Improving Cost-Effectiveness of and Outcomes From Drug Therapy in Patients With Atrial Fibrillation in Managed Care: Role of the Pharmacist

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ABSTRACT

BACKGROUND: The medical care costs for procedures, medications, and testing associated with atrial fibrillation (AF) in the United States are high and projected to increase markedly in the future as the number of Americans affected grows. The burden on patient quality of life, the health care system, and society are pharmacoeconomic considerations in managing AF.

OBJECTIVES: To identify key pharmacoeconomic considerations in managing AF and describe ways in which managed care pharmacists can improve the cost-effectiveness of and outcomes from drug therapy for AF.

SUMMARY: The high medical care costs of AF are largely the result of the high cost of hospitalization and inpatient procedures. Recurrence of AF dramatically increases costs, especially for hospital care.

Managed care pharmacists have many opportunities to provide cost-effective care to and improve outcomes in patients with AF. Policy and process review, population management, and case management are key strategies for improving outcomes in patients with AF. Pharmacist input into policy and process review, including pharmacy benefits design, formulary management, and the use of information technology, can help ensure that the use of drug therapy for AF is cost-effective. Population management strategies, such as development of clinical pathways and patient registries, seek to improve the quality, consistency, and cost-effectiveness of care and the likelihood that desired therapeutic outcomes are achieved through targeted interventions. Case management strategies focus on longitudinal care for individuals in order to improve quality. Pharmacist-managed anticoagulation services and antiarrhythmic drug monitoring are the 2 most widely known case management strategies for patients with AF. Managed care pharmacists can screen patients with AF for the use of anticoagulation, which is needed to prevent embolic stroke but is under-used, even though recommended by evidence-based guidelines. The clinical efficacy and cost-effectiveness of pharmacist-managed anticoagulation services for patients with AF are well documented. Pharmacist-managed antiarrhythmic drug monitoring is a less well-known case management strategy that facilitates early detection and intervention to minimize toxicity.

CONCLUSIONS: Managed care pharmacists can play an instrumental role in implementing strategies to improve the cost-effectiveness of and outcomes from drug therapy for AF.


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Off-Label Disclosure Statement

In this article, amiodarone is discussed for the off-label use in atrial fibrillation. While widely used for this indication, amiodarone is not approved for this use in the United States.

Pharmacoeconomics can be defined as the study of economic factors related to the cost of drug therapy, including the impact on health care systems and society. Alternatively, pharmacoeconomics can be defined as the study of cost-benefit ratios of drugs compared with other therapies or similar drugs, where costs include both financial and quality-of-life measures. The fact that drug therapy is associated with a measurable cost both financially and with respect to patient quality of life is a common theme regardless of which definition is used. One aspect of pharmacoeconomics that, because of the growing number of cases, has attracted considerable attention is the management of atrial fibrillation (AF).

Pharmacoeconomic considerations include the cost burden of managing AF on the health care system, patients, and society. The types of costs taken into consideration include the costs of procedures, medications, and testing. New technologies, including electronic medical records, as well as internet-based registry tools, have had a profound impact on the costs of managing AF and other diseases, leading to their promotion by the current presidential administration as an example of meaningful health care reform. Arguably, the largest challenge that we as a society face is how to determine which technologies—pharmacologic and nonpharmacologic—provide the greatest value for our health care dollars.

Costs of Atrial Fibrillation

Annual AF-related health care costs in the first few years after diagnosis amount to roughly $4,700 per patient in the United States. Although this figure may not seem large, the total annual cost of AF in the United States, obtained by extrapolating this figure to the 2.3 million Americans currently affected, is nearly $11 billion. Furthermore, projections of the number of Americans with AF by the year 2050 range from more than 5.6 million to nearly 16 million, so the disease’s economic impact could become enormous.
Analysis of medical, drug, and disability claims data from 16 employers and 2 million enrollees in private insurance programs in the United States during the period 1999-2002 revealed that the annual direct costs of AF (i.e., medical service and prescription drug costs), expressed in 2002 dollars, were more than 5-fold higher in 3,944 patients with AF ($15,553) than in 3,944 persons (matched 1:1 for age, gender, and health plan status) without the disease ($2,792). The indirect costs of lost work time (i.e., productivity), calculated using disability claims and data for absenteeism due to medical conditions for 603 employees, were 4-fold higher in patients with AF ($2,847) compared with persons without the disease ($713). The average annual medical service costs were $13,749, with the largest portion ($8,486; 62%) for inpatient hospital care and a lesser portion ($4,622; 34%) for outpatient care (e.g., physician office visits). Annual prescription drug costs were comparatively lower—$1,804 per patient.

