2-5-2016

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Recommended Citation

Dixon DL, Dunn SP, Kelly MS, McLlarky TR, Brown RE. Effectiveness of Pharmacist-Led Amiodarone Monitoring Services on Improving Adherence to Amiodarone Monitoring Recommendations: A Systematic Review. Pharmacotherapy. 2016;36(2):230-236. doi: 10.1002/phar.1697

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The authors listed below have no conflicts of interest and this work was not funded

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Key words: pharmacists, amiodarone, antiarrhythmic, drug monitoring

Abstract

Amiodarone remains the mostly frequently used antiarrhythmic in clinical practice and is most often used to maintain normal sinus rhythm in patients with atrial fibrillation who have failed a rate control strategy. Amiodarone has superior efficacy over other antiarrhythmics, lower risk of torsades de pointes, and a better cardiovascular safety profile in patients with structural heart disease. However, amiodarone is associated with notable non-cardiac toxicities affecting the thyroid, lungs, eyes, liver, and central nervous system. Since 2000, clinicians have been advised to follow amiodarone monitoring guidelines provided by the Heart Rhythm Society. Adherence to these recommendations in clinical practice is, however, suboptimal. Pharmacists play a major role in ensuring the safe and effective use of medications, particularly high-risk medications such as amiodarone. This qualitative review details the evidence supporting the role of pharmacist-led amiodarone monitoring services (AMS) in improving adherence to amiodarone monitoring guidelines and identifying adverse effects. Five studies were identified and, overall, these programs had a favorable impact on improving adherence to guideline-recommended monitoring standards for amiodarone. The available evidence is limited by the significant variations in study designs, outcome definitions, lack of patient randomization, and limited generalizability. Nevertheless, available studies suggest pharmacist-led AMS may improve adherence to recommended monitoring guidelines and identification of amiodarone-related adverse effects. Further study is warranted to demonstrate whether or not these services impact the overall quality of care provided to patients receiving amiodarone, which might justify broader implementation.

Introduction

Atrial fibrillation (AF) remains the most frequently observed cardiac arrhythmia in clinical practice with an estimated prevalence of nearly 6 million in the United States. Some projections estimate the prevalence of AF will double by 2050.[1] Although a rate control strategy is often preferred, antiarrhythmic medications are indicated in patients with significant symptoms despite satisfactory rate control.[2] Recent trends suggest an increase in the application of a rhythm control strategy as evident in the rise of AF ablation procedures, and a 2% per year increase in antiarrhythmic prescriptions.[3, 4]

Amiodarone is a multi-channel blocker (potassium, sodium, and calcium) and noncompetitive alpha- and beta-blocker. Although not approved by the Food and Drug Administration (FDA) for AF, amiodarone remains the most frequently prescribed antiarrhythmic used for AF, accounting for approximately 45% of all antiarrhythmic prescriptions.[4] This is primarily due to its superior efficacy in maintaining normal sinus rhythm (NSR) over other antiarrhythmics and demonstrated cardiovascular safety in patients with structural heart disease.[2] However, amiodarone is notoriously associated with multiple non-cardiac multi-organ toxicities. As such, the Heart Rhythm Society (formerly the North American Society of Pacing and Electrophysiology) published the first amiodarone monitoring guidelines in 2000,[5] which were most recently updated in 2015.[6] These guidelines are summarized in Table 1.

Adherence to amiodarone monitoring guidelines in clinical practice has been suboptimal. A retrospective cohort study at 10 health maintenance organizations found that only half of the 1,055 patients on amiodarone received the recommended monitoring for both liver and thyroid toxicity.[7] The available evidence also suggests that

adherence to baseline monitoring is much higher than follow-up monitoring.[8] This is problematic when the risk of amiodarone-related toxicities increases with longer duration of use. Furthermore, while a majority of patients receiving amiodarone experience an adverse effect in the first year of therapy, one-third of these may be preventable with appropriate long-term monitoring.[9]

One suggested approach to improving the chronic monitoring of patients receiving amiodarone therapy has been the utilization of Amiodarone Monitoring Services (AMS). Considering the role pharmacists play in ensuring the safe and effective use of medications, it is no surprise that many AMS are pharmacist-led. The objective of this qualitative review is to summarize the available evidence evaluating the effectiveness of pharmacist-led AMS in improving adherence to amiodarone monitoring guidelines and identification of previously unrecognized adverse effects.

