Second, disability was as high in migraineurs who had not been previously diagnosed as it was in previously diagnosed patients. This suggests that reasons for not seeking a diagnosis are more complex than the possibility that those who do not seek treatment have milder pain or disability than those who do seek treatment. Distress may be one factor that influences the decision to seek treatment since distress level was higher among previously diagnosed migraineurs. Finally, improved means for identifying and treating migraine are available and should be used in the managed care setting to the benefit of patients. Increased public and physician education about the symptoms and accurate diagnosis and treatment of migraine headache are needed.

DISCLOSURES
This study was supported, in part, by a grant from Pfizer, Inc.; funding was obtained by authors David J. Katzelnicks and George Sands; Sands is employed by Pfizer, Inc., Katzelnicks and author John H. Greist disclose that they have served as consultants for, participated in the speakers bureau of, and received research support from numerous pharmaceutical organizations, including Pfizer. Authors Kenneth A. Kobak, Monica King, and Mary Dominski disclose no potential bias or conflict of interest relating to this article.

Parts of this manuscript were presented at the American Association for the Study of Headache, 42nd Annual Scientific Meeting, Montreal, Canada, June 23-25, 2000. Kobak served as principal author of the study. Study concept and design were contributed by Kobak, Katzelnicks, Sands, King, and Dominski. Analysis and interpretation of data were contributed by all authors. Drafting of the manuscript was the work of Kobak, Katzelnicks, and King, and its critical revision was the work of Kobak, Katzelnicks, Greist, and Sands. Statistical expertise was contributed by Kobak, Katzelnicks, Greist, and Sands.
APPENDIX A  Sands-Taylor Migraine Questionnaire

INSTRUCTIONS: Please think of the PAST 3 MONTHS when answering these questions.

1. What percent of your migraine headache attacks are associated with head pain that is:
   1a. Mild __________%  
   1b. Moderate __________%  
   1c. Severe __________%  
   (Total should add up to 100%)

SECTION ONE: Mild Headaches
Migraine headache attacks are often associated with certain symptoms in addition to head pain. These include nausea and/or vomiting, increased sensitivity to light and/or sound. The first section deals with migraine headache attacks where the headache PAIN is of MILD severity. Please refer to only those migraine headache attacks where the headache pain is of MILD severity when answering these questions. If none of your headache pains are MILD, that is, if the head pain was moderate or severe in all of them, skip this section and go to Section Two (page 2).

2. In the past 3 months, how many migraine headache attacks have you had where the HEAD PAIN was of MILD severity?
   ❑ 1 None (IF NONE, GO TO Section Two, page 2)
   ❑ 2 1
   ❑ 3 2-3
   ❑ 4 4-5
   ❑ 5 6-8
   ❑ 6 9-12
   ❑ 7 13-18
   ❑ 8 19 or more

3. How long do your migraine headache attacks with MILD HEAD PAIN last on average?
   ❑ 1 Less than 30 minutes
   ❑ 2 31 minutes to 1 hour
   ❑ 3 1 to 2 hours
   ❑ 4 2 to 4 hours
   ❑ 5 4 to 8 hours
   ❑ 6 8 to 12 hours
   ❑ 7 12 to 24 hours
   ❑ 8 More than 24 hours

4. Do your migraine headache attacks with MILD PAIN affect your ability to function at work and/or at home?
   ❑ YES (GO TO Question 5)
   ❑ NO (GO TO Question 6)

5. For the following question, please think about how much your ability to function at work and/or at home is affected by your migraine headache attacks with MILD HEAD PAIN.

   What percent does each item below contribute to your decreased ability to function?
   5a. Head pain __________%
   5b. Increased sensitivity to light __________%
   5c. Increased sensitivity to sound __________%
   5d. Nausea and/or vomiting __________%
   (Total should add up to 100%)

SECTION TWO: Moderate or Severe Headaches
The second section deals with migraines where the headache PAIN is MODERATE OR SEVERE. Please refer to only those migraine headache attacks where the headache PAIN is of MODERATE OR SEVERE severity, that is, if they are all mild, skip this section and go to Section Three (page 4).

6. In the past 3 months, how many migraine headache attacks have you had where the HEAD PAIN was MODERATE OR SEVERE?
   ❑ 1 None (IF NONE, GO TO Section Three, page 4)
   ❑ 2 1
   ❑ 3 2-3
   ❑ 4 4-5
   ❑ 5 6-8
   ❑ 6 9-12
   ❑ 7 13-18
   ❑ 8 19 or more

7. How long do your migraine headache attacks with MODERATE-TO-SEVERE PAIN last on average?
   ❑ 1 Less than 30 minutes
   ❑ 2 31 minutes to 1 hour
   ❑ 3 1 to 2 hours
   ❑ 4 2 to 4 hours
   ❑ 5 4 to 8 hours
   ❑ 6 8 to 12 hours
   ❑ 7 12 to 24 hours
   ❑ 8 More than 24 hours

8. Do your migraine headache attacks with MODERATE-TO-SEVERE PAIN affect your ability to function at work and/or at home?
   ❑ YES (GO TO Question 9)
   ❑ NO (GO TO Question 10)

9. For the following question, please think about how much your ability to function at work and/or at home is affected by your migraine headache attacks with MODERATE-TO-SEVERE HEAD PAIN.

   What percent does each item below contribute to your decreased ability to function?
   9a. Head pain __________%
   9b. Increased sensitivity to light __________%
   9c. Increased sensitivity to sound __________%
   9d. Nausea and/or vomiting __________%
   (Total should add up to 100%)

SECTION THREE: Work and/or Home Impairment
The next three questions are about the past 3 months, not including today.

10. During the past three months, how many hours did you miss from work because of your migraine headache attacks? Include hours you missed on sick days, times you went in late, left early, etc.
    __________ hours

(Continued on next page)
Prevalence and Burden of Illness of Migraine in Managed Care Patients

**APPENDIX A** Sands-Taylor Migraine Questionnaire (continued)

11. During the past three months, how much did migraine headache attacks affect your productivity while you were working? Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If migraine headache attacks affected your work only a little, choose a low number. Choose a high number if migraine headache attacks affected your work a great deal. (Circle a number.)

<table>
<thead>
<tr>
<th>Migraines had no effect on my work</th>
<th>CIRCLE A NUMBER</th>
<th>Migraines completely prevented me from working</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

12. Now think about your regular daily activities (other than your job). This means the usual activities that you do every day, such as work around the house, shopping, child care, exercising, etc.

During the past three months, how much did migraine headache attacks affect your ability to do your daily regular activities? Think about days you were limited in the amount or kind of activities you could do, days you accomplished less than you would like, or days you could not do your regular activities as carefully as usual. If migraine headache attacks affected your daily regular activities only a little, choose a low number. Choose a high number if migraine headache attacks affected your daily regular activities a great deal. (Circle a number.)

<table>
<thead>
<tr>
<th>Migraines had no effect on my daily regular activities</th>
<th>CIRCLE A NUMBER</th>
<th>Migraines completely prevented me from my daily regular activities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
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<td>2</td>
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<td></td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

---

**SECTION FOUR: Family History of Migraine Headache Attacks**

13. Does any relative related to you by blood get similar headaches?  
   - [ ] YES  
   - [ ] NO

**SECTION FIVE: Medications**

Please indicate whether or not you have taken any of the medications below in the PAST 3 MONTHS for migraine headache attacks and how much relief you obtained from each one.

**OVER-THE-COUNTER MEDICATIONS**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Have you taken this medication?</th>
<th>If taken, indicate here (by checking the box) how much RELIEF obtained.</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. Advil</td>
<td>[ ] YES [ ] NO</td>
<td>None [ ] Some [ ] A lot [ ] Complete [ ]</td>
</tr>
<tr>
<td>15. Aleve</td>
<td>[ ] YES [ ] NO</td>
<td>a. [ ] b. [ ] c. [ ] d. [ ]</td>
</tr>
<tr>
<td>16. Aspirin</td>
<td>[ ] YES [ ] NO</td>
<td>a. [ ] b. [ ] c. [ ] d. [ ]</td>
</tr>
<tr>
<td>17. Excedrin</td>
<td>[ ] YES [ ] NO</td>
<td>a. [ ] b. [ ] c. [ ] d. [ ]</td>
</tr>
<tr>
<td>18. Excedrin Migraine</td>
<td>[ ] YES [ ] NO</td>
<td>a. [ ] b. [ ] c. [ ] d. [ ]</td>
</tr>
<tr>
<td>19. Ibuprofen (200 mg tablets)</td>
<td>[ ] YES [ ] NO</td>
<td>a. [ ] b. [ ] c. [ ] d. [ ]</td>
</tr>
<tr>
<td>20. Motrin</td>
<td>[ ] YES [ ] NO</td>
<td>a. [ ] b. [ ] c. [ ] d. [ ]</td>
</tr>
<tr>
<td>21. Nuprin</td>
<td>[ ] YES [ ] NO</td>
<td>a. [ ] b. [ ] c. [ ] d. [ ]</td>
</tr>
<tr>
<td>22. Tylenol</td>
<td>[ ] YES [ ] NO</td>
<td>a. [ ] b. [ ] c. [ ] d. [ ]</td>
</tr>
<tr>
<td>23. Other OTC medicines</td>
<td>[ ] YES [ ] NO</td>
<td>a. [ ] b. [ ] c. [ ] d. [ ]</td>
</tr>
<tr>
<td>Which ones? (list)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued on next page)
### APPENDIX A

#### Sands-Taylor Migraine Questionnaire (continued)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Have you taken this medication?</th>
<th>If taken, indicate here (by checking the box) how much RELIEF obtained.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Some</td>
</tr>
<tr>
<td>24. Amerge</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>25. Cafergot</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>26. Demerol</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>27. Dihydroergotamine (DHE) injection</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>28. Fioricet/Fiorinal</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>29. Ibruprofen (600 mg tablets)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>30. Imitrex (injection)</td>
<td>☐</td>
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</tr>
<tr>
<td>31. Imitrex (oral)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>32. Imitrex (nasal)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>33. Maxalt (oral)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>34. Maxalt (wafer)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>35. Midrin</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>36. Migranal</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>37. Percocet/Percodan</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>38. Stadol</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>39. Tylenol with codeine</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>40. Vicodin</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>41. Wigraine</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>42. Zomig</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>43. Other prescription drugs</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Which ones? (list)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>b.___________________</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
APPENDIX B  Migraine Severity Scale

We want to learn about the severity of your migraine headaches during the last three months.

When answering these questions, please refer only to your migraine headaches. Migraine headaches meet the following definition: migraine headaches last at least four hours and are associated with at least two of the following symptoms:

1) pain starting on one side of your head;
2) a throbbing or pulsating feeling in the head;
3) nausea or vomiting;
4) light or sound being more bothersome;
5) changes in vision or seeing sparkling lights;
6) numbness or tingling of your hand, arm, or face; or
7) headaches that are made worse by routine physical activity, such as walking up stairs.

Please rate only those migraine headaches that you have had in the past three months.

1. In the past three months, have you had any migraine headaches, that is, headaches that had at least two symptoms that we just described?
   - Yes
   - No (If no, GO TO #7)

2. How many migraine headaches (as just described) have you had in the past three months?
   - None
   - 1-2
   - 3-4
   - 5-6
   - 7-10
   - 11 or more

3. During the past three months, please rate separately how long your worst, your usual, and your mildest migraine headaches last.

<table>
<thead>
<tr>
<th>Worst Headache (3a)</th>
<th>Usual Headaches (3b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ 1  Less than 2 hours</td>
<td>☐ 1  Less than 2 hours</td>
</tr>
<tr>
<td>☐ 2  2-4 hours</td>
<td>☐ 2  2-4 hours</td>
</tr>
<tr>
<td>☐ 3  5-8 hours</td>
<td>☐ 3  5-8 hours</td>
</tr>
<tr>
<td>☐ 4  9-12 hours</td>
<td>☐ 4  9-12 hours</td>
</tr>
<tr>
<td>☐ 5  12-24 hours</td>
<td>☐ 5  12-24 hours</td>
</tr>
<tr>
<td>☐ 6  24-48 hours</td>
<td>☐ 6  24-48 hours</td>
</tr>
<tr>
<td>☐ 7  Over 48 hours</td>
<td>☐ 7  Over 48 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mildest Headache (3c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ 1  Less than 2 hours</td>
</tr>
<tr>
<td>☐ 2  2-4 hours</td>
</tr>
<tr>
<td>☐ 3  5-8 hours</td>
</tr>
<tr>
<td>☐ 4  9-12 hours</td>
</tr>
<tr>
<td>☐ 5  12-24 hours</td>
</tr>
<tr>
<td>☐ 6  24-48 hours</td>
</tr>
<tr>
<td>☐ 7  Over 48 hours</td>
</tr>
</tbody>
</table>

4. How much do your typical or usual migraine headaches interfere with your everyday activities?
   - No interference
   - Slight interference with social or occupational activities, but overall performance not impaired (e.g., may skip a social activity or put off some work activity but perform most work activities)
   - Definite interference with social or occupational performance, but still manageable (e.g., attends social activities but participates less than usual, definite decrease in work performance)
   - Causes substantial impairment in social or occupational performance (e.g., does not attend important social activities; leaves work or stays home from work)
   - Extreme, incapacitating (requires bed rest)

5. How much distress do your typical or usual migraine headaches cause you?
   - None
   - Mild, infrequent, and not too disturbing
   - Moderate, frequent, and disturbing, but manageable
   - Severe, very frequent, and very disturbing
   - Extreme, near constant, and disabling distress

6. How much control do you have over your migraine headaches? How successful are you in stopping them once you feel one coming on, for example, with medication, bed rest, relaxation, or other action?
   - Always
   - Usually
   - Sometimes
   - Rarely
   - Never

7. How long has it been since you’ve had your last migraine headache?
   - More than 3 months (ANSWER #7b)
   - More than 1 month (GO TO #8)
   - More than 2 weeks (GO TO #8)
   - More than a week (GO TO #8)
   - Less than a week (GO TO #8)

7b. Please indicate the date you had your last migraine headache. If you can’t remember, just make your best estimate.

   _____/_____/______ (date of last migraine)

8. How long have you had migraine headaches?
   - Less than 6 months
   - 7 to 12 months
   - 13 months to 2 years
   - 25 months to 4 years
   - More than 4 years but less than 10
   - 10 years or more
### Headache Specialist Diagnostic Patient Interview

**Instructions:** Initially, consider how many types of headaches the patient may have. Then, answer the following questions based on the patient’s migraine headaches. If migraine headaches are not present in this patient, then answer the questions based on their most severe and disabling headaches. On page 3, please evaluate patient for migraine without aura and migraine with aura as it is possible for patient to be diagnosed with neither, either, or both. Please check an answer for all questions in order to collect the most accurate data possible.

#### LOCATION OF HEADACHES

1. **Yes ☐ No ☐**
   1) Are the headaches located more on one side or the other?
2. **Yes ☐ No ☐**
   2) Do the headaches ever begin on the other side?

#### QUALITY OF HEADACHE

3. **Yes ☐ No ☐**
   3) Do you have more than one type of headache? If yes, please describe the most severe and disabling headache by answering the following questions.
   4. **Yes ☐ No ☐**
      4) Do you have nausea and/or vomiting with this type of headache?
      5. **Yes ☐ No ☐**
         5) Please describe the type of pain associated with your headache:
         5a. **Yes ☐ No ☐**
            5a) Throbbing?
         5b. **Yes ☐ No ☐**
            5b) Stabbing?
         5c. **Yes ☐ No ☐**
            5c) Pressure?
         5d. **Yes ☐ No ☐**
            5d) Tightness?

6) Please rate the average severity of your most severe and disabling headaches from 0 to 10.

```
| No Headache | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Most Severe Pain |
```

7. **Yes ☐ No ☐**
   7) Do odors or strong smells bother you more than usual during the headaches?
8. **Yes ☐ No ☐**
   8) Does sound/noise/music bother you more than usual during the headaches?
9. **Yes ☐ No ☐**
   9) Does exercise or movement worsen your headaches?
10. **Yes ☐ No ☐**
    10) Do you have any numbness or tingling in your arms or legs during your headaches? (If yes, explore timing of onset.)
11. **Yes ☐ No ☐**
    11) Do you have any weakness (decreased strength) in your arms or legs during your headaches?

#### QUALITY AND DURATION OF HEADACHE

12. ___ months
(If not converting to months, indicate # of years x 12)

13. ___ per month
14. ___ hours

#### ASSOCIATED SYMPTOMS

15. **Yes ☐ No ☐**
    15) Do you ever know that you are going to have a headache before you have one?
16. **Yes ☐ No ☐**
    16) Do you experience increased sensitivity to light?
17. **Yes ☐ No ☐**
    17) Does anything trigger or worsen your headaches?
18. **Yes ☐ No ☐**
    18) Do you see flashing lights or have any changes in your vision during or after your headaches?
19. **Yes ☐ No ☐**
    19) Do you have other symptoms with your headache?
20. **Yes ☐ No ☐**
    20) Do your parents, siblings, or children have similar headaches?
21. **Yes ☐ No ☐**
    21) Do your parents, siblings, or children have headaches associated with nausea and/or vomiting?
22. **Yes ☐ No ☐**
    22) What relieves your headaches?
22a. **Yes ☐ No ☐**
      22a) Resting in a dark or quiet room?
22b. **Yes ☐ No ☐**
      22b) Sleep?
22c. **Yes ☐ No ☐**
      22c) Vomiting?
22d. **Yes ☐ No ☐**
      22d) Taking an over-the-counter medication?
22e. **Yes ☐ No ☐**
      22e) Taking a prescription medication?
22f. **Yes ☐ No ☐**
      22f) Other?
22g. **Yes ☐ No ☐**
      22g) Nothing?
23. **Yes ☐ No ☐**
    23) Do you need/take medication to control your headaches? If yes, please list the number of pills or capsules you take per month for each medication.
APPENDIX C

Headache Specialist Diagnostic Patient Interview (continued)

**DIAGNOSTIC STUDIES**

24) Have you ever had?

- 24a) MRI
- 24b) CT scan
- 24c) Blood work
- 24d) Spinal tap
- 24e) EEG

If yes to any of the above, please list the clinically relevant findings: _______________________________________________

**INTERNATIONAL HEADACHE SOCIETY (IHS) CRITERIA DIAGNOSTIC CHECKLIST**

1.1 Migraine without aura

**Diagnostic Criteria**

25) At least 5 attacks fulfilling 26-28b

26) Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

27) Headache has at least 2 of the following characteristics:

- 27a) Unilateral location
- 27b) Pulsating quality
- 27c) Moderate or severe intensity (inhibits or prohibits daily activities)
- 27d) Aggravation by walking up stairs or a similar routine physical activity

28) During headache at least one of the following:

- 28a) Nausea and/or vomiting
- 28b) Photophobia and phonophobia

29) At least one of the following:

- 29a) History and/or physical examinations and/or neurological examinations do not suggest one of the following: headache associated with head trauma, vascular disorders, nonvascular intracranial disorders, substances or their withdrawal, nonencephalic infection, metabolic disorder, or disorders of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures.
- 29b) History and/or physical examinations and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations.
- 29c) Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

30) Patient meets diagnostic criteria for migraine without aura?

2.1 Migraine with aura

(Aura as herein used does not necessarily imply that it precedes the headache, nor does it imply any relationship with epilepsy.)

**Diagnostic Criteria**

31) At least 2 attacks fulfilling 32a-32d

32) At least 3 of the following 4 characteristics:

- 32a) 1 or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction
- 32b) At least 1 aura symptom develops gradually over more than 4 minutes, or 2 or more symptoms occur in succession.
- 32c) No aura symptom lasts more than 60 minutes. If more than 1 aura symptom is present, accepted duration is proportionally increased.
- 32d) Headache follows aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with the aura.)

33) At least 1 of the following:

- 33a) History and/or physical examinations and/or neurological examinations do not suggest one of the following: headache associated with head trauma, vascular disorders, nonvascular intracranial disorders, substances or their withdrawal, nonencephalic infection, metabolic disorder, or disorders of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures.
- 33b) History and/or physical examinations and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations.
- 33c) Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

34) Patient meets criteria for diagnosis of migraine with aura?

35) Migraine with aura ☐

Migraine w/o aura ☐
REFERENCES


Costs and Utilization of Triptan Users Who Receive Drug Prophylaxis for Migraine Versus Triptan Users Who Do Not Receive Drug Prophylaxis

LIDA R. ETEMAD, PharmD, MS; WINNIE YANG, PharmD, BCPS; DENISE GLOBE, PhD; ARIE BARLEV, PharmD, MS; and KATHLEEN A. JOHNSON, PharmD, PhD

ABSTRACT

OBJECTIVES: The objectives were 2-fold: (1) to describe the utilization patterns of new users of triptan therapy and (2) to measure the direct (pharmacy and medical) costs of migraine-related health care services in moderate-to-severe migraine patients treated with drug prophylaxis compared with migraine patients who are not treated with drug prophylaxis.

METHODS: A retrospective administrative database study was conducted from the perspective of a managed care health plan. Patients initiating triptan therapy were identified, and utilization in the 12 months following initiation of drug therapy was determined. In addition, moderate-to-severe migraine patients were identified based on the quantity of triptan medication dispensed. Patients were classified as utilizing or not utilizing migraine prophylaxis. Migraine-specific health services costs incurred in the 12 months following identification were determined. A multivariate ordinary least squares regression model was constructed to determine the impact of the use of drug prophylaxis on total cost. Utilizing the model, the difference in health services costs was predicted for each subject and the average treatment effect was computed.

RESULTS: Thirty-nine percent of new triptan users received only 1 triptan claim during the 12-month follow-up period, accounting for 11.5% of the total triptan costs incurred by the health plan for this cohort. For new triptan users, triptan use in the first or second quarter was correlated with triptan use in the entire 12-month follow-up period (r = 0.187 and 0.279, respectively). The mean migraine-related pharmacy cost per patient during the follow-up was $871; however, continuous users had mean costs ($1,505) nearly 3 times the mean costs for patients who are not treated with drug prophylaxis. Migraine-specific health services costs were identified based on the quantity of triptan medication dispensed. Patients were classified as utilizing or not utilizing migraine prophylaxis. Migraine-specific health services costs in the 12 months following identification were determined. A multivariate ordinary least squares regression model was constructed to determine the impact of the use of drug prophylaxis on total cost. Utilizing the model, the difference in health services costs was predicted for each subject and the average treatment effect was computed.

CONCLUSION: High utilizers of migraine therapy can be identified early in treatment. Drug prophylaxis for migraine is cost saving, and an intervention program that increases the use of migraine prophylaxis in potential candidates could be cost beneficial.

KEYWORDS: Migraine, Prophylaxis, Economics, Cost, Managed care

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M migraine is a chronic, episodic disorder that interrupts the patient's ability to function and decreases quality of life. It affects 17.6% of females and 5.7% of males in the United States, occurring most commonly between the ages of 25 and 55. The economic burden of migraine includes both direct and indirect costs. The direct costs are those that are experienced by the patient or the third-party payer resulting from physician office visits, emergency room or urgent care center visits, medications, diagnostic tests, and hospitalizations. Patients and employers also incur indirect costs as a result of missed days of work, decreased productivity while experiencing a migraine, and decreased quality of life.

Annual estimates for the direct costs of migraine care in the United States in 1994 have been estimated at approximately $1 billion. In 1989 and 1990, managed care patients with migraine incurred an average cost of $145 per member per month (PMPM) as opposed to $89 PMPM for those patients without migraine. Even though this time period was prior to the introduction of the triptan medications, these patients generated 3 times as many pharmacy claims as the comparison group. A study of the Idaho Medicaid population in 1998 found that migraine patients, on average, incurred $2,844.67 in prescription claims per year as compared with $998.80 for controls matched on age, sex, and residence.

Utilization of health care services is another method to assess the economic impact of migraine. Joish et al. also found that physician visit, hospital, and outpatient hospital claims were significantly higher in migraine patients. In 1994, physician office visits accounted for the greatest proportion (60%) of treatment costs, while prescription medications made up almost all of the remaining costs (30%).

The severity of attacks varies across migraine patients and can vary even across attacks within one patient. Migraine attacks may range from mild, treatable with simply over-the-counter medications, to so severe that the patient requires a day or more of bed rest. Treatment, therefore, can be complicated and must be individualized. Research analyzing migraine costs by severity level is limited; however, patients with greater severity of migraines show higher rates of consultations. Severity is generally determined by frequency of headaches, pain intensity, disability, days missed from work, and days of impaired work function.

Migraine prophylaxis may be indicated in patients with frequent or severe episodes. It has been suggested that patients experiencing more than 2 attacks per month are candidates...
for prophylaxis. Consensus guidelines for initiation of prophylaxis have not been established. As with acute therapy, the decision to incorporate pharmacologic prophylaxis in a migraineur’s regimen is individualized, based on the severity and frequency of attacks and the comorbid conditions of each patient. Medications used for prophylaxis include beta-blockers, tricyclic antidepressants, valproic acid and derivatives, selective serotonin reuptake inhibitor (SSRI) antidepressants, nonsteroidal anti-inflammatory drugs, and calcium channel blockers. The American Academy of Neurology published migraine treatment guidelines in 2000 that classified the various migraine prophylaxis drugs into 5 categories based on the evidence of efficacy and the incidence of side effects for each drug. Amitriptyline, divalproex, propranolol, and timolol were classified as “Group 1” agents: medications with proven high efficacy and mild-to-moderate adverse events.