Medical care costs associated with recurrence of AF were analyzed using data from the Fibrillation Registry Assessing Costs, Therapies, Adverse events, and Lifestyle (FRACTAL) registry of 973 patients with AF who were followed beginning at the time of diagnosis for a mean of 24 months. Patients with permanent AF for whom a rate-control strategy was chosen had the lowest medical care costs; patients for whom rhythm-control strategies were chosen typically require costly hospital admission for initiation of antiarrhythmic drug therapy. Not surprisingly, recurrence of AF dramatically increased annual medical care costs, which include costs for hospital care, outpatient services, and medications (Figure 1). Hospital costs included costs for direct current cardioversion, AF ablation, and other inpatient procedures (e.g., MAZE [open-heart surgery to create non-conductive scar tissue] procedure). Outpatient services costs included emergency room and physician office visits. Medication costs reflected laboratory monitoring costs as well as drug acquisition costs based on average wholesale prices.

Each recurrence of AF increased annual medical care costs by approximately $1,600, expressed in U.S. 2002 dollars. The largest component of the cost increase associated with AF recurrence was for hospital charges, with lesser amounts attributed to outpatient services and medications. The costs used in the analysis for some procedures ($2,300 for AF ablation, $760 for cardioversion, and $640 for a single emergency room visit without admission) were considerably higher than the annual costs for some medications (e.g., $180 for warfarin, $1,100 for amiodarone).

Pharmacist’s Role
Managed care pharmacists have many opportunities to develop, provide, and implement cost-effective strategies to improve outcomes in patients with AF. For example, a variety of approaches may be used to improve outcomes in patients with AF (Table 1). Pharmacist input into policy and process review, including pharmacy benefits design, formulary management, and the use of information technology, can help ensure that the use of drug therapy for AF is cost-effective.

Pharmacists play a vital role in advising clinicians who prescribe the problematic antiarrhythmic drug to monitor renal function. Pharmacists also should counsel patients about the risks associated with drug therapy and the warning signs of problems that warrant prompt medical attention. Talking points should be developed for the pharmacists to use when interacting with prescribers and patients. Programming electronic alerts about the need for renal function monitoring into the computerized prescriber order entry (CPOE) system is an application of information technology that can help meet the goals of improving renal function monitoring and drug safety. Establishing prescribing restrictions through the formulary management process might be considered. Creating a database of all patients receiving the medication to identify adverse effects may be useful for detecting trends and identifying underlying causes.
Policy and Process Review

Pharmacy benefits design, a component of policy and process review, is a logical approach to provide consistent care and make resources available to all patients. In the past, pharmacy benefits were designed using a one-size-fits-all approach, with a single-benefit tier. Under such benefit plans, insurance premiums were prepaid, and out-of-pocket costs for acute care were low for most patients. Recently, 3- and 4-tier pharmacy benefit plans with high deductibles and out-of-pocket costs for medications and acute care have been developed in an attempt to mitigate cost increases associated with the emergence of new technologies and therapies and a need to shift some of these costs to patients, especially patients with chronic diseases.

In today’s health care environment, formulary management has assumed a greater role than before. Formulary management involves the timely review of new drugs approved by the U.S. Food and Drug Administration (FDA). Restrictions on which clinicians may prescribe the drug (i.e., prior authorization requirements) and types of patients who may receive the drug can be established based on efficacy, safety, and cost compared with the standard of care. The development of treatment algorithms and protocols to ensure appropriate use of medications to manage diseases also may be part of the formulary management process. The need for and costs of monitoring therapy and the costs of treating adverse effects should be taken into consideration along with drug acquisition costs.

The antiarrhythmic agent dronedarone was approved by the FDA in early July 2009 for use in certain patients with AF, and the anticoagulant rivaroxaban (which is under consideration for approval for prophylaxis of venous thromboembolism following orthopedic surgery) may soon be approved by the FDA. Pharmacists can play an important role in evaluating the available clinical data, identifying knowledge gaps, and making recommendations for use of the drugs in the organization. For example, pharmacists may participate in the development of a cogent clinical pathway that alerts prescribers that dronedarone should not be used in patients with severe heart failure (HF). Few data currently are available about the comparative efficacy and safety of dronedarone and amiodarone (the standard of care, although the drug is not approved formally by FDA for patients with AF), but one drug may be preferred over the other for some patients. The development and use of treatment algorithms and protocols for patients with AF based on what is known about the efficacy and safety of dronedarone, amiodarone, and other antiarrhythmic agents can facilitate and ensure consistency in the therapeutic decision-making process.

