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JMCP EDITORIAL POLICY

EDITORIAL MISSION AND POLICIES

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JMCP EDITORIAL POLICY
Glass is something that most people probably take for granted—a material found in everyday objects such as windows, mirrors, bottles, jars, and light bulbs. Skilled glassblowers are able to use this ordinary substance to create extraordinary pieces of art.

"The art of glassblowing was first discovered in the Middle East along the Phoenician coast in 20 B.C. This new technique changed the use of glass from jewelry and ornaments to necessities. Glass containers and other items of high quality (even windowpanes) were found in the ruins of Pompeii.

"Glassblowing of vases and art objects is still done in basically the same way as it was originally done. Glassblowers (gaffers) use a hollow iron pipe about four feet long. The gaffer dips the pipe in the melt [melted glass in the furnace], and rolls a small amount of molten glass (gather) on the end, then rolls the gather against a paddle or metal plate to give it an initial shape (marvering). The gaffer then blows into the pipe creating a bubble (parison), controlling the shape and thickness by inverting the parison at the furnace and shaping and blowing it to create the form. Wooden paddles and wet newspapers held in the hand are all used to shape the glass. Glass of all types can be colored by the addition of metals, metal oxides or other compounds to the melt. The coloring agent will either suspend or dissolve in the glass." Richly colored glass chips and canes can also be rolled onto the gather and fused upon the surface of the glass in the furnace. For more information about the history and process of glassblowing, visit the Boise State University Web site. Glass containers and other items of high quality (even windowpanes) were found in the ruins of Pompeii.

One of Murano's most talented glass artists is Lino Tagliapietra, born on the island in 1934. He became an apprentice at age 12 in the glass studio of Muranese master Archimede Seguso and achieved the rank of "maestro" by the age of 21. During the next 25 years, he worked as a master glassblower at many important glass factories in Murano and Venice. Since the late 1970s, he has played a primary role in teaching Venetian glassblowing techniques to the younger generation of glassblowers throughout the United States and around the world. A partial list of educational institutions where Tagliapietra has lent his artistic expertise includes the Pilchuck Glass School, Stanwood, Washington; the Studio of the Corning Museum of Glass, New York; the Centre International de Recherche sur le Verre, Mulhonne, France; the Toyama Art School, Japan; and the University of Sydney, Australia.

Tagliapietra became known for his collaboration with other glass artists during the 1980s. The distinguished Dutch glass designer A.D. Copier may have had the greatest impact on his work. Of Copier, he said, "What did I learn from him? Not any technical skills, but more importantly, the way to see and think about glass objects as works of art." Tagliapietra also collaborated with several American artists working in glass, including Dale Chihuly and Dan Dailey. His reputation continued to grow in the 1990s, and he was widely recognized for his own unique works of art. Today, Tagliapietra is considered to be one of the greatest glass artists of all time. Susanne K. Frantz, former curator of twentieth-century glass at the Corning Museum of Glass, declared, "Lino Tagliapietra is one of the few glassmakers who can successfully transmit his own sensitivity and intellect into an inanimate object. That is what makes us respond so powerfully to his work and what makes him an artist."

Tagliapietra’s glass installation, Samba do Brasil, exemplifies his fluid, expressive technique. Intricate filigree lines enhance the curves of the blown-glass objects as they spiral upward in a sensuous dance of color and form. He has made the most of the lyrical relationship between art glass and light in the installation, and his overlapping placement of each piece has produced dramatic hues and patterns. Many more of Tagliapietra's magnificent glass installations and individual works of art can be seen at Holsten Galleries in Stockbridge, Massachusetts (www.holstengalleries.com) and Hawk Galleries in Columbus, Ohio (www.hawkgalleries.com). Some of the other U.S. galleries that represent him are: the Pismo Fine Art Glass galleries in Denver, Aspen, Vail, and Beaver Creeks, Colorado; William Traver Gallery in Seattle; Marx-Saunders Gallery in Chicago; and Heller Gallery in New York City. In Europe, his artwork can be found at the Galleria Marina Barovier gallery in Venice.

Tagliapietra’s award-winning glass art has been exhibited worldwide, and his work is in the permanent collection of numerous major museums. Several pictorial books have been written about this gifted artist and his spectacular work, including Tagliapietra: A Venetian Glass Maestro, edited by Marino Barovier, and Lino Tagliapietra: Vetri Glass Vivos Glass, edited by Giovanna Sarpellon. Sheila Marcho
Cover Editor

COVER CREDIT
Lino Tagliapietra, Samba do Brasil, glass installation, Seattle, Washington.
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SOURCES
http://chemistry.boisestate.edu/tanks/glassblowing/glassblowing_history.htm.
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☐ abstract: no more than 500 words
☐ 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.

Go to disclosure of conflict-of-interest forms: completed and signed author attestation forms (available at www.amcp.org); clearly indicate source(s) of funding and financial support.

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1. Standard journal article
(List all authors when 6 or less, if more than 6, list only the first 3 and add et al.)

2. No author given
ABSTRACT

OBJECTIVE: To determine which factors are associated with use of atomoxetine (ATX) relative to stimulant medications (STIMs) for treatment initiation in adults with attention-deficit/hyperactivity disorder (ADHD). A similar exploratory analysis of the use of ATX versus STIMs in children has been published previously.

METHODS: This was an exploratory analysis using a retrospective observational cohort design applied to administrative pharmacy and medical claims from an integrated managed care database. Patients were identified if they had at least 1 administrative claim with a diagnosis for ADHD. Treatment “initiation” was defined as a new prescription for an ADHD medication preceded by 3 months without similar therapy. Two separate analyses were done, one comparing medication starts for ATX with those of any STIM, the other comparing starts of ATX with long-acting stimulants (LA-STIMs). Logistic regression analyses of prior-year administrative claims were used to compare the frequencies of differential predictors of the use of medication.

RESULTS: There were 10,359 patients aged >18 years who initiated ATX or a STIM between April and December of 2003 and had at least 1 claim with a diagnosis for ADHD (International Classification of Diseases, Ninth Revision, Clinical Modification codes 314.0x). Approximately one third (28 of 82) of the comparisons related to patient demographics, diagnostic history, and previous treatment history was found to be related to the use of ATX versus STIMs and/or LA-STIMs. Patients were more likely to have received ATX than a STIM if they had prior diagnoses of bipolar disorder (odds ratio [OR] 1.47; 95% confidence interval [CI], 1.16-1.87), alcohol dependence (OR 1.80; 95% CI, 1.26-2.58), anxiety (OR 1.21; 95% CI, 1.05-1.40), previous use of antipsychotic medication (OR 1.55; 95% CI, 1.22-1.96), or previous antidepressant use (OR 1.14; 95% CI, 1.01-1.28). Prior use of behavioral services greater than 12 visits was associated with the use of ATX relative to STIMs (OR 1.46; 95% CI, 1.20-1.77) but not for ATX relative to LA-STIMs. Conversely, ATX was used less often than STIMs for initiation in younger adults aged 18 to 24 years (OR 0.66; 95% CI, 0.58-0.74), female patients (OR 0.89; 95% CI, 0.80-0.99), patients with personality disorders (OR 0.53; 95% CI, 0.34-0.82), and those with prior use of STIMs (OR 0.62; 95% CI, 0.56-0.69). The majority of comparisons (54 of 82) related to demographics, diagnostic history, and previous treatment history did not show statistically significant associations.

CONCLUSIONS: During the first year of ATX’s market introduction, some differences in the frequency of various clinical factors were found in adults treated with ATX compared with those patients who received STIMs. This association may suggest that STIMs and ATX are used to address different treatment needs in adults with ADHD. Future studies will need to determine the significance of the practice pattern differences inferred here and if they persist after ATX has been on the market longer.

KEYWORDS: Atomoxetine, Stimulants, Administrative claims, Treatment selection, Adult ADHD

J Manag Care Pharm. 2006;12(3):230-38

Factors Associated With Initiation With Atomoxetine Versus Stimulants in the Treatment of Adults With ADHD: Retrospective Analysis of Administrative Claims Data

DAVID L. VAN BRUNT, PhD; JOSEPH A. JOHNSTON, MD, MSc; WENYU YE, PhD; GERHARDT M. POHL, PhD; and NINA N. OHARA, PharmD

Atention-deficit/hyperactivity disorder (ADHD) is characterized by problems regulating attention and controlling behavior across social settings. Though predominantly viewed as a childhood disorder, there is growing recognition that symptoms often persist into adulthood. While the etiology of ADHD remains a matter of debate, there is a wealth of literature as to its effects. Persons with ADHD experience academic and occupational underachievement relative to their peers, have impaired social relationships with higher rates of divorce, and have higher rates of traffic violations and accidents resulting in injury. Untreated ADHD in children is also associated with an increased risk for substance abuse problems later in life.

Treatment options for ADHD include both behavioral and pharmacological therapies, with the latter more broadly applied and dominated by the use of psychostimulants. In 2003, a nonstimulant therapy became widely available, offering another pharmacologic alternative to the stimulant (STIM) group. U.S. Food and Drug Administration (FDA) approval for adult use of atomoxetine (ATX, Strattera) was granted after 2 studies of 10 weeks duration, each of which showed improvements on the Conners Adult ADHD Rating Scales. ATX differs from STIMs both in the mechanism of action and in adverse effects. Like other nonstimulants used for ADHD such as tricyclic antidepressants and bupropion, ATX can be safely used in patients with comorbid anxiety disorders, does not exacerbate tics, and lacks potential for abuse.

New treatment choices create new challenges. Physicians must balance the risks and benefits of expanding treatment alternatives to optimally care for their patients. In the early days following the approval of a new medication, this task may be
Factors Associated With Initiation With Atomoxetine Versus Stimulants in the Treatment of Adults With ADHD: Retrospective Analysis of Administrative Claims Data

particularly daunting. The available evidence upon which clinical decisions for new drugs are based often consists of results from clinical trials evaluating short-term efficacy in highly selected populations. While such trials are critical in establishing a drug’s efficacy prior to approval, trial populations and care delivery are often not representative of real-world clinical practice. This creates an information vacuum in the early days following a drug’s approval. Later, providers learn from practical clinical experience and additional studies which patients are best suited for the new agent. For instance, an interim open-label study was recently published that enrolled the patients from the initial short-term ATX trials. With a mean treatment length of 40 weeks, longer duration efficacy and safety data were added to the knowledge about ATX.

Until longer-term clinical trial data for ATX become available, examining emerging patterns of medication use may be informative for care of adult ADHD. Differences in treatment selection reflect not only marketing efforts but perceived medication successes and failures over time. In addition to providing clues as to where the drug may be most useful, managed care decision makers may find information on emerging patterns useful in deciding if use of a new product appears to be meeting previously unmet needs (versus being used interchangeably with existing and usually less costly therapies). From a risk surveillance perspective, understanding which patients are being selected for specific treatments may help provide important context in the event that adverse consequences become apparent. For instance, adverse events may be directly related to drug effects, but they also may be the result of increased baseline risk in the treatment group compared with baseline risk in the group receiving traditional therapy.

Three years after the introduction of ATX, administrative claims data are available to allow study of the early utilization patterns of ATX relative to STIM use for ADHD. We hypothesized that the use of ATX would be preferred in (1) patients with conditions that may be exacerbated by STIMs, such as tics and anxiety; (2) patients for whom present substance abuse is a concern, such as those with a history of alcohol or substance abuse; and (3) difficult-to-treat or treatment-refractory patients, such as those with comorbid psychiatric disorders (e.g., depression, psychosis, or personality disorders) or a recent history of non-pharmacological mental health treatment. In this article, we focus specifically on adults with ADHD. A similar examination in children of ATX versus STIM and long-acting stimulant (LA-STIM) use has been published previously.

### Methods

The current analyses were limited to adults (aged >18 years) because treatment priorities, diagnosis, and the importance of certain medication side effects are different for adults and children with ADHD. We focused on the examination of multiple demographic, diagnostic, and treatment factors preceding initiations of ATX and STIMs. Although bupropion and tricyclic antidepressants have been successfully used in adult ADHD and are commonly used as second-line agents, our study design intentionally excluded these drugs from the analysis since they are not approved by the FDA for the treatment of ADHD. Specific STIM medications and their categorizations are shown in Table 1 and are based upon the categorizations described by the Subcommittee on Attention-Deficit/Hyperactivity Disorder of the American Academy of Pediatrics’ Committee on Quality Improvement.

Because we were assessing the pattern of treatment in the year of ATXs introduction and because patient care often involves more than one agent over the course of time, we compared treatments based on the most recent treatment initiation for each patient. Since ATX is considered long-acting, we compared recent initiations of ATX with those of STIMs in general and with LA-STIMs specifically. This division into 2 sets of analyses created some replication of findings for STIMs as a class but also allowed for a more direct comparison between treatments of similar cost; the shorter-acting medications are readily available generically, and, thus, findings here may reflect the effect of confounding socioeconomic or other factors. Where findings are repeated across analyses, we have greater confidence that the findings are the result of differences in treatment approach rather than access per se.

Our data were drawn from the proprietary PharMetrics database. At the time of the study, this database consisted of administrative health care claims data from more than 75

<table>
<thead>
<tr>
<th>Subclass</th>
<th>Agent (Formulations or Brand Names)</th>
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</thead>
<tbody>
<tr>
<td>Short-acting stimulants</td>
<td>Methylphenidate (generic, Ritalin, Methylin)</td>
</tr>
<tr>
<td>(3–5 hour duration of action)</td>
<td>Desmethylphenidate (Focalin)</td>
</tr>
<tr>
<td></td>
<td>Amphetamine mixed salts (generic amphetamines*, Dexedrine, Dextrostat, Dexamfex, Biphetamine)</td>
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<tr>
<td></td>
<td>Methamphetamine (Desoxyn)</td>
</tr>
<tr>
<td></td>
<td>Pemoline (generic, Cylert)†</td>
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<tr>
<td></td>
<td>Modafinil (Provigil)‡</td>
</tr>
<tr>
<td>Intermediate-acting stimulant</td>
<td>Methylphenidate (generic ER/SR/CR/SA, Ritalin SR, Metadate ER, Methylin ER)</td>
</tr>
<tr>
<td>(5–8 hour duration of action)</td>
<td>Amphetamine mixed salts (generic amphetamines CR*, Adderall, Dexedrine spansules)</td>
</tr>
<tr>
<td>Long-acting stimulants</td>
<td>Methylphenidate (Ritalin LA, Metadate CD, Concerta)</td>
</tr>
<tr>
<td>(8–12 hour duration of action)</td>
<td>Amphetamine mixed salts (Adderall XR)</td>
</tr>
</tbody>
</table>

* Includes any combination of amphetamine, dextroamphetamine, or methamphetamine.
† Pemoline is no longer sold in the United States because of liver toxicity.
‡ Modafinil is not FDA-indicated for use in ADHD.
ADHD=attention-deficit/hyperactivity disorder; FDA=U.S. Food and Drug Administration.
managed care organizations covering more than 44.3 million lives. We limited our extraction of data from pharmacy and medical claims to patients with at least 1 filled prescription for ATX or STIMs and at least 1 recorded diagnosis for ADHD (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 314.0x). Because diagnoses and medication use in the 1-year period prior to drug initiation were evaluated as predictors of treatment selection, patients with less than 1 year of continuous enrollment prior to the most recent treatment initiation were excluded.

We defined a treatment “initiation” as a new prescription for an ADHD medication preceded by 3 months without similar therapy. The 3-month interval was chosen for consistency with our prior study of children,12 in which we acknowledged that gaps in treatment may occur during summer months even through college years. ATX was only first widely available in January 2003. To reduce the potential for a systematic bias related to the inclusion of very early adopters, treatment episodes were included with the first date between April 1, 2003, and December 31, 2003. Because “concurrent start” episodes (e.g., a patient’s having a qualifying treatment initiation for methylphenidate and ATX on the same day) could not be clearly assigned to only 1 comparison group, these patients were excluded from our analyses.

Pharmacy claims for ATX and STIMs were examined. STIMs with 8 to 12 hours duration of action were separately examined by comparing initiations of ATX with those of LA-STIMs in separate statistical models. A new treatment initiation was defined as a prescription for a categorized medication preceded by 3 months without that same medication or any other medication within the same treatment category (ATX, STIM, or LA-STIM). For example, a prescription for Concerta (long-acting methylphenidate) would constitute a LA-STIM initiation if, for the 3 months preceding that prescription, the patient was enrolled in the plan but showed no claim for Concerta or any other LA-STIM. This patient could, however, have received a short-acting STIM such as immediate-release (IR) methylphenidate; in that case, the prior short-acting STIM use would appear as a predictor for methylphenidate and ATX on the same day) could not be clearly assigned to only 1 comparison group, these patients were excluded from our analyses.

After categorizing patients according to their most recent pharmacological treatment initiation, selected demographic and historical diagnostic and treatment variables were assessed for the year prior to initiation for each patient (Table 2). These included the presence of common medical and psychiatric disorders (as indicated by ICD-9-CM codes within service claims) and medication use (as indicated by National Drug Code codes on pharmacy claims) within the 1 year prior to treatment initiation. Behavioral health care utilization rates were also assessed by computing the per-patient frequency of claims reflecting services for behavioral or psychological therapies (Current Procedural Terminology codes 90804 through 90831, 90842-90857, 90875-90889, 90901-90910, or 96100), visits to nonprescribing mental health specialists (such as psychologists and social workers), and claims with revenue codes consistent with the provision of nonmedication mental health therapy services as described by the Centers for Medicare and Medicaid Services (revenue codes 914, 915, 916, or 918). Behavioral health care utilization rates were categorized into “never used,” “1-12 visits,” or “>12 visits” in the past year.

Initiators of ATX were compared with STIM and LA-STIM initiators, in turn, on the basis of prior-year demographic and clinical characteristics using multivariate logistic regression. To avoid any collinearity that would result from including both an assessment of psychiatric conditions and the medications used to treat them in the same model, separate models were used to examine the associations between treatment initiation and (1) diagnostic history and (2) treatment history when adjusted for demographics and other diagnoses or treatments. Unadjusted odds ratios were also computed for age and gender. All analyses were conducted using SAS version 8.2 for Unix (Cary, NC). Coverage restrictions such as maximum age limits and formulary status (e.g., copayment tier) of the drugs in this study were not recorded in the database and were not available for evaluation in this research.