Since the introduction of the “triptan” class of medications in the early 1990s, research efforts in migraine have focused on the development of appropriate treatment strategies using this efficacious, yet comparatively expensive, class of medications. Although there has been much research on the cost-effectiveness of sumatriptan therapy, there has been relatively little work done in the area of cost-effectiveness or cost benefit of migraine prophylaxis, presumably because most are now available generically and are relatively inexpensive. A model developed by Steiner in 1995 assesses the cost-effectiveness of migraine prophylaxis but relies heavily on many assumptions. Adelman et al. developed a model to calculate the minimum number of migraine attacks per month a patient would need to experience for different types of prophylaxis to be cost effective. This method, however, is individualized per patient and would require alteration and population assumptions in order to be applied in a systematic manner in a managed care population.

In addition, there is little research in the area of utilization patterns of triptan users. Characterizing triptan utilization patterns of patients receiving this type of therapy would help to inform the development of disease management programs. Disease management programs may be most efficient when it is possible to identify potentially high utilizers of pharmaceuticals early in drug therapy since these patients may benefit most from drug prophylaxis of migraine. Therefore, information on the feasibility of early identification of high utilizers would augment a disease management intervention.

This study examined the pharmacy and medical utilization and costs of migraine patients in a managed care population and compared health services utilization trends of patients who are treated with prophylaxis with those who might be candidates but do not receive migraine prophylaxis. Triptan use patterns following initiation are evaluated to determine whether potential high utilizers may be identified early in therapy when intervention may be most cost effective. Potential differences in cost among prophylaxis groups was determined to aid in the development of quality improvement initiatives.

### Methods

#### Study Design

A retrospective claims analysis was performed utilizing pharmacy, medical, and eligibility databases from a large managed care health plan with more than 2 million members. The health plan used in the study was a mix of health maintenance organization (HMO, 40%) and preferred provider organization (PPO, 60%) health plans located in the western United States.

#### Patient Populations

Figure 1 illustrates the selection process used to define the patient populations. Commercial enrollees between the ages of 18 and 65 years who had at least 1 migraine-specific prescription claim during the time period of July 1, 1998, to May 31, 2000, were identified. Migraine-specific medications used for the purpose of identifying migraine patients included ergotamine products, isomethypene combination products, methysergide, sumatriptan, zolmitriptan, naratriptan, and rizatriptan. The first migraine-related claim (either pharmacy or medical) was identified as the index claim. Patients who did not have continuous eligibility for the health plan for the 6 months prior to and the
12 months following the index claim were excluded from the analyses. Two patient cohorts were then identified using the criteria described below.

The first analysis cohort (A) was a subset of patients who were newly started on triptan therapy. This cohort included patients who received a triptan medication as the index pharmacy claim. Patients receiving a migraine-specific medication during the 6 months prior to the index claim were excluded from this cohort. Prescription medication use in the 12 months following the index claim was determined and analyzed in order to characterize migraine-related pharmacy use in new utilizers of triptan medications.

The second analysis cohort (B) represents migraine patients and includes patients who had either (1) an International Classification of Diseases, 9th edition (ICD-9) code for migraine (346.0-346.2, 346.8, and 346.9) and at least 1 migraine-specific medication claim or (2) 2 or more migraine-specific medication claims during the specified time period. Migraine-specific medication claims were identified by the First Data Bank national drug data file definition using Smart-key code 0272 and included ergotamine products, isometheptene combination products, methysergide, sumatriptan, zolmitriptan, naratriptan, and rizatriptan (almotriptan, frovatriptan, and eletriptan were not approved for use in the United States at the time of this study).

Definition of Prophylaxis Subgroup

Patients in the second analysis cohort (B) were used to identify the subgroups used for the prophylaxis analysis. Patients receiving drug prophylaxis and potential candidates for prophylaxis were identified. The definition for potential candidates for prophylaxis was conservative in order to minimize potential bias. Patients who were potential candidates for prophylaxis were identified based on the suggested criteria that recommends use in patients with greater than 2 migraine attacks per month. Patients who were determined to be candidates could not have a claim for a medication used for prophylaxis in the 12 months following their index date and were required to possess triptan medication in sufficient quantities to treat more than 18 headaches in the first 6 months following the index migraine-related claim.

Because of the different dosing schedules of the triptan medications, the quantity of triptan medication received was standardized using a proxy unit, the triptan equivalent (TE). Each TE was equal to the maximum quantity recommended to treat 1 headache episode for each triptan medication. Table 1 depicts the quantities for each medication that were considered equivalent to 1 TE. Patients possessing greater than 18 TEs in the first 6 months following the index claim were considered potential candidates for migraine prophylaxis medication. The use of these criteria selected only those with frequent migraines (moderate-to-severe migraineurs) for the migraine prophylaxis candidates group.

Patients were considered to be on migraine prophylaxis if they had at least 2 claims for medications in the same class in any 3-month period during the 12-month follow-up period. Migraine prophylaxis medications included tricyclic antidepressants, SSRI antidepressants, mirtazapine, venlafaxine, phenelzine, beta-blockers, calcium-channel blockers, valproic acid and derivatives, gabapentin, tiagabine, topiramate, and carbamazepine. Exclusion criteria were applied in order to increase the likelihood that patients were using the medication for migraine prophylaxis versus another nonmigraine indication. Patients who received the prophylaxis medication prior to the migraine index date or who had an ICD-9 code for a disease state related to the prophylaxis medication were dropped from the analysis (i.e., patients receiving a beta-blocker/calcium channel blocker who had a diagnosis in medical claims for hypertension [ICD-9 code of 401-405, 410, 411, 413, 414] or patients receiving a tricyclic/SSRI who had a claims diagnosis of depression [ICD-9 code of 296.2, 296.3] were excluded).

In order to increase the likelihood that patients in the prophylaxis comparison group experienced migraine headaches in the same frequency as those patients identified as potential prophylaxis patients, an additional exclusion criterion was applied. The number of TEs received during the period from the index date to the date of prophylaxis initiation was calculated. Patients were excluded if they received, on average, fewer than 2 TEs per month during this time period.

### Variable Definitions

Migraine-related medical service utilizations were those associated with an ICD-9 code for migraine (346.0-346.2, 346.8, and 346.9). Costs were calculated as the amount paid by the health plan and did not include patient copays or deductibles. Patient comorbidity was determined by ICD-9 codes obtained from medical claims and was used in the identification of the subset of patients who were using prophylaxis medications.

Patients were defined as having used a migraine-specific medication other than a triptan if they had at least 1 claim for an ergotamine product, isometheptene combination product...
Patients in the migraine cohort were classified as either newly starting migraine therapy (of any type, not just triptan therapy) or continuous users. New starts were defined as those patients who did not have a migraine-specific pharmacy claim in the 6 months preceding the index claim. By definition, continuous users had an index date between July 1, 1998, and December 31, 1998; however, the index date for new starts ranged from July 1, 1998, to May 31, 2000.

**Analyses**

Triptan utilization statistics were calculated for those patients identified in the new triptan users cohort. The number of patients who received only 1 prescription for a triptan medication was calculated. The total cost of migraine-specific medications received by the cohort in the 12-month follow-up was determined. The quantity of TE received in the first quarter, second quarter, and 12 months following the index triptan claim was determined. The correlation between consumption of triptan medication early in treatment (in the first and second quarters) and the entire follow-up was calculated.

Descriptive demographic and utilization statistics were compared between the prophylaxis and prophylaxis candidate subgroups using t tests and chi-square tests where appropriate. All analyses were conducted using SAS version 8.0 (SAS Institute, 2001).

The average treatment of migraine drug prophylaxis was also determined using a method that incorporated ordinary least squares (OLS) regression analysis. Since cost data had no upper bound and the distribution was therefore skewed to the right, the log of the cost was used as the outcome variable. Taking the log of the cost resulted in a more normally distributed variable. OLS regression analysis was then used to determine the association of drug prophylaxis use with migraine-related health care costs in the follow-up period for the subset of patients identified as either using prophylaxis or being candidates for prophylaxis. The following variables were used in the model: use of drug prophylaxis, sex, age, continuous user, use of a nontriptan migraine-specific medication, number of unique migraine-specific medications used, and concurrent use of 2 or more unique triptans.

Using the model estimated by the OLS regression, a treatment effect for each patient was calculated by retransforming the logged equation (including the sample variance as a correction term) and predicting total costs for each patient utilizing his or her individual parameters. The treatment effect (TxE) for each patient was calculated as the total predicted migraine cost when the variable indicating prophylaxis use was set equal to 1 minus the total migraine cost predicted when it was set equal to 0. The average treatment effect (ATE) is then the mean of the treatment effects for the entire population:

\[
\text{ATE} = \frac{1}{n} \sum (\text{TxE})
\]

**Results**

**New Triptan Users**

A total of 5,294 patients were identified as having a new triptan prescription claim during the study time period (Cohort A).

<table>
<thead>
<tr>
<th>Percentage of Total Triptan Cost Incurred by Cohort A During the Follow-up by Utilization Characteristic</th>
<th>1 Claim Only (39% of Population)</th>
<th>&gt; 36 TE (13% of Population)</th>
<th>&lt; 36 TE (48% of Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.5%</td>
<td>49.0%</td>
<td>39.4%</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2** Prediction of 12-Month Utilization With Utilization During the 1st and 2nd Quarter Post-Triptan Initiation (Cohort A)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>1st Quarter Data</th>
<th>2nd Quarter Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation of the number of TEs received in the quarter to the number of TEs received during the entire follow-up</td>
<td>0.187</td>
<td>0.279</td>
</tr>
<tr>
<td>Odds ratio (95% CI) of receiving ≥36 TEs*</td>
<td>8.9 (7.0 - 11.4)</td>
<td>18.1 (12.0 - 27.2)</td>
</tr>
<tr>
<td>% of patients with &gt;36 TEs in the follow-up who had ≥9 TEs during the quarter</td>
<td>26.2%</td>
<td>28.5%</td>
</tr>
</tbody>
</table>

* Odds ratio for patients with ≥9 TEs (triptan equivalents) during the quarter compared with those with < 9 TEs.
Thirty-nine percent of patients received only 1 triptan claim during the 12-month follow-up period, accounting for 11.5% of the total triptan cost incurred by the health plan for this cohort (Figure 2).

The number of patients exceeding 36 TEs (the quantity sufficient to treat greater than 2 migraines per month) during the follow-up year was also calculated. Thirteen percent of new triptan users had greater than 36 TEs and accounted for 39% of the total triptan cost incurred by the cohort.

The amount of TEs received in either of the first or second quarters was correlated with the total number of TEs received in the 12-month follow-up (Table 2). Patients who received more than 9 TEs in the first 3 months following their index date were 8.9 (95% CI, 7.0-11.4) times more likely to exceed 36 TEs in the 12-month follow-up than those who received fewer than 9. Combining the first- and second-quarter data resulted in an increased correlation coefficient (0.284) as compared with either quarter alone; however, using data from either quarter correctly identified more than 26% of patients who exceeded 36 TEs in the 12-month period.

Migraine Patients
Demographic and Descriptive Statistics
A total of 8,488 patients were identified as meeting the inclusion criteria. Descriptive statistics for the overall study cohort are given in Table 3. The overall total migraine cost to the health plan per patient during the 1-year follow-up period was $989.00 per person per year (PPPY), with pharmacy costs accounting for the majority of the total costs (88.1%). Continuous users were significantly older than the new users and had significantly greater pharmacy utilization and, consequently, greater total costs.

Prophylaxis versus Prophylaxis Candidates
Table 4 describes the utilization characteristics of the subset of patients included in the prophylaxis analysis. Patients receiving drug prophylaxis were younger than those not receiving prophylaxis. Although the total costs of migraine medications were significantly lower for those receiving drug prophylaxis, those on prophylaxis had more migraine-related hospitalizations and outpatient office visits (which resulted in higher overall medical utilization cost) compared with those not receiving prophylaxis. These differences remained statistically and significantly different when the Wilcoxon rank sum test was performed to test for differences in non-normally distributed variables.

The results of the OLS regression with independent variables included are shown in Table 5. The coefficient on the treatment variable (prophylaxis use) predicts approximately a 21% decrease in total migraine cost for patients who use drug prophylaxis. Retransforming the equation, the predicted average treatment effect of migraine prophylaxis across the population was a $559.71 reduction in total migraine cost (95% CI, $514.28-$607.26) PPPY (in 1998-2001 dollars).
25 and 55 years. Although the present study had a higher percentage of females than previously reported, the previous study was a population-based study whereas the present study occurs in a treated cohort. Since women are known to seek medical treatment more often than men, this finding is not surprising and probably reflects real-world health plan treatment populations.

The migraine-related cost incurred by this population is consistent with other studies. In 1999, migraineurs in a managed care population in western Pennsylvania had an average of $97.85 per PPPM in migraine-related costs prior to a triptan quantity limit intervention. This is similar to the $989 in migraine-related health care costs PPPY ($82.42 PPPM) in our study. Unlike the study conducted by Hu et al., the pharmacy costs in our study dominated the medical costs, accounting for 88.1% of the overall cost. Due to the definition of a migraine-related medical visit (ICD-9 code for migraine in the first 2 diagnosis fields), it is possible that the true medical costs may have been underestimated due to probable undercoding of medical service claims for migraine. However, with a proportion this high, it is reasonable to conclude that pharmacy costs represent a majority of the cost of migraine therapy and that the potential under-estimate of outpatient costs would not significantly bias the total cost estimates.

Continuous triptan users utilized considerably more migraine pharmacy services than the patients newly initiating therapy. It could be postulated that this group of patients is more refractory to migraine medications. Further characterization of utilization patterns in this subset could lead to greater insight into the prevalence of dose and quantity escalation and the possibility of rebound headaches.

Predicting which patients will be high utilizers early in triptan therapy appears to be feasible. The amount of triptan used in the first 6 months following triptan initiation is correlated with the amount used in the entire 12-month period. Identification and implementation of quality assurance programs in potential high users early in treatment can be beneficial to managed care plans in reducing migraine cost burden and to patients in modifying the burden of migraines.

The majority of the migraine patients identified by medical claims with a migraine ICD-9 were new starts (78.8%). For new-start patients with a medical claim as the index claim, 17% did not receive a triptan medication in the follow-up period and 35.6% received only 1 triptan claim. Patients who received only 1 triptan claim may have been prescribed the medication to aid in diagnosis of migraine versus tension headaches (since tension headaches do not respond to triptan medications). Due to the high cost of triptan medications, however, this is not a preferred method of differential diagnosis of headaches. Since this represents a substantial portion (35.6%) of the patients identified by index medical claims, prescribers with multiple patients in this group may benefit from an intervention program that outlines the International Headache Society criteria for migraine diagnosis.

Overall, patients receiving drug prophylaxis had lower migraine-related costs than those using acute treatment alone. This information is useful to any health care payer seeking to

### TABLE 4: Demographic and Utilization Characteristics of Subjects Who Received Drug Prophylaxis Versus Subjects With No Drug Prophylaxis but Who Are Potential Candidates

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis</th>
<th>(SD)</th>
<th>No Prophylaxis</th>
<th>(SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (total = 1,124)</td>
<td>286</td>
<td></td>
<td>838</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>42.39 (10.1)</td>
<td></td>
<td>45.13 (8.8)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% female</td>
<td>82.9%</td>
<td></td>
<td>80.3%</td>
<td></td>
<td>0.3832</td>
</tr>
<tr>
<td>Median number of standardized triptan equivalents received</td>
<td>36</td>
<td></td>
<td>45</td>
<td></td>
<td>0.0335</td>
</tr>
<tr>
<td>Total number of migraine ER visits per 100 patients per year</td>
<td>23.43 (267.2)</td>
<td></td>
<td>4.06 (30.7)</td>
<td></td>
<td>0.2223</td>
</tr>
<tr>
<td>Total number of migraine hospitalizations per 100 patients per year</td>
<td>5.59 (38.0)</td>
<td></td>
<td>0.48 (6.9)</td>
<td></td>
<td>0.0242</td>
</tr>
<tr>
<td>Total number of migraine office/outpatient visits per 100 patients per year</td>
<td>185.66 (647.9)</td>
<td></td>
<td>67.66 (188.4)</td>
<td></td>
<td>0.0026</td>
</tr>
<tr>
<td>Total Rx migraine cost (PPPY)</td>
<td>$1,691.84 (1,735.8)</td>
<td></td>
<td>$2,011.71 (1,738.7)</td>
<td></td>
<td>0.0073</td>
</tr>
<tr>
<td>Total cost of migraine ER visits (PPPY)</td>
<td>$17.14 (194.06)</td>
<td></td>
<td>$2.23 (19.7)</td>
<td></td>
<td>0.1957</td>
</tr>
<tr>
<td>Total cost of migraine hospitalizations (PPPY)</td>
<td>$39.23 (383.79)</td>
<td></td>
<td>$8.15 (210.58)</td>
<td></td>
<td>0.1957</td>
</tr>
<tr>
<td>Total cost of migraine office/outpatient visits (PPPY)</td>
<td>$163.81 (714.45)</td>
<td></td>
<td>$54.06 (204.11)</td>
<td></td>
<td>0.0109</td>
</tr>
<tr>
<td>Total cost of migraine medical utilization (PPPY)</td>
<td>$219.74 (1193.56)</td>
<td></td>
<td>$65.18 (308.09)</td>
<td></td>
<td>0.0312</td>
</tr>
<tr>
<td>Total migraine costs (PPPY)</td>
<td>$1,911.57 (2371.61)</td>
<td></td>
<td>$2,076.89 (1,767.00)</td>
<td></td>
<td>0.2804</td>
</tr>
</tbody>
</table>

* Potential candidates received at least 18 triptan equivalents in the 6-month postindex period and received no migraine prophylaxis medication. ER = emergency room; Rx = prescription; PPPY = per patient per year for 1998-2001 costs.
reduce migraine-related costs. Any intervention to increase the use of migraine prophylaxis in appropriate patients that costs less than $559.71 PPPY in which drug prophylaxis is initiated has the potential to be cost saving.

Nearly 10% of the total population and 8% of the new triptan users fit the criteria for inclusion in the prophylaxis candidate subgroup. Since it is possible to identify potential prophylaxis candidates during the first 6 months following initiation of therapy, a migraine intervention program is feasible in the early stages of treatment.

Patients for this study were identified over a period of 23 months. During this time period, migraine therapy improvement initiatives in the form of physician letters to increase the use of migraine prophylaxis were undertaken by the health plan. While these types of initiatives may normally lead to possible introduction of bias, the majority of patients for this study (75%) were identified in the first 6 months of the study, alleviating this potential issue. In addition, the month of subject identification was also entered into the multivariable regression and was found to be nonsignificant, indicating that any temporal treatment pattern changes were not significant predictors of cost.

This study examined the potential economic impact of drug prophylaxis in a managed care migraine population and the feasibility of intervening early in therapy. Further study to characterize patients who receive migraine drug prophylaxis may provide additional information to the design of a clinical intervention program.

**Study Limitations**

This study only takes into account direct costs to the health plan and does not include any higher or lower costs due to beneficial effects from reduced disability or detrimental side effects of drug prophylaxis for migraine. Patients who require bed rest while experiencing a migraine attack may feel that the reduced direct costs understate the overall benefit since the reduction in number and severity of migraine episodes allows the patients to be more productive and have a higher quality of life. Others who experience less-severe migraine episodes may believe that the side effects of the medications for prophylaxis are troublesome and offset any reduction in number of migraine episodes. Further work to incorporate these aspects into a cost-effectiveness study would be beneficial from a societal standpoint.

This study has the limitations associated with any retrospective claims database analysis. Due to miscoding or absence of coding, some medical claims may be inappropriately classified as non-migraine-related when migraine care was actually provided. Patients may have an office visit for a routine check-up and also receive a prescription for a triptan medication without the visit reflecting a diagnosis code for migraine. In addition, patients may have been receiving a medication for prophylaxis for another indication without a claims diagnosis of that indication appearing during the study period (e.g., SSRIs for depression). This would lead to the inclusion of patients who were not primarily receiving their drug prophylaxis for migraine therapy. However, while we excluded patients in which competing medical indications were present in the claims in order to be methodologically conservative, patients receiving medications with a prophylaxis effect would receive this benefit of the medication regardless of the indication and this should not bias the treatment-effect results.

While claims data allow for the determination of the medications received by patients, they do not allow for determination of how medications were used. This is the principal limitation of claims data analysis, particularly when examining medications that are taken as needed rather than in a prescribed regimen. Additionally, use of over-the-counter medications was not captured. This study included patients who received sufficient quantities of triptans to treat at least 2 migraine attacks per month for the specified time period. While it is possible that patients used greater than 1 triptan equivalent to treat 1 migraine episode, did not use the entire quantity received during the time period outlined, or used medications other than triptans to treat migraine attacks, it is unlikely that these types of patterns differed between the treatment groups studied.

Patient comorbidities were not controlled for in this analysis. Due to the potential of miscoding, in many cases, it is important to adjust for other disease states that may influence health services cost. During model development, we attempted to include dichotomous variables that indicated the presence of disease states that are common comorbidities of migraine headache (e.g., depression). These variables proved to be nonsignificant. This result is most likely due to the fact that only migraine-specific cost was included in the outcome and that this cost was highly driven by migraine-specific drug use. Had total health services cost been utilized as the outcome of interest, controlling for comorbidities might have provided additional information (i.e., resulted in significant coefficients).

**TABLE 5 OLS Regression Analysis of Log Migraine-Related Costs on Prophylaxis Use**

<table>
<thead>
<tr>
<th>Variable</th>
<th>β Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>6.88</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Drug prophylaxis</td>
<td>-0.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Continuous user</td>
<td>0.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Concurrent triptan use</td>
<td>0.29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>0.01</td>
<td>0.0048</td>
</tr>
<tr>
<td>Female</td>
<td>-0.06</td>
<td>0.2501</td>
</tr>
<tr>
<td>Use of nontriptan</td>
<td>-0.11</td>
<td>0.1809</td>
</tr>
<tr>
<td>F statistic</td>
<td>26.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted R²</td>
<td></td>
<td>0.1179</td>
</tr>
</tbody>
</table>

OLS = ordinary least squares.
Medical criteria for prophylaxis initiation have not been uniformly developed and are based on not only migraine frequency but disability as well. Due to the nature of a claims database, qualitative effects of the migraine episodes could not be assessed; therefore, the quantity of triptan medication received was used as a proxy to determine if drug prophylaxis was indicated. This may have inappropriately categorized patients with frequent but less-severe migraines and those with infrequent but extremely debilitating migraines. Although we attempted to control for any variation in migraine severity and frequency by the subgroup definition, it is possible that variations in these factors may not have been fully accounted for.

Since these are real-world data not derived from a randomized, placebo-controlled trial, it is possible that selection bias may have occurred. Physicians may have based treatment decisions on clinical factors that could not be captured in the claims dataset. By implementing strict inclusion criteria, we attempted to control for this. Patients included in the subgroup analysis were similar with respect to triptan consumption prior to the initiation of prophylaxis therapy. To control for selection bias, we conducted 2 additional analyses using a model that included a propensity score and a model based on matched cases. However, the results remained the same, supporting the methodology used and the fact that appropriate inclusion and exclusion criteria were utilized to identify patients that were comparable. This study examined costs and utilization in a managed care health plan that was a mix of HMO and PPO models, and the results may not apply to other health plans.

Finally, this model explains a small proportion (12%) of variation in migraine-related medical cost between migraine patients. There are other factors that influence overall cost in addition to those we were able to determine from a claims dataset.

**Conclusion**

Migraine is a costly disorder for health plans. Identification of utilization characteristics is useful in developing disease management programs aimed at increasing quality patient care and decreasing overall costs. Since there is a strong correlation between use in the first 6 months following triptan initiation and the entire first year of follow-up, it is possible to identify high triptan utilizers early in treatment. Continuing triptan patients are much more costly than new starts. It is therefore potentially valuable to a health plan to identify patients who would benefit from an intervention program early following triptan therapy initiation. Patients receiving greater than 18 TEs in a 6-month period may benefit from the use of migraine drug prophylaxis. Migraine drug prophylaxis is cost-saving ($559.71 per patient in 1998-2001 dollars), and an intervention program that increases the use of migraine drug prophylaxis in potential candidates could be cost beneficial.