Another example is rivaroxaban, which will probably be approved initially only for the prevention of venous thromboembolism in patients undergoing hip- and knee-replacement surgery, although clinical trials of the drug for preventing embolic stroke in patients with AF are under way. The formulary management process should address the uses of rivaroxaban that will be permitted within the organization. As new clinical data become available, prescribing restrictions and treatment algorithms and protocols should be updated.

Drug utilization and safety programs are an important part of the formulary management process. Such programs may include algorithm development to guide safe and effective prescribing, prior authorization reviews, and regular drug-use evaluations. These programs should be adapted to accommodate the need for postmarketing surveillance of adverse effects from new drugs for AF and other disease states. Using dronedarone as an example, an appropriate use of clinical pharmacy services would be for proactive development of a clinical prescribing algorithm to be vetted together with cardiologists, hospitalists, and primary care physicians. In essence, this would establish a process of care that maximizes safe and effective use of dronedarone for appropriate patients. Adjunctively, periodic drug-use evaluations by pharmacy staff would provide a snapshot of overall drug use and may afford opportunities for a therapeutic “course correction” if needed.

The expanded use of information technology (e.g., electronic medical records, electronic alerts in CPOE systems) to coordinate and streamline the delivery of health care (e.g., reduce duplicate testing, facilitate evidence-based practice) has the potential to both improve patient outcomes and decrease costs. These goals have gained prominence in recent years, especially in managed care. Examples that apply to patients with AF include electronic prescriber alerts that provide clinicians with monitoring recommendations for amiodarone (or other antiarrhythmic agents) and the ability to quickly extract administrative-level data (including comorbidities, demographic characteristics, and treatment information) to assess overall quality of care provided.

Population Management

Population management strategies are based on an appreciation of the 80/20 rule—the fact that typically the majority (80%) of health care costs are incurred by a minority (20%) of patients. Population management strategies seek to improve the quality, consistency, and cost-effectiveness of care and the likelihood that desired therapeutic outcomes are achieved. In patients with AF, these outcomes might include a reduction in hospital readmission rates for AF recurrence.

The development of evidence-based clinical pathways for drug therapy management and patient registries to track safety outcomes from drug therapies are probably the 2 most important managed care population management strategies for patients with AF. These strategies facilitate the consistent delivery of high quality, cost-effective patient care. Managed care pharmacists can seek opportunities to become involved in these strategies, including the development and implementation of evidence-based clinical pathways for the management of patients with AF. Many successful examples of these strategies are available for the management of a variety of disease states, including diabetes (a
risk factor for embolic stroke in patients with AF), asthma, and depression; however, to date, there are no published examples of specific strategies for patients with AF.\textsuperscript{12-15}

**Registries.** Patient registries make a valuable contribution to population management by facilitating prompt and systematic intervention to ensure patient safety. For example, if an alert is issued by the FDA with an urgent drug recall for safety reasons, a registry can expedite the identification of patients receiving the drug, and action can be taken to prevent or minimize harm.

Registries also can be helpful for providing effective case management (i.e., ensuring proper care for individual patients). Potential disadvantages of registries include the cost of implementation and maintenance, difficulty establishing an interface with information technology infrastructure, and challenges associated with ensuring data accuracy.

Data from registries of patients with AF can be used to evaluate the clinical importance of the proarrhythmic effects from class Ic and class III antiarrhythmic drugs and critical drug interactions involving prolongation of the QT interval. Another application of registries is to support clinical initiatives to ensure that patients with AF receive safe and effective antithrombotic therapy to prevent embolic stroke. The registries can also be used to identify patients with AF who are on class Ic antiarrhythmic drugs and develop screening algorithms for coronary artery disease (CAD) because class Ic antiarrhythmic agents are contraindicated in patients with CAD or other important structural heart disease.

**Case Management**

Case management strategies focus on individuals instead of populations. The 2 most widely known case management strategies for patients with AF are pharmacist-managed anticoagulation and pharmacist-managed antiarrhythmic drug monitoring. Medication therapy management services provided through Medicare Part D are another form of case management. These services are designed to improve outcomes in patient safety and efficacy.

**Pharmacist-Managed Anticoagulation.** Anticoagulation is under-used in patients with AF, despite the fact that these patients are at increased risk for embolic stroke, and evidence-based guidelines recommend the use of anticoagulation in patients with AF.\textsuperscript{16-19} For example, one study examined adherence to these evidence-based guidelines in the 6-month period after diagnosis of AF in members of a large health plan.\textsuperscript{10} For the 444 health plan members at high risk for stroke, 48% received warfarin alone, 11% received warfarin plus aspirin, 17% received aspirin alone, and 24% received no antithrombotic therapy.\textsuperscript{16} The authors attributed lack of adherence to physicians being less likely to initiate warfarin therapy for single episodes of AF without recurrence, despite the patients’ underlying risk for stroke. They speculated that this may have been because the AF had resolved by the time the treatment decision had been made.