### Results

A total of 133,134 patients were identified as receiving medication treatment for ADHD in 2003 and having an ADHD diagnosis anywhere within their administrative claim records. Limiting this group to patients who initiated therapy between April 1, 2003, and December 31, 2003, and who had continuous enrollment for 1 full year preceding a treatment initiation resulted in 46,396 (34.8%) patients. Restricting the sample further to patients aged ≥18 years resulted in 10,359 patients (7.8%). The distribution of “most recent initiations” for these patients is shown in Table 3. Note that because the inclusion criteria for initiation requires the nonuse of similar drugs for 3 months preceding a prescription, there are more disqualifications for initiations of STIMs generally than for LA-STIMs specifically. Since each patient is categorized according to his or her most recent therapy initiation, this results in a greater number of ATX initiators for the analyses comparing ATX with STIM use than for those comparing ATX with LA-STIM use.
**TABLE 2** Demographics and Past-Year Diagnostic and Treatment History for Initiations of Atomoxetine and Stimulant Therapies

<table>
<thead>
<tr>
<th>ATX Versus STIM</th>
<th>ATX Versus LA-STIM</th>
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<tr>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>ATX</td>
<td>STIM</td>
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<tr>
<td>ATX</td>
<td>STIM</td>
</tr>
</tbody>
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| Age group (years) | | | | | |
|--------------------|----|----|----|----| |
| Age 18-24 | 829 (40.7) | 3,485 (51.1) | 796 (40.7) | 1,795 (30.3) |
| Age 25-44 | 726 (33.7) | 1,963 (28.8) | 697 (35.6) | 1,115 (18.4) |
| Age 45+ | 481 (23.6) | 1,366 (20.1) | 463 (23.7) | 657 (18.4) |

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,177 (57.8)</td>
<td>859 (42.2)</td>
<td>3,875 (56.9)</td>
</tr>
<tr>
<td>1,139 (58.2)</td>
<td>817 (41.8)</td>
<td>2,028 (56.9)</td>
</tr>
</tbody>
</table>

| Past year medication use | | | | |
|--------------------------|----|----|----| |
| Stimulant | 1,013 (49.8) | 4,246 (62.3) | 933 (47.7) | 2,293 (64.3) |
| Nonstimulant (improprin) | 379 (18.6) | 850 (12.3) | 359 (18.4) | 1,115 (35.5) |
| Antidepressants | 832 (40.9) | 2,288 (33.6) | 802 (41.0) | 1,265 (35.5) |
| TCAs | 77 (3.8) | 270 (4.0) | 74 (3.8) | 146 (4.1) |
| SSRI | 622 (30.6) | 1,712 (25.1) | 598 (30.6) | 946 (26.5) |
| Other | 335 (16.5) | 812 (11.9) | 323 (16.5) | 473 (13.3) |
| Antipsychotics | 137 (6.7) | 236 (3.5) | 132 (6.8) | 150 (4.2) |
| Typical/first generation | 10 (0.5) | 14 (0.2) | 9 (0.5) | 10 (0.3) |
| Atypical/second generation | 133 (6.5) | 231 (3.4) | 128 (6.5) | 147 (4.1) |
| Antianemics | 138 (7.8) | 331 (49) | 151 (7.7) | 202 (5.7) |
| Anxiolytics | 401 (19.7) | 1,033 (15.2) | 382 (19.5) | 569 (16.0) |

| Previous BHP§ services | | | | |
|------------------------|----|----|----| |
| Never used | 1,255 (61.6) | 4,835 (71.0) | 1,216 (62.2) | 2,365 (66.3) |
| 1-12 visits | 583 (28.6) | 1,573 (23.1) | 552 (28.2) | 936 (26.2) |
| >12 visits | 198 (9.7) | 406 (6.0) | 186 (9.6) | 266 (7.5) |

| Previous diagnosis | | | | |
|-------------------|----|----|----| |
| ADHD (314.x) | 1,443 (70.9) | 4,453 (65.4) | 1,384 (70.8) | 2,470 (69.3) |
| ADHD inattentive (314.00) | 683 (33.6) | 2,378 (34.9) | 666 (34.1) | 1,259 (35.3) |
| ADHD hyperactive (314.01 or 314.00+314.01) | 742 (36.4) | 2,034 (29.9) | 701 (35.8) | 1,195 (33.5) |
| Schizophrenia (295.xx) | 14 (0.7) | 22 (0.3) | 14 (0.7) | 10 (0.3) |
| Bipolar/mania (296.0x-296.8x, 301.13) | 128 (6.3) | 237 (3.5) | 125 (6.4) | 140 (4.1) |
| Psychosis (297, 298) | 28 (1.4) | 33 (0.5) | 27 (1.4) | 22 (0.6) |
| Depression (296.2x-296.3x, 300.4, 311) | 716 (35.2) | 1,932 (28.4) | 689 (35.2) | 1,107 (31.0) |
| Anxiety states (300.xx, 313.0) | 396 (19.5) | 944 (13.9) | 375 (19.2) | 567 (15.9) |
| Personality disorder (PD) (301.xx) | 30 (1.5) | 100 (1.5) | 30 (1.5) | 63 (1.8) |
| Nondependent drug abuse | 171 (8.4) | 231 (3.4) | 128 (6.5) | 147 (4.1) |

| * N of ATX is higher in STIM comparison due to stricter exclusions in defining STIM initiations (see Table 3).  
† Only 9 patients for ATX therapy and 227 patients for STIM therapy were aged 65 years.  
‡ Other includes MAOIs, SNRIs, mirtazapine, nefazodone, and trazodone.  
§ Behavioral health/psychology (BHP) services represent therapeutic interventions other than pharmaceutical treatment.  
|| Though all patients were required to have an ADHD claim on record to be included for analysis, this table reflects claims within the one year prior to the initiation.  
ADHD = attention-deficit/hyperactivity disorder; AIDs = acquired immune deficiency syndrome; ATX = atomoxetine; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; LA-STIM = long-acting stimulants; MAOI = monoamine oxidase inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; STIM = any stimulant; TCA = tricyclic antidepressant.  
www.amcp.org   Vol. 12, No. 3   April 2006   JMCP   Journal of Managed Care Pharmacy   233
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in the Treatment of Adults With ADHD: Retrospective Analysis of Administrative Claims Data

Table 2 shows the frequency distributions for demographic factors and past-year diagnostic and treatment history for ATX compared with STIM and LA-STIM initiations. Specific testing of these relationships was done within the adjusted logistic regression models. Compared with our predefined arbitrary referent category of patients aged 25 to 44 years, younger adults (18-24 years) showed a decreased likelihood of receiving ATX relative to both STIMs and LA-STIMs whereas no significant difference was noted for older (45+ years) adults. While no significant gender differences were observed in unadjusted analyses (Table 4), females were less likely to receive ATX than STIMs and LA-STIMs in adjusted models.

Diagnostic history was informative in treatment selection. Figure 1 depicts the diagnoses assessed within claims along with the corresponding adjusted odds ratios for ATX initiation and associated 95% confidence intervals. For the broader comparison of ATX with STIMs, but not always when comparing ATX with LA-STIMs, patients with past-year claims for alcohol and drug dependence, psychosis, bipolar disorder, and anxiety disorders were more likely to initiate treatment with ATX, whereas patients with past-year claims for personality disorder were more likely to initiate treatment with STIMs or LA-STIMs. Though the rate of tics or Tourette’s was nearly 3 times higher for ATX initiators than STIM initiators, the overall past-year prevalence of this condition (<1%) was too low for this difference to reach significance in the adjusted models.

The direction of effect for all diagnostic predictors of ATX versus LA-STIM initiation was the same as for the comparison with STIM. However, drug dependence, psychosis, and anxiety disorders—all significant positive predictors of ATX versus STIM initiation—were not significantly associated with ATX

Table 3 Sample Selection

<table>
<thead>
<tr>
<th>Source patients</th>
<th>For Comparing Initiations of ATX to STIM: 133,134</th>
<th>For Comparing Initiations of ATX to LA-STIM: 133,134</th>
</tr>
</thead>
<tbody>
<tr>
<td>Those using ADHD medication in 2003 and having one or more claims with ADHD diagnosis in claims records</td>
<td>n (%) Remaining</td>
<td>n (%) Remaining</td>
</tr>
<tr>
<td>Excluding patients with no initiations between April 1, 2003, and December 31, 2003, or without one full year of continuous enrollment</td>
<td>86,738 (65.2% of source)</td>
<td>46,396 (34.9% of source)</td>
</tr>
<tr>
<td>Excluding children (patients aged &lt;18 years)</td>
<td>36,037 (27.1% of source)</td>
<td>10,359 (7.8% of source)</td>
</tr>
<tr>
<td>Cohort of qualified adult patients</td>
<td>10,359</td>
<td>10,359</td>
</tr>
<tr>
<td>Excluding patients with no qualifying treatment initiations* for either ATX or analysis-specific comparator</td>
<td>1,481 (14.3% of cohort)</td>
<td>8,877 (85.7% of cohort)</td>
</tr>
<tr>
<td>Excluding patients with ambiguous initiation (i.e., with most-recent qualifying initiations of ATX and analysis-specific comparator on the same day)</td>
<td>28 (0.3% of cohort)</td>
<td>8,850 (85.4% of cohort)</td>
</tr>
<tr>
<td>Initiations compared Unique patients assigned by most recent qualifying initiation, relative to analysis-specific comparator</td>
<td>8,850</td>
<td>5,523</td>
</tr>
<tr>
<td>ATX</td>
<td>2,036 (23.0% of initiations)</td>
<td>1,956 (35.4% of initiations)</td>
</tr>
<tr>
<td>STIM</td>
<td>6,814 (77.0% of initiations)</td>
<td>–</td>
</tr>
<tr>
<td>LA-STIM</td>
<td>–</td>
<td>3,567 (64.6% of initiations)</td>
</tr>
</tbody>
</table>

* "Qualifying initiations" are pharmacy claims preceded by a 90-day period free of a pharmacy claim for the same or similar drug. See “Methods” for details and example.
† The ATX to LA-STIM analysis excludes patients treated primarily with medications other than ATX or LA-STIM, resulting in greater overall exclusion than for the ATX to STIM analysis.

TABLE 4 Unadjusted Association Between Patient Demographics and Atomoxetine Treatment Selection

<table>
<thead>
<tr>
<th>Medication Episodes</th>
<th>ATX Versus Stimulant</th>
<th>ATX Versus LA-STIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% Confidence Limits</td>
<td>OR</td>
</tr>
<tr>
<td>Age group (years) 18-24 (versus 25-44) 0.64 [0.57, 0.72] 0.71 [0.63, 0.81]</td>
<td>0.95 [0.83, 1.09] 1.13 [0.97, 1.31]</td>
<td></td>
</tr>
<tr>
<td>Gender Female (versus male) 0.96 [0.87, 1.06] 0.95 [0.85, 1.06]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PAHTx=atomoxetine; LA-STIM=long-acting stimulant; STIM=stimulant.
initiation compared with LA-STIM initiation.

The findings for historical medication use (Figure 2) only partly replicated the diagnostic history results. For example, antipsychotic use, like a historical diagnosis of a psychotic disorder, was significantly associated with an increased likelihood of initiating ATX as opposed to STIMs. However, while antidepressant use in the treatment model was significantly associated with ATX initiation compared with both STIM and LA-STIM initiation, this relationship was not evident for depression in the diagnosis models. Use of bupropion, indicated for major depression but commonly used off-label for treatment of adults with ADHD, was similarly associated with an increased likelihood of initiating ATX. This trend is similar to—and may, in fact, be simply a reiteration of—the trends for other antidepressants. Conversely, prior antimanic medication use was not associated with treatment selection, whereas a bipolar/mania diagnosis was. A past-year STIM prescription was associated with an increased likelihood of initiating ATX as opposed to both STIMs and for LA-STIMs specifically.

Using “no prior-year visits” as a reference category, prior use of behavioral services up to a once-monthly average rate was associated with significantly higher odds of initiating ATX as opposed to STIMs. Behavioral service utilization, however, did not predict treatment selection between ATX and LA-STIMs.

Discussion

Our findings demonstrate that in adults with ADHD, a statistically significant association was found between some demographic characteristics and clinical history, and the initiation of treatment with a STIM versus ATX.

Our first hypothesis, that ATX would be used more often in patients with conditions potentially exacerbated by STIMs, was partially supported. ATX use was more common than STIM use in patients with anxiety, but it was not more common than LA-STIM use. ATX was also not associated with preferred use in patients with tic disorders. The second hypothesis, that patients at risk for substance abuse would be less likely to initiate STIMs, likewise received partial support. ATX was preferred over STIMs and LA-STIMs in patients with histories of alcohol dependence but not in patients with histories of nondependent drug abuse. Drug-dependent patients were more likely to initiate ATX over STIMs, but there was no difference between ATX and LA-STIM use.

The third hypothesis, that difficult-to-treat patients with psychiatric comorbidities or recent counseling would more frequently initiate ATX, was also only partially supported. ATX use was more likely in patients with psychosis, bipolar disorder, or anxiety (though in the latter 2 instances the effect was present only for STIMs, not for LA-STIMs), while STIMs were associated with increased preference in patients with personality disorder. Patients who have recent prescriptions for antidepressants or antipsychotics were slightly more likely to initiate ATX. ATX was not initiated more frequently in patients with prior depression or in those patients currently taking antimanic or anxiolytic medication. With respect to recent counseling, the use of behavioral services was positively associated with increased likelihood for ATX initiation relative to STIMs in general, but this distinction was not found for ATX use relative to LA-STIM use specifically.

While the above is somewhat consistent with our expectations, some patient factors associated with STIM initiation are more

---

**FIGURE 1**

### Adjusted Odds Ratios for Atomoxetine Initiation Based on Diagnostic History and Demographics

<table>
<thead>
<tr>
<th>Factor</th>
<th>ATX vs. STIM</th>
<th>ATX vs. LA-STIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female vs. Male</td>
<td>0.89 (0.80, 0.99)</td>
<td>0.88 (0.79, 0.99)</td>
</tr>
<tr>
<td>Age 18-24 vs. Age 25-44</td>
<td>0.66 (0.58, 0.74)</td>
<td>0.71 (0.62, 0.81)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0.96 (0.83, 1.10)</td>
<td>1.12 (0.96, 1.32)</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.53 (0.26, 1.11)</td>
<td>0.94 (0.52, 1.80)</td>
</tr>
<tr>
<td>Poisoning/Ingestion</td>
<td>0.92 (0.67, 1.26)</td>
<td>0.75 (0.54, 1.03)</td>
</tr>
<tr>
<td>HIV</td>
<td>1.31 (0.86, 1.99)</td>
<td>1.11 (0.78, 1.60)</td>
</tr>
<tr>
<td>Alzheimer/Other Dementia</td>
<td>0.70 (0.32, 1.54)</td>
<td>0.60 (0.26, 1.37)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.39 (0.39, 4.93)</td>
<td>0.18 (0.07, 1.44)</td>
</tr>
<tr>
<td>Cardiac Dysrhythmias</td>
<td>0.76 (0.31, 1.13)</td>
<td>0.84 (0.54, 1.30)</td>
</tr>
<tr>
<td>Hepatitis or Cirrhosis</td>
<td>1.30 (0.74, 2.26)</td>
<td>1.00 (0.72, 1.39)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.94 (0.65, 1.36)</td>
<td>0.95 (0.77, 1.17)</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.97 (0.77, 1.22)</td>
<td>1.07 (0.83, 1.37)</td>
</tr>
<tr>
<td>COPD</td>
<td>1.33 (0.93, 1.95)</td>
<td>1.23 (0.93, 1.65)</td>
</tr>
<tr>
<td>Accidents/Injuries</td>
<td>0.98 (0.87, 1.09)</td>
<td>0.93 (0.82, 1.06)</td>
</tr>
<tr>
<td>Mental Retardiment</td>
<td>1.17 (0.81, 1.69)</td>
<td>1.02 (0.73, 1.42)</td>
</tr>
<tr>
<td>Hypersomnolence</td>
<td>1.07 (0.83, 1.37)</td>
<td>1.75 (0.51, 5.84)</td>
</tr>
<tr>
<td>Sleep Loss</td>
<td>0.87 (0.57, 1.34)</td>
<td>1.71 (0.94, 3.17)</td>
</tr>
<tr>
<td>Tic</td>
<td>1.14 (0.89, 1.45)</td>
<td>1.97 (0.97, 4.43)</td>
</tr>
<tr>
<td>Nondependent Drug Use</td>
<td>1.20 (0.97, 1.49)</td>
<td>0.90 (0.79, 1.00)</td>
</tr>
<tr>
<td>Drug Dependence</td>
<td>1.17 (0.98, 1.48)</td>
<td>1.55 (1.00, 2.21)</td>
</tr>
<tr>
<td>Alcohol Dependence</td>
<td>1.36 (0.92, 2.03)</td>
<td>0.80 (0.52, 1.28)</td>
</tr>
<tr>
<td>Personality Disorder</td>
<td>0.66 (0.43, 1.02)</td>
<td>0.53 (0.34, 0.82)</td>
</tr>
<tr>
<td>Anxiety States</td>
<td>0.93 (0.58, 1.51)</td>
<td>0.95 (0.58, 1.60)</td>
</tr>
<tr>
<td>Depression</td>
<td>1.21 (0.83, 1.75)</td>
<td>1.21 (0.83, 1.75)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>1.08 (0.92, 1.26)</td>
<td>1.11 (0.99, 1.23)</td>
</tr>
<tr>
<td>Bipolar/Mania</td>
<td>1.02 (0.92, 1.20)</td>
<td>0.87 (0.68, 1.11)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1.65 (0.88, 3.08)</td>
<td>1.47 (0.78, 2.79)</td>
</tr>
<tr>
<td>ADHD Hyperactive</td>
<td>0.97 (0.48, 2.03)</td>
<td>0.97 (0.48, 2.03)</td>
</tr>
<tr>
<td>ADHD Inattentive</td>
<td>1.99 (0.80, 5.00)</td>
<td>1.30 (0.74, 2.26)</td>
</tr>
</tbody>
</table>

ATX=atomoxetine; CI=confidence interval; COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus; LA-STIM=long-acting stimulant; STIM=stimulant.
difficult to understand. Female gender (in the adjusted models), young adulthood (18-24 years), and personality disorders were all associated with increased odds of receiving STIMs. If we make the assumption that women are more likely than men to be interested in weight loss, the finding with regard to gender may reflect a preference for STIM treatment among women (without a formal diagnosis of obesity) inclined to view the anorexic effects of STIMs as an added benefit of treatment.

We can imagine 2 possible reasons that younger adults with ADHD would be more likely to prefer STIMs over ATX than older adults with ADHD. The first is the increasing acceptance of ADHD in adults as a treatment focus in recent years. As medication treatment rates have increased along with recognition of the persistence of ADHD into adulthood, the predominance of STIM use in this age group may reflect an extension of the dominance of STIM use prior to the introduction of nonstimulant alternatives. This might also reflect an extension of prior patient experiences, to the extent that patients who had used STIMs successfully during childhood might be more inclined to reinitiate therapies previously found to be beneficial. The significant extent to which we observed that past-year STIM use could predict new initiations is certainly consistent with that idea. Older adults initiating treatment may not have as much personal history with ADHD treatment and thus come into the treatment decision with a “cleaner slate.”

A more pessimistic interpretation of this finding might be that this relationship is a reflection of the desire to divert STIM medications for abuse within the young adult population. Although diverted STIMs must ultimately have come from someone, the current data do not assess whether the patients who filled their prescriptions are the same people who are using or selling their medication. Future research would be needed to examine the supply side of diversion to understand to what degree prescriptions that are intended for insured persons in this age group end up in the hands of others.

With concerns over the diversion of prescription STIMs, we expected patients with substance-abuse histories to be directed away from STIMs, given their potential for abuse. We were, therefore, somewhat surprised to see that an overt history of nondependent drug abuse was not associated with medication selection. The more severe diagnoses of drug and alcohol dependence, however, did show a relationship in the expected direction (though the difference was not statistically significant in favor of ATX versus LA-STIMs for drug dependence).

The preference for STIM therapy in patients with personality disorders is more obscure, insofar as there is no obvious clinical reason that such patients should preferentially receive either therapy. It is possible that certain providers (e.g., psychiatrists) are both more likely to diagnose and/or code for personality disorders than other providers (e.g., primary care physicians) and more likely to use STIMs. If so, the observed treatment difference for patients with personality disorders could simply reflect unmeasured practice variation.

Patients who were prior users of psychological or behavioral health care services showed mixed results. They were more likely to be treated with ATX than general STIMs, but no preference was seen for ATX over LA-STIMs specifically.

Limitations

Our methods of patient selection may have resulted in the inclusion of some patients without ADHD since coding errors would go unnoticed in the absence of thorough medical record reviews. Such coding errors, if present, may also result in the exclusion of true ADHD patients. Although we did not measure the rate of recording errors in our database, the large sample size leads us to believe that such unrecorded errors did not introduce any systematic bias when comparing the treatments of interest. We therefore believe that our analysis provides a reasonable characterization of the differences in how these medications are being prescribed in managed care settings.

While the current methodology cannot prove cause and effect and does not address the relative effectiveness of the treatment alternatives studied, it does highlight the relative associations between clinical factors and medication choices that have emerged during the first year of ATX's availability.