**DISCLOSURES**

This study was funded through the support of a fellowship for graduate study and data extraction by Pharmacia Corporation, now part of Pfizer, Inc. Funding was obtained by author Kathleen A. Johnson. Authors Lida R. Etemad and Arie Barlev were Pharmacoeconomic Research fellows sponsored by Pfizer (formerly Pharmacia) and WellPoint, Inc., at the University of Southern California, Los Angeles, at the time of this study. Johnson discloses that she has served as a consultant for WellPoint and BMS Managed Care Information and has received numerous research grants from pharmaceutical, health care, and educational organizations. Authors Winnie Yang and Denise Globe disclose no potential bias or conflict of interest relating to this article.

Etemad served as principal author of the study. Study concept and design were contributed by Etemad, Yang, and Johnson. Analysis and interpretation of data were contributed by Etemad, Yang, and Barlev. Drafting of the manuscript was primarily the work of Etemad, and its critical revision was the work of Globe and Johnson. Statistical expertise was contributed by Etemad and Barlev.

**REFERENCES**

Relationship of Total Health Care Charges to Selective Serotonin Reuptake Inhibitor Utilization Patterns Including the Length of Antidepressant Therapy—Results From a Managed Care Administrative Claims Database

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ABSTRACT

OBJECTIVE: Administrative claims data analysis performed in the early 1990s found lower total medical costs for patients with depression who remained on antidepressant therapy with selective serotonin reuptake inhibitors (SSRIs) for at least 90 days compared with patients who discontinued therapy prior to 60 days. Over the past decade, many changes in the health care system have occurred that might impact the reproducibility of these findings. The purpose of this study was to investigate the association between SSRI utilization patterns and the use of health care services in the managed care environment.

METHODS: A large managed care claims database was used to identify patients receiving 2 or more SSRI prescriptions between June 2001 and December 2002. In order to ensure that patients were newly started on SSRI therapy, patients receiving 2 or more SSRI prescriptions between June 2001 and December 2002 were required to have 6 months of enrollment data prior to their index date, without evidence of antidepressant therapy. Continuous enrollment for 12 months following their index prescription was also required. Patients with schizophrenia, bipolar disorder, or who received antipsychotic medications were excluded from this analysis. Patients were placed into 1 of 5 mutually exclusive antidepressant utilization cohorts: (1) <90 days, (2) ≥ 90 days, (3) titration, (4) partial compliance, and (5) therapy change. Total medical costs, with and without pharmacy costs, were then compared between antidepressant utilization cohorts for 12 months of claims data.

RESULTS: There were 65,753 patients included in the study. Medical charges without pharmacy charges were lowest in the ≥90-day cohort ($5,143) compared with the partial compliance ($5,909, P<0.05), <90-day ($6,289, P<0.001), titration ($6,375, P<0.001), and therapy change ($7,858, P<0.001) cohorts. Differences in total medical charges—without pharmacy charges—were primarily influenced by inpatient charges. The addition of pharmacy charges, including the charges for antidepressants, resulted in total medical charges that were not statistically different for the ≥90-day cohort compared with the <90-day cohort, $7,454 and $7,829, respectively, P=0.006.

CONCLUSION: Medical charges—without pharmacy charges—were lower for patients remaining on antidepressant drug therapy for at least 90 continuous days compared with patients who used antidepressants for less than 90 continuous days, but total health care charges, including pharmacy charges, were not different between the 2 groups.

KEYWORDS: Selective serotonin reuptake inhibitors, Depression, Length of therapy, Compliance, Economic burden, Duration of therapy

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D epression affects between 32.6 and 35.1 million adults in the United States each year, with a lifetime prevalence of 16.2%. The economic burden of depression is estimated at $81.5 billion annually, primarily fueled by losses in productivity and excessive depression relapse rates. An important factor in controlling the clinical and economic manifestations of depression is to promote the effective use of antidepressant therapy.

Clinical practice guidelines stress the importance of adherence to antidepressant therapy for a minimum length of time. In general, these guidelines recommend acute treatment of first-episode depression patients for at least 3 months, followed by continuation of treatment for 6 to 9 months after symptoms have remitted and maintenance treatment for a minimum of 9 months after symptom resolution. Despite treatment recommendations, approximately 28% of patients reportedly discontinue antidepressant therapy within 30 days of initiating treatment. Only 60% of patients remain on therapy for longer than 90 days, and fewer than 50% remain on therapy for 6 or more months.

The clinical benefits associated with antidepressant therapy for a duration specified by treatment guidelines have been documented. These clinical benefits may also result in substantial savings in health care costs. Using data from 1991 to 1993 for 2 selective serotonin reuptake inhibitors (SSRIs), fluoxetine and sertraline, Thompson et al. demonstrated that various patterns of antidepressant use were associated with

Note: An editorial on the subject of this article, “Evidence-Based Medicine: Are SSRIs More Effective Than Placebo and What Length of Therapy Is Enough?” appears on pages 172-76 of this issue.

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An "x" indicates that all subcodes were included.

Note:
Exclusion Diagnoses
Inclusion Diagnoses


<table>
<thead>
<tr>
<th>Inclusion Diagnoses</th>
<th>ICD-9-CM</th>
</tr>
</thead>
<tbody>
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<td>Depression</td>
<td>296.2</td>
</tr>
<tr>
<td>Major depressive disorder, single episode</td>
<td>296.2</td>
</tr>
<tr>
<td>Major depressive disorder, recurrent episode</td>
<td>296.3</td>
</tr>
<tr>
<td>Neurotic depression</td>
<td>300.4</td>
</tr>
<tr>
<td>Depressive disorder, not elsewhere classified</td>
<td>311.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion Diagnoses</th>
<th>ICD-9-CM</th>
</tr>
</thead>
<tbody>
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<td>295.xx</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>296.xx</td>
</tr>
<tr>
<td>Manic disorder, single episode</td>
<td>296.0x</td>
</tr>
<tr>
<td>Bipolar affective disorder, manic</td>
<td>296.4x</td>
</tr>
<tr>
<td>Bipolar affective disorder, mixed</td>
<td>296.6x</td>
</tr>
<tr>
<td>Bipolar affective disorder depressed</td>
<td>296.5x</td>
</tr>
<tr>
<td>Bipolar affective disorder, unspecified</td>
<td>296.7</td>
</tr>
<tr>
<td>Manic-depressive psychosis, other</td>
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</tr>
<tr>
<td>Affective personality disorder, cyclothymic disorder</td>
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</tr>
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</tr>
<tr>
<td>Organic affective syndrome</td>
<td>293.83</td>
</tr>
<tr>
<td>Unspecified affective psychosis</td>
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</tbody>
</table>


Note: An "x" indicates that all subcodes were included.

significant differences in the cost of medical care. The highest costs were found in patients who switched, had augmented therapy, or who discontinued treatment early (i.e., received no more than 60 days of antidepressant therapy during the 12-month follow-up period), while patients who remained on SSRI therapy for ≥90 days had the lowest costs of the 4 groups. Only 10.2% of the 1,200 patients in the study by Thompson et al. continued SSRI therapy for ≥90 days.

It is important to investigate how the length of depression treatment impacts cost within the context of today's environment. Throughout the last 10 years, major changes in the antidepressant, mental health, and broader health care environments have occurred. Specifically, increased awareness of depression as a treatable disease, the introduction of newer SSRIs, and the growth of managed health care all have potentially impacted pharmaceutical treatment patterns and costs of care.

This study examines the association between length of antidepressant therapy and overall health care costs in a large, commercial managed care population. We seek to understand how length of antidepressant therapy and therapy changes are linked with service use in the current health care environment.

## Methods

### Data Source

Medical and pharmacy administrative claims data were extracted from the Pharmetrics Integrated Outcomes Database (Watertown, MA). At the time of data extraction, the Pharmetrics Database contained more than 1.9 billion claims from approximately 64 managed care organizations with 38 million members distributed throughout the United States.

### Sample Selection

Patients who were at least 18 years of age and who had 2 or more pharmacy claims for an SSRI (citalopram, fluoxetine, immediate-release paroxetine, controlled-release paroxetine, or sertraline; note that escitalopram was not available until August 2002) between June 2001 and June 2002 were identified from the database. The index date, defined as the date of the first prescription for an SSRI during this time frame, was ascertained for each eligible patient. There were 3 periods defined for each patient: (1) preindex prescription period—the 6-month period prior to the index date, (2) postindex follow-up period—the 1-year period after the index date, and (3) study period. Based on the preindex and postindex periods, the effective study period for the patients was between January 2001 and June 2003.

In order to ensure that patients were newly started on the current course of SSRI therapy, patients could not have received an antidepressant drug in the preindex period. Patients with schizophrenia (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 295.xx) or bipolar disorder (ICD-9-CM codes 296.0x, 296.4x, 296.6x, 296.5x, 296.7, 296.89, 301.13, 296.80, 293.83, and 296.90), or patients who received an antipsychotic medication during the preindex or postindex period were excluded from this analysis. Patients were also required to be 18 years of age and have a diagnosis of depression (ICD-9-CM codes 296.2, 296.3, 300.4, or 311). Claims data for patients meeting all selection criteria were extracted for 12 months after the index date (postindex period) and placed into cohorts based upon the antidepressant utilization patterns. (See Table 1.)

### Cohort Classification

Patients were placed into 1 of 5 mutually exclusive cohorts determined by antidepressant utilization patterns within 12 months of initiating antidepressant therapy. Initially, patient-level overlapping prescriptions were collapsed into 1 prescription, based on the national drug code of that prescription. Collapsing prescriptions ensures that similar medications prescribed over the same period are not counted twice. Any overlap was added to the end of the collapsed prescription to give a conservative estimate of treatment duration. After this initial collapse of drug claims, the claims were again collapsed across all drug types (tricyclic antidepressant, SSRIs, and bupropion or venlafaxine) to determine days of continuous therapy. Utilization cohorts were chosen based on earlier efforts in this area and are consistent with published guidelines for acute-phase depression care. The cohorts are defined in Table 2.
Comorbidity Assessment
To assess comorbidities across the cohorts, the Charlson Comorbidity Index, with Dartmouth-Manitoba and Deyo modification, was utilized. This index contains 19 categories of comorbidities, primarily defined by ICD-9-CM diagnosis codes. Higher scores represent a higher burden of comorbidity. Charlson index scores for this study were derived by evaluating the presence of various ICD-9-CM codes in the 6-month period before each patient’s index date.

Analysis and Measurement of Outcomes
Once patients were placed into cohorts, health care charges within the 12-month period following their index date were evaluated. Health care expenditures were defined as the total provider submitted charges for (1) physician visits, (2) inpatient hospitalizations, (3) outpatient hospital encounters, (4) emergency department visits, (5) antidepressant prescription medications (6) all prescription medications, and (7) other services (laboratory, radiological, and similar ancillary services). Statistical differences in charges across the patient cohorts were determined by utilizing an analysis of covariance model, controlling for differences in age, gender, presence of anxiety, mental health specialty care, preperiod charges (e.g., care provided by a psychiatrist or mental health professional), and the Charlson Comorbidity Index. Differences in the demographic characteristics across cohorts were assessed by chi-square tests for categorical variables and t tests for continuous variables. The alpha level of statistical significance was preset at 0.05.

Results
Baseline Characteristics
There were 65,753 patients who met all inclusion criteria and were subsequently analyzed for antidepressant utilization patterns. The distribution of patients receiving pharmacy claims for SSRIs included in the analysis was as follows: citalopram 24% (n = 15,771), fluoxetine 23% (n = 15,175), immediate-release paroxetine 24% (n = 16,012), sertraline 29% (n = 18,768), and controlled-release paroxetine <1% (n = 24). As shown in Figure 1, the highest percentage of patients discontinued therapy within 90 days of initiating treatment (36%). Only 16% of patients remained on therapy for >90 days without evidence of a therapy change, titration in dose, or being partially compliant.

Table 3 shows the demographic characteristics of the SSRI cohorts. Patients remaining on SSRI therapy for ≥ 90 days had lower illness severity by the 3 proxy measures (diagnosis for comorbid anxiety disorder [defined as panic disorder, social anxiety disorder, obsessive compulsive disorder, posttraumatic stress disorder, or generalized anxiety disorder], use of mental health specialty care, and the Charlson comorbidity score) compared with the >90-day group. Patients discontinuing therapy within 90 days of treatment tended to be younger than patients in the remaining cohorts, all of whom remained on

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;90 days</td>
<td>Patients not having at least 90 days of continuous therapy after their index date. Patients with more than a 15-day treatment gap between subsequent prescriptions were assumed to have discontinued therapy at the ending date of the prescription prior to the 15-day treatment gap. It was permissible for patients in this group to have dose adjustments or switch antidepressant agents.</td>
</tr>
<tr>
<td>≥90 days</td>
<td>Patients having 90 days or more of continuous therapy. These patients were required to have no gaps in treatment greater than 15 days, no claims for antidepressants other than their index study agent, and no evidence of a titration in SSRI dose.</td>
</tr>
<tr>
<td>Partial compliance</td>
<td>Patients having at least 90 days of continuous therapy, with evidence of one or more 15-day gaps in therapy after 90 days. These patients were also required to have no claims for an antidepressant other than their index study agent and no evidence of a titration in SSRI dose.</td>
</tr>
<tr>
<td>Upward titration</td>
<td>Patients having at least 90 days of continuous therapy, with evidence of an increase in dosage at some point after starting antidepressant treatment. These patients were also required to have had no claims for antidepressants other than their index study agent and no gaps in treatment greater than 15 days.</td>
</tr>
<tr>
<td>Therapy change</td>
<td>Patients having at least 90 days of continuous therapy, with evidence of receiving another antidepressant (switch or augmentation) during the study period. These patients were required to have had no gaps in treatment greater than 15 days.</td>
</tr>
</tbody>
</table>

Note: The index drugs were SSRIs (citalopram, fluoxetine, immediate-release paroxetine, controlled-release paroxetine, or sertraline), but the follow-up observation period included assessment of all antidepressant drug therapy.

Figure 1 Distribution of Antidepressant Patients by Compliance Category*

* N = 65,753 (See Table 4 for complete data.)
therapy for at least 90 continuous days. Patients experiencing a change in therapy and patients in the titration group both appeared to have higher illness severity as measured by the 3 proxies (the Charlson Comorbidity Index, the percentage of patients having comorbid anxiety, and use of mental health specialty care) compared with the >90-day group.

**Total Medical Charges**

Total medical charges for 12 months were highest in patients having a change in therapy ($7,858) during the study period, while patients in the ≥90-day cohort had the lowest total medical charges ($5,143) (Table 4). Differences in total medical costs between the <90-day (P < 0.001), titration (P < 0.001), partial compliance (P < 0.05), and therapy change (P < 0.001) cohorts were statistically significant compared with the ≥90-day cohort. Differences in total medical charges were primarily driven by inpatient charges, which were highest in the therapy change ($2,386) and <90-day ($2,094) cohorts, and lowest in the ≥90-day ($1,446) cohort. Charges for physician services followed a similar trend, being lowest in the ≥90-day cohort. When patients remaining on therapy for 180 days or more (n = 8,548, 82.9% of the ≥90-day cohort) were separated from the ≥90-day cohort and compared with the <90-day cohort, medical charges were ($1,089) lower for the >180-day group (P < 0.001).

**Table 3** Patient Characteristics and Use of SSRI Drug Therapy

<table>
<thead>
<tr>
<th></th>
<th>&lt;90 Days (n = 23,231)</th>
<th>≥90 Days (n = 10,311)</th>
<th>Partial (n = 8,858)</th>
<th>Titration (n = 8,019)</th>
<th>Change (n = 13,334)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% female</td>
<td>76.0%*</td>
<td>72.8%</td>
<td>74.9%†</td>
<td>76.3%*</td>
<td>78.0%*</td>
</tr>
<tr>
<td>Mean age (years ± SD)</td>
<td>42.1* ± 12.7</td>
<td>45.5 ± 11.3</td>
<td>44.6* ± 11.8</td>
<td>43.8* ± 11.6</td>
<td>44.0* ± 11.1</td>
</tr>
<tr>
<td>Comorbid anxiety disorder</td>
<td>24.3%*</td>
<td>19.0%</td>
<td>19.3%</td>
<td>25.3%*</td>
<td>28.4%*</td>
</tr>
<tr>
<td>Mental health specialty care†</td>
<td>28.9%*</td>
<td>24.1%</td>
<td>24.4%</td>
<td>30.5%*</td>
<td>37.3%*</td>
</tr>
<tr>
<td>Mean Charlson comorbidity score</td>
<td>0.96†</td>
<td>0.89</td>
<td>0.90</td>
<td>0.96†</td>
<td>1.10†</td>
</tr>
<tr>
<td>Preperiod medical charges</td>
<td>$2,342</td>
<td>$2,261</td>
<td>$2,068</td>
<td>$2,348</td>
<td>$2,803</td>
</tr>
</tbody>
</table>

* P < 0.001 when compared with the ≥90-day cohort.
† P < 0.05 when compared with the ≥90-day cohort.
§ Mental health specialty care is defined as care provided by a psychiatrist or mental health professional.
SSRI = selective serotonin reuptake inhibitor.

**Table 4** Annual Average-per-Patient Hospital, Medical, and Pharmacy Charges ($)*

<table>
<thead>
<tr>
<th></th>
<th>&lt;90 Days (n = 23,231)</th>
<th>≥90 Days (n = 10,311)</th>
<th>Partial (n = 8,858)</th>
<th>Titration (n = 8,019)</th>
<th>Change (n = 13,334)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>2,094</td>
<td>1,446</td>
<td>2,040</td>
<td>1,996</td>
<td>2,386</td>
</tr>
<tr>
<td>Outpatient</td>
<td>1,427</td>
<td>1,302</td>
<td>1,319</td>
<td>1,499</td>
<td>1,868</td>
</tr>
<tr>
<td>Emergency department</td>
<td>309</td>
<td>159</td>
<td>177</td>
<td>238</td>
<td>302</td>
</tr>
<tr>
<td>Physician</td>
<td>1,434</td>
<td>1,290</td>
<td>1,334</td>
<td>1,584</td>
<td>2,007</td>
</tr>
<tr>
<td>Other†</td>
<td>1,025</td>
<td>947</td>
<td>1,038</td>
<td>1,058</td>
<td>1,296</td>
</tr>
<tr>
<td>All medical charges</td>
<td>6,289†</td>
<td>5,143</td>
<td>5,909†</td>
<td>6,375†</td>
<td>7,858†</td>
</tr>
<tr>
<td>SSRI therapy charges</td>
<td>508</td>
<td>886</td>
<td>802</td>
<td>1,066</td>
<td>1,172</td>
</tr>
<tr>
<td>Medical + SSRI charges</td>
<td>6,797†</td>
<td>6,029</td>
<td>6,711†</td>
<td>7,441†</td>
<td>9,030†</td>
</tr>
<tr>
<td>Other pharmacy charges</td>
<td>1,032</td>
<td>1,424</td>
<td>1,236</td>
<td>1,503</td>
<td>1,939</td>
</tr>
<tr>
<td>Total charges</td>
<td>7,829</td>
<td>7,453</td>
<td>7,947§</td>
<td>8,944§</td>
<td>10,969§</td>
</tr>
</tbody>
</table>

* These are provider submitted charges for services rendered within 1 year of initiating treatment; e.g., 1-year costs for patients who initiated treatment in June 2001 would consist of all costs incurred from June 2001 through May 2002.
† "Other" includes laboratory, radiological, and similar ancillary services.
§ P < 0.001 when compared with the ≥90-day cohort.
§ P < 0.05 when compared with the ≥90-day cohort.
SSRI = selective serotonin reuptake inhibitor.
Medical, Antidepressant, and Total Pharmacy Charges

When total medical charges were combined with antidepressant-related pharmacy charges (Table 4), patients having a change in therapy experienced the highest costs ($9,030), while patients in the ≥90-day cohort experienced the lowest costs ($6,029). The costs for medical and antidepressant pharmacy charges for the ≥90-day cohort were lower than the costs for the other utilization cohorts. When all pharmacy charges, including antidepressant drug therapy, were added to total medical charges, the total charges were not different between the <90-day cohort ($7,829) and the ≥90-day cohort ($7,545), P = 0.606.

Discussion

The purpose of this analysis was to evaluate differences in resource utilization resulting from various patterns of antidepressant use and longer length of drug therapy. Results of this study provide some support for the earlier findings that patients remaining on therapy for at least 90 days without drug therapy changes incur lower health care charges (absent pharmacy charges), and patients requiring a therapy change incur higher health care charges.12

The data presented here also provide some support for earlier findings that patients adhering to antidepressant therapy for at least 90 days achieve improved outcomes.10,11,15,16 Studies of Medicaid14 and privately insured populations15 have found that patients treated for the recommended duration of antidepressant therapy (a minimum of 90 days for acute treatment) had a lower likelihood of depression relapse than individuals remaining on therapy for less than the minimum duration. Assuming that increased resource utilization may in part reflect relapse, the current study is consistent with these earlier findings.

Medication selection is an important factor in increasing adherence to antidepressants and decreasing therapy change since 43% of patients who discontinue antidepressant therapy within 30-days cite adverse events from the medication as the primary cause of early discontinuation.17 Selecting therapies that have demonstrated a lower incidence of side effects may lessen the need for changing therapies, enhance patient medication compliance, and reduce overall health care costs. This is especially true for patients with a comorbid anxiety disorder, such as panic disorder, in that these patients appear to be particularly sensitive to the side effects of antidepressants.10,19 The current study found that patients who needed some type of therapy change, either an augmentation or switch in treatment, were significantly more likely to have a comorbid anxiety disorder.

Also of interest is the finding that non-depression-related pharmacy charges were higher in patients who received continuous antidepressant drug therapy for ≥90 days. Given previous work documenting a link between depression and poor compliance,20 it is plausible that improved depression treatment may lead to better compliance with other medications. It is also possible that certain individuals are more adherent to, or higher utilizers of, a range of chronic medications. Future analyses should evaluate the effect of improved antidepressant treatment patterns on non-depression-related medication compliance and associated health care costs.

Limitations

The ability to draw causal relationships between adherence to therapy and cost of care is not possible with the cross-sectional study design. We were also unable to adjust for all potentially confounding variables. While we attempted to measure severity of illness and health status with 3 proxy measures, it is possible that unmeasured patient characteristics led both to medication discontinuation, therapy change, titration, and the increased likelihood of use of health care service uses. Our study adjusted for a wide range of confounders, but caution should always be exercised when making inferences of causality from retrospective analysis of medical claims data.

Since economic and resource utilization data were obtained from retrospective claims, the reason(s) for patient discontinuation, therapy change, titration, or partial compliance could not be determined and may be related to factors other than efficacy or tolerability. Patient-specific data, such as chart review data, are critical for better understanding these reasons and developing interventions to improve adherence to therapy.17 While it is plausible that resource utilization could be used as a proxy measure of effectiveness, we did not directly assess the effectiveness of antidepressant treatment patterns in reducing the clinical signs and symptoms of depression. It may be inappropriate to use resource utilization in this manner if the true effectiveness of these agents is not reflected in medical charges within a 1-year period of initiating treatment. Readers should also note that we reported per-patient-per-year medical and pharmacy costs since all patients were continuously eligible from 12 to determine the values expressed in resource utilization per patient per month. We excluded patients who received only 1 antidepressant pharmacy claim, and discontinuation of therapy after filling 1 prescription has been reported to be as high as 30% of patients initiating SSRI treatment.

Finally, the claims data only provided information on patterns of drug therapy derived from dispensed prescriptions rather than actual use of medications by patients. Pharmacy records tend to overestimate compliance as compared with gold-standard electronic compliance monitoring systems.21 Additionally, the use of drug samples could not be accounted for with our methodology. We have no reason to believe that drug sampling would differentially affect patients in the various cohorts; however, if the use of drug samples is substantial, it is likely to be a source of patient misclassification in our method. Misclassification could also occur if a physician recommended a decrease in the frequency or dose of a prescription after the prescription was filled.
Despite the limitations of this study, this research provides current data on the relationship between SSRI antidepressant drug use and total health care resource consumption. It is not possible to conclude from these data that titrating or changing therapy are inappropriate treatment patterns. However, selecting the right medication for the right person in initial therapy may decrease the need for titration or therapy change. Future research should seek to better explain the many patient, provider, and treatment-related factors that may affect the relationship between medical care that is concordant with treatment guidelines and patient outcomes, including the total cost of care.

DISCLOSURES

Funding for this study was provided by GlaxoSmithKline (GSK) and was obtained by authors Michael T. Eaddy, Matthew W. Sarnes, and Timothy S. Regan. Eaddy, Sarnes, Regan, and author Laura E. Frankum are employed by Applied Health Outcomes, which serves as a consultant firm for GSK. Author Benjamin G. Druss received an honorarium from GSK for his participation in this article. Eaddy and Regan disclose that they participate in speakers bureaus for GSK, presenting various aspects of their research. Eaddy served as principal author of the study. Study concept and design were contributed primarily by Eaddy. Analysis and interpretation of data were contributed by all authors. Drafting of the manuscript was primarily the work of Eaddy, Druss, and Regan. Statistical expertise and administrative, technical, and/or material support were provided by Eaddy.