Each year 40,000 preventable strokes at a cost of $600 million have been attributed to the underuse of warfarin in Americans with AF, largely because of what some people consider an exaggerated fear of adverse effects.\textsuperscript{20} Major hemorrhage and thromboembolic complications are serious concerns associated with the use of anticoagulation. The need for close monitoring to prevent these complications may serve as a deterrent to the use of anticoagulation. It also provides impetus to develop new anticoagulants that do not require such close monitoring.

The clinical efficacy and cost-effectiveness of pharmacist-managed anticoagulation services are well documented.\textsuperscript{20-23} These services are readily integrated into most managed care settings because the resources needed to support the services (e.g., clinical laboratory services, information technology) are widely available. For example, outcomes from a centralized clinical pharmacy anticoagulation service, conducted primarily by telephone, were compared with those from conventional anticoagulation management by physicians in a retrospective, observational cohort study of 6,645 ambulatory patients receiving warfarin at a large nonprofit, group-model health maintenance organization.\textsuperscript{21} Roughly 40% of patients had AF or atrial flutter. The primary outcome was complications from warfarin therapy (fataal or nonfatal major bleeding or thromboembolic complications). The pharmacy anticoagulation service was associated with a 39% reduction in the primary outcome compared with physician-managed anticoagulation (hazard ratio [HR] = 0.61, 95% confidence interval [CI] = 0.42-0.88). This reduction was largely due to a 62% reduction in the risk of cerebrovascular accident (CVA), and other thromboembolic complications (HR = 0.38, 95% CI = 0.21-0.69). The incidence of CVA was significantly lower with pharmacist-managed anticoagulation (0.4%) than with physician-managed anticoagulation (1.4%). The risk of major bleeding was reduced by 7% in the pharmacist-managed group (HR = 0.93, CI = 0.54-1.59). Nonetheless, major hemorrhage remains a safety concern with the use of anticoagulation.

The development and implementation of pharmacist-managed anticoagulation services can pose challenges, especially in private practice settings. Such services are resource intensive, and the cost is not universally reimbursed by third-party payers. Furthermore, the patient outreach methods employed, including direct patient care visits, point-of-care testing, at-home patient self-testing, telephone management, and online management, differ, which could affect outcomes. In addition, it is possible that these pharmacist-implemented strategies might face resistance from patients and physicians. Nevertheless, several studies reported that both these groups were generally supportive of such initiatives.\textsuperscript{24}

The cost-effectiveness of pharmacist-managed anticoagulation services has been demonstrated despite the need for costly resources.\textsuperscript{20,22} The estimated annual cost savings from such services for patients receiving warfarin for a variety of indications, including AF, ranges from $1,621 to $4,072 per patient.\textsuperscript{20,22} Much of the cost savings is derived from a reduction in thromboembolic complications (by nearly 80% at 1 pharmacist-managed...
anticoagulation clinic), which leads to fewer emergency room visits and hospitalizations.20

The costs of pharmacist-managed anticoagulation services for ambulatory patients with AF in a group-model health maintenance organization were quantified and analyzed based on the risk for stroke.25 The monthly cost per patient (calculated in terms of U.S. 2000 dollars) for anticoagulant medications and dispensing fee, laboratory testing fees (including international normalized ratio tests), and clinical pharmacist specialist fees was $19.09 (37% of the total cost), $18.38 (36%), and $13.78 (27%), respectively. These costs did not differ significantly based on the level of risk for stroke (i.e., high, intermediate, and low). The cost of the clinical pharmacist represented a relatively small part of the cost of pharmacist-managed anticoagulation services compared with drug costs and laboratory testing fees.