A further limitation is the availability of data on systemic factors that may affect care—for example, the rate of dispensation through mail-service pharmacies, plan limits such as noncoverage of STIMs in adults, or the formulary tier status of the drugs under study. Because our database contained information from many diverse health plans, a broad range of these and other systemic factors associated with initiation with Atomoxetine versus Stimulants in the Treatment of Adults With ADHD: Retrospective Analysis of Administrative Claims Data

**Factors Associated With Initiation With Atomoxetine Versus Stimulants**

![Figure 2](attachment:image.png)

**Adjusted Odds Ratios for Atomoxetine Initiation Based on Treatment History and Demographics**

<table>
<thead>
<tr>
<th>Factors</th>
<th>ATX vs. STIM</th>
<th>STIM vs. ATX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female vs. Male</td>
<td>0.83 (0.75, 0.93)</td>
<td>0.93 (0.87, 1.00)</td>
</tr>
<tr>
<td>Age 18-24 vs. Age 25-44</td>
<td>1.33 (1.20, 1.53)</td>
<td>1.17 (1.02, 1.33)</td>
</tr>
<tr>
<td>1-12 BHP Visits vs. Never Used</td>
<td>1.46 (1.20, 1.77)</td>
<td>1.14 (0.90, 1.45)</td>
</tr>
<tr>
<td>&gt;12 BHP Visits vs. Never Used</td>
<td>1.05 (0.92, 1.20)</td>
<td>1.16 (0.94, 1.45)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>1.10 (0.89, 1.36)</td>
<td>1.26 (1.12, 1.42)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>1.16 (0.98, 1.36)</td>
<td>1.28 (1.13, 1.47)</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>1.41 (1.14, 1.79)</td>
<td>1.49 (1.14, 1.95)</td>
</tr>
<tr>
<td>Antithyroid</td>
<td>1.14 (0.85, 1.54)</td>
<td>1.33 (1.06, 1.63)</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>1.22 (1.04, 1.45)</td>
<td>1.16 (0.90, 1.45)</td>
</tr>
<tr>
<td>Nonstimulant</td>
<td>1.05 (0.89, 1.23)</td>
<td>1.16 (0.94, 1.45)</td>
</tr>
<tr>
<td>Stimulant</td>
<td>0.97 (0.85, 1.11)</td>
<td>1.28 (1.13, 1.47)</td>
</tr>
<tr>
<td>0.3 0.4 0.5 0.8 1 1.5 2 2.5 3</td>
<td>Favors STIM or LA-STIM</td>
<td>Favors ATX</td>
</tr>
</tbody>
</table>

ATX = atomoxetine, BHP = behavioral health/psychological, CI = confidence interval, LA-STIM = long-acting stimulant; STIM = stimulant.
factors was likely represented. Whether or not these systemic factors directly impact utilization or drug choice by providers is an important policy-related question and merits future study.

Similarly, the effect of provider specialty was unmeasured because of limitations in our ability to confidently determine provider specialty from claims. Often, the “provider” was not an individual specialist but a clinic that may have contained providers of diverse specialties. In addition, where specialty could not be clearly identified, the PharMetrics database imputed this based on practice patterns; as a result, the “psychiatric” specialty may in fact represent psychologists, psychiatrists, and social workers. To avoid statistical confounding with our “behavioral care” variable, we chose to omit provider specialty as an independent variable for this study.

Besides limited information on systemic factors affecting care, the exclusion of bupropion and tricyclic antidepressants leaves unexamined the utilization patterns of these commonly used agents for adult ADHD. As with other nonstimulants (with evidence supporting off-label use in adult ADHD), further research is merited.

Our study shares the limitations of all research conducted using administrative claims. As administrative rather than research tools, claims cannot be considered as accurate or reliable as the data derived from cohort clinical trials that follow patients over time; our data are observational and cannot provide insights into cause and effect.

Conclusions

To our knowledge, this is the first examination of emerging patterns of treatment with ATX and STIMs for adults with ADHD; previously published research examined initiation of ATX and STIMs in children and adolescents with ADHD. The significance of patient demographics, clinical histories, and prior behavioral service use suggest that ATX and STIMs may be used for different purposes in the treatment of adults with ADHD. Future research into health service utilization patterns and outcomes, including relative effectiveness over time for ATX versus STIMs, should consider potential differences between patients receiving these treatment alternatives.

Disclosures

Funding for this research was provided by Eli Lilly and Company and was obtained by author David L. Van Brunt. Van Brunt and authors Joseph A. Johnston, WenYu Ye, Gerhardt M. Pohl, and Nina N. Ohara, are employed by Eli Lilly and Company and disclose that they receive company stock within employee 401(k) plans. They state that their employer reviews their work prior to disclosure to ensure that they have not violated any federal regulations or privacy laws or disclosed any trade secrets, and that the information being disclosed is scientifically accurate. However, the authors attest to the fact that the scientific content is their own and that company policy encourages the disclosure of findings from all research, regardless of whether or not the outcome of that research is favorable to the company’s products (which include ATX). Similar research of administrative claims data for children with ADHD was published in November 2005 in Pharmacotherapy (Van Brunt DL, Johnston JA, Pohl G, et al. Predictors of pharmaceutical treatment selection for children with ADHD following the introduction of ATX. Pharmacotherapy. 2005;25(11):1541-49).

Van Brunt served as principal author of the study. Study concept and design were contributed by Van Brunt, Johnston, and Pohl, with input from Ye and Ohara. Data collection was the work of Ye and Van Brunt, with input from Johnston and Pohl, data interpretation was primarily the work of Ye, Van Brunt, and Johnston, with input from Pohl and Ohara. Drafting of the manuscript and its revision were primarily the work of Van Brunt, with input from Johnston and the other coauthors.

REFERENCES

Factors Associated With Initiation With Atomoxetine Versus Stimulants in the Treatment of Adults With ADHD: Retrospective Analysis of Administrative Claims Data


Relationship of Blood Pressure Control to Adherence With Antihypertensive Monotherapy in 13 Managed Care Organizations

THOMAS J. BRAMLEY, PhD, RPh; PHILIP P. GERBINO, PharmD; BRIAN S. NIGHTENGALE, PhD, RPh; and FERIDE FRECH-TAMAS, MPH, RPh

ABSTRACT

OBJECTIVE: This study was conducted to evaluate the relationship between medication compliance and blood pressure (BP) control among members of 13 managed care organizations with essential hypertension (HTN) who received antihypertensive monotherapy for at least 3 pharmacy claims prior to the blood pressure measurement.

METHODS: This was a retrospective review of medical and pharmacy claims over a 4-year period (1999-2002) from 13 U.S. health plans. Data were collected by trained health professionals from randomly selected patient medical records per Health Plan Employer Data and Information Set (HEDIS) technical specifications. Patients were selected if they (1) had received monotherapy or fixed-dose combination therapy (administered in one tablet or capsule) during the time BP was measured (thus those with no BP drug therapy were excluded); (2) had received 3 or more antihypertensive pharmacy claims for the antihypertensive drug therapy prior to BP measurement; and (3) had one or more antihypertensive pharmacy claims after BP was measured. Control of BP was defined according to guidelines of the Sixth Report of the Joint National Committee (JNC 6) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (<140/90 mm Hg, or <130/85 mm Hg for patients with diabetes). Medication adherence was measured using the medication possession ratio (MPR), and MPR was used to classify patients into 3 adherence levels: high (80%-100%), medium (50%-79%), and low (<50%). The relationship between medication adherence and BP control was assessed using a logistic regression model.

RESULTS: There were 1,017,181 patients with a diagnosis of HTN in medical claims data from which 10,734 (10.6%) were randomly selected for chart review. There were 1,032 patients (9.6%) in the sample who had a diagnosis of HTN but who were excluded because they had no HTN drug therapy. Of the total 9,894 patients (92.2%) who were excluded from the sample, 3,029 patients (28.2%) met all other inclusion criteria but were receiving more than one HTN drug. Of the 840 patients on HTN monotherapy, the mean age was 59 ± 12.2 years; 422 (50%) were women, 16% had diabetes, and 43% had dyslipidemia. The monotherapy HTN drug was an angiotensin-converting enzyme inhibitor (27% of patients), calcium channel blocker (22%), beta-blocker (20%), or diuretic (11%). Of the 840 patients, 629 (74.8%) were determined to have high medication adherence (MPR > 0.8), medium adherence (0.5 < MPR < 0.8), and low adherence (MPR < 0.5). The relationship between medication adherence and BP control was assessed using a logistic regression model.

CONCLUSION: These results demonstrate that 75% of these health plan members with a diagnosis of essential HTN who were selected for receipt of at least 4 pharmacy claims for HTN monotherapy exhibited high medication adherence. However, only 43% of high-adherence patients attained their target (JNC 6) blood pressure goal compared with 33% to 34% of patients with medium or low adherence to antihypertensive monotherapy.

KEYWORDS: Antihypertensive therapy, Compliance, Medication possession ratio, Hypertension

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CARDIOVASCULAR disease, the leading cause of death and disability in the United States, is associated with inadequate blood pressure (BP) control. The relationship between BP and risk of cardiovascular events is positive, continuous, consistent, and independent of other risk factors. Unfortunately, BP control is particularly poor among hypertensive patients at the highest risk for cardiovascular events, including patients with diabetes and older patients with systolic hypertension (HTN).

Randomized controlled trials conducted over the last 4 decades have provided evidence to support the effectiveness of BP lowering to reduce the risks of cardiovascular disease. Pharmacologic treatment of high BP can reduce the risk of stroke by 30% to 40% and myocardial infarction (MI) by 20% to 25%. Failure to reach BP treatment goals contributes to the burden of HTN complications. Results of the Cardiovascular Health Study suggest that undertreating systolic BP of >140 mm Hg accounts for 34% of strokes and 22% of MIs in older adults. Recent population data indicate that only 31% of all hypertensive individuals are controlled to <140/90 mm Hg. Thus, almost 70% of the more than 50 million Americans with high BP are at increased risk of cardiovascular complications due to the failure to reach goal BP.

Although poor BP control can be attributed to several factors, one pivotal reason is the problem of long-term patient compliance with therapy. Lack of compliance with BP-lowering medication is a major reason for poor control of BP. Reasons for poor compliance vary. Patients with high BP may fail to take their medication because of the chronic nature of HTN and its absence of overt symptoms; other reasons that have been studied include the adverse effects of medication, complicated drug interactions, and the failure to reach goal BP.
regimens, lack of understanding about HTN management, lack of motivation, and the challenge to individual patients' health beliefs. It is assumed that good compliance with a prescribed antihypertensive regimen is associated with better BP control and the potential for improved long-term outcomes. Persistence with a highly effective and well-tolerated antihypertensive treatment regimen can be expected to improve BP control and long-term outcomes, although few studies exist that support these assumptions.

One way to measure medication compliance is the medication possession ratio (MPR). The MPR indicates medication acquisition and is distinct from medication consumption, as measured by tablet counts. The MPR is a ratio of medication received over a defined interval of time. Although electronic monitoring of compliance would likely increase measurement accuracy, this type of monitoring is not available when conducting retrospective research with administrative claims. Use of the MPR relies on assumptions regarding patient behavior; for example, that patients consistently consume their acquired antihypertensive therapy throughout the measurement period. While an MPR of 100% is an ideal, indicating that a medication is in the patient's possession for every day of the treatment period, an MPR of at least 80% is considered a proxy for continuous use. The MPR is useful in assessing adherence to medications intended for long-term use, such as antihypertensive medications, when long gaps in treatment may lead to adverse outcomes.

The present study was conducted to determine the relationship between medication adherence and BP control in a managed care population receiving antihypertensive monotherapy. Patients receiving monotherapy were selected to simplify the measurement of therapy compliance and increase the confidence in a causal relationship between compliance and BP control.

### Methods

A retrospective, population-based study was conducted utilizing medical and pharmacy claims and medical records from 13 health plans across the United States from 1999 to 2002 as specified by the Health Plan Employer Data and Information Set (HEDIS) technical specifications. Claims data were used to identify patients with an International Classification of Diseases, Ninth Revision (ICD-9) code indicating the diagnosis of essential HTN (401.x) during the first 6 months of the measurement year. To be included in this study, there also had to be the notation of a diagnosis of HTN in the medical record on or before the first 6 months of the measurement year as defined by the HEDIS HTN performance measure. The HEDIS measure requires medical record review to confirm the diagnosis of HTN and to evaluate BP control. A total of 1,017,181 patients were identified with a diagnosis of essential HTN in the medical claims. By plan, patients were randomly selected for chart review to produce a representative sample of patients for each plan via a random number process generated using SAS Statistical Software version 8.0 (SAS Institute Inc., Cary, NC). This process ensured no patient or health characteristics influenced the selection of patients for chart review.

Records were included from patients who (1) had received antihypertensive monotherapy (defined as 1 agent) or fixed-dose combination (administered in 1 tablet or capsule) during the time BP was measured (patients switching therapy but maintaining monotherapy status remained in the study); (2) had received 3 or more antihypertensive pharmacy claims prior to BP measurement in the 270 days preceding BP measurement; and (3) had one or more antihypertensive pharmacy claims after BP was measured (Table 1). In other words, all patients included in the final analysis had received at least 4 pharmacy claims for HTN monotherapy. Only patients who received monotherapy (including fixed-dose combination) were included, in an attempt to reduce the confounding influence of HTN severity and permit selection of a more homogeneous population with regard to HTN severity.

Also, the inclusion of monotherapy patients simplified measurement of therapy compliance and increased confidence in a causal relationship between compliance and BP control. Inclusion of patients receiving other regimens such as dual therapy may increase the external validity, but little “real-world” research exists examining the association between compliance and BP control. Therefore, a simplified approach in patients receiving monotherapy was done to evaluate if any association existed. A single BP value was used from each patient who

### Table 1: Sample Selection

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Number (%) of Patients Dropped</th>
<th>Number (%) of Patients Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomly selected for chart review analysis*</td>
<td>–</td>
<td>10,734 (100)</td>
</tr>
<tr>
<td>Patients with both pharmacy and medical claims†</td>
<td>1,032 (9.6)</td>
<td>9,702 (90.4)</td>
</tr>
<tr>
<td>Patients with pharmacy claims overlapping BP date‡</td>
<td>5,010 (46.7)</td>
<td>4,692 (43.7)</td>
</tr>
<tr>
<td>Patients with 3 or more antihypertensive Rxs pre-BP date</td>
<td>757 (7.1)</td>
<td>3,935 (36.6)</td>
</tr>
<tr>
<td>Patients with 1 or more antihypertensive Rxs post-BP date</td>
<td>66 (0.6)</td>
<td>3,869 (36.0)</td>
</tr>
<tr>
<td>Patients receiving antihypertensive monotherapy</td>
<td>3,029 (28.2)</td>
<td>840 (7.8)</td>
</tr>
</tbody>
</table>

* 1,017,181 patients with an HTN diagnosis (ICD-9-CM code 401.x for essential hypertension) in medical claims data from which 10,734 (10.6%) were randomly selected for chart review.
† Only 1 medical claim with an HTN diagnosis was required.
‡ June 1, 1998, was the earliest date of service for a pharmacy claim and the latest date was September 30, 2002.

BP= blood pressure; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; HTN = hypertension; Rx = prescription
fulfilled all 3 criteria, and the date of the BP measurement was selected to ensure that it occurred during the compliance measurement period. BP measurements were obtained from readings recorded in medical charts either by nurses or physicians. Control of BP was defined according to the then-current guidelines of the Sixth Report of the Joint National Committee (JNC 6) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (<140/90 mm Hg, and <130/85 mm Hg for patients with diabetes). The use of BP controls as defined in the JNC 6 guidelines permitted a continuous measure of BP to be converted into a dichotomous variable representing control: yes or no. All diagnosis code fields were reviewed, and patients with codes for diabetes, hyperlipidemia, and heart failure also were identified.

Medication Possession Ratio and Other Measures of Interest
Medication adherence rates were generated using the MPR, defined as the supply of medication in days divided by the total number of days in the study period (actual treatment days), then multiplied by 100 to convert to a percentage. This definition of MPR is similar to that employed in previous studies. The numerator was the sum of all days supplied regardless of whether prescriptions involved overlapping days. The number of days was counted beginning from the fill date of the patient’s first pharmacy claim to the fill date of the patient’s last pharmacy claim. The days supply of the last observed pharmacy claim was not included in the summation of the supply of medication. As no antihypertensive pharmacy claim activity occurred after the last observed pharmacy claim, adherence to the last prescription could not be determined. While electronic measurement of compliance is often done in prospective studies, MPR is a well-accepted methodology to measure medication use in research with administrative pharmacy claims. Adherence was capped at 100%, i.e., MPR values greater than 1.0 were reduced to 1.0.

The MPR measure of adherence can be influenced by use of 90-day and larger supplies from mail-service pharmacies. Fewer than 9% of all pharmacy claims had days supply quantities ≥90 days. Patients were categorized into 3 adherence groups: high (80%-100%), medium (50%-79%), and low (<50%). These categories were specified a priori and based on a study by Psaty et al. that indicated that patients who took less than 80% of their hypertensive medication were at a 4-fold risk for acute cardiac events than patients who took 80% or more of their medications. In addition, several other studies have used 80% as a cut-off point when assessing compliance in HTN and other disease states as well.

Potential factors associated with adherence in this study included age, gender, prescription count of nonantihypertensive medications, and severity of illness adjusted according to the Charlson Comorbidity Index. The Charlson index contains 19 categories of comorbidities and includes scores from 0 to ≥6, according to the absence or presence of comorbid disorders, which are indicated by ICD-9 codes and was assessed up to 270 days prior to the date of the BP recording.

### TABLE 2
Characteristics of the Study Population Taking Antihypertensive Medication (N=840)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>418 (49.8)</td>
</tr>
<tr>
<td>Women</td>
<td>422 (50.2)</td>
</tr>
<tr>
<td><strong>MPR</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 80%</td>
<td>629 (74.9)</td>
</tr>
<tr>
<td>50%-79%</td>
<td>165 (19.6)</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>46 (5.5)</td>
</tr>
<tr>
<td><strong>Antihypertensive drug class</strong></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>223 (26.5)</td>
</tr>
<tr>
<td>ARB</td>
<td>25 (3.0)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>168 (20.0)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>187 (22.3)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>91 (10.8)</td>
</tr>
<tr>
<td>Fixed-dose combination</td>
<td>10 (1.2)</td>
</tr>
<tr>
<td>Other (e.g., alpha-blocker)</td>
<td>136 (16.2)</td>
</tr>
<tr>
<td><strong>BP control to &lt;140/90 mm Hg</strong></td>
<td></td>
</tr>
<tr>
<td>(&lt;130/85 mm Hg for patients with diabetes)</td>
<td>341 (40.5)</td>
</tr>
<tr>
<td><strong>Comorbid disease</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>132 (15.7)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>362 (43.1)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10 (1.2)</td>
</tr>
<tr>
<td>None of the above</td>
<td>455 (54.1)</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; MPR = medication possession ratio.

### Statistical Analysis
The relationship between BP control and medication adherence was assessed using a logistic regression model. In this regression analysis, BP control was modeled as a function of adherence controlling for age, gender, Charlson index, HTN medication class, and count of the number of non-HTN medications. One indicator variable for adherence was constructed whereby those subjects with an MPR of at least 80% were compared with those with an MPR of less than 80%. Three indicator variables were for HTN medication class whereby ACE inhibitors, beta-blockers, and calcium channel blockers were compared with all other HTN medication classes (i.e., diuretics, alpha-blockers, fixed-dose combination). All statistical analyses were performed using the SAS Statistical Software version 8.0 (SAS Institute Inc., Cary, NC). The a priori level of significance was α = .05.

### Results
The characteristics of the managed care study population (N = 840) are summarized in Table 2. Patients had a mean age of 59 ± 12.2 years (range, 22-93 years). Most patients had uncontrolled BP (60%) according to JNC 6 guidelines. The majority of patients were in the high-adherence category with a mean MPR of 87%. The most commonly prescribed antihypertensive agents were angiotensin-converting enzyme (ACE)
inhibitors, calcium channel blockers (CCBs), beta-blockers, and diuretics. Table 3 summarizes the severity measures by MPR category. Overall, patients were generally healthy, with an overall Charlson index score of <1.

Blood pressure was controlled to JNC 6 goal in 270 patients (42.9%) in the high-adherence group versus 56 patients (33.9%) in the medium-adherence group and 15 patients (32.6%) in the low-adherence group \( (P = 0.06, \text{Table~3 and Figure~1}) \).