REFERENCES

Clinical Monograph for Drug Formulary Review: Erectile Dysfunction Agents

HELEN ELOISE CAMPBELL, BS, PharmD

ABSTRACT

BACKGROUND: Significant advances in the pharmacologic treatment of erectile dysfunction (ERD) have occurred in recent years, most notably the introduction of sildenafil, the first oral selective phosphodiesterase type 5 (PDE5) inhibitor, in 1998. Sildenafil quickly gained acceptance by the medical community and the public because of its broad efficacy for different types of ERD and its ease of use. Two PDE5 inhibitors, vardenafil and tadalafil, have since joined sildenafil to compete in the ERD market. 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 ERD drugs as part of drug formulary management process and decision making by the Pharmacy & Therapeutics (P&T) committee.

OBJECTIVE: To provide readers with a comprehensive clinical monograph on ERD drugs written from a managed care perspective.

METHODS: The PBM clinical monograph 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 prepared 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 pharmacoeconomic data.

RESULTS: Despite the lack of head-to-head comparative studies, all 3 PDE5 inhibitors appear to have equivalent efficacy in the treatment of general ERD and ERD associated with diabetes and postprostatectomy. Sildenafil has additional efficacy data in the management of ERD associated with spinal cord injury and antidepressant medications. Tadalafil has the longest duration of action (up to 36 hours); this feature can be both beneficial (greater sexual spontaneity) or possibly detrimental (greater exposure to drug, delayed adverse events). All 3 PDE5 inhibitors appear to be generally well tolerated and have similar contraindications and warnings. However, vardenafil is the only PDE5 inhibitor with a cardiac conduction precaution. Alprostadil products are recommended in current ERD guidelines as second-line therapy for those who have not responded or cannot take the oral PDE5 inhibitors. Overall, higher clinical efficacy rates are achieved with intracavernous than with transurethral administration.

CONCLUSION: A large amount of clinical efficacy and safety data has been published since the market launch of sildenafil in 1998. Sildenafil has the greatest body of efficacy and safety evidence. No comparative studies have been conducted with any of the PDE5 inhibitors. Differences in study populations, primary end points, and measurement tools make comparisons difficult. However, all PDE5 inhibitors appear to be roughly equivalent in efficacy, with minor differences in adverse event profiles. Until more comparative data are available, economic considerations will be a significant factor in choosing ERD products for formulary inclusion.

KEYWORDS: Erectile dysfunction, Sildenafil, Vardenafil, Tadalafil, Drug monograph, Outcomes-based formulary, Evidence-based medicine

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Editors' 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 utilization 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

Erectile dysfunction (ERD) has been defined as the persistent (lasting at least 6 months) inability to attain and maintain erection sufficient to permit satisfactory sexual performance. Although ERD is not a life-threatening disorder, it has a profound impact on the quality of life of those who suffer from it. ERD increases progressively with age, but it is not an inevitable consequence of aging. Other age-related conditions may increase the risk of developing ERD.

Based on the Massachusetts Male Aging Study, the probability of ERD of any degree is 40% among 40-year-old men and 70% among 70-year-old men.1,2 Many diseases—and many medications—may lead to erectile dysfunction. Therefore, an individual evaluation and identification of the underlying causes as well as a reduction in polypharmacy and a substitution of medications should be some of the first approaches in the management of ERD.3

Significant advances in the pharmacologic treatment of ERD have occurred in recent years, most notably the introduction in 1998 of sildenafil, the first oral selective phosphodiesterase type 5 (PDE5) inhibitor. Sildenafil quickly gained acceptance by the medical community and the public because of its broad efficacy for different types of ERD and its ease of use. Recent guidelines published by the European Association of Urology and the American Association of Clinical Endocrinologists include sildenafil as first-line pharmacologic therapy in the treatment of ERD when nonspecific therapy is appropriate.4,5

Author

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Clinical Monograph for Drug Formulary Review: Erectile Dysfunction Agents

Two PDE5 inhibitors, sildenafil and tadalafil, have joined sildenafil to compete in the ERD market. However, PDE5 inhibitors do not work for all patients, and some individuals may have contraindications that preclude their use. Other first-line options include the use of vacuum devices or investigational oral drugs such as oral yohimbine, trazodone, phentolamine, and, in Europe, sublingual apomorphine. Efficacy data is sparse and conflicting for the off-label use of trazodone, yohimbine, and phentolamine in the treatment of ERD.4

U.S. Food and Drug Administration (FDA)-approved agents recommended as second-line alternatives in ERD guidelines include intracavernosal alprostadil therapy (direct delivery of the drug to the erectile chambers) and transurethral alprostadil delivery (direct delivery to the urethra) (Table 1).

This monograph will present a short overview of the etiology, risk factors, pathophysiology, and diagnosis of ERD. The focus of this monograph will be an evaluation of pharmacology, pharmacodynamics, pharmacokinetics, clinical efficacy, and the safety of the pharmacologic treatments that are approved by the FDA for the management of ERD.

Testosterone injection, oral tablets, gels, and transdermal systems are indicated for the treatment of ERD associated with hypogonadism. The review of testosterone preparations for the treatment of hypogonadism will be the subject of a separate monograph.

# II. Overview of ERD

## Pathophysiology

Penile erection depends on one or two main mechanisms: reflex erection or psychogenic erection. It is a hemodynamic event regulated by the relaxation of the arterial and corporal smooth muscle. The penis consists of paired erection chambers (corpora cavernosa) that are filled with erectile tissue (corporal sinusoids) composed of smooth muscles. Relaxation of the smooth muscle of the corpora cavernosa is mediated by the release of acetylcholine by the parasympathetic nerves. Acetylcholine causes the endothelial cells to release a non-adrenergic, noncholinergic carrier of relaxation signal—nitric oxide. Nitric oxide may stimulate guanylate cyclase to produce cyclic guanosine monophosphate (cGMP), therefore causing a relaxation of the trabecular smooth muscle. Penile erection is a result of neurally mediated increased arterial inflow into the corporal bodies and an increased amount of oxygen that stimulates nitric oxide synthesis by cavernosal nerves and endothelium, along with a decrease or cessation of venous outflow.5-7

The corporal smooth muscle is contracted when the penis is flaccid. The contraction is due to the presence of a normally present adrenergic tone. Smooth muscle relaxation occurs with erection. There are a number of other receptors in penile smooth muscle, including those responsive to vasoactive intestinal polypeptide, dopamine, histamine, prostaglandin, and various others.5-7

## Etiology and Risk Factors of ERD

Vascular disease is the most common etiology of ERD in elderly men. The risk of vascular ERD increases with smoking, hypercholesterolemia, and diabetes. In addition, many diseases, such as diabetes, stroke, and Parkinson’s disease, can cause autonomic dysfunction. This can impair the penile arterial vasodilation, maintaining the vascular constriction, and therefore preventing erection. Furthermore, a number of medications have been associated with ERD. Medications with anticholinergic properties, such as antidepressants, antipsychotics, and antihistamines, block parasympathetic-mediated penile artery vasodilation and trabecular smooth muscle relaxation.8 Causes contributing to ERD may be related to a number of disorders, which are listed in Table 2.

ERD is clearly a symptom of many conditions, and certain risk factors have been identified, some of which may be preventable. Diabetes mellitus, hypogonadism, hypertension, vascular disease, high cholesterol or low-density lipoprotein cholesterol, alcohol ingestion, depression, lack of sexual knowledge, poor sexual techniques, and many chronic diseases have all been identified as risk factors. In addition, age is a strong indirect risk factor because it may be associated with increased likelihood of direct risk factors. Smoking is another indirect risk factor that may increase the effects of other risk factors, such as hypertension or vascular disease. Knowledge of the risk factors can guide patients to prevention strategies.5-7,9,10

### Table 1: Monograph Review Agents: Erectile Dysfunction

<table>
<thead>
<tr>
<th>Type of Disorder</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Atherosclerosis, penile Raynaud’s phenomenon, cardiovascular disease, diabetes</td>
</tr>
<tr>
<td>Neurological</td>
<td>Spinal cord damage, cerebrovascular accident, Peripheral neuropathy, diabetic autonomic neuropathy</td>
</tr>
<tr>
<td>Hormonal/endocrine</td>
<td>Hypogonadism, hyperthyroidism, hyperglycemia (poorly controlled diabetes)</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Performance anxiety, depression</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Pelvic radiation, lumbar sympathectomy, prostatectomy, Renal transplant, spinal cord resection</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Dutereics, sympatholytics, nonselective beta-blockers, alpha-blockers, direct vasodilators, calcium channel blockers, antidepressants, antipsychotics, anxiolytics, opioids, cimetidine</td>
</tr>
</tbody>
</table>

### Table 2: Causes of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Type of Disorder</th>
<th>Example</th>
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</tr>
<tr>
<td>Hormonal/endocrine</td>
<td>Hypogonadism, hyperthyroidism, hyperglycemia (poorly controlled diabetes)</td>
</tr>
<tr>
<td>Psychogenic</td>
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<tr>
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<td>Pelvic radiation, lumbar sympathectomy, prostatectomy, Renal transplant, spinal cord resection</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Dutereics, sympatholytics, nonselective beta-blockers, alpha-blockers, direct vasodilators, calcium channel blockers, antidepressants, antipsychotics, anxiolytics, opioids, cimetidine</td>
</tr>
</tbody>
</table>
Diagnosis of ERD

ERD may be associated with several abnormalities of the endocrine, neurological, and vascular system. Thus, an appropriate evaluation of all men with ERD should include a medical and sexual history, physical exam, psychosocial evaluation, and appropriate laboratory studies.3

Endocrine evaluation includes hemoglobin A1C, a morning serum testosterone, prolactin, luteinizing hormone, and follicle-stimulating hormone (FSH) levels. Other tests, such as complete blood count, urinalysis, creatinine, lipid profile, fasting blood sugar, and thyroid function may be indicated to exclude an unrecognized underlying systemic disease. Neurologic causes may be associated with a history of diabetes, spinal injury, or cerebrovascular accident; a detailed medical history will be essential to identify them. In addition, nocturnal penile tumescence testing may be useful when a primary psychogenic ERD is suspected. An erectile response to an intracavernosal injection of pharmacological test dose of a vasodilatory agent, such as papaverine or PGE1, indicates adequate arterial and vено-occlusive function. For patients who favor noninvasive treatments, such as the oral PDE5 inhibitors, pharmacological injection, intraurethral suppository, or vacuum constrictor devices, no further diagnostic tests are necessary. On the other hand, for patients with unsatisfactory response, penile implant surgery or further diagnostic tests may be appropriate.3

III. Pharmacology/Pharmacodynamics

FDA-Approved Therapy

Alprostadil (Caverject, Edex, and MUSE)

Prostaglandin E1 (alprostadil) is one of the prostaglandins, naturally occurring acidic lipids with a variety of pharmacological effects, including vasodilatation, inhibition of platelet aggregation, and stimulation of intestinal and uterine smooth muscle. It acts by relaxing the trabecular smooth muscles of the corpus cavernosum and increasing the diameter of cavernous arteries, and this leads to erection. In animal studies, the degree and duration of cavernous smooth muscle relaxation appears to be dose dependent.11-15

PDE5 Inhibitors (Sildenafil, Vardenafil, and Tadalafil)

The mechanism of penile erection involves relaxation of the corpus cavernosal smooth muscle. This occurs through release of nitric oxide during sexual stimulation, which results in increased concentrations of cGMP. Sildenafil, vardenafil, and tadalafil are all competitive inhibitors of the type 5 cGMP-specific PDE5 enzyme.14-16 The result is an enhancement of the effect of nitric oxide secondary to a decrease in degradation of cGMP. PDE5 inhibitors have no effect in the absence of sexual stimulation.

There are 11 families of phosphodiesterase isoenzymes that have been identified in mammalian tissue. While PDE1 through 6 have been extensively studied, PDE7 through 11 have been recently discovered, and thus less is known regarding their distribution and function in the human body.

Sildenafil, vardenafil, and tadalafil are all more selective for the PDE5 isoenzyme than for all other PDE isoenzymes. However, degrees of selectivity vary among the agents, depending on the isoenzyme in question. As illustrated in Table 3, sildenafil is 80 times more selective for PDE5 than for PDE1, but greater than 80 times more selective for PDE6, an isoenzyme heavily concentrated in the retina of the eye.17,18 In contrast, tadalafil is greater than 700 times more selective for PDE5 than for the PDE6 isoenzyme. This selectivity ratio pattern may explain why the side effect of blue-tinged vision or changes in blue-green color discrimination is reported with sildenafil but is
not expected to occur with tadalafil use. On the other hand, tadalafil is only 14 times more selective for the PDE5 than the PDE11 isoenzyme than sildenafil and vardenafil, which have much higher selectivity ratios. The low selectivity ratio of tadalafil for PDE11, an isoenzyme heavily concentrated in the testes and skeletal muscle, led investigators to conduct safety studies to ascertain what effect tadalafil would have on spermatogenesis. However, 6-month, daily-dosing, placebo-controlled studies with 10 and 20 mg/day of tadalafil produced no clinically relevant effect on spermatogenesis as measured by sperm count and sperm morphology and motility. Additionally, no effect was observed on hormones related to spermatogenesis (luteinizing hormone, FSH, testosterone) with chronic tadalafil use.19

### Hemodynamic Effect

The PDE5 inhibitors all work as vasodilators. Because PDE5 is found in the smooth muscle of the systemic arteries and veins, these agents all have potential to interact with the cardiovascular system. Since many men with ERD also have coexisting hypertension, diabetes, and cardiovascular disease, significant hemodynamic effects from PDE5 inhibitor use could be clinically important. Table 4 summarizes the hemodynamic changes seen with the PDE5 inhibitors in normal healthy volunteers and patients with coronary artery disease. All 3 agents produce minor changes in systolic and diastolic blood pressure, but these changes do not alter response to exercise testing. Careful analysis of population data and vardenafil, sildenafil, and tadalafil clinical data do not show an increase in serious cardiac events associated with PDE5 inhibitor use.15-24

All PDE5 inhibitors are contraindicated with concomitant administration of nitrates because significant hypotension can result. Sildenafil, vardenafil, and tadalafil are also contraindicated for use with alpha-blockers for the same reason. One exception to this rule is that tadalafil can be safely administered with tamsulosin 0.4 mg daily.14-16

### Effect on Cardiac Conduction

Vardenafil in therapeutic (10 mg) and supratherapeutic (80 mg) doses produced increases in the QT interval similar to that of 400 mg of moxafloxicin. While the clinical impact of these changes is unknown, the coadministration of vardenafil with Class IA and Class III antiarrhythmic medications should be avoided. Patients with congenital QT prolongation should also avoid vardenafil use.15

### IV. Pharmacokinetics

The pharmacokinetics of the ERD agents are summarized in Table 5. Sildenafil and vardenafil reach peak plasma concentrations at about 1 hour after administration; tadalafil reaches peak concentrations at 2 hours. Although not well studied, efficacy data for all 3 PDE5 inhibitors indicate that onset of action is earlier (17 to 40 minutes) than when peak serum concentrations are reached.25-28 Although all 3 PDE5 inhibitors vie for the claim of earliest onset, only well-designed comparative studies will help answer the question of which agent is the fastest acting. There are no studies that directly compare the onset, duration, or overall efficacy of the PDE5 inhibitors. Unlike sildenafil and vardenafil, peak serum concentrations of tadalafil are not affected by a high-fat meal.14-16 All 3 PDE5 inhibitors undergo extensive hepatic metabolism and require some dosage adjustment with hepatic dysfunction. The most striking difference between tadalafil, vardenafil, and sildenafil is the long half-life of tadalafil (17.5 hours). This long half-life translates into a prolonged duration of action for tadalafil (up to 36 hours), earning it the name of “le weekend” drug in France.

### TABLE 4: Hemodynamic Effects of PDE5 Inhibitors

<table>
<thead>
<tr>
<th>Lowering of systolic and diastolic BP (standing readings, hemodynamic changes are less when supine)</th>
<th>Sildenafil</th>
<th>Vardenafil</th>
<th>Tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy volunteers</td>
<td>↓ 8 mm systolic</td>
<td>↓ 7 mm systolic</td>
<td>Healthy volunteers</td>
</tr>
<tr>
<td>↓ 6 mm diastolic</td>
<td>↑ heart rate 4 BPM</td>
<td>↑ 8 mm diastolic</td>
<td>↓ 5 mm diastolic</td>
</tr>
<tr>
<td>↑ heart rate 4 BPM</td>
<td>↔ heart rate</td>
<td>NA</td>
<td>↔ heart rate</td>
</tr>
<tr>
<td>No effect as compared with placebo on heart rate or blood pressure during exercise testing in patients with known or probable CAD</td>
<td>CAD patients</td>
<td>↓ 7 mm systolic</td>
<td>CAD patients</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>↓ 4 mm diastolic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↔ heart rate</td>
<td></td>
</tr>
<tr>
<td>Effect on exercise test</td>
<td>No effect on ischemic response to exercise in patients with known or probable CAD</td>
<td>Did not affect total treadmill exercise time to angina but did delay onset of ST segment changes in symptomatic patients with stable CAD</td>
<td>Did not reduce total exercise or time to ischemia</td>
</tr>
</tbody>
</table>

BP = blood pressure; BPM = beats per minute; CAD = coronary artery disease; NA = not available; PDE = phosphodiesterase.
The bioavailability of intracavernous administration of alprostadil has not been studied. The absorption with transurethral administration of alprostadil appears to be biphasic, with 80% of the dose being absorbed within 10 minutes.11-13 The onset of action after intracavernous injection is within 2 to 5 minutes of administration. The onset of action after transurethral administration is slower, at about 5 to 10 minutes. Following intracavernous and transurethral administration of alprostadil, the drug is either metabolized locally or cleared from the penis into the systemic circulation and then metabolized by the lungs. The mean peripheral plasma concentrations are not significantly greater than baseline levels of endogenous alprostadil. The metabolites are excreted primarily by the kidney. Within 24 hours following administration, about 90% of the dose was excreted in urine, and the remaining 10% was excreted in feces. The effect of age, gender, and renal or hepatic failure on the pharmacokinetics of alprostadil has not been evaluated. However, patients with pulmonary disease may have reduced ability to clear the drug because of pulmonary first-pass metabolism of prostaglandin E1.11-13,29

### Considerations in the Interpretation of ERD Drug Trials

There are no head-to-head studies comparing the efficacy of one PDE5 inhibitor with another. While it may be tempting to compare the efficacy results seen with tadalafil and vardenafil with sildenafil, this practice is fraught with error since studies may have differing designs, study populations (age, ERD etiology, ERD severity, comorbidity, prior ERD drug use), and outcomes measures.30

### Outcomes Measures Used in ERD Drug Trials

There are several primary and secondary efficacy measures commonly used in ERD clinical studies. The most common included the International Index of Erectile Function (IIEF), Sexual Health Inventory for Men (SHIM), Sexual Encounter Profile (SEP) Diary, and global assessment questions. A brief definition of each measurement tool is provided.30

### International Index of Erectile Function (IIEF)

The IIEF is a validated self-administered questionnaire used to assess therapeutic efficacy of ERD therapy. It is comprised of 5 domains:

1. Erectile function (Questions 1-5 and 15, total maximum score of 30; score of 26 = normal erectile function; 22-25 = mild ERD; 17-21 = mild-to-moderate ERD; 11-16 = moderate ERD; and 1-10 = severe ERD). Of the ERD domain questions, 2 questions are often isolated as separate outcomes measures. The questions are: “When you attempted intercourse, how often were you able to penetrate your partner?” (IIEF question 3) and “During sexual intercourse, how often were you able to maintain your erections?” (IIEF question 4).

2. Libido

3. Orgasmic function

4. Sexual satisfaction

5. Overall satisfaction

IIEF outcomes may be reported in a variety of ways: change
TABLE 6 Erectile Dysfunction Placebo-Controlled Studies: General Population

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Treatment Details</th>
<th>N</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fink31 (2002)</td>
<td>Sildenafil vs. Placebo</td>
<td>3,229</td>
<td>• Efficacy increased with increasing vardenafil dose.</td>
</tr>
<tr>
<td>Design and baseline characteristics:</td>
<td></td>
<td></td>
<td>MC, R, PC, fixed-dose study</td>
</tr>
<tr>
<td>Systematic review of R, PC studies of sildenafil in ERD of various etiologies</td>
<td></td>
<td></td>
<td>Mean age: 52 years</td>
</tr>
<tr>
<td>Patient age: mean age 55 years, 21% 65 years or older</td>
<td></td>
<td></td>
<td>Etiology of ERD: organic 27%-33%, psychogenic 25%-30%, mixed 36%-48%</td>
</tr>
<tr>
<td>Ethnicity: white 70%, Asian 21%, African American 5%</td>
<td></td>
<td></td>
<td>Baseline ERD severity: mild 26%-28%, moderate 34%-37%, severe 32%-36%</td>
</tr>
<tr>
<td>Comorbid conditions: HTN 30%, coronary artery disease 8%, diabetes 21%, depression 5%</td>
<td></td>
<td></td>
<td>Prior sildenafil use: 30%-45% of patients in each treatment group had severe ERD at baseline.</td>
</tr>
<tr>
<td>Design and baseline characteristics:</td>
<td></td>
<td></td>
<td>Efﬁcacy increased with increasing vardenafil dose.</td>
</tr>
<tr>
<td>Sildenafil 25 mg-100 mg or placebo x 12 weeks</td>
<td></td>
<td></td>
<td>• Efficacy increased with increasing vardenafil dose.</td>
</tr>
<tr>
<td>Fixed-dosage design: sildenafil vs. placebo</td>
<td></td>
<td></td>
<td>• Efficacy increased with increasing vardenafil dose.</td>
</tr>
<tr>
<td>Results:</td>
<td></td>
<td></td>
<td>• Efficacy increased with increasing vardenafil dose.</td>
</tr>
<tr>
<td>Flexible-dosage design: sildenafil vs. placebo</td>
<td></td>
<td></td>
<td>• Efficacy increased with increasing vardenafil dose.</td>
</tr>
<tr>
<td>Mean % successful intercourse: 57% vs. 21%, WMD 34% (CI, 29-38)</td>
<td></td>
<td></td>
<td>• Efficacy increased with increasing vardenafil dose.</td>
</tr>
<tr>
<td>% improvement in erection: 78% vs. 25%</td>
<td></td>
<td></td>
<td>• Efficacy increased with increasing vardenafil dose.</td>
</tr>
<tr>
<td>IIEF Q.3 scores: 3.8 vs. 2.3</td>
<td></td>
<td></td>
<td>• Efficacy increased with increasing vardenafil dose.</td>
</tr>
<tr>
<td>IIEF Q.4 scores: 3.6 vs. 2.1</td>
<td></td>
<td></td>
<td>• Efficacy increased with increasing vardenafil dose.</td>
</tr>
</tbody>
</table>

(Continued on next page)
**TABLE 6 Erectile Dysfunction Placebo-Controlled Studies: General Population (continued)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and baseline characteristics</th>
<th>Drug regimen and duration</th>
<th>Outcomes measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linet36 (1993)</td>
<td>MC, DB, R, parallel design, fixed-dose study</td>
<td>Caverject (intracavernous alprostadil) 2.5 mcg (N = 57), 5.0 mcg (N = 60), 10 mcg (N = 62), 20 mcg (N = 58), placebo (N = 59)</td>
<td>Clinical evaluation of erection quality, RigiScan evaluation of erection quality</td>
<td>No response to placebo by either clinical or RigiScan evaluation. Men responding with full erection ranged from roughly 20% (2.5 mcg dose) to 50% (20 mcg dose) by either clinical or RigiScan assessment.</td>
</tr>
</tbody>
</table>
| Albrecht abstract37 (1997) | PC, DB, MC, crossover study | Edex (intracavernous alprostadil) 1 mcg-20 mcg or placebo | Erection adequate for successful intercourse (physician and patient assessments) | Study 2. Home phase  
% adequate erections: intracavernous alprostadil 73%-74% vs. placebo 7%-13%  
Median time to erection: intracavernous alprostadil 10 minutes  
Median duration of erection: intracavernous alprostadil 59 minutes |
| Padma-Nathan39 (1997) | MC, DB, PC study | MUSE (transurethral alprostadil) 125 mcg, 250 mcg, 500 mcg, or 1,000 mcg, placebo | 3 month, at-home phase (transurethral alprostadil responders) | In-clinic phase: 66% of men had at least 1 erection adequate for intercourse.  
At-home phase: transurethral alprostadil vs. placebo, erections resulting in intercourse: 65% vs. 19%, P<0.001 |

**Comments:**
- Compared with placebo, tadalafil significantly improved all efficacy outcomes.
- High placebo response rate reflects higher proportion of subjects with mild ED at study entry.
- Prolonged erection (+6 hours): intracavernous alprostadil 3% vs. placebo 0.4%
- Bleeding: intracavernous alprostadil 6% vs. placebo 3%
- Pain: intracavernous alprostadil 31% vs. placebo 9%
- Prolonged erection (4-6 hours): intracavernous alprostadil 3% vs. placebo 0.4%
- Bleeding: intracavernous alprostadil 6% vs. placebo 3%
- Pain: intracavernous alprostadil 31% vs. placebo 9%

CI = confidence interval; DB = double blind; ERD = erectile dysfunction; HTN = hypertension; IIEF = International Index of Erectile Function; MC = multicenter; MUSE = Medicated Urethral System for Erection; PC = placebo controlled; Q = question; R = randomized; RBI = relative benefit increase; RRI = relative risk increase; SEP = Sexual Encounter Profile; WMD = weighted mean difference.