In the future, rivaroxaban, dabigatran, and other new alternatives to warfarin that do not require close laboratory monitoring may become available, possibly increasing the use of anticoagulation in patients with AF who are unable or unwilling to take warfarin or whose physician was disinclined to initiate anticoagulation.8-10 The cost of these new medications may be competitive with that of warfarin if the costs of laboratory testing and monitoring by clinicians are taken into consideration. However, the new agents probably will not initially supplant warfarin for certain high-risk patients (e.g., patients with AF and mechanical valve prostheses as well as known thrombophilies) because of the established clinical effectiveness of warfarin in these patients.26

Until new drugs or devices that eliminate the need for warfarin become available, pharmacist-managed anticoagulation services are a cost-effective means for improving clinical outcomes in patients with AF. Because there is evidence of underuse of warfarin in patients with AF, managed care pharmacists can improve outcomes by screening patients for the need for therapy.16-18

Antiarrhythmic Drug Monitoring. Pharmacist-managed antiarrhythmic drug monitoring services have been developed to prevent or minimize toxicity and drug interactions, although fewer outcomes data are available for these services than for pharmacist-managed anticoagulation services.27,28 Antiarrhythmic drug monitoring services often focus on amiodarone, which is associated with long-term extracardiac toxicities (e.g., thyroid dysfunction, pulmonary fibrosis, hepatotoxicity, corneal deposits, optic neuritis) and interactions with numerous commonly used medications.20-31

A variety of effective approaches have been used in antiarrhythmic drug monitoring programs. An electronic alert about the need for testing to detect toxicity in patients receiving amiodarone was incorporated into the CPOE system at a Veterans Administration health system.27 A template was used to retrieve past test results, detect trends (changes in test results over time suggesting possible adverse reactions), and allow surveillance for toxicities. A retrospective observational study compared the rate of testing for 341 patients with amiodarone prescriptions written in the 6-month period before implementation of a computerized interactive template with 316 patients with prescriptions written after implementation. The template was used to retrieve the patients’ liver, thyroid, and pulmonary function test results as well as the chest x-ray and ophthalmologic slit lamp examination reports from the electronic medical record. The template then offered links to order sets that automated test reordering and was used to track past test results in 172 of the 316 patients. In these 172 patients, there were significant increases in adherence to recommended testing for amiodarone toxicity compared with the period before implementation; increases were observed in the rate of testing of liver function tests (from 64% to 89%), thyroid function tests (from 56% to 85%), and pulmonary function tests (from 21% to 29%); chest x-rays (from 35% to 75%); and eye examinations (from 39% to 69%). However, the rate of testing after implementation of the electronic alert in the 144 patients for whom the template was not used to track past test results did not increase significantly compared with the 6-month period before implementation of the electronic alert. Providing automated decision support to the prescriber probably was cost neutral because the information technology was already established, although the study did not address costs. There was room for improvement in adherence to testing during amiodarone therapy despite the use of the electronic alert and template for monitoring past test results.

A multidisciplinary case management approach was used in an ambulatory clinic to monitor amiodarone therapy in 60 patients with various arrhythmias (ventricular arrhythmias as well as AF) who were receiving amiodarone.26 Patients were referred to the clinic by primary physicians. A multidisciplinary team composed of a cardiovascular pharmacist, nurse, and physician specialists created a database with the patient medical history, current drug therapy, and baseline laboratory values, and various tests (e.g., liver, thyroid, and pulmonary function tests, chest X-rays) were scheduled in accordance with published guidelines. The mean duration of follow-up was 16 months before referral to the clinic and 9 months after referral. The number of patients with guideline-recommended laboratory testing increased from 14 (23%) before referral to 54 (90%) after enrollment in the clinic (P<0.001). Previously unrecognized adverse events (e.g., pulmonary fibrosis, QT interval prolongation, liver enzyme elevation, hypothyroidism, hyperthyroidism, asthma exacerbation) were detected in 21 (35%) patients after referral to the clinic. Amiodarone was discontinued in 6 (10%) patients, including 4 patients with suspected pulmonary toxicity. The amiodarone dosage was adjusted in 29 (48%) patients. Thus, establishing the multidisciplinary clinic facilitated the prompt detection of toxicity from amiodarone and provided the opportunity for early intervention to minimize harm.

In the future, the need for pharmacist-managed...
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antiarrhythmic drug therapy services may be diminished by the introduction of new antiarrhythmic agents with improved safety or the increased use of ablation procedures or other non-pharmacologic interventions for AF. However, the availability of dronedarone is unlikely to eliminate the use of amiodarone based on the current clinical results. If the role of antiarrhythmic agents in AF management decreases, pharmacists might change their focus to primary prevention of AF through improved pharmacologic management of hypertension and other AF risk factors. Certain antihypertensive therapies (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) may play a role in AF prevention.12

Conclusions

The growing cost of AF in the United States and the problems associated with drug therapies used to manage AF represent both challenges and opportunities for pharmacists in managed care. Managed care pharmacists can play an instrumental role in improving the cost-effectiveness of and outcomes from drug therapy in patients with AF through a variety of strategies.

REFERENCES


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