Methods

Search Strategy

We conducted a search of English language publications from database inception through October 30, 2015 using PubMed, CINAHL (EBSCOHost), Web of Science, Cochrane Library and ProQuest Dissertations & Theses. The search was divided into three concept groups, including the terminology used to describe “amiodarone,” “pharmacists,” and “drug monitoring.” Medical Subject Headings (MeSH) and equivalent controlled vocabulary and keywords were utilized in each database as appropriate. Additionally, a reference list of the retrieved publications was searched to identify publications not identified in the database search. The search results and process of screening and study selection is illustrated in Figure 1.

Studies were included if they described an AMS that included pharmacists and reported outcomes that included adherence to amiodarone monitoring guidelines and/or incidence of patients that experienced a previously unrecognized amiodarone-related adverse event. Published studies of multidisciplinary models were included if the role of the pharmacist was clearly described and a primary component of the intervention. For purposes of this review, pre-post studies were considered acceptable. Broad drug monitoring programs that did not focus on amiodarone were excluded. Abstracts, letters to the editor, and editorials were also excluded from this review.

Results

Two investigators (DD, MK) independently identified five articles that met our inclusion criteria. A summary of included studies is listed in Table 2. Study sites included outpatient clinics at an academic medical center,[10] integrated healthcare systems,[11-13] and a private, university-affiliated cardiology clinic.[14] The respective study designs included three unmatched retrospective cohort studies[11-13] and two uncontrolled pre-post studies.[10,14] Adherence to amiodarone monitoring guidelines was a primary clinical outcome for all of the studies,[10-14] while the reporting of amiodarone-related adverse effects was reported in all but one study.[15]

Study methods included physician-pharmacist protocols or algorithms,[11,14] electronic tracking tools,[13] and face-to-face outpatient clinic visits.[10,11,14] Pharmacists' primary role in each study involved ensuring monitoring parameters were obtained or scheduled. Additional interventions included recommending antiarrhythmic dose adjustments, identifying and making recommendations for managing drug-drug interactions and/or adverse drug reactions, obtaining medication histories, and providing

patient education. Several of the monitoring programs were interdisciplinary collaborative-care models that included other healthcare professionals, such as electrophysiologists,[10] general cardiologists,[13,14] and registered nurses,[14] but pharmacists served in a primary role in each of these.

Evaluation of Clinical Outcomes

Retrospective Cohort Studies

Three studies evaluated adherence to amiodarone monitoring guidelines by comparing patients followed by an AMS to a retrospective cohort of patients that did not participate in the AMS (i.e., usual care). The study follow-up period after implementation of the AMS was 12 months for each of these studies. Overall, patients followed by the AMS had significantly higher rates of adherence to the recommended amiodarone monitoring guidelines compared to usual care. Adherence to the recommended baseline monitoring parameters varied between studies, but generally occurred in less than 50% of the patients.[11-13]

Graham et al[11] reported no difference between groups at baseline, except for eye exams, which occurred more frequently in the intervention group. Johnson et al[13] observed adherence to baseline monitoring of alanine transaminase (ALT) and electrocardiogram (ECG) was significantly higher in the intervention group compared to usual care. Spence et al.[12] reported baseline monitoring of ALT, thyroid stimulating hormone (TSH), pulmonary function tests (PFT), and chest x-ray occurred more frequently in the intervention group. All three studies reported significantly higher adherence to follow-up liver function test (LFT) monitoring in the intervention group compared to usual care, although the recommended monitoring of LFT in the study by

Graham et al[10] occurred twice as frequently as the studies by Johnson et al.[13]

Incidence of identified adverse events was reported in two studies.[11,13] Graham et al.[11] reported 17% of patients in the AMS group had a documented TSH elevation, compared to 10% of patients in the control group (p=0.23). Thyroid abnormalities were also the most common adverse event reported by Johnson et al,[13] but the overall rate of confirmed amiodarone-related adverse events was significantly lower in patients followed by the AMS (5.4% vs. 9.3%; p=0.031).

Longitudinal Studies

Two studies[10,14] analyzed the effectiveness of the AMS using a pre/post-intervention study design. Sanoski et al[9] reported that recommended laboratory monitoring occurred in only 23% of patients before referral to the AMS. Before enrolling in the AMS, the patients were followed by their primary physician for a mean of 16.3 $\pm$ 25.5 months. After a mean follow-up of 9.2 $\pm$ 5.5 months in the AMS, 90% of patients received recommended laboratory monitoring (p<0.001). Overall adherence rates to amiodarone monitoring parameters were not reported by Tafreshi et al,[14] but the study did report an increase in PFT monitoring from only 5% at baseline to 77.5% after referral to the AMS.