IIEF Question 3 or SEP Question 2: “When you attempted intercourse how often were you able to penetrate your partner?”  
IIEF Question 4 or SEP Question 3: “During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?”  
Global efficacy question 1: “Did treatment improve your erections?”  
Global efficacy question 2: “Did treatment improve your ability to have sexual intercourse?”
TABLE 7  Erectile Dysfunction Placebo-Controlled Studies: Special Populations


Design and baseline characteristics:
MC, R, DB, PC, flexible-dose-escalation study
Patient age: mean age: 55 years; 21% ≥ 65 years
Comorbid conditions: type 1 diabetes 19%, type 2 diabetes 81%, HTN 53%, ischemic heart disease 26%
ERD type (all patients): organic 96%, mixed 4%
Duration: 5.3-5.8 years

Drug regimen and duration:
Sildenafil (N = 136)
25 mg-100 mg as needed but no more than once daily
Placebo (N = 132)
Duration: 12 weeks

Outcomes measures: mean % successful intercourse, global efficacy (improvement in erections), IIEF score Q.3, IIEF score Q.4, IIEF erectile domain

Results:
Sildenafil vs. placebo
Mean % successful intercourse 48% vs. 12%, P<0.001
% improvement in erections 3.2 vs. 2.0, P<0.001
IIEF Q.3 scores
56% vs. 10%, P<0.001
2.9 vs. 1.6, P<0.001

Comments:
• In an analysis of subgroups, sildenafil efficacy was not affected by age, duration of ERD, or the duration of diabetes.
• Common adverse events included headache, dyspepsia, and respiratory tract disorder (sinus congestion or drainage).
• No discontinuations due to adverse events


Design and baseline characteristics:
MC, R, DB, PC study
Mean age: 59 years
Comorbidities: type 2 diabetes

Drug regimen and duration:
Sildenafil (N = 110)
25 mg-100 mg as needed but no more than once daily
Placebo (N = 109)
Duration: 12 weeks

Outcomes measures: global efficacy (improvement in erections), IIEF score Q.3, IIEF score Q.4, IIEF erectile domain

Results:
Sildenafil vs. placebo
Mean % successful intercourse 49% vs. 12.4%, P<0.001
% improvement in erections 3.2 vs. 2.0, P<0.001
IIEF Q.3 scores
56% vs. 10%, P<0.001
2.9 vs. 1.6, P<0.001

Comments:
Results are very similar to those attained earlier by Rendell40 (1999).


Design and baseline characteristics:
MC, R, DB, PC, flexible-dose-escalation study
Mean age: 48 years
Etiology of ERD: type 1 diabetes
Comorbidities: HTN 32%, cardiovascular disease 36%

Drug regimen and duration:
Sildenafil (N = 95)
25 mg-100 mg as needed but no more than once daily
Placebo (N = 93)
Duration: 12 weeks

Outcomes measures: global efficacy (improvement in erections), IIEF score Q.3, IIEF score Q.4, IIEF erectile domain

Results:
Sildenafil vs. placebo
% improvement in erections 3.61 vs. 2.71, P<0.001
Mild-moderate ERD: 30% vs. 10% IIEF Q.4 scores
Severe ERD: 30% vs. 10% IIEF Q.4 scores
65% vs. 11% IIEF Q.4 scores
3.25 vs. 2.19, P<0.001

Comments: Overall, men with mild-to-moderate ERD at baseline had higher scores for all efficacy measures than those participants with severe disease.


Design and baseline characteristics:
MC, R, PC, parallel group, fixed-dose study
Mean age: 57 years
ERD type: type 1 and type 2 diabetes
Baseline ERD severity: severe 56%, moderate 23%, mild 6%
Comorbidities: HTN 53%, depression 10%
Prior sildenafil use: 58%

Drug regimen and duration:
Vardenafil 10 mg (N = 149 )
Vardenafil 20 mg (N = 141 )
Placebo (N = 140)
Duration: 12 weeks

Outcomes measures: IIEF erectile function domain scores, SEP Q.2 (penetration), SEP Q.3 (successful intercourse), global efficacy (improvement in erections)

Results:
Vardenafil vs. placebo
Improvement in IIEF scores
5.9-10.8 vs. 1.4; P<0.0001
SEF Q.2
61%-64% vs. 36%; P<0.0001
57%-72% vs. 13%; P<0.0001

Comments:
• Efficacy was usually greater for vardenafil 20 mg than with vardenafil 10 mg.
• Both dosage levels of vardenafil were statistically superior to placebo in improving IIEF scores, successful intercourse, and improvement in erections.
• Significant treatment response occurred regardless of ERD severity.
• Adverse events included headache, flushing, rhinitis, and transient vision changes (haziness).


Design and baseline characteristics:
MC, R, PC, parallel group, fixed-dose study
Mean age: 56 years
ERD severity: severe 72%
Comorbidities: HTN 37%, hypercholesterolemia 18%

Drug regimen and duration:
Tadalafil 10 mg (N = 73 )
Tadalafil 20 mg (N = 72 )
Placebo (N = 71)
Duration: 12 weeks

Outcomes measures: IIEF erectile function domain scores, SEP Q.2 (penetration), SEP Q.3 (successful intercourse), global efficacy (improvement in erections)

Comments:
Efficacy was usually greater for tadalafil 20 mg than with tadalafil 10 mg.
Both dosage levels of tadalafil were statistically superior to placebo in improving IIEF scores, successful intercourse, and improvement in erections.
Significant treatment response occurred regardless of ERD severity.
Adverse events included headache, flushing, rhinitis, and transient vision changes (haziness).

(Continued on next page)
### TABLE 7  Erectile Dysfunction Placebo-Controlled Studies: Special Populations (continued)

<table>
<thead>
<tr>
<th>Drug regimen:</th>
<th>Sildenafil 50 mg-100 mg (N = 120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes measures:</td>
<td>13-question survey designed to determine preoperative and postoperative erectile function, response to sildenafil and side effects</td>
</tr>
<tr>
<td>Results:</td>
<td></td>
</tr>
<tr>
<td>Response rates by age</td>
<td></td>
</tr>
<tr>
<td>Bilateral nerve sparing</td>
<td>Unilateral nerve sparing</td>
</tr>
<tr>
<td>Age &lt;55 years</td>
<td>80%</td>
</tr>
<tr>
<td>56-65 years</td>
<td>45%</td>
</tr>
<tr>
<td>&gt;66 years</td>
<td>33%</td>
</tr>
<tr>
<td>Non-nerve sparing</td>
<td>no response</td>
</tr>
<tr>
<td>Comments:</td>
<td>Highest response rates with younger age and bilateral nerve-sparing procedure</td>
</tr>
</tbody>
</table>

Tadalafil vs. Placebo in Postprostatectomy ERD  
N = 440

### Design and baseline characteristics:
- R, DB, PC, parallel group, fixed-dose study
- Patient age: 60 years
- ERD type: postprostatectomy, 73% had bilateral nerve-sparing procedures
- ERD severity: severe 67%-74%, moderate 12%-19%, mild-moderate 11%-14%
- Comorbidities: HTN 29%-32%, hypercholesterolemia 21%, depression 1%-7%, past smoker 46%-53%
- Prior sildenafil use: 80%

### Drug regimen and duration:
- Vardenafil 10 mg (N = 146)
- Vardenafil 20 mg (N = 149)
- Placebo (N = 145)
- Duration: 12 weeks

### Outcomes measures: IIEF erectile function domain scores, SEP Q.2 (penetration), SEP Q.3 (successful intercourse), global efficacy (improvement in erections)

| Results: | |
| Improvement in IIEF scores in erection | Improvement in IIEF scores by baseline ERD severity |
| 60%-65% vs. 13%, P<.0001 | Mild-moderate 25%-20% vs. 16% |
| Improvement in SEP Q.3 by baseline ERD severity | Moderate 19%-23% vs. 13% |
| Mild-moderate 70%-74% vs. 48% | Severe 11%-13% vs. 7% |
| Moderate 52%-67% vs. 19% | |
| Severe 24%-28% vs. 4% | |

### Comments:
- Patients with mild ERD at study entry had the highest response rates.

### Design and baseline characteristics:
- MC, R, DB, PC, parallel group, fixed-dose study
- Mean age: 60 years
- Etiology of ERD: bilateral nerve-sparing prostatectomy
- ERD severity: severe ERD 63%

### Drug regimen and duration:
- Tadalafil 20 mg (N = 201)
- Placebo (N = 102)
- Duration: 12 weeks

### Outcomes measures: IIEF erectile domain, SEP Q.2 (penetration), SEP Q.3 (successful intercourse), global efficacy (improvement in erections)

### Results:
- Zagaia (2000)  
Sildenafil in Postprostatectomy ERD  
N = 120

### Design and baseline characteristics:
- Open-label, retrospective study
- Age: <55 years 23%, 56-65 years 54%, >65 years 23%
- ERD etiology: postprostatectomy
- Prostatectomy types: bilateral nerve sparing 49%, unilateral nerve sparing 32%, non-nerve sparing 29%
- Comorbidities: HTN 29%-32%, hypercholesterolemia 21%, depression 1%-7%, past smoker 46%-53%
- Prior sildenafil use: 80%

### Drug regimen and duration:
- Tadalafil 20 mg (N = 303)

### Outcomes measures: IIEF erectile domain, SEP Q.2 (penetration), SEP Q.3 (successful intercourse), global efficacy (improvement in erections)

| Results: | |
| Global efficacy-improvement in erection | Improvement in IIEF scores by baseline ERD severity |
| 60%-65% vs. 13%, P<.0001 | Mild-moderate 25%-20% vs. 16% |
| Improvement in SEP Q.3 by baseline ERD severity | Moderate 19%-23% vs. 13% |
| Mild-moderate 70%-74% vs. 48% | Severe 11%-13% vs. 7% |
| Moderate 52%-67% vs. 19% | |
| Severe 24%-28% vs. 4% | |

### Comments:
- Patients with mild ERD at study entry had the highest response rates.

### Design and baseline characteristics:
- Open-label, retrospective study
- Age: <55 years 23%, 56-65 years 54%, >65 years 23%
- ERD etiology: postprostatectomy
- Prostatectomy types: bilateral nerve sparing 49%, unilateral nerve sparing 32%, non-nerve sparing 29%
- Comorbidities: HTN 29%-32%, hypercholesterolemia 21%, depression 1%-7%, past smoker 46%-53%
- Prior sildenafil use: 80%

### Drug regimen and duration:
- Tadalafil 20 mg (N = 303)

### Outcomes measures: IIEF erectile domain, SEP Q.2 (penetration), SEP Q.3 (successful intercourse), global efficacy (improvement in erections)

### Results:
- Vardenafil vs. Placebo in Postprostatectomy ERD  
Tadalafil vs. Placebo in Postprostatectomy ERD  
N = 440

### Design and baseline characteristics:
- R, DB, PC, parallel group, fixed-dose study
- Patient age: 60 years
- ERD type: postprostatectomy, 73% had bilateral nerve-sparing procedures
- ERD severity: severe 67%-74%, moderate 12%-19%, mild-moderate 11%-14%
- Comorbidities: HTN 29%-32%, hypercholesterolemia 21%, depression 1%-7%, past smoker 46%-53%
- Prior sildenafil use: 80%

### Drug regimen and duration:
- Vardenafil 10 mg (N = 146)
- Vardenafil 20 mg (N = 149)
- Placebo (N = 145)
- Duration: 12 weeks

### Outcomes measures: IIEF erectile function domain scores, SEP Q.2 (penetration), SEP Q.3 (successful intercourse), global efficacy (improvement in erections)

### Results:
- Vardenafil vs. placebo

### Comments:
- Patients with mild ERD at study entry had the highest response rates.

### Design and baseline characteristics:
- MC, R, DB, PC, parallel group, fixed-dose study
- Mean age: 60 years
- Etiology of ERD: bilateral nerve-sparing prostatectomy
- ERD severity: severe ERD 63%

### Drug regimen and duration:
- Tadalafil 20 mg (N = 201)
- Placebo (N = 102)
- Duration: 12 weeks

### Outcomes measures: IIEF erectile domain, SEP Q.2 (penetration), SEP Q.3 (successful intercourse), global efficacy (improvement in erections)
### Table 7: Erectile Dysfunction Placebo-Controlled Studies: Special Populations (continued)

<table>
<thead>
<tr>
<th>Drug regimen and duration:</th>
<th>Sildenafil vs. Placebo (N = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil 25 mg-100 mg</td>
<td>Placebo (N = 78)</td>
</tr>
<tr>
<td>Duration: 12 weeks</td>
<td></td>
</tr>
</tbody>
</table>

**Outcomes measures:** global efficacy questions, IIEF erectile domain function, treatment response: yes to global efficacy questions 1-2 and score ≥21 on erectile function domain of IIEF questionnaire, HAM-D: Beck Depression inventory, life satisfaction checklist.

**Results:**
- ERD treatment responders
  - Sildenafil vs. placebo
    - 73% vs. 14%

**Effect on depression measures**
- ↓ in HAM-D scores of 10.6 and 2.3 in treatment responders
- 76% of responders showed a >50% decline in HAM-D scores vs. 14% of nonresponders
- Life satisfaction improved in responders

**Comments:**
- Sildenafil was effective in this group of depressed men.
- Successful treatment was associated with improvement in depression scores and quality of life.
- Headache, dyspepsia, flushing, and abnormal vision were most frequent adverse events.

### Design and baseline characteristics:
- R, PC, 2-way crossover, flexible-dose-escalating study
- Mean age: 45 years
- Etiology of ERD: secondary to SSRI antidepressant treatment

#### Nurnberg52 (2003)  Sildenafil vs. Placebo in Patients With Depression  N = 90

**Drug regimen and duration:**
- Sildenafil 25 mg-100 mg
- Placebo
- Duration: 12 weeks
- Average 5 doses per treatment group

**Outcomes measures:** CGI-SF, IIEF erectile function, Arizona Sexual Experience Scale, HAM-D

**Results:**
- Sildenafil vs. placebo
  - Improvement in CGI-SF (primary measure)
    - 54.5% vs. 4.4%, P < 0.001
  - IIEF erectile function and other overall satisfaction measures were significantly improved for sildenafil subjects vs. placebo

**Comments:**
- Mean depression scores remained constant and were consistent with remission.
- Headache, dyspepsia, flushing, nasal congestion, palpitations, insomnia, and abnormal vision were most frequent adverse events.

---

**TABLE 7**

**Clinical Monograph for Drug Formulary Review: Erectile Dysfunction Agents**

**Results:**

<table>
<thead>
<tr>
<th>Drug regimen and duration:</th>
<th>Sildenafil vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tadalafil vs. placebo</td>
<td></td>
</tr>
<tr>
<td>Improvement in IIEF</td>
<td>54% vs. 32%, P &lt; 0.001</td>
</tr>
<tr>
<td>5.3 vs. 1.1, P &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Outcomes measures:**
- Median 8.5 doses of sildenafil
- Duration: 6 weeks on each treatment
- Subjects in remission from depression
- Mean SSRI use: 27 months

**Design and baseline characteristics:**
- R, DB, PC, 2-way crossover, flexible-dose-escalating study
- Mean age: 38 years
- Etiology of ERD: post-SCI

### Tadalafil vs. Placebo

**Results:**
- Improvement of erections: 55% vs. 0%, P < 0.001
- % of successful intercourse attempts, IIEF erectile function domain Q.3 and Q.4 for sildenafil vs. placebo

**Comments:**
- Most common adverse events were headache, facial flushing, nasal congestion, dyspepsia, and visual disturbances.
- Significant improvement persisted even when patients with no residual erectile function at baseline were included.
- Response to sildenafil for subjects with SCI is comparable to response seen in ERD subjects with other comorbid conditions.

---


**Drug regimen and duration:**
- Sildenafil 50 mg-100 mg or placebo for 6 weeks then crossover to placebo or sildenafil for an additional 6 weeks
- Duration: 6 weeks on each treatment
- Median 8.5 doses of sildenafil

**Outcomes measures:**
- Global efficacy question 1: “Did treatment improve your ability to have sexual intercourse?”
- Global efficacy question 2: “When you attempted intercourse how often were you able to penetrate your partner?”
- Global efficacy question 3: “During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?”
- Global efficacy question 4: “Did treatment improve your ability to have sexual intercourse?”

**Results:**
- Significant improvement persisted even when patients with no residual erectile function at baseline were included.
- Response to sildenafil for subjects with SCI is comparable to response seen in ERD subjects with other comorbid conditions.

---

**Seidman51 (2001)  Sildenafil vs. Placebo in Patients With Depression  N = 152**

**Design and baseline characteristics:**
- MC, R, DB, PC, flexible-dose-escalating study
- Mean age: 56 years
- Etiology of ERD: major depressive disorder (untreated)

**Results:**
- Improvement in CGI-SF (primary measure)
  - 54.5% vs. 4.4%, P < 0.001
  - IIEF erectile function and other overall satisfaction measures were significantly improved for sildenafil subjects vs. placebo

**Comments:**
- Mean depression scores remained constant and were consistent with remission.
- Headache, dyspepsia, flushing, nasal congestion, palpitations, insomnia, and abnormal vision were most frequent adverse events.

---

**CGI-SF = Clinical Global Impression-Sexual Function; DB = double blind; ERD = erectile dysfunction; HAM-D = Hamilton Depression Scale; HTN = hypertension; IIEF = International Index of Erectile Function; MC = multicenter; PC = placebo controlled; Q = question; R = randomized; SCI = spinal cord injury; SEP = Sexual Encounter Profile; SHIM = Sexual Health Inventory for Men; SSRI = selective serotonin reuptake inhibitor.**

**IIEF Question 3 or SEP Question 2:** “When you attempted intercourse how often were you able to penetrate your partner?” **IIEF Question 4 or SEP Question 3:** “During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?” **Global efficacy question 1:** “Did treatment improve your erections?” **Global efficacy question 2:** “Did treatment improve your ability to have sexual intercourse?”
Sexual Health Inventory for Men (SHIM)

The SHIM is an abbreviated version of the IIEF questionnaire and was designed to allow a more rapid diagnosis of ERD and assignment of ERD severity. The instrument has 6 questions, with a maximum score of 30. ERD is present if the SHIM score is 21 or less. The SHIM primarily measures erectile function, and it does not address measures of orgasmic function, libido, and satisfaction.

Sexual Encounter Profile (SEP) Diary

Assessments of individual sexual encounters are provided by SEP diaries. The SEP diary is intended to be an immediate-recall diary of encounters. The diaries contain 6 questions for the patient and 4 questions for the partner. SEP questions 2 and 3 are very similar to questions 3 and 4 of the IIEF erectile function domain. However, the SEP questions are answered yes or no while the IIEF questions are assigned a numerical score. In IIEF score from baseline, normalization of IIEF erectile function domain, mean improvement in erectile function score, and percentage improvement over baseline, to name a few.

Sexual Health Inventory for Men (SHIM)

Global Assessment or Global Efficacy Questions

Global assessment or efficacy questions are often used as secondary outcomes measures. The 2 most common questions are: “Did this treatment improve your erections?” and “Did treatment improve your ability to have sexual intercourse?”

Clinical Efficacy Summary

General ERD Population: PDE5 Inhibitors

Sildenafil, vardenafil, and tadalafil significantly improve IIEF erectile function domain scores and improve erection quality as compared with placebo in large, double-blind, randomized, controlled trials in the general ERD population. There are several outcomes measurements reported in ERD clinical studies.
but perhaps the most meaningful improvement to the patient is the rate of successful intercourse. In a meta-analysis of 14 randomized, placebo-controlled, flexible-dose studies, the subjects on sildenafil 25 mg to 100 mg had a successful intercourse rate of 57% as compared with a rate of 21% with placebo.31 Combined data from 2 fixed-dose sildenafil studies showed a successful intercourse rate of 43%, 50%, and 51% for the 25 mg, 50 mg, and 100 mg dose, respectively, as compared with the placebo group, which had rates of 14% to 17%.31 In general, higher sildenafil doses were associated with higher efficacy rates. Also included in the meta-analysis were additional analyses examining efficacy in subgroups stratified by age, race, ERD baseline severity, and ERD etiology. Sildenafil was as efficacious in the Asian and African American subjects as in

### TABLE 9 Miscellaneous Studies: Failed Previous Erectile Dysfunction Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and baseline characteristics</th>
<th>Drug regimen and duration</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engel30 1998</td>
<td>MUSE (Transurethral Alprostadil) in ICI PGE1, Papaverine or Phentolamine Failures N = 452</td>
<td>In-office phase: Titration to response with 125 mcg, 1,000 mcg of transurethral alprostadil At-home phase: 3 months treatment with transurethral alprostadil or placebo</td>
<td>Outcome measures: Physician and patient assessment of erection, patient diaries</td>
<td>58% of patients previously unresponsive to ICI PGE1 achieved an adequate erection at least once during the in-office phase. 47% of this group reported at least 1 successful intercourse during the at-home phase vs. 12% for placebo. Most efficacy measures were significantly higher for transurethral alprostadil than placebo.</td>
</tr>
<tr>
<td>Shabsigh56 (2000)</td>
<td>Edex (Intracavernous Alprostadil) in Sildenafil Failures N = 134</td>
<td>Subjects treated with sildenafil 5 mg, 100 mg for 4 weeks (N = 134); Nonresponders or partial responders (N = 67) with IIEF score of 3 or less given intracavernous alprostadil and titrated in-office until response (up to 40 mcg) At-home phase: 6 weeks of treatment with on-demand intracavernous alprostadil</td>
<td>Outcomes measures: IIEF Q.3 (penetration) and Q.4 (maintenance of erection for successful intercourse), erectile response score (physician and patient assessment)</td>
<td>Mean dose of intracavernous alprostadil 28 mcg, 94% of patients were able to achieve an adequate erectile response as per physician assessment. 89% and 85% of patients had an improvement of 1 or more in IIEF score for Q.3 and Q.4, respectively.</td>
</tr>
</tbody>
</table>

**DB** = double blind; **ERD** = erectile dysfunction; **ICI** = intracavernous injection; **IIEF** = International Index of Erectile Function; **MC** = multicenter; **MUSE** = Medicated Urethral System for Erection; **PC** = placebo controlled; **PGE1** = prostaglandin E1; **Q** = question; **SEP** = Sexual Encounter Profile.

**IIEF Question 3 or SEP Question 2: “When you attempted intercourse, how often were you able to maintain your erection after you had penetrated your partner?” IIEF Question 4 or SEP Question 3: “During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?” Global efficacy question 1: “Did treatment improve your erections?”

**Outcomes measures:** IIEF Q.3 (penetration) and Q.4 (maintenance of erection for successful intercourse), erectile response score (physician and patient assessment)
whites, who comprise the majority of subjects in ERD studies. While the rate of successful intercourse varied depending on age, ERD severity, and ERD etiology, sildenafil use resulted in significantly greater rates for each subgroup as compared with placebo.31

In one large, randomized, fixed-dose study, vardenafil, at doses ranging from 5 mg to 20 mg, was able to produce a significantly greater rate of erections adequate for intercourse—50% to 65%—compared with a placebo rate of 32%, which is higher than the reported placebo average of 20%. The high placebo rate seen in this study is intriguing because 30% to 45% of subjects were classified by investigators as having severe ERD. An increase in efficacy was seen with increasing vardenafil dose.32 Vardenafil significantly improved IIEF erectile function domain scores as compared with placebo regardless of patient age, ERD etiology, or baseline ERD severity.33

In an integrated analysis of 5 multicenter, double-blind, randomized, fixed-dose studies, tadalafil 2.5 mg, 5 mg, 10 mg, and 20 mg resulted in significantly higher rates of successful intercourse, 36%, 42%, 61%, and 75%, respectively, compared with a placebo rate of 32%.34 Another multicenter, double-blind, randomized, fixed-dose study compared the duration of efficacy of 20 mg tadalafil with placebo.35 At 24 hours postadministration, a 53% rate of successful intercourse attempts was reported in the tadalafil group compared with a 29% rate in the placebo group. Tadalafil remained significantly more efficacious than placebo at 36 hours postdose, with a rate of 59% compared with 28%.36 The results of this study confirm the long duration of tadalafil, which would be anticipated from its prolonged half-life of 17 hours.

No comparative studies have been done to assess relative efficacy of any one PDE5 inhibitor to another. Until large comparative studies prove otherwise, the efficacy of these products seems roughly equivalent; however, direct comparisons of efficacy and safety should not be made, given the many variables present in populations studied and outcomes measures used.