Highly adherent patients were 45% more likely to achieve BP control than patients with medium or low adherence to HTN monotherapy, after controlling for age, gender, HTN medication class, and comorbidities \( (\text{odds ratio} \ [\text{OR}] = 1.45; \ P = 0.026) \). Additionally, a higher total number of nonhypertensive medications was associated with a lower rate of BP control \( (\text{OR} = 0.95; \ P = 0.007, \text{Table~4}) \).

The high HTN medication adherence group received a higher proportion of pharmacy claims with a larger average days supply. The mean days supply per pharmacy claim was 39.4 for the high-adherence group versus 32.8 days for the medium-adherence group and 30.2 days for the low-adherence group \( (P < 0.001, \text{Table~3}) \).

Discussion

These results suggest that adherence to antihypertensive medications is associated with a higher proportion of HTN patients who reach target BP control. To our knowledge, no other research has established an association between medication adherence and BP control in a real-world setting. In addition, this study begins to explore the magnitude of this association. Such assessments are necessary and provide valuable data for groups such as the American Heart Association’s Task Force on Compliance. In fact, this task force was charged with determining “if sufficient data exist to make specific recommendations about compliance.”27 Control to the target goal of <140/90 mm Hg (<130/85 mm Hg for patients with diabetes), according JNC 6 guidelines in effect at the time that these data were collected, was achieved in 43% of high-adherence patients compared with BP control rates of only 34% and 33% for medium and low adherence, respectively. Prior to adjustment, these ratios were not significant \( (P = 0.06) \).

Of note is the finding that a higher number of medications other than the HTN monotherapy was associated with a lower likelihood of reaching goal BP. One explanation for this finding is the difference in severity scores of the patients—the Charlson index score was apparently higher in the low-adherence group, but \( P = 0.12 \) for the comparison \( (\text{Table~3}) \). However, this was controlled in the regression analysis, using the Charlson index. In a systematic review of randomized controlled trials of interventions to improve compliance with BP-lowering medication,8 it was shown that increasing the complexity of a medication regimen results in decreased medication compliance. In 7 of 9 studies included in the review, simplifying the dosing regimen was found to increase compliance; specifically, reducing the number of daily doses appeared related to higher compliance with antihypertensive medication.8 Other studies have shown that a higher number of total medications is related to lower patient compliance and that both the class of medication prescribed and the number of tablets taken each day are important factors in patient compliance.25-33 In this study, patients were taking an average of at least 6 distinct nonantihypertensive medications.

Blood pressure control is potentially determined by multiple factors, including the underlying pathophysiology of HTN; age, severity of disease, health habits, and presence of comorbid illness; compliance with medication; and the impact of health care systems.34 Most Americans with poor BP control have health insurance coverage, availability, and access to medical care.33-35

Several reports suggest that a major factor in inadequate BP control is clinical inertia, or the physician’s failure to titrate or combine medications when seeing a patient with uncontrolled
BP. It is of interest to compare the BP control rate in this study with that reported in a recent, similarly designed study using a retrospective review of patient records and refill history, in which only 34.8% of treatment-compliant, hypertensive, male veterans had BP levels <140/90 mm Hg. In that study, the percentage of patients whose BP was controlled increased in proportion to the number of antihypertensive drugs taken, with the highest BP control seen in nondiabetic patients receiving 2 or more agents and in diabetic patients receiving 3 or more antihypertensive agents. Furthermore, there was a strong inverse relationship between the number of antihypertensive drugs and systolic BP readings ($r^2$ coefficient of determination) = .87; $P = 0.001$.

The JNC 7 report lowered the blood pressure goal for diabetics even further, to <130/80 mm Hg. These low BP goals are difficult to achieve, especially in patients with diabetes. Results of recent, large clinical trials have shown that monotherapy is unable to bring BP to goal levels in most patients. In the largest antihypertensive drug trial ever conducted, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), only 30% of patients achieved BP <140/90 mm Hg with monotherapy. This evidence, together with that from other published studies, has increased the recognition among practitioners that goal BP is achieved in the majority of patients only when 2 or more antihypertensive medications are employed.

Approximately half of the patients in the present study were taking either ACE inhibitors or CCBs. The proportion of patients taking angiotensin receptor blockers (ARBs) was small (3%).

Limitations
Foremost among the limitations of this study was the use of only one BP measurement. Second, the potential influence of mail-service pharmacy on the measure of medication adherence was not considered in the study design, and the proportion of mail-service claims was not measured or reported in the results. The high-adherence group in this study received an average 39.4 days supply per HTN pharmacy claim compared with 32.8 days per HTN claim in the medium-adherence group and 30.2 days per HTN in the low-adherence group ($P = 0.001$).

Third, due to the retrospective nature of the study, some potential confounding factors were not available for the model, such as smoking, family history of cardiovascular disease, socioeconomic status, and other risk factors. Fourth, this analysis was limited to patients receiving monotherapy, and the results may not be generalizable to patients receiving common regimens such as dual or triple therapy to control BP. Fifth, formulary status and copayment tier were not determined in the study.

**Figure 1** Blood Pressure Control According to JNC 6 by Category of Medication Adherence

![Blood Pressure Control Graph]

*P = 0.06 prior to adjustment; $P = 0.026$ in regression analysis.

The level of blood pressure control was 43% in the 629 patients who were highly compliant versus 34% for 165 patients with medium compliance and 33% in 46 patients with low compliance.


**Table 4** Blood Pressure Control—Logistic Regression Model Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High adherence*</td>
<td>1.45</td>
<td>1.04-2.02</td>
<td>0.026</td>
</tr>
<tr>
<td>Female</td>
<td>1.18</td>
<td>0.88-1.59</td>
<td>0.27</td>
</tr>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.98-1.00</td>
<td>0.10</td>
</tr>
<tr>
<td>ACE inhibitor†</td>
<td>0.79</td>
<td>0.54-1.15</td>
<td>0.23</td>
</tr>
<tr>
<td>Beta-blocker†</td>
<td>0.80</td>
<td>0.53-1.20</td>
<td>0.28</td>
</tr>
<tr>
<td>Calcium channel blocker†</td>
<td>0.72</td>
<td>0.49-1.05</td>
<td>0.10</td>
</tr>
<tr>
<td>Charlson index</td>
<td>1.01</td>
<td>0.91-1.12</td>
<td>0.82</td>
</tr>
<tr>
<td>Number of nonhypertensive medications</td>
<td>0.95</td>
<td>0.92-0.98</td>
<td>0.007</td>
</tr>
</tbody>
</table>

* Reference group was medium and low adherence.
† Reference group was all other HTN classes (i.e., diuretics, fixed-dose combination, alpha-blocker).
ACE = angiotensin-converting enzyme; HTN = hypertension.
present study and may influence measurement of medication adherence using administrative claims data 45.

While the present study focused on monotherapy (including 10 patients [1.2%] who received fixed-dose combination therapy), to reduce the complexity in measuring medication adherence, the results show that blood pressure control was attained in only 43% of patients who had MPR values ≥80%. This suggests that these patients were not dosed properly and many probably required more than monotherapy to attain BP goal. This supports JNC 7 guidelines, which recommend combination therapy for patients with stage 2 HTN without compelling indications (e.g., heart failure, diabetes, chronic kidney disease). In addition, combination therapy should be considered for patients with stage 1 HTN without compelling indications and for patients with compelling indications regardless of stage. Even though many of these patients may have been treated inappropriately with a single HTN agent, the results still indicate that greater BP control is associated with higher medication adherence as measured by the MPR.

**Conclusion**

Across 13 MCOs, 75% of members who received at least 4 pharmacy claims for an antihypertensive medication during the study period exhibited high medication adherence with antihypertensive monotherapy, but only 43% of high-adherence patients attained their target blood pressure goal compared with approximately one third of patients with either medium or low adherence with antihypertensive monotherapy.

**DISCLOSURES**

Funding for this research was provided by Novartis Pharmaceuticals Corporation and was obtained by author Thomas J. Bramley. Author Feride Frech-Tamas is an employee of Novartis Pharmaceuticals Corporation. The other authors disclose no potential bias or conflict of interest relating to this article.

An abstract of this paper was presented at the 19th Annual Scientific Meeting of the American Society of Hypertension, New York, New York, May 22, 2004, and published in The American Journal of Hypertension. (Am J Hypertens. 2004;17(5 part 2):222A.) Bramley served as principal author of the study. Study concept and design were contributed primarily by Bramley, with input from authors Philip P Gerbino, Brian S. Nighthengale, and Frech-Tamas. Data collection was the work of Bramley; data interpretation was the work of all authors. Drafting of the manuscript was primarily the work of Bramley; with input from Nighthengale, Frech-Tamas, and Gerbino; its revision was the work of all authors.

**REFERENCES**


Assessment of Clinical, Service, and Cost Outcomes of a Conversion Program of Sumatriptan to Rizatriptan ODT in Primary Care Patients With Migraine Headaches

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ABSTRACT

OBJECTIVE: Managed care organizations can increase the value of drug therapy by negotiating discounts on drug acquisition costs with pharmaceutical manufacturers and promoting use of preferred drugs, including the conversion of patients to preferred medications. This investigation was designed to assess conversion success, migraine drug utilizations, and patient satisfaction with a clinical pharmacist-managed conversion program from sumatriptan to rizatriptan ODT, both forformulary drugs.

METHODS: This was a retrospective cohort study conducted in a managed care organization for patients aged 18 years or older who had picked up at least one outpatient prescription for any sumatriptan dosage form at the pharmacy between January 2002 and June 2002. Patients’ pharmacy and medical data were reviewed to assess eligibility (e.g., no history of rizatriptan failure) for conversion from sumatriptan to rizatriptan orally disintegrating tablet (ODT). There was no copayment difference for members for rizatriptan ODT versus sumatriptan. A questionnaire was developed to assess 2 domains: (1) patient satisfaction with the medication conversion process and (2) preference for rizatriptan ODT or sumatriptan. A random sample of 315 patients who initiated conversion to rizatriptan ODT was surveyed. Electronic pharmacy claims were reviewed to determine the number of patients who were successfully converted from sumatriptan to rizatriptan ODT. Pharmacy expenditures and total health care utilization and expenditures in the 180 days prior to baseline and after the conversion (follow-up) to rizatriptan ODT were compared for the cohorts of subjects who were successfully converted and those patients who were not successfully converted.

RESULTS: Therapeutic conversion from sumatriptan to rizatriptan ODT was attempted in 457 patients; 214 (47%) were successfully converted. The only difference between the 2 cohorts at baseline for the 6 months prior to attempted conversion was a higher mean number of sumatriptan doses per patient per month (PPPM) in the 243 failed conversions (mean 3.5, SD 2.9) compared with the 214 successful conversions (mean 2.8, SD 2.8, P = 0.003). The median triptan doses increased by 1.0 PPPM in both cohorts (P = 0.862), from 2.0 to 3.0 doses PPPM in the group of successful conversions and from 2.7 to 4.0 in the group of unsuccessful conversions. The survey response rate was 55% for both successful and for unsuccessful conversions. More than 90% of the patients in both cohorts were satisfied with the level of care provided by the clinical pharmacy staff during medication conversion, and there was no difference between the 2 cohorts in patient satisfaction (P = 0.761). Rizatriptan ODT was preferred by 68.0% and 8.5% of successful and failed conversion subjects, respectively (P = 0.001). Using representative group purchase prices, triptan expenditures for successful conversion subjects were reduced by a median of $-2.0 (6.2%) PPPM while triptan expenditures for unsuccessful conversions increased by a median of $1 (P = 0.001). There were no differences for either cohort in median PPPM changes in migraine-related office visits (0.0 median change in office visits, P = 0.748) or office-visit costs ($0 median change, P = 0.861) for preconversion versus postconversion attempts. Regression modeling identified that lower total counts of sumatriptan doses filled during baseline period was an independent predictor of successful conversion to rizatriptan ODT (P < 0.001). There was an average of 3.5 triptan medication fills per patient for successful conversion during the 6-month follow-up period, with 76% of these subjects filling at least 2 prescriptions for rizatriptan ODT during this period.

CONCLUSIONS: This conversion program for sumatriptan to rizatriptan ODT was successful in converting almost half of primary care patients to the preferred product despite the absence of a copayment incentive for members to agree to the conversion. There were no measurable medical or economic consequences of the conversion, and patient satisfaction with the quality of care was maintained. Future efforts are likely to have a higher success rate if focused on converting patients with less-severe migraine headaches, as measured by the need for baseline rescue medication, since lower acuity was the only independent predictor of successful conversion in this conversion program for 2 triptan drugs.

KEYWORDS: Clinical pharmacy specialist, Triptans, Therapeutic interchange, Patient satisfaction

It is estimated that 6% of men and 18% of women in the United States suffer from migraine headaches. Approximately 10% of primary care office visits are for headaches, with the majority being for migraines. The impact of migraine headaches on pain, disability, and general health results in a significant financial burden as it is estimated that the U.S. spends $14 billion annually on migraine treatment, including missed workdays and associated loss of productivity.

Migraine treatment consists of preventive and abortive therapy. The goals of preventive treatment are to decrease the severity, duration, and frequency of migraine attacks. Abortive therapy is required to treat migraine headaches when or if prophylactic medications do not prevent attacks. Patient preference surveys reveal that an ideal antimigraine agent would treat a migraine attack quickly and consistently while minimizing related symptoms such as nausea and vomiting, have minimal side effects, and be easy to use.

Serotonin agonists, more commonly known as triptans, are most often used for abortive treatment of moderate to severe migraines. Several different triptan agents are available in a range of dosage forms. Unfortunately, among the agents, there are few direct comparisons with adequate sample sizes and power that support recommending one agent over another. When no clear evidence of superiority exists, economic pressures may encourage substitution of one agent over another in this high-cost medication class. Reports assessing patient satisfaction with migraine medications and medication conversion strategies within the triptan class are limited.

Authors

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Due to changes in drug purchase contracts, it became economically advantageous in late 2001 to consider using rizatriptan orally disintegrating tablets (ODT, Maxalt MLT) for Kaiser Permanente Colorado (KP CO) patients who were using sumatriptan (Imitrex) products. Given that triptans can account for a significant percentage of a health care organization's drug budget and efficacy and tolerability profiles appear equal among triptans, a decision was made to actively intervene to shift drug use from sumatriptan to rizatriptan ODT in patients who were naïve to the alternative product and willing to make this change. Both of these products remained on KP CO's formulary, and there was no copayment incentive for members to convert to rizatriptan ODT from sumatriptan. A clinical pharmacy specialist-managed program to actively convert patients utilizing sumatriptan to rizatriptan ODT was undertaken within this health maintenance organization (HMO) from January to June 2002.

The purpose of this study was to examine, among sumatriptan-receiving migraine sufferers who initiated conversion to rizatriptan ODT, the following: (1) satisfaction with the care they received from their clinical pharmacy specialist during the conversion process, (2) preference for and satisfaction with the efficacy and tolerability of rizatriptan ODT versus sumatriptan, (3) medication and health care services utilization and expenditures associated with the conversion program, and (4) patient characteristics predictive of a successful conversion to rizatriptan ODT.

Methods

Setting

This study was conducted in a not-for-profit group-model HMO with enrolled members receiving care at 16 medical offices in the Denver/Boulder metropolitan area. Each medical office is staffed by 1 to 3 primary care clinical pharmacy specialists (PCCPSs) who assist health care providers and patients with medication-related problems and promote cost-effective use of medications. Approval was obtained from the KP CO Institutional Review Board for this study.

Study Design

This study used a retrospective cohort design. Patients were surveyed regardless of whether they were successfully or unsuccessfully converted from sumatriptan to rizatriptan ODT. The 2 principal domains of the survey were satisfaction with clinical pharmacy services and satisfaction with the triptan medications that the patients used. In addition, integrated electronic pharmacy and medical record data were examined to assess the successful conversion rates during the 180 days after the conversion attempt and to measure changes in migraine medication and health care service utilization and expenditures during the 180 days before and after conversion initiation. An apriori sample size calculation revealed that for an ±8% survey sampling error, a minimal sample size of 150 patients was required. Assuming an estimated 50% response rate, questionnaires were sent to 315 patients.

Patient Population

Patients aged ≥18 years who had picked up at least one prescription for any sumatriptan dosage form (tablet, nasal spray, or subcutaneous injection) at the pharmacy between the dates of January 1, 2002, and June 30, 2002, were identified from electronic pharmacy claims data. Patients whose membership had been terminated or who had died within 6 months of the program being initiated were excluded. Patients’ electronic medical records were reviewed by PCCPS staff to assess eligibility for conversion from sumatriptan to rizatriptan ODT. Patients with a history of failing rizatriptan ODT due to intolerance or self-reported lack of efficacy or whose provider did not authorize conversion were ineligible for medication conversion. PCCPS staff contacted eligible patients by telephone, starting in August 2002, and offered conversion from sumatriptan to rizatriptan ODT. Patients who agreed to convert were instructed to finish their sumatriptan doses before filling their new prescription for rizatriptan ODT.

Outcome—Patient Satisfaction

To assess patient satisfaction with the conversion process, a questionnaire was developed to assess 2 domains: (1) patient satisfaction with the medication conversion process, including an assessment of care given by the primary care clinical pharmacy specialist, and (2) preference for rizatriptan ODT or any sumatriptan product, including oral tablet, intranasal spray, or subcutaneous injection. Items for these domains were compiled from validated questionnaires. Domain #2 was assessed only among patients who had received at least 1 prescription for rizatriptan ODT after conversion from sumatriptan. Responses to the questions were recorded on a 5-point scale ranging from “completely disagree” to “completely agree.” These responses were converted to a 3-point scale combining “completely agree [or disagree]” and “somewhat agree [or disagree]” and maintaining a neutral response.

Questionnaires were mailed to a sample of patients randomly selected from the eligible patients who were contacted by the PCCPS. Each questionnaire was coded with a unique patient identification number different from the KP CO health record number in order to maintain patient confidentiality. The first mailing of the questionnaire took place in October 2002, followed by a second mailing one month later to patients who failed to respond to the first survey. An introduction letter that explained in detail the background history and the reasons for the mailing was mailed together with the questionnaire.

