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Standardizing Therapeutic Drug Monitoring for Clinic Patients on Amiodarone

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Abstract

The side effects of amiodarone can be severe and potentially lethal (Vassallo & Trohman, 2007). Amiodarone is frequently prescribed for supraventricular arrhythmias, specifically atrial fibrillation, without any standardized monitoring for adverse effects. In this quality improvement (QI) project, providers were encouraged to use a protocol containing evidence-based recommendations built into the Electronic Health Record (EHR) when prescribing amiodarone in outpatient encounters. Providers were emailed with education on the protocol and how to use it. A survey was sent to providers seven weeks later to assess the usefulness and ease of use of the protocol. EHR reports were run to assess how often the protocol was used pre- and post-email and how many amiodarone orders were placed within the study timeline.

Results show providers only marginally thought the protocol was useful and easy to use. Providers perceived that they did not prescribe amiodarone often enough to use the protocol. However, EHR reports showed that the protocol was used only 2% of the time amiodarone was prescribed. Survey scores were positive; however, qualitative feedback indicated that providers perceived they did not have the opportunity to use the protocol. Despite evidence-based education, most providers did not use the protocol.
Introduction

Problem Formation

Although amiodarone is only approved by the Federal Drug Administration (FDA) to treat ventricular arrhythmias, many cardiologists, electrophysiologists, and advanced practice providers specializing in cardiology and electrophysiology use amiodarone therapy to treat persistent supraventricular arrhythmias, specifically atrial fibrillation (afib); (Vassallo & Trohman, 2007). Amiodarone is considered a class III antiarrhythmic potassium-channel blocker (Florek & Girzadas, 2020). Unlike other class III antiarrhythmics, amiodarone also has beta-adrenergic receptor blocking, calcium-channel blocking, and sodium-channel blocking effects (Florek & Girzadas, 2020). Since amiodarone has multiple unique pharmacological mechanisms, standardized monitoring tests should guide providers in safely prescribing amiodarone.

Background

As the most common arrhythmia disorder, afib affects 1% of the world’s population and 9% of people 75 years and older (Nesheiwat et al., 2020). It also occurs more frequently in men than women and Caucasians than other races. Two million Americans have a current afib diagnosis, and experts predict the incidence of afib will double or triple by 2050 (Nesheiwat et al., 2020).

Problem Statement

Will providers report that a protocol for therapeutic drug monitoring of amiodarone that is automated in the EHR is useful and easy to use? Will providing education on evidence-based practice recommendations for the early detection of common and severe side effects increase protocol use?
**Needs Assessment**

Amiodarone is frequently prescribed for supraventricular arrhythmias, specifically afib, without any standardized monitoring for adverse effects. The goal is for all patients to receive timely, evidence-based monitoring. Providers (physicians and advanced practice providers) do not have a standardized, evidence-based protocol when prescribing amiodarone. Providers are not up to date on current guidelines based on varying requirements for monitoring. This variation from provider to provider demonstrates a knowledge gap. Gaps in skill and practice include providers not knowing how to use a protocol, not knowing how to refill medications electronically, and not having a protocol. The method used to identify these gaps was direct observation from clinic providers, including nurse practitioners (NP), Physician Assistants (PA), and medical doctors (MD). Gaps in skill and practice were also identified by the practice site's director of cardiology.

**Significance**

Consequences of afib arise from the atrioventricular (AV) asynchrony and the rapid increase in rate and irregularity of the ventricular contractions. The rapid ventricular response (RVR) can lead to left ventricular hypertrophy (LVH), causing patients to be more symptomatic than those without RVR. This population benefits most from the return to normal sinus rhythm (NSR); (Zimetbaum, 2007).

The side effects of amiodarone can be severe and potentially lethal (Vassallo & Trohman, 2007). Adverse effects manifest in 15% of patients within the first year of amiodarone use and up to 50% with long-term use (Florek & Girzadas, 2020). Pulmonary toxicity, thyroid disorders, prolonged QT on electrocardiogram (ECG), skin
discoloration, corneal deposits, liver toxicity, and many drug-drug interactions are the most common side effects (Florek & Girzadas, 2020). Close monitoring of side effects with long-term therapy is needed to avoid harm with the long half-life.

Amiodarone is more effective in maintaining NSR than any other antiarrhythmic medication (Zimetbaum, 2007). However, due to its highly lipophilic component and a large volume of distribution, there is a delay in the onset of action and a long elimination half-life (Zimetbaum, 2007). This delay in the onset of action is why side effects from amiodarone can take months to appear. As amiodarone continues to outperform other antiarrhythmics in sustaining NSR, clinicians would benefit from a useful and easy-to-use protocol to monitor for signs and symptoms of side effects.

Protocols are often built into the electronic health record (EHR) through SmartSets. In the EHR, a provider can order a group of orders that all relate to one outcome. In a SmartSet, groups of orders are bundled together, making it convenient for the provider to order multiple related orders simultaneously.

The benefits and the side effects of amiodarone are well documented in current literature. What is significantly lacking is evidence that automated protocols built into the EHR decrease unwanted side effects. It is also not well documented if providers believe protocols to be useful and easy to use. This QI project will contribute to the literature to show if having an evidence-based automated protocol will not only increase use but also if providers find protocols helpful in providing evidence-based care.