General ERD Population: Alprostadil

Intracavernous and transurethral administration of alprostadil, while not usually considered first-line therapy, is also effective in the management of ERD in the general population. In alprostadil studies, efficacy is most often measured by physician and patient assessment of erection quality. In one large, multicenter, randomized, fixed-dose study, intracavernous administration of alprostadil at doses of 2.5 mcg, 5 mcg, 10 mcg, and 20 mcg resulted in 20%, 30%, 35%, and 50%, respectively, of men achieving full erections.37 The mean duration of erection was 37 minutes, and the duration was related to dose. Five men had prolonged erections; in 2 men, the erections lasted 4 hours or more. Penile pain was reported by 23% of intracavernous alprostadil subjects. In a 6-month self-injection extension of the study, the intracavernous alprostadil responders reported being able to have intercourse after the injections 94% of the time.38 In another placebocontrolled crossover study, intracavernous alprostadil 1 mcg to 40 mcg resulted in 73% to 74% of erections deemed adequate for intercourse (patient assessment) as compared with rates of 7% to 13% for placebo.39 The median duration of erection was 59 minutes, and prolonged erections lasting 4 to 6 hours were noted in 3% of subjects taking intracavernous alprostadil. The average intracavernous alprostadil dose was not reported in this study. Penile pain and bleeding were other common adverse events.39

Transurethral alprostadil was significantly more effective than placebo in 2 double-blind, placebo-controlled studies.40,41 In these studies, using transurethral alprostadil doses ranging from 125 mcg to 1,000 mcg, the rates of erections deemed adequate for intercourse were 49% to 66%. In the at-home phase of one of the studies, transurethral alprostadil resulted in a successful intercourse rate of 65% compared with a placebo rate of 19%. Incidence of penile pain ranged from 9% to 19%, hypotension was 3%, and there were no reports of priapism or prolonged erections.40,42

Two open-label studies compared the efficacy of transurethral alprostadil versus intracavernous alprostadil. In one study, the intracavernous alprostadil product was an extemporaneous preparation43; in the other, the Edex preparation was used.44 In both studies, intracavernous injections of alprostadil resulted in significantly higher erectile assessment scores or IIEF erectile function domain scores as compared with transurethral alprostadil. In one study, transurethral alprostadil was better tolerated with a lower discontinuation rate due to penile pain;41 however, the other study reported similar rates of penile pain and a marked patient preference for injection over transurethral therapy.44

General ERD Population: Failures on Previous ERD Therapy

One open-label, multicenter study reported that intracavernous alprostadil, in doses up to 40 mcg, was effective in failures with sildenafil therapy. In this study, sildenafil failures had a score of 1.2 or less on the IIEF erectile domain questions 3 and 4. A score of 1 means that sildenafil was almost never or never effective. Use of intracavernous alprostadil resulted in the IIEF scores improving by 2.75 to 2.63 points for 85% to 90% of patients. Penile pain was present in 30% of all intracavernous alprostadil subjects.45

One open-label, multicenter study examined the efficacy of vardenafil 5 mg to 20 mg in the treatment of ERD in 134 patients determined to be unresponsive to sildenafil. Unresponsiveness was defined as failure with sildenafil on at least 4 out of 6 attempts, with at least one of those attempts at the 100 mg dosage level. Sildenafil failures were randomized to receive either vardenafil (N = 231) or placebo (N = 226) for a treatment period of 12 weeks. Vardenafil use resulted in significantly higher IIEF erectile domain scores than placebo.
and higher rates of maintenance of erection sufficient for intercourse (46% vardenafil versus 16% placebo; P < .001). Overall, 62% of vardenafil subjects stated that their erections were improved compared with 15% of those in the placebo group.57

**Special Populations**

**Diabetes**

Several double-blind, placebo-controlled studies have been performed to evaluate the efficacy of sildenafil, vardenafil, and tadalafil in the management of ERD associated with type 1 and type 2 diabetes.40-44 No direct comparative studies have been performed to assess relative efficacy of one PDE5 inhibitor to another. However, well-designed studies have reported the following rates of successful intercourse: sildenafil 48% versus placebo 12%; vardenafil 49% to 54% versus 23%; tadalafil 28% to 29% versus 1.9%.44 The lower success rate seen with tadalafil may be due to the high percentage (72%) of patients with severe ERD enrolled in the study.

**Postprostatectomy**

As with diabetes, several clinical studies have assessed the efficacy of all of the currently available PDE5 inhibitors in the management of ERD postprostatectomy. In this patient population, response to treatment is dependent on subject age, baseline ERD severity, and the type of prostatectomy surgery. In general, bilateral nerve-sparing surgery is associated with the best chance for response with non-nerve-sparing procedures having the lowest response to therapy. However all PDE5 inhibitors are potentially effective in the management of postprostatectomy ERD.45-49

**Post-Spinal-Cord Injury**

Of the PDE5 inhibitors, only sildenafil has been studied in the management of ERD resulting from spinal cord injury. This patient population differs not only in the etiology of ERD but also in age since the average spinal cord injury patient in clinical studies is much younger (38 years) as compared with the ERD patient in the general population (56 years). In one randomized, placebo-controlled crossover study in 178 spinal cord injury patients, doses of sildenafil 50 mg to 100 mg resulted in an intercourse success rate of 55% versus 0% for placebo. Thus, success rates for sildenafil in ERD secondary to spinal cord injury approach rates seen in subjects with other comorbid conditions.50

**Depression**

One double-blind, placebo-controlled study has evaluated the efficacy of sildenafil in the management of ERD in patients with depression. Most patients in this study had a diagnosis of mild or moderate major depression and were not treated with antidepressants. Sildenafil 25 mg to 100 mg or placebo was given for 12 weeks. At the end of the study, significantly more patients on sildenafil than placebo (73% versus 14%) had a treatment response as defined by IIEF erectile function treatment scores and positive responses to 2 global efficacy questions. Successful treatment was also associated with an improvement in Hamilton Depression scores and quality-of-life measures.51

Sildenafil was more effective than placebo (55% versus 4.4%; P < .001) in improving Clinical Global Impression-Sexual Function scores in a study with 90 patients with ERD secondary to treatment with selective serotonin reuptake inhibitor antidepressants. All patients were in remission from major depression and remained on antidepressants during treatment with sildenafil for 6 weeks.52

**Effectiveness Studies**

Overall, in controlled clinical studies, sildenafil has an efficacy rate of roughly 60% in the broad ERD population.51 However, in the real-world setting, refill rates for sildenafil are not as high as would be expected. Of patients tracked for 1 year, only 52% filled a second prescription during that 12-month period and 31% filled greater than 7 prescriptions.53 In another study, patients in a clinic were followed for 2 years to evaluate their response to sildenafil.54 Two surveys were conducted. The first survey went to 200 men who had recently been given a prescription for sildenafil. Of these 200 men, only 151 (75%) actually tried the drug. Of those who tried the drug, an overall success rate of 74% was reported. The most common doses used were 50 mg (n = 88) and 100 mg (n = 61). While 38% of patients reported side effects, none discontinued therapy from drug intolerance. Two years later, a second survey was sent out; only 82 patients participated. Of those patients, 17% discontinued because of loss of efficacy and 20% needed to increase their dose by 50 mg. There was no correlation between frequency of use and the need to increase the dose. While the authors concluded that tachyphylaxis to sildenafil was responsible for study results, it is not clear if this is the case.55 Other reasons for reduced effect over time could have included psychological factors as well as worsening of underlying comorbid conditions, especially progressive vascular disease or poorly controlled diabetes.

Efficacy results in controlled clinical studies are rarely, if ever, duplicated in the real-world setting, and the experience with ERD is no different. However, McCullough et al. did report on several studies designed to identify and improve success rates with sildenafil therapy.60 The intensive disease management approach utilized in one of the studies yielded impressive results. Overall, 55% of men not previously successful with sildenafil became successful after intensive reeducation and counseling, which included regular follow-up visits with information as to how to take the drug, titration to maximum dose, and a minimum trial of 8 attempts for efficacy assessment. Controlling risk factors for ERD as recommended in current treatment guidelines also was a successful strategy, although
men with only 1 risk factor were more likely to respond to intervention than men with multiple risk factors. 60

VI. Adverse Events

PDE5 Inhibitors

Tadalafil, sildenafil, and vardenafil were well tolerated in clinical studies with headache, flushing, and dyspepsia occurring as the most common adverse events. There are no comparative safety data to compare rates of common adverse events, but based on the rates seen in placebo-controlled studies, there appears to be little difference in safety profiles for these most commonly reported events. Discontinuations secondary to adverse events were low for all 3 PDE5 inhibitors, ranging from 1% to 5%. Changes in color vision, which has been reported with sildenafil use, are less frequent with vardenafil and rarely reported with tadalafil. However, tadalafil does seem to be associated with more reports of myalgia and back pain than vardenafil or sildenafil. The muscle aches and back pain usually occur within 12 to 24 hours after tadalafil administration and resolve within 48 hours. Approximately 0.5% of patients discontinued tadalafil because of back pain or myalgia. 14-16

Serious Cardiac Events

Cardiac mortality rates in the tadalafil clinical study database (N > 4,000 subjects) are consistent with the expected rate in a male population. Across all studies, the incidence rate of myocardial infarction was 0.43 per 100 patient years in the tadalafil-treated patients compared with 0.6 per 100 patient years in the placebo-treated population, which was also consistent with the incidence rate observed with an age-standardized male population. 61

The cardiac safety of sildenafil has been extensively studied.

<table>
<thead>
<tr>
<th>TABLE 10</th>
<th>PDE5 Inhibitors: Selected Adverse Events Occurring &gt;2% in Placebo-Controlled Studies 14-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>Sildenafil/Placebo (%)</td>
</tr>
<tr>
<td>Headache</td>
<td>16/4</td>
</tr>
<tr>
<td>Flushing</td>
<td>10/1</td>
</tr>
<tr>
<td>Rhinitis/nasal congestion</td>
<td>4/2</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7/2</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>3/0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>NR</td>
</tr>
<tr>
<td>Increased creatinine kinase</td>
<td>NR</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>NR</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2/1</td>
</tr>
<tr>
<td>Back pain</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Myalgia</td>
<td>&lt;2</td>
</tr>
<tr>
<td>NR = not reported.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 11</th>
<th>Selected Adverse Events: Intracavernous and Transurethral Alprostadil 11-13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local side effects</td>
<td>Caverject (Intracavernous Alprostadil) (%)</td>
</tr>
<tr>
<td>Injection site ecchymosis</td>
<td>2</td>
</tr>
<tr>
<td>Injection site hematoma</td>
<td>3</td>
</tr>
<tr>
<td>Penile edema</td>
<td>1</td>
</tr>
<tr>
<td>Penile fibrosis</td>
<td>3</td>
</tr>
<tr>
<td>Penile pain</td>
<td>37</td>
</tr>
<tr>
<td>Penile rash</td>
<td>1</td>
</tr>
<tr>
<td>Penis disorder</td>
<td>3</td>
</tr>
<tr>
<td>Prolonged erection</td>
<td>4</td>
</tr>
<tr>
<td>Priapism</td>
<td>0.4</td>
</tr>
<tr>
<td>Testicular pain</td>
<td>NR</td>
</tr>
<tr>
<td>Urethral bleeding—minor</td>
<td>NR</td>
</tr>
<tr>
<td>Urethral burning</td>
<td>NR</td>
</tr>
<tr>
<td>Systemic side effects</td>
<td>Headache</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
</tr>
<tr>
<td>Hypotension</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>4</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>2</td>
</tr>
<tr>
<td>* Erections lasting 4 to 6 hours. † Not listed, but &lt; 1% rate of erections lasting &gt; 6 hours. NR = not reported.</td>
<td></td>
</tr>
</tbody>
</table>
Pooled results from 53 clinical studies indicated no difference between the incidence of death or myocardial infarction in men with ERD receiving sildenafil or placebo. In a United Kingdom study, 5,601 patients with ERD showed no evidence of increased risk of myocardial or ischemic heart disease during the first 4.9 months of sildenafil therapy. This low risk is supported by open-label safety data from subjects who have been taking sildenafil for up to 4.5 years.

Vardenafil has been shown to prolong the cardiac conduction as evidenced by a prolonged QT interval at therapeutic and supratherapeutic doses (Section VII, Contraindications/Precautions). Vardenafil increases the QT interval in a dose-dependent manner.15

**Intracavernosal and Transurethral Alprostadil**

The type and degree of side effects reported in the 2 intracavernous alprostadil formulations are very similar. Controlled comparative studies are available that directly compared the adverse event rates of these 2 products. As might be expected from a penile injection, local side effects (ecchymosis, hematoma, edema, pain) are prominent with both. Transurethral alprostadil is also associated with a significant occurrence of penile pain, urethral burning, and bleeding. The 2 comparison studies that compared transurethral alprostadil with intracavernous alprostadil injections had conflicting results regarding penile pain and discontinuations due to adverse events. Prolonged erection or, in some cases, priapism, can occur with intracavernous alprostadil and transurethral alprostadil.

Tables 10 and 11 display selected common adverse events as reported in respective product labeling for the currently marketed PDE5 inhibitors and the alprostadil intracavernosal and transurethral products. Direct comparisons between adverse events rates cannot be made as the event rates displayed are not derived from comparative studies.

**VII. Contraindications/Precautions**

The contraindications, warnings, and precautions for sildenafil, tadalafil, and vardenafil are extremely similar. No
(80 mg) doses produced increases in the QT interval similar to that of 400 mg of moxifloxacin. While the clinical impact of these changes is unknown, the coadministration of vardenafil with Class IA and Class III antiarrhythmic medications should be avoided. Patients with congenital QT prolongation should also avoid vardenafil use.15

The contraindications, warnings, and precautions for intracavernousal and transurethral products are exactly the same with one exception. Transurethral alprostadil should not be used for sexual intercourse with a woman who is
pregnant or could become pregnant, unless the couple uses a condom barrier. This precaution is based on animal data that showed embryotoxic effects when alprostadil was administered as a subcutaneous bolus to pregnant female rats (transurethral alprostadil product information). Table 13 lists the contraindications, warnings, and precautions as stated in intracavernous and transurethral alprostadil product information.11-13

### VIII. Drug/Food Interactions

Drug and food interactions with PDE5 inhibitors are presented in Table 14.

### IX. Use in Pregnancy/Nursing

Transurethral alprostadil should not be used for sexual intercourse with a woman who is pregnant or could become pregnant, unless the couple uses a condom barrier.13

Vardenafil, sildenafil, and tadalafil are listed as Pregnancy Category B drugs. While no evidence of fetal or embryonic toxicity was found in animal studies, there are no adequate and well-controlled trials of vardenafil, sildenafil, or tadalafil in pregnant women.14-16

In animal studies, tadalafil and vardenafil were secreted into the milk of lactating rats at concentrations 2.4-fold (tadalafil) and 10-fold (vardenafil) greater than found in the plasma. It is not known if these agents are excreted in human breast milk. There is no information on sildenafil and lactation.14-16

### X. Indications/Dosing

The indications, usual adult dose, and dose for special populations for all FDA-approved ERD drugs are listed in Tables 15 and Table 16.11-16

### XI. Conclusion

All 3 PDE5 inhibitors have significant efficacy in the treatment of general ERD and ERD associated with diabetes and post-prostatectomy. Placebo-controlled trials have also shown sildenafil to have efficacy for patients with ERD associated with depression and spinal cord injury.

There are no head-to-head clinical studies comparing the efficacy and safety of sildenafil with vardenafil or tadalafil. Sildenafil has by far the highest number of controlled studies confirming its safety and efficacy and is recommended as first-line ERD therapy when a nonspecific therapy is appropriate. The PDE5 inhibitors differ in their duration of action. Sildenafil and vardenafil seem to have similar duration of action of about

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**TABLE 16 Indications and Dosage for Alprostadil**

<table>
<thead>
<tr>
<th>FDA indication</th>
<th>Caverject (Intracavernous Alprostadil)</th>
<th>Edex (Intracavernous Alprostadil)</th>
<th>MUSE (Transurethral Alprostadil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology; intracavernous alprostadil is also indicated as an adjunct to other diagnostic tests in the diagnosis of erectile dysfunction.</td>
<td>Intracavernous alprostadil is indicated for the treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology.</td>
<td>Transurethral alprostadil is indicated for the treatment of erectile dysfunction.</td>
<td></td>
</tr>
<tr>
<td>Usual adult dose</td>
<td>The dose of intracavernous alprostadil should be individualized for each patient by careful titration under supervision by the physician. Dosage should be initiated at 2.5 mcg and gradually titrated upward according to response and erection duration. For spinal cord injury patients, lower initial doses of 1.25 mg are recommended. No more than 2 doses during an initial titration should be given in 24 hours. Dosage range 2.5 to 60 mcg; mean dose in clinical studies was 17.8 mcg. The recommended frequency is 3 times weekly with 24-hour periods between doses.</td>
<td>The dose of intracavernous alprostadil should be individualized for each patient by careful titration under supervision by the physician. Dosage should be initiated at 2.5 mcg and gradually titrated upward according to response and erection duration. For spinal cord injury patients, lower initial doses of 1.25 mg are recommended. No more than 2 doses during an initial titration should be given in 24 hours. Dosage range 1 to 40 mcg; mean dose in clinical studies was 21.9 mcg. The recommended frequency is 3 times weekly with 24 hour periods between doses.</td>
<td>The dose of transurethral alprostadil should be individualized for each patient by careful titration under supervision by the physician. Dosage should be initiated at 125 to 250 mcg and gradually titrated upward in a stepwise manner until the patient achieves an erection adequate for intercourse. Dosage range 125 to 1,000 mcg. Most men in clinical studies required the 500 or the 1,000 mcg dose to achieve an adequate erection. The maximum frequency is 2 administrations within a 24-hour period.</td>
</tr>
</tbody>
</table>
4 hours, while tadalafil has a duration of action of up to 36 hours. This prolonged duration of action may be a significant advantage for tadalafil since it could allow for increased sexual spontaneity. However, from a side-effect standpoint, it may not be an advantage to have prolonged levels of tadalafil in the systemic circulation.

Tadalafil, sildenafil, and vardenafil have similar common and nonserious adverse events. Yet, tadalafil does have a higher rate of myalgias and back pain that can take several hours to resolve. Vardenafil and especially tadalafil seem to have less propensity for visual changes. However, vardenafil does produce changes in cardiac conduction at therapeutic doses.
This could be especially significant if vardenafil is coadministered with CYP3A4 inhibitors because these drugs interfere with vardenafil metabolism.

Injectable or transurethral alprostadil remains recommended second-line therapy if first-line therapy is ineffective or contraindicated. Injectable alprostadil results in a quicker onset and a higher success rate than transurethral alprostadil, but it may also have a higher rate of prolonged erections or priapism.

Table 17 contains the clinical summary grid that compares and contrasts effectiveness, efficacy, safety, and clinical attributes of the 6 products currently used for the treatment of ED. Table 18 lists definitions of some of the outcomes terms used in the clinical summary grid. Table 19 contains the comparative costs for a single dose of the ERD agents discussed in this study.

### REFERENCES


### TABLE 18 Outcome Terms in Evidence-Based Medicine

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</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 that matters (POEM)</td>
<td>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>
</tbody>
</table>

### TABLE 19 Comparative Costs for Erectile Dysfunction Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cost per Average or Usual Dose ($)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracavernous alprostadil injection (Caverject)</td>
<td>29.50</td>
</tr>
<tr>
<td>Intracavernous alprostadil injection (Edex)</td>
<td>28.00</td>
</tr>
<tr>
<td>Transurethral alprostadil insert (MUSE)</td>
<td>22.00</td>
</tr>
<tr>
<td>Sildenafil (Viagra)</td>
<td>9.09</td>
</tr>
<tr>
<td>Vardenafil (Levitra)</td>
<td>9.20</td>
</tr>
<tr>
<td>Tadalafil (Cialis)</td>
<td>8.90</td>
</tr>
</tbody>
</table>

* Cost obtained from www.drugstore.com on December 26, 2004, for a single dose, based on the average doses used in clinical studies or the usual dose in the package insert.

Note: In actual deliberations, the P&T committee is provided with the WellPoint Pharmacy Management national net cost per claim for the most recent calendar quarter available.
Clinical Monograph for Drug Formulary Review: Erectile Dysfunction Agents


Evidence-Based Medicine: Beware of Results From Randomized Controlled Trials and Research With Administrative Claims Data

The “New Physician Survey” sponsored by the American Academy of Family Practice found that “coding and documenting care” was the most frustrating aspect of professional life for family physicians.1 “Managed care” and “keeping up with journals” were the second and third most frustrating aspects of professional life for family physicians. It would appear that none of these 3 factors has lost intensity, and a survey of family physicians today would likely produce similar results.

In a previous issue of the *Journal of Managed Care Pharmacy*, neurologist John Barbuto brought light to an underrecognized aspect of outcomes research—misCODing of medical claims performed by medical practices for convenience or, more purposefully, for reimbursement.2 Barbuto’s observations are important, and similar letters from the front lines of medicine and pharmacy practice should be regular features of *JMCP*, to remind us, in the science of outcomes research, that our careful calculation of summary statistics and measures will be limited by the underlying quality of the administrative claims data. A recent review and evaluation of the literature concluded that physicians whose practices include larger proportions of Medicaid and managed care patients seem more willing to deceive third-party payers to obtain coverage and provider reimbursement.3

The significance of this assertion is considerable in managed care and managed care pharmacy. At one extreme, outcomes research based on administrative claims data cannot inform and can do little more than guide. At the least, it is incumbent upon outcomes researchers and readers of outcomes research based on administrative claims data to attempt to assess the threats to validity in each study. For example, what is the magnitude of the incentive (or need) to miscode or upcode a particular diagnosis or patient severity (ICD-9-CM) or a particular procedure (CPT-4)? As pointed out by Barbuto, tension headache would tend to be underreported, particularly in managed care administrative claims, while migraine would tend to be overreported.

So, perhaps we can be more comfortable with relying upon the results of randomized controlled trials (RCTs) for the evidence in evidence-based medicine—or maybe not. Experts at Oxford University, led by An-Wen Chan, a researcher in clinical medicine, assessed the published results of 102 scientific trials that produced 122 published journal articles and 3,736 outcomes.4 Overall, 50% of efficacy and 65% of harm outcomes per trial were not reported completely. Statistically significant outcomes had a higher odds ratio (OR) of being fully reported compared with nonsignificant outcomes for both efficacy (pooled OR, 2.4; 95% confidence interval [CI], 1.4–4.0) and harm (pooled OR, 4.7; 95% CI, 1.8–12.0) data. In comparing published articles with protocols, 62% of trials had at least 1 primary outcome that was changed, introduced, or omitted. Eighty-six percent of survey responders (42 of 49) denied the existence of unreported outcomes despite clear evidence to the contrary. This under-reporting of clinical trial outcomes that are not significant and the failure to provide undesirable outcomes undercuts evidence-based medicine. This manipulation of the medical literature also contravenes official guidelines on reporting medical research.5 The bias in the medical literature to not report negative or unfavorable outcomes is augmented by bias in selective reporting of results in the RCTs that are published.

Evidence-Based Medicine: Are SSRIs More Effective Than Placebo and What Length of Therapy Is Enough?

A previous issue of *JMCP* included the results of a study of 100 medical charts randomly selected from 3,037 patients who were prescribed an antidepressant drug in primary care.6 The researchers found that 40% of the charts documented not one of the symptoms of major depression as defined in the fourth edition of the *Diagnostic and Statistical Manual* (DSM-IV), 30% of the charts had only 1 qualifying symptom for major depression recorded, 12% had 2 symptoms, and only 7% of the charts had 5 or 9 symptoms of major depression. In other words, 90% of the patient charts had insufficient documentation of symptoms to justify prescribing antidepressant drug therapy for treatment of major depression, according to DSM-IV criteria. These results may not be too surprising but certainly call into question the severity of depression suffered by the patients who are receiving antidepressant drug therapy in primary care, and the 7% of patient charts that did have documentation of sufficient qualifying criteria may overstate the actual incidence of actual major depression since there was probably selection bias in the results (access to patient charts was obtained voluntarily from physician offices and access to 79 charts was denied). This study also found a significant lack of patient follow-up, with only 37% of the patient charts containing documentation of patient outcomes of drug therapy.

The absence of sufficient qualifying symptoms of major depression in patients receiving antidepressant drug therapy in primary care may not be a major concern if the drugs are safe and have few adverse effects. It has long been clear that the selective serotonin reuptake inhibitors (SSRIs) may not be much more effective than placebo in the majority of patients diagnosed with depression. The placebo response in antidepressant clinical trials is typically in the range of 40%,7,8 and psychiatrist Arif Khan, who studied the placebo effect in 96 antidepressant drug trials submitted to the U.S. Food and Drug Administration (FDA) between 1979 and 1996 found that the effect of the antidepressant could not be distinguished from that of the placebo in 52% of the randomized controlled trials (RCTs).9 However, there is reliable evidence that patients with more severe depression respond better to antidepressant drug therapy.10 Now, more data are emerging that the SSRIs may be worse than not helpful—they may be harmful, particularly in
children, adolescents, and older adults.