Outcome—Conversion Rate

Electronic pharmacy claims data were analyzed to determine if patients were successfully converted from sumatriptan to rizatriptan ODT. Patients were categorized as “initiated conversion to rizatriptan ODT” if they had received one or more prescriptions for rizatriptan ODT or if a prescription had been ordered but not picked up at the pharmacy and there was a note in the patient’s
Assessment of Clinical, Service, and Cost Outcomes of a Conversion Program of Sumatriptan to Rizatriptan ODT in Primary Care Patients With Migraine Headaches

### TABLE 1 ICD-9-CM Codes Used to Capture Migraine-Related Office Visits and Costs

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>307.81</td>
<td>Tension headache</td>
</tr>
<tr>
<td>784.0</td>
<td>Headache</td>
</tr>
<tr>
<td>346.00</td>
<td>Classical migraine without mention of intractable migraine</td>
</tr>
<tr>
<td>346.01</td>
<td>Classical migraine with intractable migraine, so stated</td>
</tr>
<tr>
<td>346.10</td>
<td>Common migraine without mention of intractable migraine</td>
</tr>
<tr>
<td>346.11</td>
<td>Common migraine with intractable migraine, so stated</td>
</tr>
<tr>
<td>346.20</td>
<td>Variants of migraine without mention of intractable migraine</td>
</tr>
<tr>
<td>348.80</td>
<td>Other forms of migraine without mention of intractable migraine</td>
</tr>
<tr>
<td>346.81</td>
<td>Other forms of migraine with intractable migraine, so stated</td>
</tr>
<tr>
<td>346.90</td>
<td>Unspecified migraine without mention of intractable migraine</td>
</tr>
<tr>
<td>346.91</td>
<td>Unspecified migraine with intractable migraine, so stated</td>
</tr>
</tbody>
</table>


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**FIGURE 1 Adjusted Odds Ratios for Atomoxetine Initiation Based on Diagnostic History and Demographics**

- **84 Disenrolled or Deceased**
  - 260 Excluded:
    - Low Sumatriptan Utilizer (34%)
    - Patient Wasn’t Contacted (30%)
    - Prior Rizatriptan ODT Failure (14%)
    - Patient Refusal (13%)
    - Followed by Neurology (7%)
    - Other (2%)
  - 717 Continuously Eligible
  - 457 Initiated Conversion From Sumatriptan to Rizatriptan ODT
  - 214 Successful Conversions
  - 243 Failed Conversions:
    - 146 Switched Back to Sumatriptan (60%)
    - 63 Taking Both Medications (26%)
    - 34 Never Picked Up Rizatriptan ODT (14%)
  - 315 Sampled for Satisfaction Questionnaire
  - 173 (54.9%) Returned Questionnaires
  - 82 Successful Conversions (55.0% Response Rate)
  - 91 Failed Conversions (54.8% Response Rate)

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Outcome—Drug and Medical Visit Utilization and Expenditures

The perspective of the payer was used for the economic analyses. Medication expenditures were calculated as the total cost of triptan medications and other medications indicated for migraine-abortive therapy in the Kaiser Permanente Management of Migraine Headaches Guidelines (i.e., isometheptine compound, dihydroergotamine, ergotamine and caffeine suppositories, ketorolac, and meperidine). Expenditures for these medications dispensed 180 days prior to (baseline) and after (follow-up) the switch date for each patient were tabulated in 2002 U.S. dollars. Pharmacy expenditures for rizatriptan ODT were calculated using representative group purchasing costs (i.e., 2002 Federal Ceiling Prices, which are the average manufacturer’s price [approximately 8% less than average wholesale prices (AWPs)] less 24% for brand-name medications).13 These prices represent the net effective discount that large group purchasers such as the Veteran’s Administration, large managed care organizations (MCOs), and pharmacy benefit managers (PBMs) may obtain with contract pricing.11 For sumatriptan and other migraine medications, discounted 2002 AWP costs, which represent costs that can be obtained by MCOs and PBMs without large group-purchasing contracts (i.e., brand agent less 12% and lowest-listed generic AWP less 36%) were used.14,15 All medication expenditures are expressed as per-patient-per-month (PPPM) values.

To assess health care services utilization, headache-related clinic and/or urgent care visits during the baseline and follow-up periods were identified using electronic medical record databases. These databases were queried for International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes pertaining to headache (Table 1). Expenditures were assigned to these visits using the 2001 and 2002 Resource-Based Relative Value Scale, depending upon the date of the visit.16

Statistical Analysis

The distributions of observations for interval-level and ratio-level baseline and outcome variables were assessed. Mean differences between groups for normally distributed data were compared using the independent samples t tests. Median differences between groups for nonnormally distributed data (i.e., office visits,
Assessment of Clinical, Service, and Cost Outcomes of a Conversion Program of Sumatriptan to Rizatriptan ODT in Primary Care Patients With Migraine Headaches

Results

A total of 801 patients were screened for conversion from sumatriptan to rizatriptan ODT (Figure 1). PCCPS staff successfully contacted and initiated conversion in 457 of these patients. Nearly one half (47%) of these conversions were successful. The reasons for not initiating conversion were: (1) low sumatriptan utilization (defined as less than one sumatriptan refill per 4 months) (34%), (2) unable to contact the patient (30%), (3) history of failing treatment with rizatriptan ODT (14%), (4) patient refusal (13%), and (5) patient required care from a specialist (i.e., neurologist) (7%).

The majority of subjects were middle-aged and female (Table 2). The mean number of sumatriptan doses received per patient per month (PPPM) in the 180 days prior to conversion initiation was 2.7 and 3.5 for successfully converted subjects versus failures, respectively (P = 0.003). One hundred seventy-three (55%) of the 315 questionnaires were returned. The proportion of successful conversions in the group that returned a questionnaire (82 of 173, 47%) was equivalent to that in the entire sample evaluated (214 of 457, 47%) (P = 0.969).

Characteristics of the 173 patients who responded to the questionnaire (responders) were compared with the 142 patients who did not respond (nonresponders). The 2 groups did not differ in terms of gender (P = 0.811); baseline dosage form of sumatriptan (tablets P = 0.100, spray P = 0.414, injection P = 0.475); and total count of baseline sumatriptan doses (tablets P = 0.443, spray P = 0.826, injection P = 0.661). Responders were slightly older than the nonresponders (mean age = 49.9 vs. 46.8 years, respectively; P = 0.017); however, this did not appear to be clinically meaningful.

The majority of respondents were satisfied with the level of care provided by their PCCPS, regardless of whether they converted to rizatriptan ODT successfully or not (Figure 2). Most respondents rated the care they received from the clinical pharmacist the same as that from other health care professionals (64.6% and 59.4% for conversion failures and successes, respectively, P = 0.761). Sixty-eight percent of the successfully converted respondents preferred rizatriptan ODT to sumatriptan, while only 8.5% of patients who failed conversion rated rizatriptan ODT as the preferred medication (P < 0.001, Figure 3). Successful conversion respondents rated rizatriptan ODT as providing faster and more complete headache relief (51.9% and 45.0%, respectively) while failure respondents reported that sumatriptan provided faster and more complete headache relief (78.3% and 75.9%, respectively, both P < 0.001). As an additional measure of satisfaction, refill rates for rizatriptan ODT in the follow-up period were assessed. Seventy-eight percent of successfully converted subjects filled at least 2 rizatriptan ODT prescriptions, suggesting that most patients were sufficiently satisfied with rizatriptan ODT to refill their prescription for this medication.

Using group purchase costs estimated to be representative, triptan expenditures in the 180 days after conversion attempt were reduced compared with baseline in successful conversions but not in failed conversions (a median reduction of -$2 PPPM in successful conversions versus an increase of $8 PPPM in failed conversions, P < 0.001) (Table 3). There were no differences in the baseline and follow-up changes between the cohorts in (1) nontriptan migraine medication expenditures (P = 0.748) and (2) migraine-related office visits (P = 0.611) and migraine-related office visit expenditures (P = 0.861). Regression modeling identified the total count of sumatriptan doses filled during the 180 days prior to conversion attempt as an independent predictor of successful conversion to rizatriptan ODT (β-coefficient = -0.016, P = 0.006). The negative correlation indicates that, with all other characteristics being equivalent, fewer sumatriptan doses received during the baseline period increased the likelihood of successful conversion (Table 4).

Discussion

Converting patients from a given medication to a “preferred” agent within the same class has become a common practice in the health care community when opportunities exist for same or better clinical or humanistic outcomes at lower cost.6,17 To our knowledge, this is

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**TABLE 2** Baseline Subject Characteristics for 6 Months Prior to Conversion

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Successful Conversions (n = 214)</th>
<th>Failed Conversions (n = 243)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) [SD]*</td>
<td>48.3 [11.7]</td>
<td>49.7 [10.4]</td>
<td>0.154</td>
</tr>
<tr>
<td>Male (%)</td>
<td>10.8</td>
<td>14.3</td>
<td>0.248</td>
</tr>
<tr>
<td>% of patients who used this</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sumatriptan dose form†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tablet</td>
<td>70.6</td>
<td>73.0</td>
<td>0.571</td>
</tr>
<tr>
<td>Subcutaneous injection</td>
<td>24.3</td>
<td>28.3</td>
<td>0.335</td>
</tr>
<tr>
<td>Nasal spray</td>
<td>13.1</td>
<td>10.7</td>
<td>0.421</td>
</tr>
<tr>
<td>Total</td>
<td>108.0</td>
<td>112.0</td>
<td></td>
</tr>
<tr>
<td>Mean no. of sumatriptan doses PPPM [SD]‡</td>
<td>2.7 [2.8]</td>
<td>3.5 [2.9]</td>
<td>0.003</td>
</tr>
<tr>
<td>Tablet</td>
<td>2.1 [2.6]</td>
<td>2.6 [2.8]</td>
<td>0.039</td>
</tr>
<tr>
<td>Subcutaneous injection</td>
<td>0.2 [0.8]</td>
<td>0.4 [1.0]</td>
<td>0.037</td>
</tr>
<tr>
<td>Nasal spray</td>
<td>0.4 [1.5]</td>
<td>0.4 [1.7]</td>
<td>0.865</td>
</tr>
</tbody>
</table>

*At time of conversion initiation.
†The totals exceed 100% because some patients were using more than one sumatriptan dose form.
‡ PPPM = per patient per month.
Assessment of Clinical, Service, and Cost Outcomes of a Conversion Program of Sumatriptan to Rizatriptan ODT in Primary Care Patients With Migraine Headaches

Overall, we found that respondents were satisfied with the care they received from their clinical pharmacy specialist during the conversion process. This is an important finding since headache sufferers, as a group, tend to be among the most dissatisfied patients.18 Even respondents in our study who failed medication conversion reported satisfaction with the care they received from the clinical pharmacy specialist. Medication conversion programs utilizing different types of medications have evaluated patient satisfaction with care and reported mixed results. Grace et al. performed a medication conversion program with HMG-CoA reductase inhibitors in 942 patients in a Veteran's Administration medical center.19 Like ours, this program involved clinical pharmacists in the conversion process. Unlike our study, where satisfaction was measured in both successful and unsuccessful conversions, patient satisfaction was measured only in subjects who continued on their new medication and met their low-density lipoprotein cholesterol goal. Of the 755 subjects surveyed, 93.6% reported satisfaction with the care they received at the clinic.19

We found that a large majority of subjects (87%) in our program who failed conversion to rizatriptan ODT expressed an overall preference for sumatriptan. This is not a surprising finding considering that all of the subjects who initiated conversion in our study had been sumatriptan users, and most had been using this medication for months or even years. Clinical trials with triptans have reported comparable patient preference, efficacy, and tolerability between sumatriptan and rizatriptan ODT,2,4,5,8 but the design of these clinical trials were substantially different from our study in that they compared parallel groups of subjects who were not stabilized on one of the study medications (as was the case in our study). Research with 2 medications from a different class of drugs also with no significant differences in efficacy or safety found that about half of the patients converted from omeprazole to lansoprazole reported worsening symptoms of heartburn.20

Nearly half of the subjects (47%) in our study who initiated conversion were successfully converted from sumatriptan to rizatriptan ODT. This result was accomplished without change in the number or cost of migraine-related office visits. A similar conversion rate (41%) was reported by Savani et al. in a conversion program for sumatriptan to other triptans.21 However, Savani et al. found that medication and health care cost savings were generated only among the subjects for whom the switch was successful, leading the authors to conclude that there was no economic justification for switching from sumatriptan to another triptan.21 Our study differed in that our conversion program was carried out by clinical pharmacy specialists who, if desired, were available to

[Figure 2: Satisfaction With Clinical Pharmacy Specialist's Care in Conversion Failures Versus Conversion Successes*]

* The response rate was 55.0% in the successful conversions and 54.8% in the failed conversions.
F = failed conversions  S = successful conversions.

How would you rate the care you received from the clinical pharmacist for your migraines compared with interactions with other health care professionals?

- The clinical pharmacist spent an appropriate amount of time with me on the phone.

- The clinical pharmacist was professional and helpful.

- The clinical pharmacist seemed knowledgeable about the recommended medication change.
patients for personal consultation. The medication conversions made by Savani et al. were carried out in a general practitioner's office and didn't necessarily include the same education and opportunity for direct telephone follow-up provided in our study.21

We found important decreases in medication expenditures, using estimated representative group purchasing costs, for the subjects successfully converted to rizatriptan ODT that offset the small rise detected among conversion failure subjects. We expected no effect of this triptan conversion program on migraine-related office visit utilization or expenditures and found no evidence for a change in migraine-related office visit use or expenditures. Thus, our findings support implementation of pharmacist-directed conversion programs for triptan medications when health plans are able to reduce the acquisition costs of preferred drugs through negotiation with pharmaceutical manufacturers.

We found that subjects who had received greater numbers of sumatriptan doses in the 180 days prior to conversion initiation tended to be less likely to convert to rizatriptan ODT. This finding suggests that a triptan conversion intervention may be less successful with patients who use more of the triptan medication due to reasons that might include poor control of migraines, higher severity of illness, or simply more familiarity with the triptan that is the target of the intervention. Furthermore, this suggests that triptan conversion programs may require more than passive intervention to be successful with higher-use patients, particularly in the absence of a copayment or other incentive for members to participate in the conversion. Previously published research in this group-model HMO for statin, cholesterol-lowering statin drugs found that a clinical-pharmacy-directed conversion program for simvastatin to lovastatin in which members had a copayment incentive to use the preferred drug was associated with a 95.5% success rate in conversions, with improved clinical outcomes and cost savings.22

While we did convert nearly half of the enrolled migraine patients from sumatriptan to rizatriptan ODT, we believe that this result could be improved. Given the substantial number of migraine patients in this HMO who were not contacted during this program, it is possible that a systematic contact system utilizing mail or phone would increase the number of conversions. Systematically providing prophylactic medications to patients could

---

**FIGURE 3** Triptan Preference in Conversion Failures versus Conversion Successes*

* The response rate was 55.0% in the successful conversions and 54.8% in the failed conversions.
* F = failed conversions   S = successful conversions.

---

<table>
<thead>
<tr>
<th>Preference</th>
<th>F (%)</th>
<th>S (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I prefer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My headache relief is faster with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My sensitivity to light and sound is relieved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My nausea relief is more complete with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My headache relief is more complete with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I experience fewer side effects with</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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* P = < 0.001
TABLE 3  Per-Patient-Per-Month [PPPM] Migraine Medication and Medical Office Utilization and Costs in the 180 Days Before and After Conversion Among Patients Successfully and Unsuccessfully Converted to Rizatriptan ODT

<table>
<thead>
<tr>
<th>Migraine Medication and Medical Office Utilization</th>
<th>Successful Conversions n = 214</th>
<th>Unsuccessful Conversions n = 243</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preconversion triptan doses</td>
<td>2.0 (2.7)</td>
<td>2.7 (3.5)</td>
<td>0.882</td>
</tr>
<tr>
<td>Postconversion triptan doses</td>
<td>3.0 (3.6)</td>
<td>4.0 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Change in triptan doses</td>
<td>1.0 (0.9)</td>
<td>1.0 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Preconversion triptan expenditures†</td>
<td>$35 ($50)</td>
<td>$46 ($67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postconversion triptan expenditures†</td>
<td>$32 ($42)</td>
<td>$57 ($73)</td>
<td></td>
</tr>
<tr>
<td>Change in triptan expenditures</td>
<td>$-2 ($-58)</td>
<td>$8 ($66)</td>
<td></td>
</tr>
<tr>
<td>Preconversion nontriptan migraine medication doses†</td>
<td>0.0 (4.9)</td>
<td>0.0 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Postconversion nontriptan migraine medication doses†</td>
<td>0.0 (4.1)</td>
<td>0.0 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Change in nontriptan migraine medication doses</td>
<td>0.0 (0.8)</td>
<td>0.0 (-0.3)</td>
<td>0.970</td>
</tr>
<tr>
<td>Preconversion nontriptan medication expenditures†</td>
<td>$0 ($2)</td>
<td>$0 ($1)</td>
<td></td>
</tr>
<tr>
<td>Postconversion nontriptan medication expenditures†</td>
<td>$0 ($2)</td>
<td>$0 ($1)</td>
<td></td>
</tr>
<tr>
<td>Change in nontriptan medication expenditures</td>
<td>$0 (-$0)</td>
<td>$0 (+$0)</td>
<td>0.748</td>
</tr>
<tr>
<td>Preconversion migraine-related office visits†</td>
<td>0.0 (0.1)</td>
<td>0.0 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Postconversion migraine-related office visits</td>
<td>0.0 (0.1)</td>
<td>0.0 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Change in migraine-related office visits</td>
<td>0.0 (-0.0)</td>
<td>0.0 (-0.0)</td>
<td></td>
</tr>
<tr>
<td>Preconversion migraine-related office visit expenditures</td>
<td>$0 ($10)</td>
<td>$0 ($4)</td>
<td></td>
</tr>
<tr>
<td>Postconversion migraine-related office visit expenditures</td>
<td>$0 ($8)</td>
<td>$0 ($3)</td>
<td></td>
</tr>
<tr>
<td>Change in migraine-related office visit expenditures</td>
<td>$0 (-$2)</td>
<td>$0 (-$1)</td>
<td>0.861</td>
</tr>
</tbody>
</table>

* P value determined by Wilcoxon rank sum test.
† Based on medication costs estimated to be representative of group purchase contracts for rizatriptan ODT and discounted average wholesale prices (AWPs) for other migraine medications, i.e., 2002 Federal Ceiling Prices, which are the average manufacturer's price (approximately 8% less than AWPs) less 24% for brand-name medications. (Available at: http://www.ppx.com/issues/drug_glossary.htm. Accessed March 21, 2006.)
‡ Nontriptan medications included in this category: sumatriptan, dihydroergotamine, ergotamine and caffeine tablets, ergotamine and caffeine suppositories, ketorolac, and meperidine.
§ The ICD-9-CM codes used to capture migraine-related office visits and costs are shown in Table 1. Expenditures were assigned to these office visits using the 2001 and 2002 Resource-Based Relative Value Scale, depending upon the date of the visit.* ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification ODT=orally disintegrating tablet.

TABLE 4  Model* of Ability to Predict Conversion Success from Subjects’ Baseline Characteristics

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>β-Coefficient</th>
<th>P Value</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.0085</td>
<td>0.331</td>
<td>0.99 (0.96-1.01)</td>
</tr>
<tr>
<td>Male</td>
<td>-0.3182</td>
<td>0.279</td>
<td>0.73 (0.41-1.30)</td>
</tr>
<tr>
<td>Sumatriptan doses received†</td>
<td>-0.0166</td>
<td>0.006</td>
<td>0.98 (0.97-0.99)</td>
</tr>
<tr>
<td>Other migraine drug doses received†</td>
<td>0.0016</td>
<td>0.154</td>
<td>0.10 (0.09-1.01)</td>
</tr>
<tr>
<td>Migraine office visits†</td>
<td>0.2135</td>
<td>0.080</td>
<td>1.24 (0.98-1.57)</td>
</tr>
</tbody>
</table>

* Hosmer and Lemeshow Goodness-of-Fit, P = 0.700.
† Number of doses counted during the 180 days prior to the conversion attempt; includes the combined number of doses for all 3 dosage forms: tablets, nasal spray, and injection.

Assessment of Clinical, Service, and Cost Outcomes of a Conversion Program of Sumatriptan to Rizatriptan ODT in Primary Care Patients With Migraine Headaches

have improved clinical and economic outcomes. Drug prophylaxis for migraine reduces expenditures on abortive therapies, and an intervention program that increases the use of prophylaxis could be cost beneficial.23,24 Focusing conversion efforts on patients who are low or moderate utilizers of triptan medications may also increase the proportion of conversion successes. In addition, a systematic method for tracking patient follow-up after the conversion may assist in maintaining conversion, especially among patients who are using both sumatriptan and rizatriptan ODT after initiating conversion. Updated guidelines for therapeutic interchange25 constitute a helpful tool for future conversion projects within health care organizations since measuring the impact of the conversion programs is one of the current requirements.

Limitations

Among the limitations of the present study is the absence of a control group of triptan patients who were not subject to the conversion program. Thus, our results may be only suggestive of the possible outcomes of an intervention to convert patients from sumatriptan to rizatriptan ODT. Second, our assessment of migraine severity was limited to the total counts of triptan doses used in the preperiod. Therefore, the role that disease severity played in the failure to convert patients to rizatriptan ODT could not be thoroughly assessed.

The patient satisfaction questionnaire was not a validated instrument but was composed of items from validated instruments.5-9,10,12 Because the individual items were assessed as individual outcomes, we believe they are valid measures. Potential recall bias may have been introduced by surveying patients after their conversion attempt. However, subjects were surveyed within 10 months of their conversion attempt and provided detailed instructions as to the nature of the survey in an attempt to limit the potential for recall bias.