Previously unrecognized adverse effects were identified, post-referral to the AMS, in 35% and 19% of patients in the studies by and Sanoski et al[10] and Tafreshi et al,[14] respectively. The most commonly detected adverse effects in both studies were thyroid-related and pulmonary toxicities. Unrecognized thyroid abnormalities were reported in 13% of patients by Sanoski et al[10] and 9% of patients by Tafreshi et al.[14] Pulmonary fibrosis was diagnosed in 6.7% of the patients followed by the AMS in the

study by Sanoski et al.[10] Unspecified pulmonary toxicity was recognized in 9.1% of the patients in the Tafreshi et al study.[14]

Discussion

An extensive search of available literature revealed five studies that evaluated the impact of pharmacist-led AMS on adherence to amiodarone monitoring guidelines, and identification of previously unrecognized adverse effects. The available evidence favors the use of pharmacist-led AMS to ensure patients receiving chronic amiodarone therapy are appropriately monitored. Greater involvement of pharmacists in the monitoring of patients receiving long-term amiodarone therapy could improve the safe use of this high-risk medication.

Interestingly, our review found that thyroid abnormalities and pulmonary toxicity were the most commonly observed amiodarone-related toxicities. Thyroid function abnormalities are common with amiodarone and of concern given the known effects these abnormalities have on cardiac contractility and output, blood pressure, and arrhythmia pathogenesis.[15] One study found a 60% increased risk of mortality in heart failure patients with an ejection fraction $\leq$35% and baseline or new-onset abnormal thyroid function during the study follow-up period.[16] Unsurprisingly, new onset thyroid abnormalities were nearly four times more common in patients receiving amiodarone.[16] These data highlight the importance of thyroid function monitoring in patients receiving amiodarone as early identification and treatment may prevent fatal adverse sequelae in patients with cardiovascular disease.

While one of the studies included in our review[10] specifically reported the rates of pulmonary fibrosis, others were more vague and simply reported rates of general

pulmonary toxicity. This is important considering amiodarone-induced pulmonary toxicity can manifest itself in various ways with the most serious being pulmonary fibrosis associated with acute respiratory distress syndrome.[17] While the mortality rate of amiodarone-induced pulmonary fibrosis has been reported to be as high as 10%, an early diagnosis may improve survival in these patients.[5] Thus, a high clinical suspicion in a patient with unexplained dyspnea should warrant immediate evaluation. Appropriate follow-up may help identify those with possible pulmonary toxicity before the development of irreversible pulmonary fibrosis.

As demonstrated in this study, current amiodarone monitoring practices remain suboptimal, potentially due to the fractured care across general and specialty caregivers. Team-based models of care including pharmacists, have been shown to improve cardiovascular clinical outcomes,[18] reduce preventable adverse effects,[19] and readmission rates.[20] Despite the potential benefit of such collaborative practice models, broader inclusion of pharmacists in medical practices is limited by lack of a formalized reimbursement structure.[21] The case could be made that ensuring proper monitoring of amiodarone, and possibly other antiarrhythmics, may have a favorable impact on reducing healthcare costs. A rhythm control approach costs approximately $5,000 more per person than rate control and has been linked to a higher rate of hospitalizations.[22] The advent of efforts to restructure payment models based on quality of care in the private sector may provide financial justification for broader implementation of pharmacist-led AMS. Ultimately, the economical feasibility of AMS is beyond the scope of this review and warrants further study.

The following limitations should be considered when interpreting the findings of

this qualitative review. We found significant variations in study designs and outcome definitions, and none of the studies randomized patients. The retrospective nature of these studies does not rule out the possibility of missing data and inability to capture data outside of integrated health care systems to confound these findings. For these reasons, it was not feasible to combine results and perform a meta-analysis. Additionally, the available amiodarone monitoring guidelines are not evidence-based, in the sense that no studies have tested whether prospective monitoring actually prevents amiodarone-related adverse effects. With that said, a notable number of patients in these studies required dose adjustments, therapy discontinuation, and had previously unrecognized and new onset adverse effects due to amiodarone. This suggests that prospective monitoring may be an effective means to mitigate the adverse effects associated with amiodarone.

Conclusion

To our knowledge, this is the first compilation of available studies evaluating the effectiveness of pharmacist-led AMS. Our review of the literature identified five studies of pharmacist-led AMS to improve amiodarone monitoring and identify potential amiodarone-related adverse effects. This preliminary evidence suggests these programs can improve adherence to amiodarone monitoring guidelines and recognition of amiodarone-related adverse effects. However, the study quality was generally poor and we found no prospective, randomized studies. A national shift toward quality-based payment models may justify further consideration of pharmacist-led AMS to monitor patients receiving chronic amiodarone therapy, but additional studies are warranted.

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