For about 15 years, the SSRIs were generally considered nearly as safe as placebo. In 2003, the questions regarding the risk-benefit ratio for SSRIs and all antidepressants used in children and adolescents became more numerous and louder. On December 6, 2004, the Medicines and Healthcare products Regulatory Authority (MHRA) in the United Kingdom released a letter to health care professionals\textsuperscript{11} and a questions and answers document\textsuperscript{12} that addressed the prescribing advice for SSRIs (including venlafaxine) in adults. This followed a similar announcement from MHRA on December 2003 regarding the use of SSRIs in children and adolescents in which recommendations against the use of paroxetine and venlafaxine in persons younger than 18 years were reiterated from previous announcements from MHRA on these subjects in June and September 2003.\textsuperscript{13} The earlier advice in 2003 included the recommendations that (a) paroxetine, venlafaxine, sertraline, citalopram, and escitalopram were contraindicated in pediatric major depressive disorder (MDD) and (b) these drugs, including fluvoxamine, should not be prescribed as new therapy to patients younger than 18 years with depressive illness. The advice in December 2004 regarding treatment of depression with SSRIs in adults included 2 attachments, one from the National Institute for Clinical Excellence (NICE) in which maintenance treatment with antidepressants is recommended for “patients who have had two or more depressive episodes in the recent past, and who have experienced significant functional impairment during the episodes, should be advised to continue antidepressants for 2 years.”

The controversy surrounding the proper use of SSRIs and all antidepressants boiled at year-end 2004 and into 2005, upending much of the conventional wisdom in the appropriate use and length of therapy with antidepressants. It was inevitable that some experts would argue for the reduced use of antidepressants, particularly in persons younger than 18 years, and a return to some experts would argue for the reduced use of antidepressants, length of therapy with antidepressants. It was inevitable that much of the conventional wisdom in the appropriate use and antidepressants boiled at year-end 2004 and into 2005, upending 2 years.”

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In the wake of this renewed controversy over the use of antidepressant pharmacotherapy, what is the optimum initiation point and what is the optimum duration of therapy? Preskorn recommends in his book, \textit{Outpatient Management of Depression}, a minimum of 4 to 5 months of antidepressant therapy, but longer duration may be advisable depending upon (a) “the stage of the illness” and (b) “the specific characteristics of the patient.”\textsuperscript{15} Preskorn elaborates on the point that some patients will be reluctant to start or continue pharmacotherapy, and the decision to initiate drug therapy should be influenced by factors such as severity, duration of the depression episode, and family history. The recent NICE guidelines have been criticized for being unhelpful in treating the bulk of depressive disorders (mild-to-moderate depression and/or the associated mixed anxiety and depressive disorders), and, in fact, the NICE review found insufficient evidence that these conditions are responsive to antidepressant medication or specific psychological treatments.\textsuperscript{16}

In May 2002, the U.S Preventive Services Task Force (USPSTF) recommended routine screening for depressive disorders in those primary care settings that have established systems for diagnosis, effective treatment, and follow-up care.\textsuperscript{17} This recommendation overturned the prior report in 1996 in which the USPSTF found that there was insufficient evidence to recommend for or against routine use of standardized questionnaires to screen for depression in primary care patients. However, the USPSTF found in May 2002 that there was still not sufficient evidence to recommend for or against routine screening of children or adolescents for depression. Meta-analysis of the medical literature published through August 2001 suggested that depression screening and feedback reduced the risk for persistent depression (relative risk, 0.87 [95% confidence interval (CI), 0.79 to 0.95]). The USPSTF recommendation for routine screening for depression in adults, including diagnosis, effective treatment, and follow-up, was couched with the caveat that follow-up systems of care based upon quality improvement were likely to be more effective than detection and treatment, even when detection and treatment are coupled with patient and provider feedback.\textsuperscript{18}

Up to 80% of patients with major MDD will relapse during their lifetime, and maintenance cognitive behavioral therapy has been estimated to avert 52% of recurrent depression during the 5 years after an episode of major depression, and maintenance pharmacotherapy could avert 50% of cases of recurrent depression over 5 years of treatment.\textsuperscript{19} Simon and VonKorff found in 1995 that primary care physicians missed psychological distress in 36% of the patients later found to have major depression, but these authors concluded that the missed cases appeared to have milder and more self-limited depression and that (scarce) treatment resources should be directed to more intensive follow-up and relapse prevention among the patients currently being treated.\textsuperscript{20}

In this issue of JMCP, Eaddy, Druss, Sarnes, Regan, and Frankum found that total medical costs were not lower for patients who take SSRIs or other antidepressants for 90 days or longer compared with persons who take antidepressants for fewer than 90 days.\textsuperscript{21} Interpretation of their results is complicated by the fact that the <90 days group actually received an average of approximately 150 total days of SSRI drug therapy during the 365-day follow-up period (because the authors defined this group of patients to include a gap in therapy [at least 15 days]), and, therefore, this group appears to comprise early discontinuation as well as episodic SSRI use. The <90 days group also had an apparent higher severity of illness as measured by 3 proxy measures: Charlson Comorbidity Index, comorbid anxiety disorder, and use of “mental health specialty care” (i.e., psychiatrist or other mental health professional).
The data reported by Eaddy et al. also permit no conclusions about causality; i.e., one cannot say from these data that taking antidepressants for 90 days or more does not save money by reducing total medical costs. What these data do show is that there may not be a direct relationship between the length of therapy with SSRIs (or other antidepressants) and total medical costs. It is also important to recognize that Eaddy et al. did not examine specifically the adverse events associated with antidepressant drug therapy, although the medical costs associated with adverse events from antidepressants would have been captured in their data.

More than 10 years ago, using administrative claims data from 1991 to 1993, Thompson et al. found that only 4.8% of sertraline users and 10.9% of fluoxetine users (combined 10.2%) continued therapy for at least 90 days. Eaddy et al. found 10 years later that 16% of patients continued SSRI therapy for 90 days or longer.

Both the research by Eaddy et al. and Thompson et al. categorize patients into groups that may not be inconsistent with depression treatment guidelines. For example, the research reported by Thompson et al. 10 years ago included 4 of 5 patient groups in which SSRI antidepressant use may have been near-compliant and adequate, such as the upward titration group in which drug therapy was continued with the original SSRI for at least 60 days but the dose was increased. Thompson et al. found that 19.1% (229 of 1,200) of patients received 60 days or less of SSRI antidepressant therapy, but even this “early discontinuation group” received up to 8 weeks of either fluoxetine or sertraline therapy. Stated another way, 100% of SSRI patients in the Thompson et al. research received at least 60 days of therapy or experienced a change of SSRI, had SSRI therapy augmented with another antidepressant, or experienced a change in SSRI dose, all of which would not be inconsistent with clinical practice guidelines for treating major depressive disorder and would, in fact, appear to be consistent with the recommendation to monitor and alter drug therapy as often as every 1 to 2 weeks.

When assessing the benefit-risk relationship, there is evidence that SSRIs and other antidepressants pose additional potential harm beyond low efficacy and the possible higher risk of suicide. A little known apparent risk associated with the use of antidepressants, particularly SSRIs, is the possibility of adverse gastrointestinal (GI) events, particularly in older adults. A longitudinal study of 317,824 elderly persons observed for 132,812 person-years and who started taking an antidepressant between 1992 and 1998 found a bleeding rate of 7.3 per 1,000 person-years. The use of SSRI antidepressants was found to increase the risk of bleeding significantly by 10.7% for octogenarians and 9.8% for those with a history of GI bleeding, with risk increasing with the degree of inhibition of serotonin reuptake. Persons aged 80 years or older were particularly at risk of an adverse effect of SSRIs on GI bleeding. The degree of serotonin reuptake inhibition was defined as low (bupropion and most of the tricyclics), intermediate (amitriptyline, fluvoxamine, imipramine, and venlafaxine), or high (clomipramine, fluoxetine, paroxetine, and sertraline), using criteria developed from Tatsumi et al. The absolute differences in bleeding between antidepressant groups were greatest for octogenarians (10.6 bleeds per 1,000 person years for low inhibition of serotonin reuptake, vs. 14.7 bleeds per 1,000 person years for high inhibition of serotonin reuptake; the number needed to harm was 244) and those with previous upper GI bleeding (28.6 bleeds per 1,000 person years for low vs. 40.3 bleeds per 1,000 person years for high inhibition of serotonin reuptake; number needed to harm was 85).

A separate epidemiologic study conducted in Denmark found 3.6 times more bleeding episodes than was expected among users of SSRI antidepressants. All users of antidepressants in the county of North Jutland, Denmark, from January 1, 1991, to December 31, 1995, were identified in the Pharmaco-Epidemiologic Prescription Database of North Jutland. In the Hospital Discharge Register, hospitalizations for upper GI bleeding were searched among the 26,005 users of antidepressant medications and compared with the number of hospitalizations in the population of North Jutland who did not receive prescriptions for antidepressants. During periods of SSRI use without use of other drugs associated with upper GI bleeding, there were 55 upper GI bleeding episodes, which represented a rate that was 3.6 times more than expected (95% CI, 2.7-4.7), corresponding to a rate difference of 3.1 per 1,000 treatment years. Combined use of an SSRI with nonsteroidal anti-inflammatory drugs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1-19.5) and 5.2 (95% CI, 3.2-8.0), respectively. Non-SSRI antidepressants increased the risk of upper GI bleeding to 2.3 (95% CI, 1.5-3.4), while antidepressants without action on the serotonin receptor had no significant effect on the risk of upper GI bleeding. The researchers also found that the risk of GI bleeding with SSRI use returned to unity (1.0) after termination of SSRI use.

In the administrative claims database research reported by Eaddy et al., it would have been interesting to know the incidence of outpatient and inpatient visits for GI bleeding events. We do know from the data presented by Eaddy et al. that the apparent differences in total medical charges, without pharmacy claims, were the result of differences in inpatient hospital charges. It would have been interesting and perhaps quite helpful to know what diagnostic groups accounted for those inpatient costs for the longer-duration versus shorter-duration users of SSRIs.

Charbonneau et al. reported a relationship between adequate duration of antidepressant drug therapy and risk of hospitalization (odds ratio [OR] 0.90), but the 95% CI includes 1.00 (0.81-1.00), i.e., no obvious risk. The relationship between adequate duration of antidepressant therapy and risk of psychiatric hospitalization...
specifically was slightly more convincing, OR, 0.82; 95% CI, 0.69-0.96. Charbonneau et al. found “adequate duration” of antidepressant therapy in 45% of the subjects in the administrative claims database, and adequate duration was defined as only 79% of days of antidepressant use in 90 days; i.e., 9.5 weeks of therapy in a 12-week period.

The uncertainty regarding the optimum length of antidepressant drug therapy is evidenced in the physician-patient relationship. There appears to be a very large discrepancy between physician expectations of the length of SSRI antidepressant therapy and patient expectations. Bull et al. found that 72% of physicians who prescribed SSRI antidepressants for patients in a health maintenance organization reported asking these patients to take the antidepressants for at least 6 months, but only 34% of SSRI patients reported that their physician asked them to take the SSRI antidepressant for this length of time. Patients who discussed adverse effects with their physicians were less likely to discontinue therapy than patients who did not discuss them (OR, 0.49; 95% CI, 0.25-0.95). Patients who reported discussing adverse effects with their physicians were more likely to switch medications (OR, 5.60; 95% CI, 2.31-13.60).

Discontinuation of SSRI therapy was associated with fewer than 3 follow-up visits for depression, adverse effects, and lack of therapeutic response to medication. Bull et al. concluded that discrepancies exist between instructions that physicians report they communicate to patients and what patients remember being told. Explicit instructions about expected duration of therapy and discussions about medication adverse effects throughout treatment may reduce discontinuation of SSRI use. More to the point of the study by Eaddy et al., Bull et al. found that patients with 3 or more follow-up visits were more likely to continue using the initially prescribed antidepressant medication. This suggests that medical visit costs might be higher in patients who continue SSRI drug therapy longer than 90 days.

If it is true that only about one third of patients heard their physicians recommend that SSRIs should be taken for at least 6 months, it should not be surprising that only about one third of patients continue with SSRI drug therapy at 6 months (and by their classification schemes, Eaddy et al. found 16% and Thompson et al. found 10.2% of patients used 90 days or more of continuous SSRI drug therapy). McManus et al. found in a cohort study using a national dispensing claims database involving patients eligible for Social Security entitlements in Australia that only 38% of “new users” of SSRIs continued the drug therapy after 6 to 8 months. Weilberg et al. also found that most patients (64%) had only a single trial of antidepressants. The 51% ratio of “inadequate” treatment according to Weilberg et al. represented 42.5% of total courses of antidepressant drug therapy and 15% of total managed care organization drug costs.

In a particularly poignant bit of irony, some researchers are concerned that children who receive methylphenidate and other pharmacotherapy for attention deficit hyperactivity disorder (ADHD) may develop depression later in life. At the very least, the possibility that stimulant drug use in childhood may be associated with depression in later life increases the importance of a true positive diagnosis of ADHD and additional attention to the risks and benefits of pharmacologic treatment of a condition that overlaps with normal childhood behavior.

So, there is much to evaluate in the medical literature that we do know about, but what about the research findings that are not published? As noted above, the medical literature has a definitive bias in the publication of positive study results. The AMCP Format for Formulary Submissions emphasizes the submission of and evaluation by drug formulary (pharmacy and therapeutic) committees, unpublished as well as published articles. Without the arguments set forth here, one might perceive this recommendation as superfluous, a matter of being complete for the sake of completeness. However, in this context of evaluating the benefit-harm balance in antidepressant drug therapy, the need for examination of unpublished studies is far from superfluous. Examination and evaluation of the unpublished literature are an essential part of defining the evidence in evidence-based medicine.

In April 2004, Whittington, Kendall, Fonagy, et al. reported the results of a meta-analysis of data from RCTs that evaluated the use of SSRIs versus placebo in participants aged 5 to 18 years. Their pooled data were derived from unpublished studies as well as articles that were published in a peer-reviewed journal and included in a review by the U.K. Committee on
Safety of Medicines. The published articles would lead one to conclude that the evidence pointed to benefits outweighing risks in the treatment of childhood depression with SSRIs, particularly fluoxetine. However, the data from the unpublished studies lead to the opposite conclusion, that the risks outweighed the benefits of treatment of childhood depression with SSRIs, except fluoxetine. Specifically, data from 2 published trials suggested that fluoxetine has a favorable benefit-risk profile, and the unpublished data supported this finding. Published results from 1 trial of paroxetine and 2 trials of sertraline suggest equivocal or weak positive benefit-risk profiles. However, in both cases, addition of unpublished data indicated that risks outweigh benefits. Data from unpublished trials of citalopram and venlafaxine showed unfavorable benefit-risk profiles. Overall, the published data suggested a favorable benefit-risk profile for some SSRIs; however, addition of unpublished data indicated that risks could outweigh benefits of these drugs (except fluoxetine) to treat depression in children and young people.

In an editorial accompanying the work by Whittington et al., impassioned writers decried the commercial interest in clinical research and the medical literature and its consequences in clinical practice when physicians follow the alleged evidence from the published literature. The Lancet editors also pointed to excerpts printed the previous month (March 2004) in the Canadian Medical Association Journal from an internal drug company memorandum that demonstrated how the company sought to manipulate the results of published research. For example, the memo stated, “it would be unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.” Despite the prohibition of treatment of children with SSRIs (except fluoxetine) imposed by the U.K. Committee on Safety of Medicines in 2003, the FDA in April 2004 “failed to act appropriately on information provided to them that these drugs were both ineffective and harmful in children.” This editorial concluded, “In a global medical culture where evidence-based practice is seen as the gold standard of care, these failings are a disaster.”24 In October 2004, the FDA requested new “black box” labeling on 32 antidepressants warning of increased risk of suicidality when used in children,25 followed by a request for all manufacturers to include notice of the new risk warning in direct-to-consumer advertisements on or before February 11, 2005.26

United States, the Last Venue for Direct-to-Consumer Advertising, Props Up the Erectile Dysfunction Market

Researchers at the Harvard School of Public Health, Massachusetts Institute of Technology, and Harvard Medical School for the Kaiser Family Foundation found that direct-to-consumer advertising (DTCA) accounted for about 12% of the growth in prescription spending in 2000 or about two thirds of the increase in prescription spending that year. Each additional dollar of DTCA generated $4.20 in prescription spending, a more than 4-fold return on investment. DTCA accounted for 14% of total prescription promotional spending in 2000, and the remaining 86% was spent on physician promotion, including 55% for drug samples, 29% for physician detailing, and 2% for medical journal advertising.27

In 2005, New Zealand joins a long list of countries that have banned DTCA of prescription drugs, leaving the United States as the only industrialized country to allow full DTCA of prescription drugs.28 The reasons for opposition to DTCA include increased use of drug and medical services, leading to increased wealth for pharmaceutical, advertising, and media companies.29 Prohibition of DTCA was found by an Australian review to produce a net benefit for the community as a whole,30 and a report presented in the Canadian legislature in 2004 recommended against DTCA, stating that “drug advertisements could endanger rather than empower consumers by minimizing risk information and exaggerating benefits” and “could contribute to increased or inappropriate drug consumption.”31

Mansfield, Mintzes, Richards, and Toop call for a complete ban on DTCA of prescription drugs, arguing that DTCA does more harm than good. Mansfield et al. cited the study released in 2001 by the National Institute for Health Care Management Research and Educational Foundation in which DTCA was most profitable for expensive new drugs as well as 2 other studies in which even unbranded advertising (i.e., of a disease state) can increase the use of sumatriptan for migraines, or terbinafine, at the expense of itraconazole, for onychomycosis.32

Impotence is the most common condition identified in physician visits attributable to DTCA, accounting for 16% of DTCA physician visits, compared with anxiety (9%) and arthritis (7%), the second and third most common conditions associated with DTCA-precipitated physician visits.33 Further evidence of the value of DTCA in generating sales of drugs for erectile dysfunction (ERD) can be found in the decision by GlaxoSmithKline (GSK) in January 2005 to sell to marketing partner, Bayer AG, its share of the marketing rights for vardenafil (Levitra) outside the United States. GSK attributed its decision to slow market growth for the ERD drugs and bans on DTCA outside the United States—to the fact that it is difficult to sell ERD drugs without consumer ads.34 Vardenafil accounted for about 13% of the total $1.3 billion in U.S. sales of ERD drugs in 2004.

Campbell, in this issue of JMCP presents in near-identical facsimile the clinical monograph for ERD drugs that was presented to the pharmacy and therapeutics (P&T) committee of one of the largest pharmacy benefits managers in the United States.35 As with the clinical monograph by Fisher in a previous issue of JMCP,36 one purpose of these articles is to make public specific examples of the “evidence” that is considered in the process of evidence-based decision making by drug formulary.
Managed care pharmacists and other professionals responsible for the cost-effective use of ERD drugs in pharmacy benefit plans will no doubt be interested to know that more than half of the ERD tablets consumed in the United States in the first half of 2004 came from physician samples, up from 30% in the year-earlier period. Perhaps this means that managed care pharmacists and administrators have finally found a combination of DTCA and drug sampling that they can support—or maybe not.

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Editorial Subjects—In This Issue and in Previous Issues


2004 JMCP Award for Excellence Conferred to Delate, Fairman, Carey, and Motheral

“Randomized Controlled Trial of a Dose Consolidation Program” Wins Top JMCP Award

The article by Thomas Delate, PhD; Kathleen A. Fairman, MA; Shelly Carey, MMR; and Brenda R. Motheral, PhD, was selected for the 2004 JMCP Award for Excellence based upon 5 criteria, in order of importance: potential impact on the profession or knowledge, relevance to managed care pharmacy today, scientific merit and sound methodology, clarity of purpose and hypothesis, and writing quality and readability. The judges concluded that this article employed a sound methodology to test the impact of a tool used in managed care pharmacy. The findings of this study might be used by others in decision making about allocating scarce resources to influence the outcomes of managed care pharmacy interventions.

The 2004 JMCP Award for Excellence was determined in January 2005 by 7 judges, 3 from the JMCP Editorial Advisory Board (Fadia Shaya, PhD, MPH; Steven Pepin, PharmD, BCPS; and Kent Summers, PhD) and 4 from the pool of top peer reviewers in 2004 (Lisa Edwards, PharmD; Marilyn Stebbins, PharmD; Joshua Benner, PharmD, ScD; and Scott Bull, PharmD). This article appeared in the September/October 2004 issue of JMCP.

REFERENCE

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 subjected 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.
Medication Therapy Management Programs: To Optimize Pharmacy Outcomes

To the Editor:
The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) has introduced Medication Therapy Management (MTM) as a program requirement for prescription drug plan sponsors and Medicare Advantage plans under the new prescription drug benefit that will become available in 2006. MTM is defined as a program of drug therapy management and medication administration. The goal of MTM is to ensure that drugs provided to eligible beneficiaries are appropriately used to (a) optimize therapeutic outcomes through improved medication use and (b) reduce the risk of adverse events, including adverse drug interactions.

The potential benefits of MTM appear to be clear. There are numerous programs and initiatives throughout the country in a wide range of settings that fall within the continuum of activities and services that would be defined as MTM services. Nevertheless, MTM is in its formative stage with no specific “best practices” or quality assurance standards yet articulated or fully evaluated.

The American Society of Health-System Pharmacists (ASHP) and the Academy of Managed Care Pharmacy (AMCP) convened two Executive Sessions on Medication Therapy Management programs to bring together stakeholders with both an understanding of the concepts of medication therapy management and the need to operationalize those concepts. During these sessions, many aspects of MTM were discussed. Active dialogue was encouraged as participants were asked to share opinions on opportunities and issues related to the implementation of MTM under MMA. Consensus was not sought on any aspect of the discussion. The following document is a summary of the discussion.

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Editor’s note: This summary is published simultaneously in the March 15, 2005, issue of the American Journal of Health-System Pharmacists.

Summary of the Executive Sessions on Medication Therapy Management Programs
Bethesda, Maryland
June 14 and August 18, 2004
Pharmacists and other health care professionals, as well as Medicare beneficiaries, had reason to welcome passage of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173). The act requires, among other things, that all prescription drug plan sponsors participating in Medicare Part D and Medicare Advantage plans providing a drug benefit under Part D offer a medication therapy management (MTM) program to help ensure that drugs are used to “optimize therapeutic outcomes through improved medication use and to reduce the risk of adverse events, including adverse drug reactions,” in certain high-risk patients.

The Medicare beneficiaries targeted by the MTM program are those who have multiple chronic conditions, are taking multiple medications, and are likely to incur high drug costs. The opportunity for the MTM program to influence the quality and cost of care purchased by Medicare is extraordinary. Just under 80% of Medicare beneficiaries have multiple chronic conditions, and 20% of Medicare beneficiaries have five or more chronic conditions, with the latter group accounting for over two thirds of Medicare spending. In general, health care spending for a person with one chronic condition is 2 times greater than spending for someone without any chronic conditions, while spending is about 14 times greater for someone with five or more chronic conditions.

For these patients, the law provides access to a range of professional services designed to improve the safety and efficacy of drug therapy. For pharmacists, this presents a new and important opportunity to collaborate with patients and other health care professionals to improve medication-use outcomes. The federal government hopes that the act will not only bring about better patient outcomes but also will moderate the rate at which health care and drug costs have increased in recent years.

The Centers for Medicare and Medicaid Services (CMS), which will administer the new benefit, is well aware of the complex issues surrounding the act’s implementation. In fact, the proposed rule implementing the 2006 prescription drug benefit, issued by CMS on July 24, 2004, is unusual in that it seems to raise as many questions as it answers. As CMS develops the final regulations governing the act’s implementation, it is seeking input on such major issues as the criteria for eligibility for MTM services, the scope of core services to be provided, and the qualifications of service providers.

To provide an opportunity for individuals in the private sector who will be responsible for implementing the MTM programs to explore these issues, the American Society of Health-System Pharmacists (ASHP) and the Academy of Managed Care Pharmacy (AMCP) recently convened two Executive Sessions on Medication Therapy Management Programs. The first session was held on June 14, 2004; the second took place on August 18. Both sessions were held at ASHP headquarters in Bethesda, Maryland. Participating were approximately 25 leaders representing pharmacy benefits management companies (PBMs), health plans, health care organizations, and state and national pharmacy organizations.
Participants engaged in frank and productive discussions but remained fully cognizant of antitrust requirements.

This report summarizes for the pharmacy community and drug plan sponsors the group's discussions with the aim of facilitating the successful implementation of MTM programs. Any specific views expressed were those of the individuals expressing them, and no endorsement is implied by other participants or the organizations that employ them.

**First Executive Session**

In welcoming remarks on June 14, ASHP Executive Vice President and Chief Executive Officer Henri R. Manasse, Jr. noted that an executive session is a forum designed to provide a safe space for the confidential discussion of critical social issues. The topic central to MTM—the safe and effective use of prescription medications by a vulnerable segment of the Medicare population—is one such issue. The participants in the executive session are leaders who are capable of using their spheres of influence to disseminate and advocate for any recommendations that emerge from the day's discussions. Although ASHP and AMCP would publish the meeting proceedings in their respective journals, none of the comments would have attribution, and the report summarizing the proceedings would be submitted to all participating organizations for review before publication.