We excluded patients followed by the neurology department of this HMO. This exclusion was based on the clinical judgment that these patients were likely to be more complicated and require more intensive therapy than those typically seen in primary care. In addition, we did not account for the costs of the clinical pharmacy specialists or other administrative costs in the economic analysis. Since the specialists were available for consultation for
both cohorts, we believe that this cost most likely would have been borne equivalently by both cohorts. Nevertheless, the administrative costs in conducting any clinical intervention are an important factor in determining the economic value of the intervention, and other organizations will no doubt choose to estimate this cost when assessing the potential cost-effectiveness of a conversion program in their patient population.

Two other methodological limitations may be important. We followed subjects for 180 days after conversion initiation. A longer follow-up period may have provided different results since the above-mentioned large retrospective U.K. study reviewed results of their triptan conversion project over a 15-month period. Nevertheless, we are confident that the outcomes in our investigation were assessed after a meaningful length of time. Second, future research might consider defining conversion success after 2 pharmacy claims rather than 1 pharmacy claim for the preferred drug. Some migraineurs experience infrequent success after 2 pharmacy claims rather than 1 pharmacy claim for the preferred drug. Some migraineurs experience infrequent migraines and may use leftover medication from an earlier prescription. A second pharmacy claim for the converted drug would provide more assurance of the successful conversion.

**Conclusions**

Without a copayment incentive for members to change therapy, the conversion of sumatriptan to rizatriptan ODT was successful in nearly half of the patients for whom conversion was attempted, without adverse medical or economic consequences, while maintaining patient satisfaction with the quality of their care. In the era of rising health care costs, conversion projects may help health care organizations increase affordability while maintaining high patient satisfaction and quality of care.

**DISCLOSURES**

No outside funding supported this study. The authors disclose no potential bias or conflict of interest relating to this article. This work was presented at the 23rd Annual Western States Residency Conference. May 2003, Asilomar, California. Author Olga E. Gershovich served as principal author of the study. Study concept and design were contributed by Gershovich and author Sarah J. Billups, with input from author Caroline Kicklighter Hoffman. Data collection was primarily the work of Gershovich, with input from Billups and author Nikki Carroll; data interpretation was the work of Billups and author Thomas Delate, with input from Gershovich and Carroll. Drafting of the manuscript and its revision were primarily the work of Gershovich, with input from Billups, Delate, and Hoffman.

**REFERENCES**

Adherence to the NASPE Guideline for Amiodarone Monitoring at a Medical University

COURTNEY L. BICKFORD, PharmD, BCPS, and ANNE P. SPENCER, PharmD, BCPS

ABSTRACT

OBJECTIVE: Amiodarone is an effective antiarrhythmic, but the clinical usefulness of this agent is complicated by its extensive side-effect profile, which necessitates careful patient selection and frequent monitoring. The purpose of this study was to quantify adherence to published recommendations for baseline monitoring when initiating inpatient amiodarone therapy at a university teaching hospital and determine whether appropriate serial monitoring of chronic amiodarone therapy (≥6 months) is occurring in the outpatient setting.

METHODS: A retrospective review of electronic medical records was conducted for inpatients at the Medical University of South Carolina (MUSC) who received amiodarone between November 1, 2003, and March 31, 2004, and for a subset of outpatients who had received amiodarone therapy for at least 6 months. Their medical records were reviewed for demographic data; reason for, date of initiation of, and duration of amiodarone therapy; and the occurrence of laboratory and diagnostic tests. The amiodarone guideline from the North American Society of Pacing and Electrophysiology (NASPE) was used as the measure of appropriate monitoring for baseline and follow-up chest x-rays (CXRs), liver function tests (LFTs), thyroid function tests (TFTs), and pulmonary function tests (PFTs).

RESULTS: Over the 5-month period from November 1, 2003, through March 31, 2004, 277 adult patients received oral amiodarone as inpatients at MUSC. Of these, 45 patients (16%) were initiated on chronic amiodarone therapy during their hospital admission. Baseline assessments of CXRs, LFTs, and TFTs occurred in 82% to 87% of these patients. Baseline assessment of PFTs occurred in 24% of patients, and 55% of these assessments included a diffusion capacity (DLCO). Overall, only 5 (11%) of the 45 patients initiated on amiodarone received all recommended monitoring tests. Twenty patients with available outpatient records in the MUSC system were identified as receiving chronic amiodarone therapy. Baseline assessments of LFTs, TFTs, and CXRs occurred in approximately 75% to 95% of these patients; baseline assessment of PFTs occurred in ≤30%, and 83% of these included a DLCO. Chronic monitoring at recommended time intervals for LFTs and TFTs occurred in 35% and 20% of patients, respectively, whereas annual CXRs were performed appropriately in 50% of patients.

CONCLUSION: Our data suggest that opportunities exist for improved monitoring of amiodarone therapy according to the NASPE guidelines and provide support for the development of a protocol to ensure continuous amiodarone monitoring.

KEYWORDS: Amiodarone, Monitoring, Adverse effects, Safety, Guidelines

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Amiodarone (Cordarone) is approved by the U.S. Food and Drug Administration for the treatment of life-threatening ventricular arrhythmias. However, it is also commonly used for atrial fibrillation. Although amiodarone is an effective antiarrhythmic, the clinical usefulness of this agent is complicated by its extensive side-effect profile, which necessitates careful patient selection and frequent monitoring. Amiodarone is an iodine-containing compound that is structurally similar to thyroxine. Since the drug has a long elimination half-life of 16 to 180 days (mean, 52 days), it takes months for blood concentrations to reach steady state. The oral bioavailability of amiodarone is variable, ranging from 35% to 65%, and excretion via the kidneys is negligible. Amiodarone is metabolized in the liver and has a major metabolite, desethylamiodarone, which is pharmacologically active.

Because amiodarone has a large volume of distribution and is highly lipophilic, it accumulates and has the potential to cause toxicity in multiple organs, including the liver, lungs, thyroid, and skin (see Table 1). Whereas some adverse effects of amiodarone are relatively mild in nature (e.g., nausea, corneal microdeposits, photosensitivity, and skin discoloration), others can require intervention to avoid serious consequences. Serial monitoring of liver transaminase, for example, is imperative in order to detect elevated levels. Elevated liver enzymes may be benign and decline despite continued amiodarone use, or they may signal the development of hepatitis, which can be fatal. If hepatitis develops, amiodarone should be discontinued immediately and appropriate supportive therapies initiated.

Hypothyroidism can be medically managed fairly easily with the addition of levothyroxine to the medication regimen and appropriate follow-up to ensure appropriate thyroid replacement. However, undetected hypothyroidism can be very detrimental to the patient, especially one with cardiovascular comorbidities. Hyperthyroidism can be more emergent in nature, especially in the patient with underlying cardiovascular disease. Based on patient-specific factors, the management strategy may include withdrawal or continuation of amiodarone, use of antithyroid medications, corticosteroids, or surgical resection of the thyroid.

An insidious and potentially fatal toxicity associated with amiodarone therapy is interstitial pneumonitis. Its onset is characterized by dyspnea and a subacute cough, both of which are fairly nonspecific and common in the patient population prescribed amiodarone. Baseline pulmonary function tests (PFTs) and chest radiographs are essential in the event interstitial pneumonitis is suspected, as interval changes consistent with this diagnosis are preferred over an isolated assessment of these
Between 34% and 93% of patients experience some type of adverse effect during the course of amiodarone therapy, with most occurring within the first year of therapy. Discontinuation of amiodarone due to adverse effects has been reported in 2% to 26% of patients. Because the frequency of some adverse effects is associated with cumulative amiodarone exposure (i.e., dose and duration of treatment), careful and continuous follow-up and monitoring are essential throughout the course of amiodarone therapy to identify significant toxicity and allow a management plan to be initiated. It is surprising that a medication with such a large number of serious adverse effects that are not extremely rare is commercially available without a structured monitoring program to ensure patient safety. It is also surprising that no evidence-based monitoring guidelines are available.

Adherence to the NASPE Guideline for Amiodarone Monitoring at a Medical University

**TABLE 1** Toxicities Associated With Amiodarone Use and Monitoring Recommendations

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Incidence</th>
<th>Package Insert Recommendations</th>
<th>NASPE Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFT elevation (&gt;3 times normal)</td>
<td>4%-50%&lt;sup&gt;5,13,16&lt;/sup&gt;</td>
<td>– Baseline – Regularly</td>
<td>– Baseline – Every 6 months</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>&lt;3%&lt;sup&gt;6&lt;/sup&gt;</td>
<td>– Baseline – Every 6 months</td>
<td></td>
</tr>
<tr>
<td>Pulmonary toxicity</td>
<td>2%-17%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>– Baseline – Every 3-6 months</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2%-10%&lt;sup&gt;13&lt;/sup&gt;</td>
<td>– Baseline</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1%-22%&lt;sup&gt;8&lt;/sup&gt;</td>
<td>– Baseline – Periodically</td>
<td>– Baseline – Every 6 months</td>
</tr>
</tbody>
</table>

CXR = chest x-ray; D<sub>1</sub>CO = diffusion capacity, a subset of the PFT; LFT = liver function test; NASPE = North American Society of Pacing and Electrophysiology; PFT = pulmonary function test; TFT = thyroid function test.

NASPE recommendations were used for this study.

Based on our own assessments during routine patient care, we sensed that laboratory and radiographic tests were not being obtained as recommended for many patients receiving amiodarone. Since chronic amiodarone therapy is associated with several commonly occurring adverse effects, some of which result in substantial morbidity, an assessment of adherence to published recommendations seemed a worthy endeavor. In a university-based teaching hospital with multi-disciplinary, hospital-based practitioners providing inpatient care, and clinic-based practitioners providing the majority of outpatient care, it remains unclear who is responsible for monitoring amiodarone therapy. Anecdotally, some practitioners feel that the initial prescriber is responsible, but this is not a realistic expectation for the longitudinal parameters if therapy is initiated during hospitalization. Others feel that the primary care provider, who is usually clinic-based and will see the patient for the long term, should be the professional responsible for follow-up monitoring of amiodarone therapy, including evaluation of laboratory values. In a referral center, continued contact with many patients is not assured. If cardiologists are involved in outpatient care, noncardiologists will often assume that the cardiologists are managing all cardiac medications, including the recommended monitoring. The case could be made that the pharmacist involved in patient care should be the responsible clinician; however, pharmacists are not reliably present in all clinic and hospital settings. Ultimately, it is not clear who in our health system is responsible for amiodarone monitoring, and this uncertainty increases the likelihood of either suboptimal amiodarone monitoring or significant overlap and unnecessary duplicate monitoring.
Adherence to the NASPE Guideline for Amiodarone Monitoring at a Medical University

TABLE 2  Baseline Characteristics and Amiodarone Monitoring Tests for Patients Initiated on Amiodarone as an Inpatient*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amiodarone Patients (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>67 years (38-84)</td>
</tr>
<tr>
<td>Men, number</td>
<td>35 (78%)</td>
</tr>
<tr>
<td>Race, number</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>23 (51%)</td>
</tr>
<tr>
<td>African American</td>
<td>20 (45%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Reason for amiodarone therapy, number (%)</td>
<td></td>
</tr>
<tr>
<td>Atrial arrhythmias</td>
<td>32 (71%)</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>8 (18%)</td>
</tr>
<tr>
<td>Both</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Daily amiodarone dose, mean (range)</td>
<td>330 mg (100-1,600)</td>
</tr>
<tr>
<td>Length of chronic therapy (≥6 months), average (range)</td>
<td>2.2 years (0.67-5)</td>
</tr>
<tr>
<td>Baseline monitoring tests (%)</td>
<td></td>
</tr>
<tr>
<td>LFT</td>
<td>39 (87)</td>
</tr>
<tr>
<td>TFT</td>
<td>37 (82)</td>
</tr>
<tr>
<td>CXR</td>
<td>39 (87)</td>
</tr>
<tr>
<td>PFT</td>
<td>11 (24†)</td>
</tr>
<tr>
<td>DlCO (N = 11)</td>
<td>6 (55)</td>
</tr>
</tbody>
</table>

† Includes patients for whom PFTs were scheduled to be performed after discharge.
CXR = chest x-ray; DlCO = diffusion capacity, a subset of the PFT; TFT = thyroid function test.

Objectives

The objectives of this study were to quantify adherence to published recommendations for baseline monitoring when initiating inpatient amiodarone therapy at a university teaching hospital and to determine whether appropriate serial monitoring of chronic amiodarone therapy (≥6 months) is occurring in the outpatient setting.

Methods

The NASPE makes several recommendations for monitoring patients on amiodarone. For the purposes of this study, we chose to focus on the 4 recommendations listed in Table 1 since monitoring of chest radiographs (CXRs), liver function tests (LFTs), thyroid function tests (TFTs), and PFTs detect the major adverse effects associated with amiodarone therapy.

The Medical University Hospital is a 700-bed tertiary-care teaching institution affiliated with the Medical University of South Carolina (MUSC). It serves as a statewide referral center for both inpatient care and numerous outpatient primary care and specialty clinics. Institutional Review Board (IRB) approval was obtained, and a retrospective, electronic medical record review was conducted. Adult inpatients who received oral amiodarone therapy from November 1, 2003, through March 31, 2004, were identified via the MS-MEDS pharmacy medication order-entry database. Two types of patients were included in this study. The first group consisted of MUSC inpatients initiated on amiodarone therapy during hospitalization, thus permitting an assessment of amiodarone baseline monitoring. The second group consisted of patients with an MUSC outpatient provider, who received chronic amiodarone on an outpatient basis. This group permitted assessment of serial amiodarone monitoring.

Patients were excluded for the following reasons: they were admitted on prior amiodarone therapy and followed by a non-MUSC provider postdischarge because of the inability to obtain their medical records to document appropriate monitoring; they were cardiothoracic (CT) surgery patients (because these patients are commonly prescribed a limited course of amiodarone therapy postoperatively for atrial fibrillation prophylaxis); and they were scheduled to receive amiodarone therapy for a short duration (<1 month), as indicated in the discharge summary.

Study patients' medical records were reviewed by the primary author for the following information: demographic data; date of initiation of amiodarone therapy; reason for amiodarone therapy; duration of amiodarone therapy; and baseline laboratory and diagnostic tests, including CXRs, LFTs, TFTs, and PFTs. If PFTs were scheduled on an outpatient basis according to the discharge summary, this was also captured. Appropriate follow-up monitoring for LFTs and TFTs was defined as every 6 months, yearly for CXRs, and based on symptoms for PFTs according to the NASPE guidelines (Table 1). Data were entered into an Excel spreadsheet, and descriptive statistics were applied to determine the proportion of patients who received appropriate amiodarone baseline and follow-up monitoring.

Results

Over the 5-month period, 277 adult patients admitted or initiated on oral amiodarone therapy at MUSC were identified for our study. Excluded patients were 146 CT surgery patients and 52 short-term (<1 month) amiodarone patients, leaving 79 patients for possible analysis. Of the 79 patients identified, 45 (57%) were initiated on amiodarone therapy during their admission at the medical university. A majority of these patients were men, (78%) with a mean age of 67 years, who were on amiodarone for atrial arrhythmias (Table 2). Additionally, outpatient records within the MUSC system were available for 20 of the 79 patients to allow assessment of chronic amiodarone monitoring.

Of the 45 patients initiated on amiodarone while hospitalized, baseline LFTs, TFTs, CXR, and PFTs occurred in 39 (87%), 37 (82%), 39 (87%), and 11 (24%) patients, respectively (Table 2). Of the 11 patients who received baseline PFTs, only 6 of these (55%) included a diffusion capacity test (DlCO, a subset of the PFT). Overall, only 5 (11%) of the 45 patients...
received all baseline monitoring tests (Table 2).

Of the 20 patients receiving chronic amiodarone and followed by a MUSC provider, baseline assessment of LFTs, TFTs, and CXRs occurred in 19 (95%), 15 (75%), and 15 (75%) of patients, respectively (Table 3). Baseline PFTs occurred in only 6 (30%) of patients, 5 (83%) of which included a DLCO (Table 3). The average duration of amiodarone therapy was 2.2 years (range, 0.67 to 5 years). Of these 20 patients, LFTs and TFTs every 6 months occurred in 7 (35%) and 4 (20%) of patients, respectively. Lastly, of the 20 chronic amiodarone patients, 16 patients had been on amiodarone for longer than 1 year, and a yearly CXR was performed in 8 (50%) of these patients. Overall adherence to the NASPE guideline for outpatient patients receiving chronic amiodarone therapy is summarized in Table 3.

### Discussion

Several of the adverse effects associated with chronic amiodarone use are serious and occur with enough frequency that vigilant assessment and monitoring are recommended and encouraged. In this retrospective analysis, we identified clinical practice guidelines developed by NASPE for amiodarone monitoring and used these as our model to evaluate appropriate monitoring practices of amiodarone therapy at MUSC. When we evaluated this monitoring model at our institution, we discovered that there was opportunity for improvement, particularly in obtaining PFTs at baseline. At our institution, only 24% of patients initiated on amiodarone therapy received PFTs at baseline. This is almost a 2-fold lower adherence rate than that reported by Stelfox and colleagues, in which 52 (52%) of 99 outpatients at a tertiary care hospital received baseline PFTs. However, our institution does appear to have a slightly better adherence rate to monitoring baseline LFTs, TFTs, and CXRs (75% to 95%), compared with their 56% to 61% adherence rate.

Overall, both this study and the study published by Stelfox and colleagues provide some insight regarding the amount and occurrence of chronic amiodarone monitoring. However, it is questionable whether these results are applicable to other health care systems. The number of referrals treated at each institution likely affects the providers’ view of the utility of obtaining baseline parameter measurements within their health system and likely influences the sense of responsibility they and other providers feel for ensuring appropriate follow-up monitoring. However, the magnitude and clinical importance of these influences are not known.

Currently, there are no broadly accepted guidelines that are consistently applied to patients receiving amiodarone. The package insert does not provide specific monitoring recommendations, and only one clinical practice guideline from an authoritative body exists for amiodarone monitoring. The complexity of amiodarone monitoring may also contribute to the failure to monitor as recommended. A number of strategies could be used to improve amiodarone monitoring through coordinating the ordering and execution of laboratory and diagnostic tests. This could be done by developing an electronic order set or protocol for amiodarone monitoring, to be initiated and/or by developing computerized prescribing aids that would remind the practitioner to monitor the tests on follow-up visits.

### Table 3: Adherence to Amiodarone Monitoring Recommendations for Outpatients

<table>
<thead>
<tr>
<th>Test</th>
<th>N (% Adherence)</th>
<th>Test</th>
<th>N (% Adherence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFT</td>
<td>19 (95)</td>
<td>Every 6 months LFT</td>
<td>7 (35)</td>
</tr>
<tr>
<td>TFT</td>
<td>15 (75)</td>
<td>Every 6 months TFT</td>
<td>4 (20)</td>
</tr>
<tr>
<td>CXR</td>
<td>15 (75)</td>
<td>Yearly CXR (N=16)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>PFT</td>
<td>6 (30)*</td>
<td>DLCO (N=6)</td>
<td>5 (83)</td>
</tr>
</tbody>
</table>

* Includes patients for whom PFTs were scheduled to be performed after discharge.

CXR = chest x-ray; DLCO = diffusion capacity, a subset of the PFT; LFT = liver function test; PFT = pulmonary function test; TFT = thyroid function test.

Multidisciplinary clinics have also been shown to have a higher adherence rate to amiodarone monitoring guidelines. A specialized amiodarone clinic at the University of Illinois at Chicago provided care to its patients according to accepted monitoring guidelines, and increased adherence to guidelines from 23% prior to referral to 90% after clinic enrollment. After a mean enrollment of 9 months, previously unrecognized...
adverse effects were detected in 35% of patients. While the number of these adverse effects that would have been detected if previous follow-up had been continued is not known, this rate is nonetheless impressive. If patients are not adequately monitored, the risks of amiodarone therapy may outweigh its beneficial antiarrhythmic effects. Unfortunately, there are no additional outcome data associated with amiodarone monitoring guideline adherence. Yet, based on the frequency and seriousness of the adverse effects associated with the use of amiodarone, it seems likely that early detection through the recommended laboratory and radiographic assessments would result in improved patient outcomes.