One purpose of the first session was to provide an introduction to the scope and variety of current MTM-type services and the settings in which they are offered. Representatives from an academic health center, a state Medicaid pharmaceutical case management program, a health maintenance organization, and three PBMs shared information about their programs that are relevant to MTM. Participants then discussed elements that are key to the successful participation of drug plan sponsors in an MTM program, namely the core elements of an MTM program, enrollee eligibility criteria, and the similarities and differences between the services provided by integrated networks and those offered by stand-alone drug plan sponsors.

At the meeting's end, participants agreed that they had engaged in a productive discussion and expressed the desire to reconvene.

**Second Executive Session**

As the August 18 meeting opened, AMCP Executive Director Judith A. Cahill summarized some basic assumptions and established objectives for the day. These objectives were as follows:

- Provide an opportunity for interested parties to discuss and gain a better understanding of the MTM program requirement in the Medicare Prescription Drug, Improvement, and Modernization Act and the proposed regulations that would facilitate implementation of that requirement.
- Develop a broad framework for drug plan sponsors to meet the MTM program requirement, with a focus on defining the core elements of an MTM program and measurement criteria to determine whether a plan's MTM program is achieving the objectives as set forth in the statute—optimization of therapeutic outcomes for beneficiaries by promoting appropriate medication use, detection and reduction of adverse drug events, increased adherence to medication regimens, and identification of patterns of overuse and underuse of medications.
- Encourage meeting participants to consider the discussions that occurred during these meetings as their organizations develop comments on the MTM program requirement for submission to CMS on the proposed regulations and as they begin to develop their organizations' MTM program.

Cahill stated that the general design of the MTM program defined in the proposed rule shows that CMS had heeded the advice offered by the Pharmacist Provider Coalition (PPC), a group of pharmacy organizations whose goal is to ensure that pharmacists are recognized as providers in Medicare Part B. PPC had endorsed and shared with CMS seven core principles that it believes should guide CMS and drug plan sponsors in the implementation of the MTM provisions of the Part D prescription drug benefit.

In the preamble to the proposed rule, CMS has shown that it is flexible and open to suggestions. It has not produced a dictum or a directive; indeed, noting lack of extensive experience in the design of MTM programs and wanting to encourage innovation, CMS chose to suggest options and welcome comments on how the programs can be more sharply defined.

Although much is uncertain, the preamble makes several important points that served as a foundation for the day's discussions. With respect to defining core MTM program elements, the preamble mentions several services in addition to those named in the statutory language, such as assessment of health status, education of family members, coordination of therapy, and collaboration among providers. The preamble reiterates that MTM services are distinct from drug dispensing. It also underscores that MTM services must be patient-specific.

The statute sets forth three eligibility criteria: Enrollees must (1) have multiple chronic diseases, (2) take multiple Part D-covered drugs, and (3) be likely to incur annual drug costs that exceed a certain level. CMS proposes to give drug plan sponsors the discretion to further define the beneficiary categories as part of their benefit design, even for the criteria the statutory language explicitly designates to be defined by the U.S. Secretary of Health and Human Services.

The law designates pharmacists as MTM providers, but it also allows others to provide MTM services. It does not define who these other providers might be.

The law provides that drug plan sponsors shall pay MTM providers on the basis of the “time and resources used” to provide services, but the proposed rule does not give drug plan sponsors any additional guidance.
MTM programs are to be included as components of the Medicare drug benefit that would be offered by prescription drug plan sponsors under Part D and Medicare Advantage plans providing a drug benefit under Part C; there is no separate payment for the MTM program. This poses a particular challenge for drug plan sponsors that offer a drug-only benefit because they will not reap the benefit MTM promises in terms of reduced visits to physicians’ offices and hospital emergency rooms. In fact, the program may at times increase drug costs; therefore, some participants recommended that CMS consider allocating a separate payment for MTM services, even though that is not consistent with the statutory requirement.

CMS is requesting information on current best practices, quality-assurance considerations, and the development of tools, such as scorecards, that will enable beneficiaries to compare MTM programs offered by drug plan sponsors.

Discussion Themes

On the basis of comments made at both sessions, it was evident that participants held a number of baseline assumptions. Among the most important are the following:

- With MTM, the government has made a major commitment to the safety of drug therapy. The program acknowledges a societal imperative to take measures to effect optimal patient outcomes for a group of high-risk individuals. As it enters this new territory, CMS can benefit from guidance from the pharmacy profession and drug plan sponsors. Assistance in defining core MTM services is essential. Meeting participants agreed that MTM should go beyond traditional pharmacy services, dispensing and counseling, and brown-bag medication reviews, though recognizing the value of such services.

- MTM programs offer an enormous opportunity to pharmacy, and pharmacy is, in general, prepared for the challenge. The basic structure or capacity for realizing MTM goals is in place; however, it will have to be intensified. Working relationships must be modified and expanded, and contractual relations must be established. The profession may also have to consider creating new credentialing programs and enriching the pharmacy curriculum, particularly in such areas common to the Medicare population (e.g., geriatrics and services for disabled patients).

- Although some MTM services will reduce drug costs, MTM programs cannot always be expected to do so; some compliance and adherence programs designed to optimize therapeutic outcomes may result in higher drug spending. CMS and drug plan sponsors cannot expect a quick financial return on investment when drug cost is the only consideration. For this reason, as well as the uncertainties currently surrounding the program, some plans may initially be reluctant to apply to participate.

- Because the investment is large and the stakes are high, accountability will be essential. Measuring short- and long-term outcomes and ensuring individual and organizational competence will be vital. Pharmacy-management-specific criteria are also essential. The lack of data and data latency will be problematic but not insurmountable.

- CMS’s desire for input from pharmacy will encourage the innovative thinking needed to ensure high-quality, cost-effective MTM services.

Core Elements of MTM Programs

The purpose of an MTM program, according to the preamble of the proposed regulations, is to “provide services that will optimize therapeutic outcomes for targeted beneficiaries.” Such programs may include elements designed to promote enhanced enrollee understanding, increased enrollee adherence, and detection of adverse events. Possible services noted in the preamble include performing patient health status assessments, formulating prescription drug treatment plans, managing high-cost and specialty medications, evaluating and monitoring patient response to drug therapy, providing education and training, coordinating medication therapy with other care management services, and participating in state-approved collaborative drug therapy management.

Seven of the services listed in the proposed rule also appear in a document entitled “Medication Therapy Management Services Definition,” which was approved by a group of 11 national pharmacy organizations in July 2004. The box (above) lists the services agreed upon by the pharmacy organizations; items appearing in italics (i.e., items a, b, d, f, g, h, and i) also appear in the proposed rule.
Attendees generally agreed that MTM could include a broad scope of services beyond the traditional counseling associated with dispensing services and that pharmacy should be able to not only assume responsibility for providing these services but also be held accountable for the outcomes of such services.

At the same time, members noted that the elements would require fine-tuning to be useful. Such elaboration would be needed both to limit the scope of work and to make it possible to assess outcomes. For example, in its application, a drug plan sponsor might state that it would be responsible for the prevention of medication-related problems for a designated list of medications but not for drugs in general.

A key service not mentioned on either list was prevention. In keeping with their professional mission and the goal of this legislation, pharmacists should, it was suggested, take a more proactive role in preventing the progression of chronic disease. To emphasize pharmacy's expanded role in the continuity of care, the suggestion was made to include in the list references to services that can be provided at specific stages in the care process where gaps commonly occur. One such time is at discharge from a hospital.

While participants agreed that this spectrum of services should be available to every eligible enrollee, each practice setting may not provide all services. For participating drug plan sponsors, the goal will be to design a system in which a patient meeting the plan’s criteria will be ensured of receiving appropriate services, whether from the plan itself or through a contract or subcontract between the plan and another entity or individual.

Identification of Target Beneficiaries

MTM services are of potential value to every patient, but drug plan sponsors are not required to provide them to every beneficiary. Resource allocation is essential. Drug plan sponsors must develop a rationale that establishes the criteria on which they will determine MTM eligibility, with the understanding that, for a variety of reasons, some patients will not receive services from which they would otherwise benefit.

The proposed rules define eligibility broadly, stating that MTM beneficiaries are enrollees who have multiple chronic diseases, are taking multiple Part D-covered drugs, and are likely to incur annual drug costs that exceed a certain level.

Multiple chronic diseases. Existing data on the incidence and prevalence of chronic diseases in the Medicare population should be a prime source. Resource allocation is essential. Drug plan sponsors must develop a rationale that establishes the criteria on which they will determine MTM eligibility, with the understanding that, for a variety of reasons, some patients will not receive services from which they would otherwise benefit.

When determining the conditions on which their programs will focus, drug plan sponsors must bear in mind these types of considerations.

Multiple drugs. The extent of multiple drug use among the elderly and the wide differences in the costs of drug products make setting this criterion exceptionally difficult. A patient may be taking only one drug, but, if it is the wrong drug, this could have far-reaching implications for that patient's health outcome. Rather than establishing a cutoff definition of drugs on the basis of numbers alone, it might be beneficial for plans to use additional criteria beyond “the use of multiple medications.” These could relate, for example, to particular combinations of drugs, the nonuse of indicated drugs for certain diagnoses, or situations in which patients stop and resume therapy with drugs used to treat chronic diseases.

Costs. Defining eligibility on the basis of a single financial figure is problematic in many respects. The desirable figure for such a determination depends on one’s perspective. The prescription drug plan, the government, and taxpayers would want a different figure, for example, than would beneficiaries. Moreover, it is not just the big-ticket items that contribute to overall health care costs. A patient who spends relatively little on drugs can be at risk for high overall health care costs if the medications are not used appropriately.

If a cost threshold is set, a drug plan sponsor probably would not want to design its plan so that an enrollee becomes eligible for MTM only after having reached that set dollar amount. It would be preferable to use modeling to determine that the enrollee was on track to meet or exceed the amount and then initiate MTM to prevent that cap from being reached.

Other criteria. Patient populations other than those meeting the statutory definition of high risk, having multiple chronic diseases, taking multiple medications, and incurring high drug costs might benefit greatly from MTM. Among these are beneficiaries who see multiple physicians and multiple pharmacists or those who otherwise show a lack of evidence of coordination of care. Also, Medicaid-eligible Medicare beneficiaries may pose different socioeconomic or lifestyle-related risks.

Participants noted that drug plan sponsors might want to use predictive modeling tools to help identify targeted patients.

Importance of Outreach

Identifying potential eligible beneficiaries is only the first step in delivering MTM services. Once these individuals are identified, there must be a structured means to help them access services. This must be multifaceted, using not only the plans to identify beneficiaries but also physician and pharmacist referral.

Beneficiary participation in MTM programs will be voluntary; thus, an individual who meets the enrollment criteria may be identified and informed of the service but refuse to participate. Some informed seniors, on the other hand, might ask their pharmacists whether they can participate. That situation will
most likely not be the norm at the onset of benefit implementation. It will be necessary to reach out to potential benefit recipients, invite them to participate, and then follow up to ensure service coordination.

As pharmacists reach out to patients, they may confront a stark reality. With respect to pharmacy services, many patients have low expectations. In many cases, their only wish is to be assured that they have received the right medication. MTM gives pharmacists broader responsibilities and will require a corresponding rise in patient expectations.

Perhaps because of their greater dependence on medications, older Americans are often more likely than younger persons to have established a trusting relationship with a pharmacist. Nonetheless, many patients view their physician as the ultimate authority on medication use. Teaching a patient to expect these services from his or her pharmacist will require an educational outreach to beneficiaries and relationship building among pharmacists, physicians, and others in the beneficiary's network of care. The drug plan sponsor must reach out to patients and other caregivers with information about the program and what it can accomplish.

Outreach efforts must touch physicians as well. Physician buy-in is essential to the success of MTM programs. When issues relating to collaborative patient management arise, many physicians say they understand the need for such relationships but note that they are not familiar with the pharmacists practicing in community settings. In such a situation, physicians may be reluctant to collaborate with pharmacists.

Building relationships with physicians is essential. Community pharmacy residency programs may be one small way to build interprofessional trust in the community setting. Other methods must be explored, and MTM, by emphasizing continuity of care, can spur their development.

Finally, outreach efforts should include patients' family members and other nonprofessional caregivers. These individuals are especially important in the provision of care to the elderly population. Caregivers themselves, as well as enrollees, may need MTM services.

A Strengths-Based Approach

MTM services will be patient-specific, focused on achieving the desired outcomes in an individual patient. Participating drug plans must design their programs and configure their services in the way that will best ensure attainment of this goal. In some cases, the dispensing pharmacist may be the pharmacist who provides all or most of a patient's MTM services; in others, it will not. A patient who purchases drugs through the mail, for example, could receive MTM services from pharmacists on staff with the mail-order service or from a local pharmacy provider. A patient who purchases drugs at a local pharmacy could receive MTM services from another MTM provider.

Meeting participants emphasized the need for a strengths-based approach; drug plan sponsors must develop a plan that capitalizes on its strengths, defines its services, and then lets the patient choose the plan in which he or she wishes to enroll.

Plan sponsors are likely to base their program on existing strengths and capabilities and then make arrangements to ensure that its enrollees can secure needed additional services elsewhere. The plan sponsor would design an MTM program that would identify potential enrollees at the time they entered the plan, bring them into the MTM program, create the scope of services around patients’ needs, and use triage, where necessary, to ensure that patients receive necessary services. Some meeting participants noted that a drug plan sponsor with a mail-service (or mail-order) pharmacy may use its clinical pharmacy call center as a starting point for the provision of MTM services. A community pharmacy, or any other setting, would use a similar strengths-based strategy—devising an MTM patient care approach (from identification and enrollment to actual provision of services) based on its current strengths.

There may be service bifurcation as plans call on their different internal strengths and rely on networks or contracts to ensure that enrollees receive specialized services or services that entail the collaboration needed to offer continuity of care. MTM programs will continue to evolve to best meet the needs of individual patients.

Referral for MTM Services

A comprehensive menu of services is meaningless if it is underused. For this reason, the manner in which services are triggered is a major concern. In preparing its proposal, the drug plan sponsor must articulate its criteria for determining that a patient needs MTM services and provide opportunities for multiple points of referral. Ideally, anyone in the continuum of care should be able to make a referral, including community pharmacists, who are often in an ideal position to identify patients in need of such services.

Reliance on any single source would be too limiting. Experience with other federally supported programs has shown that if referral is dependent on physicians alone, for example, it is likely that many patients will be missed and that MTM services will be underused.

These points of referral might be episodic and related to a particular point in the continuum of care. For example, they might occur when a patient is discharged from the hospital to home or to an assisted-living facility.

Plans must also develop a plan for determining how they will ensure the delivery of services. The patient should be referred to the provider; the drug plan sponsor would then decide whether its model accommodates the service requests.

To ensure continuity of care, it was noted that recommendations made through MTM programs would need to be coordinated with the initiatives of the new Chronic Care Improvement Program.
Qualifications of MTM Providers

The act does not set educational or experiential criteria for pharmacists or other qualified providers of MTM services. Pharmacists seem to be seen as the primary providers of MTM services; however, this is not explicit. Meeting participants agreed that drug plan sponsors would need some flexibility to determine who qualifies under their program and might consider prospective providers’ training, education, and experience.

A graduate of a doctor of pharmacy (PharmD) program should be capable of providing core MTM services, most group members agreed, even though a recent graduate may lack the in-depth experience needed to handle the most complex cases. Some new graduates and seasoned practitioners may need additional education and training in geriatrics to meet the needs of this population. Pharmacists with certification in certain specialties are well prepared to provide core MTM services in those specialty areas, although their numbers are insufficient to limit the provision of MTM services to these pharmacists. Pharmacists with a bachelor of science degree and no certification, but with years of experience in the appropriate setting, are also well qualified to provide MTM services.

Meeting participants suggested several ways of tackling these interlocking challenges. First, any drug plan sponsor should ensure that its work force is diverse and complementary in terms of experience, skills, and knowledge. Plans can set an educational and experiential profile and use it as a reference point when hiring new employees or contracting with community-based pharmacists or other MTM providers. Plans should offer incentives that encourage their work force to attain new levels of achievement.

It was suggested that the profession may need to explore new credentialing paradigms. The entry-level PharmD degree and specialty certification have brought a new level of excellence to the profession. Other forms of recognition, tailored to the needs of MTM programs, could be developed.

One participant suggested that CMS could eventually develop conditions of participation for plans. Given the diversity of program settings and patients’ needs, defining meaningful baseline criteria would be difficult.

Ensuring that pharmacists are prepared to provide high-quality MTM services in sufficient capacity to meet the needs of MTM programs is ultimately a deployment issue for the entire profession. It will require collaboration among employers and educational institutions. The latter must make sure that their curricula prepare graduates adequately to provide MTM services. Employers must realize that pharmacists, no matter how knowledgeable and skilled, must practice in a professional work environment that is conducive to providing high-quality patient care services in order for MTM to be successful.

The proposed rule states that, in addition to pharmacists, other health care providers can have roles in MTM. Who these professionals might be and what roles they might assume will depend on enrollee characteristics, core elements, and health care settings defined elsewhere in the drug plan sponsor’s proposal.

Ensuring Accountability

Those attending the executive sessions had no doubt that CMS will hold drug plan sponsors and those who work for or contract with them accountable for the outcomes of MTM services. They prefaced their discussions of accountability with two overarching thoughts. The first is that being held accountable for the outcomes of MTM services is a landmark—pharmacists will move beyond simply being responsible for such services. The second idea, expressed succinctly by one attendee, is that good management requires accountability mechanisms: “You cannot manage what you cannot measure.”

Although agreeing on the need for accountability, participants had many questions concerning how it will be ensured under MTM. A basic question is: Who will be held accountable? The plan and the provider may not be the same entity. If the drug plan sponsor is held accountable, how will it delegate accountability to the provider?

Outcomes measures for an integrated network will differ from those of a freestanding plan. Although some measures will be shared, others will not. Issues relating to collaboration and continuity of care, for example, must be addressed by integrated plans. Sponsors of such plans are also interested in total outcomes, expressed by such criteria as reductions in overall hospitalizations. Stand-alone plans do not currently have the medical data on which to evaluate the role their services play in achieving such a goal.

One solution, stimulated by MTM discussions, is to design plans in a manner that will blend the population-based focus of PBMs with the traditional individual responsibility of the provider. MTM will require the formation of networks. To make the program work, a means must be found to merge pharmacy claims data with medical data.

The need for data is an overriding problem. National data, available from the National Committee for Quality Assurance’s HEDIS (Health Employee Data and Information Set) and Medicare’s quality improvement organizations, can be tapped. High-quality outcomes measures, such as the Study of Clinically Relevant Indicators for Pharmacological Therapy (SCRIPT) measures developed by CMS and the Medication Appropriateness Index developed by the Veterans Affairs Measurement Excellence and Training Resource Information Center, will likewise be helpful, particularly when geared specifically to the geriatric population.

The bottom line with respect to data, as one participant noted, is that “you’ve got to work with what you have.” Good work can be done in ensuring accountability, even though the data are not perfect or complete. At the same time, given the
importance of data sharing, information technology will be crucial to the success of programs from multiple standpoints—for transferring information among health care providers, between plans and providers, and between providers and patients and for capturing claims data and other information needed for measuring outcomes and determining costs. CMS may want to consider investing in a means to ensure efficient data transfer that can be used by all program participants. Such a tool would be invaluable in ensuring inter-program consistency.

Need for MTM-Specific Outcome Criteria
Ultimately, CMS will most likely be the source of the data most needed by drug plan sponsors to assess both long- and short-term outcomes of MTM programs. If, as these programs get under way, CMS could develop criteria to compare the impact of different MTM programs on Medicare beneficiaries’ overall health needs, it would create a more complete picture with which to measure MTM programs’ success. CMS is developing the capacity to issue monthly claims feeds. It will provide these data to the Chronic Care Improvement Program participants and could also make them available to drug plan sponsors.

In light of the absence of direction from CMS and access to historical data, the profession itself should develop a set of measures that drug plan sponsors and CMS can use to assess the success of MTM programs. Participants from pharmacy organizations suggested that they could, through their respective foundations, create a subcommittee that could survey the literature, hold a research-based discussion, and develop such indicators.

The assumption underlying any such effort should be that a reduction in overall drug costs is just one criterion on which to rate the success of a program. Some aspects of MTM will increase drug costs.

Working on this premise, participants sought to identify some cost-, condition-, and process-specific guidelines that could be used as criteria to assess MTM services. Among those named were adherence to the medication regimen and decreases in rehospitalization rates. Some criteria can be condition-specific; however, given that enrollees will have multiple conditions and that the effects of these conditions are more than additive, focusing on conditions alone yields limited data. The National Center for Health Statistics has data on Medicare beneficiaries that may be helpful in setting these types of criteria.

Patient satisfaction is an outcome measure. Plans will need to devise ways to secure patient-satisfaction data from enrollees themselves. If patients are not satisfied, they will change plans. Such measurement tools need not be overly sophisticated. Questions such as “Was your pharmacist responsive to your needs?” or “Did you have access to the pharmacist?” could serve as a starting point. Plans should likewise survey physicians to gauge their satisfaction with pharmacy services.

As valuable as discrete indicators are, there is a danger that, in focusing on them, the overall objective of enhanced patient care through improved medication use could be lost. Plans cannot focus too much on certain indicators, no matter how informative, at the expense of others. Ensuring an appropriate balance should be the responsibility of drug plan sponsors.

Economic Incentives for Participation
Among the many factors that surround the design and implementation of MTM services, none is more important—or less predictable—than how many drug plan sponsors will decide to apply to participate in the programs, particularly at the outset.

Because MTM programs are currently so loosely defined, many uncertainties exist. Noting that the program may add financial risk, one participant suggested that participating plans might want to ensure the MTM segment of their plans against financial loss. Yet another issue is the fundamental difference in care needs, even among this identified high-risk population. One participant praised the program structure because, by offering the possibility of risk adjustment, it will offer plans an incentive to manage complex patients. Previously, plans might have been reluctant to accept such patients because of a fear of adverse economic consequences. Under MTM, a plan that successfully manages patients with diabetes, for example, may choose to try to attract this patient group because of the risk adjustment.

Some stand-alone plans may see few economic incentives—and a great deal of work—associated with offering an MTM program. Others may view the program as a way to create win-win situations for themselves and their beneficiaries.

Participants presumed that CMS will expect a return on its investment, although it has also made a commitment, with MTM, to safe drug use. The Bush administration has placed a strong emphasis on competition in the marketplace, and CMS may see program applications as an opportunity to identify and test a broad range of programs and ensure that it gets the best outcomes for the smallest investment. For the drug plan sponsor, the goal will be to submit a bid that is low enough to get the business but high enough to make participation feasible.

With respect to economic incentives, participants underscored two important elements. First, CMS must assess the MTM component of proposals separately from drug costs and must use consistent, well-defined criteria in making these assessments. The MTM segment of a plan’s proposal should account for a specific percentage of the overall score. If MTM services do not receive separate treatment, participants will lack the incentive to perform them well.

Second, CMS must set realistic expectations. If a plan proposes to serve 3% of its Medicare enrollees, CMS cannot demand that it serve 6%, unless CMS is willing to accept a corresponding decrease in the breadth of services provided to each of these individuals as well as less-desirable results. Tradeoffs will have consequences.
To the Editor:

In reviewing a recent article for JMCP publication consideration, I had the opportunity to truly understand the importance of peer review. A good general concept is not sufficient—the information must be accurate and presented in a clear manner.

As a manager of clinical pharmacy services for a moderate-sized Medicaid managed care plan, there were numerous subjects that I considered to be of critical interest for managed care pharmacists. Volumes of information are published on new medications, and I had limited time to read them. When I did read, I expected the literature to be clear and of high quality. As a result, I selected a limited group of journals that I viewed as my weekly or monthly “must reads.”

JMCP was one of them. Until taking the time and seizing the opportunity both to author and participate in peer review for JMCP, I never valued the magnitude of importance that quality peer review provides. As authors, we often become so passionate about our ideas and publication submissions that we do not recognize or appreciate the need for a second opinion or clarification. Peer review provides that opportunity.

In my review of a recent manuscript on the economic impact of the use of various psychotropics, I felt that including critical information related to the rationale behind comparing selected agents would clarify the authors’ objective in writing the article. This is one of several suggestions that were made by reviewers with the intent of increasing the clarity of the article.

Managed care pharmacy encompasses an ever-expanding magnitude of clinical areas, and the range of disease states and topics that formulary managers and P&T committees encounter on a daily basis makes it critical that the articles they read are both comprehensible and accurate. Managed care practitioners rely heavily on the experts in their fields to paint a clear picture of both the concept and the details. For that reason, it is essential that publications such as JMCP have, and continue to nurture, a team approach in the writing and review of high-quality literature. Good authors and focused reviewers working together provide the best chance for production of quality publications.

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