Limitations

The foremost limitation of this study is that it is a care process evaluation and does not address clinical outcomes.

Second, the results are based on retrospective medical record review, in which the data were limited to those files available in the MUSC computer database systems and pulmonary function laboratory records. This leads to potentially incomplete data for patients who received additional outpatient care from non-MUSC providers (approximately 50% of the patients assessed had an outside provider).

Third, the data collection period for this study, the 5-month period ending March 31, 2004, preceded the warning letters sent to pharmacists and other health care professionals at year-end 2004, regarding the life-threatening arrhythmias and cardiovascular and hepatic toxicity associated with the use of amiodarone. It is possible that outpatient monitoring of amiodarone improved in 2005 following the heightened attention to the black-box warning in amiodarone labeling.

Fourth, only those patients on chronic amiodarone therapy who were admitted to the hospital during the 5-month time frame of data collection and followed by MUSC providers were identified, making it likely that many chronic amiodarone patients receiving outpatient care within our health system were not identified.

Fifth, baseline and follow-up laboratory tests could have been obtained for reasons other than initiation or monitoring of amiodarone therapy, leading to an elevated level of monitoring due to hospitalization or other complaint. For example, a CXR is often obtained when a patient is admitted for any pulmonary or cardiac complaint, not just because the patient is on amiodarone therapy. Also, PFTs may have been obtained if the patient had an underlying pulmonary condition such as asthma, chronic obstructive pulmonary disease, lung cancer, or sarcoidosis. Physicians indicated in only 2 out of the 11 PFTs obtained for patients in our review that these tests were related to initiation of amiodarone therapy. The indication for pulmonary function testing is required on paperwork submitted by the requesting physician, and these data were captured for the small number of tests ordered at MUSC in our sample. All other PFTs were at least partly obtained for other reasons. Lastly, because this study included a small number of patients, these data can only provide a very rough estimate of adherence to amiodarone monitoring guidelines at this university-affiliated teaching institution.

However, given these limitations, the results indicating that patients on amiodarone therapy are not adequately monitored for adverse effects are not discordant with the one other report in the literature. With the paucity of data available concerning amiodarone monitoring, our results provide justification for a gross assessment of this issue in other health care settings, for a prospective assessment in a university-affiliated setting, and for an investigation exploring the relationship between quality of amiodarone monitoring and patient outcomes.

Amiodarone is an effective antiarrhythmic, but its use is associated with many serious adverse effects. Close clinical observation and routine laboratory monitoring are necessary components of the management of patients on long-term amiodarone therapy. Serial monitoring of CXRs, LFTs, TFTs, and PFTs allows for early detection of toxicity and permits the discontinuation of amiodarone and/or initiation of appropriate treatment before serious or irreversible sequelae occur.

Conclusion

The NASPE guidelines for the monitoring of patients receiving amiodarone were published in 2000. Data collected for the 5-month period ending March 31, 2004, revealed a 75% to 95% adherence rate for all amiodarone baseline monitoring parameters except for baseline PFTs, for which the adherence rate was ≤30%. Recommendations for chronic monitoring of outpatients receiving amiodarone were followed in ≤50% instances in the set of patients for whom outpatient data were available.

DISCLOSURES

No outside funding supported this study. The authors disclose no potential bias or conflict of interest relating to this article. Author Courtney L. Bickford served as principal author of the study. Study concept and design were contributed by Bickford and author Anne P Spencer. Data collection was the work of Bickford; data interpretation was primarily the work of Bickford, with input from Spencer. Drafting of the manuscript was primarily the work of Bickford; its revision was primarily the work of Spencer.

REFERENCES

Adherence to the NASPE Guideline for Amiodarone Monitoring at a Medical University


Case Report: Lack of Control of Diabetes and Weight Gain in a Patient on Initiation and Rechallenge of Therapy With Olanzapine

Summary
The following is a case report analysis intended to draw attention to the need for better care coordination by describing the observed relationship of olanzapine to metabolic changes manifested as uncontrolled diabetes mellitus and weight gain. A 47-year-old male with bipolar I disorder/hallucinations presented to the Veterans Affairs Medical Center (VAMC) with suicidal ideations. He was referred to the psychiatry service where he was treated with olanzapine. He was followed exclusively by the psychiatry service for more than a year. During that time, weight issues and diabetes status were not addressed. Upon presenting to the primary care service a year and a half later, the patient was taking 40 mg per day of olanzapine and had gained 62 pounds, a 30% increase in body weight; glycosylated hemoglobin (A1c) was 11.1%. The patient was enrolled in a weight-loss clinic, and his diabetes medications were adjusted. Subsequently, olanzapine was discontinued because of weight gain and uncontrolled diabetes. Blood sugar and A1c were finally stabilized one month after discontinuation of olanzapine (A1c, 6.9%). The patient experienced a relapse in his bipolar disorder, and olanzapine was restarted at 20 to 40 mg per day. His blood sugar became uncontrolled, he gained 13 pounds, and his A1c increased to 9.4%.

Background
Atypical antipsychotics were developed in order to decrease side effects that are associated with first-generation antipsychotics. While the atypical antipsychotics have fewer or no extra-pyramidal side effects, they have been associated with metabolic changes, such as glucose dysregulation and weight gain. All atypical antipsychotics have the potential to cause these changes, but clozapine and olanzapine appear to have the highest risk.1-2 In March 2004, at the request of the U.S. Food and Drug Administration, a section detailing the link between atypical antipsychotics and hyperglycemia and diabetes mellitus was added to the olanzapine package insert, as well as to the inserts of all other atypical antipsychotics.3,4 This new warning states that “patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.”5 The Consensus Statement developed by the American Diabetes Association (ADA) and the American Psychiatric Association (APA) outlines a more specific approach. Monitoring of blood glucose is recommended at baseline, 12 weeks, and annually, while measurement of body mass index is recommended at baseline, 4 weeks, 8 weeks, 12 weeks, quarterly, and annually. It is also recommended that patients who gain ≥5% of their initial weight should consider switching to an alternate agent.6

Olanzapine is an atypical antipsychotic currently indicated for the treatment of schizophrenia and bipolar disorder. The mechanism of action is unclear, but it has binding affinity for serotonin 5HT2A/2C, dopamine D1-4, muscarinic M1-5, histamine H1, and alpha1-adrenergic receptors.1,2,4 The typical dose ranges from 5 to 20 mg daily.7 The first reported case of olanzapine-induced hyperglycemia dates back to 1998.8 Since that time, olanzapine’s potential to cause hyperglycemia as well as weight gain has been established1-16; however, the frequency or severity of these reactions is still undetermined.

The VAMC is a managed care organization that utilizes a national drug formulary. There are approximately 150 VAMCs in the United States. Because of the large number, VAMCs are categorized into Veterans Integrated Service Networks (VISNs). There are 22 VISNs in the United States. Each VISN has the ability to review, vote on, and add certain medications to their formulary that might not currently be on the national formulary. Treatment options are monitored through computerized records (i.e., medication refill history; appointment schedules; and lab values, such as A1c). All VAMC patient records are computerized, which allows practitioners to have access to all medical notes, including primary care and sub-specialties. VAMC also allows the dissemination of information on treatment guidelines or clinical pathways to practitioners.

Despite provider education on the recommendations from the ADA and APA, providers do not always take an active role in monitoring their patients. Because of this, uncontrolled disease states caused by atypical antipsychotics may lead to patient nonadherence as well as higher health care costs pertaining to negative outcomes from new disease states. The following case details the hyperglycemic events and weight gain issues associated with olanzapine therapy not only on initiation but also upon rechallenge. It also emphasizes the need for continuous monitoring and care coordination among providers.

Case Report
A 47-year-old white male presented for his first visit to the outpatient primary care clinic on February 27, 2002. His past medical history was significant for type 2 diabetes (unknown date of diagnosis), osteoarthritis, bipolar I disorder/hallucinations, and alcohol abuse (abstinent since 1991). His medications prior to this visit were depakote, clonazepam, olanzapine, glipizide XL, and metformin (doses and frequencies unknown). The patient’s weight at initial visit was 208 pounds. His diabetes status and blood work were not evaluated at this visit because the patient expressed suicidal ideations and was referred to the psychiatric emergency clinic.

He was to come back within a week to get his blood drawn, but he did not follow through. He did come in 3 months later and had a fasting blood sugar of 144 mg/dL. His psychiatric disorder was followed closely by the mental health clinic for the next year, but his diabetes status and weight were not addressed during this time frame. He was initially prescribed olanzapine...
On August 25, 2004, the patient saw his psychiatrist and requested that his olanzapine be discontinued because of his weight gain and his inability to lose the weight. The olanzapine was tapered as follows: 10 mg every evening for 2 weeks, then 5 mg every evening for 2 weeks, and then stopped. His mental health care provider did not initiate another antipsychotic to replace olanzapine even though the patient's note stated that he was reluctant to stop the olanzapine because he was “doing so well on it.”

He was then seen in the primary care clinic on October 21, 2004, one month after discontinuing his olanzapine. During this time, his blood sugars dropped significantly. His average for the previous 2 weeks was 114 mg/dL, with a range from 53 to 185 mg/dL (19 readings; 21% below goal, 47% within goal, 32% above goal). His insulin was decreased to 80 units in the morning and 70 units in the evening. During that same time, the patient saw his psychiatrist and requested that olanzapine be restarted because he was hearing voices. Olanzapine was restarted at 20 to 40 mg every evening (he was taking 40 mg). There is no reason stated as to why a dose of 20 to 40 mg was chosen, since the 40 mg dose is again above the recommended maximum dose.

On November 3, 2004, his blood sugar average was 209 mg/dL with a range of 174 to 283 mg/dL (unknown number of readings, 100% above goal). His insulin 70/30 was increased back to 85 units in the morning and 75 units in the evening.

Two weeks later, he presented to the clinic with a blood sugar average of 262 mg/dL and a range of 202 to 340 mg/dL (11 readings, 100% above goal). Insulin was increased to 95 units in the morning and 85 units in the evening.

He returned in January 2005 and weighed 281 pounds and had an A1c of 9.4%. His mental health care provider kept him on olanzapine and never addressed the issue of weight gain again.

**Discussion**

Koller and colleagues reviewed cases of hyperglycemia associated with olanzapine from the Med Watch Drug Surveillance System. The time of onset of hyperglycemia ranged from 2 days to 45 months, with the majority occurring at 6 months or fewer. They also discovered that, while the onset of hyperglycemia may have been rapid and severe, the association was not dose dependent.

The reason for hyperglycemia associated with the use of olanzapine is not clear. While weight gain may play a role, other causalities likely exist. There are several theories about how olanzapine can induce hyperglycemia. One theory postulates that serotonin (5-HT₁₅) antagonism has the ability to cause low insulin secretion by blunting the response of the pancreatic beta cells. Other theories include a dysregulation of the sympathetic system and insulin resistance due to alteration of the receptor-binding characteristics. Lastly, it has been hypothesized that atypical antipsychotics may decrease the half-life of glucose transporters. Therefore, there are fewer transporters to carry glucose. The mechanism of action...
Worsening of glucose control upon rechallenge was also apparent with this patient. He demonstrated hyperglycemia, with a significant weight gain (approximately 37% of initial body weight). The ability of olanzapine, to cause weight gain is well documented.

Medications that antagonize serotonergic transmission, such as olanzapine, may cause an increase in food consumption. The amount of weight gain correlates with the agents’ affinity for H₁ receptors. Also, the sedative effects of atypical antipsychotics can lead to a sedentary lifestyle, thus contributing to weight gain.

There is literature to support the idea that weight gain may be minimized with nutritional intervention. This patient did attend weight-control classes but was unable to reverse the weight gain. Also, a case report found that by improving negative symptoms in a patient with schizophrenia, weight gain was minimized because she became motivated to diet and exercise regularly.

As with most retrospective case reports, not all pertinent information was available about our patient. For example, a baseline A1c was not obtained, and there was no explanation as to why doses exceeding the recommended maximum dose were used. He was also lost to follow-up in the primary care clinic for more than one year. During this time frame, the patient was being closely evaluated for his bipolar disorder in the mental health clinic. While the mental health care provider evaluated the efficacy of the olanzapine, he never addressed or evaluated the possible side effects (such as weight gain and glucose deregulation) during the course of treatment.

Records at this facility are computerized, thereby allowing practitioners to view all notes from patients’ visits. The mental health care provider was able to see that the patient had not had a primary care follow-up appointment for more than a year. While diabetes status and weight issues are usually addressed by a primary care provider, these issues should also have been addressed by the patient’s mental health care provider.

DISCLOSURES
The author discloses no potential bias or conflict of interest relating to this article.

REFERENCES
Timeline and Potential Impact of CMS’s Drug Competitive Acquisition Program (CAP)

Section 303(d) of the 2003 Medicare Modernization Act mandated creation of a drug Competitive Acquisition Program (CAP) for Part B drugs and biologicals administered “incident to” a physician’s service. CMS’s rationale for the CAP is shown in Inset 1. The intended January 1, 2006, launch date was delayed in order to allow CMS to reconsider key program provisions.1

Anticipated Timeline and Events for CAP

- Several prospective CAP vendors submitted applications to CMS by the December 22, 2005, deadline.
- Announcement of CAP vendor awards was expected by early March 2006.
- A minimum of 2, and up to 5, awarded vendors must sign CMS contracts in order for CAP implementation to proceed.2
- CAP is voluntary for physicians. The first step in CAP implementation will be 2006 physician election of CAP versus “buy-and-bill,” scheduled to commence in early April 2006.4
- Launch of CAP is projected for the first week of July 2006.4
- In October, physician CAP versus buy-and-bill election will commence for the 2007 calendar year.3
- Six months after CAP launch (approximately December 31, 2006) will mark approved CAP vendors’ first opportunity to terminate CMS contracts (the author’s extrapolation from original terms of vendor contract).6

What Impact Will CAP Have on Stakeholders?

CAP-electing physicians. In its proposed rule, CMS cites benefits that will accrue to CAP-electing physicians. However, CMS has not acknowledged the additional administrative burden of CAP for these physicians, which, in this author’s view, constitutes offsetting harms, including obligations to separately track drugs and biologicals shipped to the physician office but discontinued before patient administration; cooperate with the CAP vendor in disposition of partially used vials of drug; submit drug claims within 14 days of administration; and participate in grievance procedures initiated by the CAP vendor.8

Patients served by CAP-electing physicians. Patients are potentially impacted both clinically and administratively. Patients may be impacted clinically by potential treatment delay because nonemergent drugs and biologicals must be ordered from the CAP vendor for each patient, not taken from physician office drug inventory. Patients may be impacted administratively in that their cost-share obligation will be to the CAP vendor, not to the treating physician. If patients are unable to meet their cost-share obligations, then, according to regulation, CAP vendors must inform them of the availability of 1, 2, or all 3 of the following forms of assistance: (1) referral to a bona fide and independent charitable organization, (2) implementation of a reasonable payment plan, and/or (3) a full or partial waiver of the cost-sharing amount. If patients’ cost-share obligation remains unpaid after a specified time period after referral, and if the CAP vendor does not make available other assistance alternatives, then the CAP vendor may withhold further shipments of drugs and biologicals for that patient.9

CAP vendors. CAP has been designated average-selling-price (ASP) exempt (see Inset 2 for the definition and calculation of ASP) for the first 3 years of the program.10 Regulations provide CAP vendors with the ability to specify (select) manufacturers within multisource Healthcare Common Procedure Coding System (HCPCS) categories. However, regulations provide no basis for vendor leverage in product selection within single-source HCPCS categories. Furthermore, regulations

Inset 1

“Beginning January 1, 2006, physicians will have a choice between (1) obtaining these drugs from entities selected to participate in the CAP in a competitive bidding process, or (2) acquiring and billing for competitively biddable Part B covered drugs under the ASP drug payment methodology. The provisions for acquiring and billing for drugs through this new system, as well as additional information about this new drug payment system, are described in this proposed rule. The competitive acquisition program may provide opportunities for Federal savings to the extent that aggregate bid prices are less than 106 percent of ASP.

“However, the CAP has other purposes than the potential to achieve savings. The competitive acquisition program provides opportunities for physicians who do not wish to be in the business of drug acquisition. Engaging in drug acquisition may require physicians to bear financial burdens such as employing working capital and bearing financial risk in the event of nonpayment for drugs. The CAP is designated to reduce this financial burden for physicians. In addition, physicians who furnish drugs often cite the burden of collecting coinsurance on drugs and that drug coinsurance can represent large amounts for a beneficiary and physician. The Competitive Acquisition Program eliminates the need for physicians to collect coinsurance on CAP drugs from Medicare beneficiaries.”3

Inset 2

“Section 303(c) of the Medicare Modernization Act (MMA) revised the drug payment methodology by creating a new pricing system based on a drug’s ASP [average selling price]. Effective January 2005, Medicare pays for the vast majority of Part B-covered drugs and biologicals using a drug payment methodology based on the ASP. In accordance with section 1847A of the Social Security Act (the Act), manufacturers submit the ASP data for their products to us on a quarterly basis. These data include the manufacturer’s total sales (in dollars) and number of units of a drug to all purchasers in the United States in a calendar quarter (excluding certain sales exempted by statute), with limited exceptions. The sales price is net of discounts such as volume discounts, prompt pay discounts, cash discounts, free goods that are contingent on any purchase requirement, chargebacks, and rebates (other than rebates under section 1927 of the Act). The Medicare payment rate is based on 106 percent of the ASP, less applicable deductible and coinsurance, and is updated quarterly.”10
disallow vendor use of drug formularies and related controls over physician prescribing. Due to these limitations, it is unlikely that brand manufacturers will extend physician class-of-trade pricing to CAP vendors. This will have important implications for vendor profitability. CAP vendors will also be subject to Local Coverage Decisions, including Least Costly Alternative policies, as they apply to the regions of the country in which CAP physician offices are located. Application of these policies may generate claims denials and/or reductions in allowed reimbursement. Another problem is that because manufacturers have designated exclusive provider arrangements for some products, CAP vendors may experience difficulty accessing these products at a cost that is reasonable given contracted reimbursement. Finally, expensive single-source products, particularly those in competitive therapeutic categories, will drive CAP vendor financial results—not less-expensive multisource products. This is due to a sharply limited upside gross defined by 6% of product’s ASP balanced against significant per-prescription supply costs, projected unbilled waste, projected CMS claims denials, and projected patient bad debt on cost-share responsibilities.

Manufacturers of CAP drugs and biologicals. CAP vendors’ limited supply role, coupled with lack of influence over choice or use of single-source products, provides vendors no contracting leverage with manufacturers of these products. In addition, this writer anticipates that few physicians will elect CAP in 2006, minimizing manufacturers’ CAP market share exposure. Together, these factors limit brand manufacturers’ interest in CAP. The situation is quite different with respect to multisource products: CAP physicians must submit “prescriptions” to CAP vendors at an HCPCS code level, without specifying manufacturer, vial size, or packaging. In response, CAP vendors will supply only those National Drug Code (NDC) numbers with respect to which they are contracted with CMS. In other words, it is likely that CAP vendors will use their significant negotiating leverage with manufacturers of multisource products to generate preferred supplier arrangements tied to favorable pricing relative to ASP.

CMS. In addition to competition between CAP vendors for CMS contracts, the term “competitive acquisition” also implies—and program success is indeed dependent upon—CAP vendors’ negotiating leverage in the acquisition of drugs and biologicals. Unfortunately, negotiating leverage is only available with respect to multisource products, which, as discussed previously, will not be the main drivers of CAP vendor financial experience. Having removed what it considers excess funding through implementation of ASP + 6% reimbursement for Part B drugs and biologicals, this author believes that CMS is unlikely to achieve additional savings through CAP—and may even experience a net cost increase compared with the same products paid for under buy-and-bill. This conclusion is driven by the following considerations. First, anticipating difficulty in negotiating favorable product acquisition cost with brand manufacturers, prospective CAP vendors are not likely to have bid significantly below the ASP + 6% upper limit permitted by CMS. Second, CMS is likely to incur new incremental cost to fund CAPs administrative structure and services.

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DISCLOSURE
The author discloses that he has provided advice to a company in preparation of its CAP vendor application to CMS, performed its HCPCS-level CAP financial analysis, and assisted in development of its CAP business strategy. He has also consulted with several biotechnical manufacturers regarding the pros and cons of contracting with CAP vendors.

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5. Medicare Program. Revisions to payment policies under the physician fee schedule for calendar year 2006 and certain provisions related to the competitive acquisition program of outpatient drugs and biologicals under Part B. CMS 1502-FC, CMS 1325-F. Federal Register. Vol. 70. No. 223:70257 (November 21, 2005).
March 2006 yielded 8,833 citations. The initial enthusiasm for articles indexed by PubMed on the subject of COX-2 inhibition of rofecoxib on September 30, 2004.\(^3\) Inhibition versus NSAIDs following the U.S. market withdrawal of anti-inflammatory drugs (NSAIDs). Ortiz summarized much of the evidence on the subject of the relative value of the COX-2 inhibitors versus NSAIDs following the U.S. market withdrawal of rofecoxib on September 30, 2004.\(^3\)

In the September 2005 issue of JMCP, Stockl et al. found that users of COX-2 inhibitors did not have a reduced risk of GI bleed events compared with users of NSAIDs who had similar baseline characteristics.\(^4\) In that study of 35,007 pairs of COX-2 inhibitor and NSAID users, there were 375 cases of GI bleed among 19,201 follow-up years for COX-2 users, or 19.5 cases per 1,000 person-years, versus 228 cases of GI bleed among 12,680 follow-up years for NSAID users, or 18.0 cases per 1,000 person-years. There was no difference in the risk of GI bleed for COX-2 versus NSAID users (relative risk 1.07; 95% confidence interval [CI], 0.90-1.26), and even among high-risk patients, the relative risk of a GI bleed for COX-2 inhibitor users was 0.995 (95% CI, 0.84-1.19).

In December 2005, Hippisley-Cox et al. found that the use of naproxen, diclofenac, and rofecoxib (Vioxx) but not celecoxib (Celebrex) was associated with increased risk of an upper GI event, defined as peptic ulcer or hematemesis. The adjusted odds ratios were 2.12 (95% CI, 1.73-2.58) for naproxen, 1.96 (95% CI, 1.78-2.15) for diclofenac, 1.56 (95% CI, 1.30-1.87) for rofecoxib, and 1.11 (95% CI, 0.87-1.41) for celecoxib. While Stockl et al. matched COX-2 inhibitor users with nonselective NSAID users, Hippisley-Cox et al. matched COX-2 or NSAID users with a first-ever diagnosis of upper GI event with controls matched for age, sex, calendar time (between August 1, 2000, and July 31, 2004), and practice (among 367 general practices in the United Kingdom). Like Stockl et al., Hippisley-Cox et al. concluded that there was no consistent evidence of protection from GI events for the COX-2 inhibitors compared with nonselective NSAIDs.\(^3\)

These 2 congruent findings in 2 different countries involving 70,014 patient records in Stockl et al. and 98,274 patient records in Hippisley-Cox et al. for the same approximate time period provide additional evidence of the apparent lack of value of COX-2 inhibitors in preventing or reducing the incidence of adverse upper GI events. In October 2005, between the publication dates for Stockl et al. in September and Hippisley-Cox et al. in December, Abraham et al. concluded from their review of 303,787 high-risk Veterans Administration patients that only 27.2% (n = 82,766) were prescribed NSAIDs safely in 2002, based on “evidence-based guidelines.” Abraham et al. defined guideline adherence as the coincident use of gastroprotection with a nonselective NSAID or use of a COX-2 inhibitor in high-risk patients. A high-risk patient was aged 65 years or older, used a corticosteroid or anticoagulant concurrently, had a history of peptic ulcer, or had a high average daily dose of NSAIDs (e.g., 1,500 mg per day of naproxen, 200 mg per day of diclofenac, or 2,400 mg per day of ibuprofen). An interesting question not addressed by Abraham et al. has to do with the unnecessary use of COX-2 inhibitors in patients not at risk of upper GI events. Johnsen et al. found that 81% of the users of COX-2 inhibitors were not in the high-risk category for upper GI events.\(^7\)

Further, the evidence supports the use of alternatives to the COX-2 inhibitors in patients at elevated risk of a GI bleed. Chan et al. established that omeprazole 20 mg per day plus diclofenac 75 mg twice daily was comparable to celecoxib 200 mg twice daily in the incidence of recurrent GI bleed in patients at high risk for GI bleed, after accounting for coincident aspirin use and status of infection with Helicobacter pylori.\(^8\) Setting aside the potential for adverse cardiovascular events associated with COX-2 inhibitors, the availability of over-the-counter omeprazole (Prilosec OTC) means that it is possible in 2006 to treat 4 patients at high risk of a GI event with omeprazole 20 mg daily plus 75 mg diclofenac twice daily for the same cost ($1.32 per day per patient, Table 1) for each high-risk patient treated with celecoxib 200 mg twice daily ($5.28 per day per patient).

The market withdrawal of rofecoxib on September 30, 2004, created an opportunity for another nontraditional NSAID—meloxicam (Mobic)—routed by some as a “COX-1½.” It is probably no coincidence that meloxicam, an NSAID not caught up directly in the COX-2 inhibitor controversy, led the price increases for all brand name drugs in January 2005. The manufacturer raised the price of the meloxicam 7.5 mg tablet by 7% and by 11% for the more commonly used 15 mg tablet.\(^9\)

Despite the same label warning as other NSAIDs regarding cardiovascular risk and GI risk,\(^10\) meloxicam leads the NSAID drug class in 2006 in average cost per 30-day supply. Discount prices in March 2006 for a standardized 30-day supply were $124 for meloxicam 15 mg per day and ranged from $79 for 1 capsule of celecoxib 200 mg per day or $158 per month for 2 capsules per day (Table 1). Comparing these prices with actual managed care organization (MCO) prices regardless of drug strength showed that meloxicam had an average MCO cost (before rebate and before member cost-share) of $132 per 30-day supply in early 2006. Approximately half of the pharmacy claims and half of total days of meloxicam therapy are accounted for by the 15 mg tablet, with an average of 1.02 tablets per day. The other half of meloxicam pharmacy claims and total days of
therapy in 2006 are for the 7.5 mg tablet, with an average of 1.35 tablets per day.† The average actual MCO cost for celecoxib was $113 per 30-day supply in early 2006 (an average of 1.33 units per day), suggesting that actual use involves a mixture of celecoxib strengths (100 mg, 200 mg, or 400 mg capsules) and either 1 or 2 capsules per day. Therefore, in actual use, meloxicam had a price premium of 15% compared with celecoxib in the first 3 months of 2006.

In order to understand better why the U.S. market embraced meloxicam in 2005 and 2006, it is helpful to recall the regulatory history of the COX-2 inhibitors. On September 30, 2004, the U.S. Food and Drug Administration (FDA) requested the market withdrawal of rofecoxib (Vioxx) due to safety concerns associated with an apparent increased risk of cardiovascular events, particularly heart attack and stroke.‡ Six months later, on April 7, 2005, the FDA asked the manufacturer of valdecoxib (Bextra) to voluntarily withdraw the drug from the market.† Steve Galson, acting director of the FDA Center for Drug Evaluation and Research, said that, at the time, there was “no added advantage, and a special risk,” in the higher rate of adverse skin reactions with Bextra, and “the cardiovascular risks of these drugs are what we consider a class effect.”  §

The media attention surrounding the market withdrawal of these two COX-2 inhibitors and the ensuing litigation against the manufacturer of rofecoxib alleging patient harm was associated with a 40% slide in celecoxib sales in 2005 (Figure 1); celecoxib dropped from rank #6 in total community pharmacy sales in 2003 to rank #26 in 2005. The decline in sales of celecoxib was picked up, in large part, by a 118% increase in meloxicam sales in 2005. Meloxicam rose from rank #111 in total expenditures in 2003 to rank #26 in 2005. The decline in sales of celecoxib was picked up, in large part, by a 118% increase in meloxicam sales in 2005. Meloxicam rose from rank #111 in total expenditures in 2003 to rank #38 in 2005.

The plummeting sales of the COX-2 inhibitors as a class have resulted mostly from the attention of the public and health care professionals to the apparent increased cardiovascular risk, not primarily from failure to protect patients from adverse GI events. Comparison of the adverse event data across all NSAIDs and COX-2 inhibitors shows a low incidence of myocardial infarction (<1%) for all NSAIDs except tolmetin (3%-9%), rofecoxib (3.5%-10%), valdecoxib (1.6%-2.1%), celecoxib (<2%), and meloxicam (<2%).

In the assessment of relative value of COX-2 inhibitors versus NSAIDs, it is important to remember that the FDA (a) allowed the manufacturer of rofecoxib (Vioxx) to add to its product label the results of the VIGOR (Vioxx Gastrointestinal Outcomes Research) trial that suggested a GI protective effect compared with naproxen, although subsequent controversy swirled years later, in 2005 and 2006, surrounding the selective omission of 3 deaths of patients who took rofecoxib; (b) never permitted a claim of less GI harm for any NSAID or COX-2 inhibitor except rofecoxib; and (c) rejected the request from the manufacturer of celecoxib to drop the warning of possible GI adverse effects from the label.

### Table 1

<table>
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<th>Drug</th>
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<th>Cost per Day ($)†</th>
<th>Cost per 30-Days ($)</th>
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<td>Meloxicam 15 mg‡</td>
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<td>Naproxen 500 mg</td>
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<td>0.77</td>
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<td>Naproxen + omeprazole OTC</td>
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<tr>
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<td>1.32</td>
<td>40</td>
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</table>

* Price data obtained from www.drugstore.com for packages of 90 units or 180 units, except 42 units per package for omeprazole OTC. Accessed March 17, 2006.
‡ Meloxicam 15 mg is the more common dose per day in actual use. Based on pharmacy claims with dates of service in 2006 through March 15, approximately 50% of the pharmacy claims and 50% of the days of therapy with meloxicam are accounted for by the 15 mg tablet, with an average 1.35 units per day, and 50% of pharmacy claims and 50% of the days of therapy with meloxicam are contained in the product information as reproduced by Drug Facts and Comparisons (Clinisphere version ISBN 1-57439-036-8). St. Louis, MO: Wolters, Kluwer Health, Inc. February 2006. Accessed March 17, 2006.

### Figure 1

Community Pharmacy Sales in 2003-2005* for Celecoxib and Meloxicam

* Data from Verispan Source Prescription Audit (SPA):
Disappointment would be in store for those who assume that there is clinical evidence of the superiority of meloxicam over the traditional NSAIDs in GI protection. The early clinical trials (the drug was approved by the FDA for use in arthritis patients on April 14, 2000\textsuperscript{21}) suggested that meloxicam was equal in efficacy to traditional NSAIDs and may have some advantage in GI protection. For example, the manufacturer sponsored a study of 774 patients with osteoarthritis of the hip or knee and a flare that concluded that meloxicam had a lower rate of GI adverse events compared with diclofenac, but this difference was not for bleeding events; rather, it was for all GI adverse events such as nausea and diarrhea.\textsuperscript{20} Also, this study by Yocum et al., like the other clinical trials used to obtain FDA approval of meloxicam, was of short duration—only 12 weeks. It is also noteworthy that Yocum et al. pooled the adverse GI event data for all 3 doses of meloxicam, including the 3.75 mg dose per day that did not prove superior in efficacy to placebo.

Later, in a meta-analysis of data from randomized, controlled trials (RCTs) published through January 2003, Richy et al. found that meloxicam had possible superiority to both naproxen and diclofenac in relative risk of GI complications for NSAID users compared with nonusers, but the risk of GI complications was not different for meloxicam users versus NSAID users compared with nonusers, and adjusting for these risk factors revealed that COX-2 inhibitors were associated with a lower risk of GI hemorrhage—but meloxicam was not associated with a lower risk of GI hemorrhage.

In conclusion, it is possible to treat 3 to 4 patients with therapeutically equivalent regimens of naproxen plus omeprazole OTC or diclofenac plus omeprazole OTC for the total cost equivalent to treat 1 patient with celecoxib. Drawing upon the research of Johnsen et al. in which only 19% of users of COX-2 inhibitors were at increased risk of a GI bleed, 81% of the use of celecoxib could have been either naproxen or diclofenac or other traditional NSAIDs and 19% could have been omeprazole OTC and either naproxen or diclofenac, at lower cost (Table 1). Applying these ratios of use of therapeutically equivalent, lower-cost therapies, consumers and third-party payers overspent by $4.45 billion on celecoxib over the last 3 years. Since there is no evidence of the superiority of meloxicam over other NSAIDs, overspending on meloxicam in the United States was $1.38 billion over 3 years, a total avoidable waste of $5.83 billion. Surely, we could have found better use for this money.

So, this is another example of cheaper is better. Evidence-based medicine supports the use of the lower-cost therapies, including omeprazole plus either naproxen or diclofenac, over the use of celecoxib in patients at increased risk of upper GI bleed.\textsuperscript{26} Regarding meloxicam, when it becomes equivalent in price to its NSAID clinical peers, perhaps it will be a reasonable COX-2 pretender in “the Emperor’s new clothes.”\textsuperscript{27}

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Editorial Subjects—In This Issue and in Previous Issues
Step Therapy Is Not Appropriate for Antiepileptic Drugs

To the Editor:

We read with interest the article by Payakachat and colleagues, comparing the clinical practice guidelines for treatment of new-onset epilepsy in adults. While we appreciate their efforts to provide a careful review of available treatment guidelines and consideration of how these guidelines might be applied in managed care, we strongly disagree with their conclusion that older agents (i.e., phenobarbital, carbamazepine, phenytoin, and valproate) are the preferred first-line treatments for new-onset epilepsy. Their conclusions appear to be based upon a rather narrow consideration that only accounts for efficacy in controlling seizures. As the authors correctly note, broader data on the effectiveness, outcomes, tolerability, and quality of life are lacking in the published literature. However, the authors underemphasize important aspects of epilepsy as a disorder and characteristics of antiepileptic drugs that must be a part of therapeutic and formulary decision making. Indeed, the guidelines that are included in the article make specific statements about drug selection in epilepsy contrary to the conclusion of Payakachat et al. The following are important factors, essential to therapeutic decisions in new-onset epilepsy, that had they been included would probably have led to a different conclusion.

Epilepsy is a heterogeneous disorder. Seizures are often merely the primary clinical manifestation of an underlying neurological abnormality or disease. Although seizures may appear to be similar in clinical presentation or electrographically, the underlying pathology can be very different from one patient to the next. Until better diagnostic tools are available to determine the underlying pathophysiology of seizures, it is important to have a broad group of drugs with respect to mechanisms of action and adverse events from which selections can be made.

The published guidelines clearly demonstrate that drugs need to be matched to the seizure type and/or seizure syndrome. Without careful attention to this detail, incorrect antiepileptic drugs may be selected and could result in exacerbation of seizures rather seizures and primary generalized seizures. Initiation of carbamazepine or phenytoin in a patient with certain types of primary generalized seizures will often result in increased seizure frequency.9-14 In all of the guidelines, some of the seizure syndromes only have a single older and newer drug recommended as first-line therapy. Typically, the older agent is valproate, which is associated with numerous adverse effects and teratogenicity.

This evaluation and recommendation does not account for the numerous adverse effects associated with older antiepileptic drugs. Older agents are associated with side effects that often result in discontinuation, impairment of lifestyle, or, in rare cases, life-threatening conditions. In several clinical trials, the newer antiepileptic drugs have demonstrated greater tolerability compared with the older agents.6,8 Beyond these acute adverse effects, chronic adverse effects such as osteopenia and osteoporosis are clearly associated with the older antiepileptic drugs.9,10 Recent studies have also provided increased understanding of the teratogenicity of the older agents, especially phenobarbital and valproate, making them less than optimal options for women of child-bearing potential.11-14

The newer agents are clearly associated with fewer drug interactions.15 All of the older drugs are hepatically metabolized, are potent inducers or inhibitors of hepatic enzymes, and some are highly protein bound. Not only do these features make them prone to influences by other medications, but their effects on hepatic enzymes will change the efficacy of other drugs the patient may be taking. One example is the clear interaction between many of the older agents and hormonal contraceptives, rendering the hormonal contraceptive much less effective.15-19

Newer antiepileptic drugs often involve renal elimination, do not induce or inhibit hepatic enzymes to the extent of the older drugs, and are typically free of drug interactions. This is a key factor when selecting an antiepileptic drug in patients who are taking multiple medications.

We believe that a recommendation for antiepileptic drug selection must take into account all of these factors to form a comprehensive evidence-based approach. Restrictions on new antiepileptic drug use in a stepped formulary approach fails to recognize the highly heterogeneous nature of epilepsy and forces patients to be exposed to drugs that are not well tolerated, carry greater risk for chronic adverse effects and teratogenicity, and complicate the therapeutic regimen with multiple drug interactions. A more thorough analysis of all available data should be initiated prior to making formulary decisions regarding antiepileptic drug use for epilepsy in managed care.

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REFERENCES


The Authors Respond

Comparison of Clinical Practice Guidelines in the Initial Pharmacological Management of New-Onset Epilepsy in Adults

We appreciate the consideration given to our article by Welty, Faught, and Privitera; however, we disagree. The authors make a vague statement, “the guidelines that are included in the article make specific statements about drug selection in epilepsy contrary to the conclusion of Payakachat”; however, after making this statement they proceed to cite several primary research articles and do not actually support this claim from the text of the guidelines.

Their title “Step therapy is not appropriate for antiepileptic drugs” is misleading because our article was an examination and comparison of guidelines. The guidelines do not advocate step therapy nor were we acting as advocates of step therapy. Our intent was to compare guideline recommendations. This is not tantamount to advocating step therapy. Rather, we observed that published guidelines did not clearly delineate supremacy of the newer drugs over the older drugs.

Guidelines are intended as general guides. They do not preclude deviation when specific circumstances warrant it. The authors note exceptions or special circumstances that they advocate as advantageous for the newer drugs. However, it is notable that the authors of the guidelines did not find these issues sufficiently convincing to discount the use of older drugs in all cases.

The authors introduce some subjects that are “non sequiturs” for our article. The authors state, “Epilepsy is a heterogeneous disorder. Seizures are often merely the primary clinical manifestation of an underlying neurological abnormality or disease.” However, our article is not about epilepsy as a disease nor about seizures as a manifestation of varied diseases. The authors go on to say, “Although seizures may appear to be similar in clinical presentation or electrographically, the underlying pathology can be very different from one patient to the next.” Our article was also not about the specific pathology underlying seizures. The authors continue, “Until better diagnostic tools are available to determine the underlying pathophysiology of seizures, it is important to have a broad group of drugs with respect to mechanisms of action and adverse events from which selections can be made.” Again, our article was not about seizure diagnosis, nor underlying pathophysiology, nor the importance of having treatment options. Rather, our article compared the conclusions reached in published treatment guidelines.

Also notable is the observation that the guidelines do not make a strong case for the use of newer drugs over the older drugs. This is not the same as precluding use of the newer drugs. Rather, in the era of cost-conscious health care, we only observed that the guidelines do not make a strong case for the newer drugs in the initial management of newly diagnosed epilepsy. And, the newer drugs are more expensive—thus
supporting the notion of giving first consideration to the older drugs. Certainly in those circumstances where specific drugs have advantages for a particular patient, the guidelines do not advocate against their use. Rather, the guidelines provide generalizations as a place to start in the initial management of newly diagnosed, uncomplicated cases, as we stressed in our article.

In total, it seems the authors have the most difficulty with the recommendations of the guidelines. However, this is a different issue for a different audience. The authors are free to put their concerns before the authors of the guidelines. We are not the authors of the guidelines. Instead, given that it is accepted current strategy to generate guidelines for reference by practitioners, and that guidelines are delineated by consensus from groups of experts, we saw it as reasonable to compare published guidelines on the topic of initial treatment of new-onset, adult epilepsy.

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