As the nursing profession strives to implement evidence-based care, literature that reflects the usefulness and ease of use of automated protocols will decrease the provider burden of ensuring the most up-to-date guidelines are being used. We have
seen this implemented in primary care for the primary prevention of common diseases with vaccine reminders and secondary prevention measures with diabetes screening, colonoscopies, and mammograms (Bangash et al., 2020). This project aimed to contribute to the nursing profession by taking a model already implemented in primary care for primary and secondary prevention and using that model for therapeutic drug monitoring patients on amiodarone.

**Purpose Statement**

This QI project aimed to determine if an amiodarone monitoring protocol would be perceived as useful and easy to use. The protocol utilized the most up-to-date research to make ordering therapeutic drug monitoring easier. It also aimed to see if education on the evidence-based protocol would increase its use in the EHR. Usefulness and ease of use were measured with a survey after asking prescribing providers to use the protocol when prescribing amiodarone for seven weeks.

**Objectives**

MDs/PAs/NPs were encouraged to use the protocol for prescribing and refilling amiodarone. Current research findings determined which tests are needed and how frequently they need to be completed by patients on amiodarone therapy. It also discerned which tests are not evidence-based in detecting adverse effects.

At the project’s practice site, there is an amiodarone refill SmartSet available in outpatient encounters already available for use. Through an informal survey of providers, most did not realize the SmartSet was available. After running an EHR report, the data showed that this SmartSet had never been used by any provider at the practice site. This SmartSet included more recommendations than what the literature supports.
Education was provided on the most up-to-date recommendations for monitoring and accessing the protocol in the EHR.

Email list-serves of cardiology and electrophysiology providers were used to distribute education on evidence-based recommended monitoring tests. The email contained informed consent and a hyperlink to the survey administered through Google forms. A password-protected laptop stored the data.

**Theoretical Framework**

An active implementation framework was used for this QI project. “The Active Implementation Frameworks (AIFs) are an evidence-based set of frameworks to use when attempting to put into practice any innovation of known dimensions” (Blanchard et al., 2017). The AIFs are an evidence-based set of frameworks developed following a systematic review and synthesis of the implementation evaluation literature (Blanchard et al., 2017).

There are five themes present in AIFs, the first being Usable Innovations. The researcher needs to ensure that education on the innovation or program can be taught effectively enough to be used properly. The program needs clear descriptions. “An innovation needs to be teachable, learnable, doable, and readily assessed in practice if it is to be used effectively to reach all students” (AIRN, 2022).

The second theme seen in AIFs is an implementation team. The implementation team assists in the full, effective, and sustained use of the program or innovation. Teams define and utilize infrastructure to improve outcomes. The third theme is implementation drivers. The drivers engage leadership and assure organizational support, (NIRN, 2014).
The fourth theme seen in AIFs is the implementation stages. This is an outlined non-linear timeline for project implementation. The four common stages in the implementation process are exploration, installation, initial implementation, and full implementation. The fifth theme is the improvement cycle, where all the people and support structures from the previous themes come together to Plan, Do, Study, Act (PDSA) (NIRN, 2014). This last theme is a cycle to ensure continued improvement in an effective and useful manner.

To assess if this QI project is useful, clear descriptions and program components needed to be identified. Operational definitions also needed to be clearly stated, and the fidelity and usefulness needed to be objectively measured with an evidence-based tool. Prior to the QI project, there was no program or practice process for using the SmartSets with therapeutic drug monitoring for patients on amiodarone at the project site. There was a SmartSet used in other settings within the healthcare organization.

This QI project lead conducted a systematic review of the literature on the adverse effects of amiodarone use and their occurrence rates to determine usable innovations. Organizational leadership was evaluated to see if the need for an evidence-based protocol for therapeutic drug monitoring of patients on amiodarone is needed or wanted. After the needs assessment, evidence-based recommendations were implemented through the EHR. The improvement cycle was considered critical in updating and changing the methods as feedback from the organizational stakeholders is integral for continual improvement.
Literature Review

In a review of six high-quality, level I studies (Ad et al., 2016; Diederichsen et al., 2016; Gillinov et al., 2016; Jennings & Baker, 2016; Ruzieh et al., 2019; Vamos & Hohnloser, 2016), one high-quality level III (Harmon, 2020), and two high-quality Level V (Pokorney et al., 2020; Vorperian et al., 1997), the evidence shows that monitoring for side effects in amiodarone patients is essential. One Level V good quality case study (Kapelios, 2018) showed how systemic the side effects of amiodarone are and how the side effects can mimic other illnesses.

Ad et al., 2016 showed that the most critical concern in treating patients with amiodarone is the associated side effects. However, treatment for a brief period (three months) with close monitoring is safe and effective. Vorperian et al. (1997) found a higher likelihood of experiencing several amiodarone-related adverse effects with exposure to low daily doses of amiodarone. Although low-dose amiodarone may be well tolerated, it is not free of adverse effects. The likelihood of experiencing adverse events related to amiodarone was higher than that of placebo. The overall rate of adverse events was low, and severe adverse events were rare (Ruzieh et al., 2019). Gillinov et al., (2016) focused on the clinical effectiveness of amiodarone. Strategies for rate control and rhythm control to treat postoperative atrial fibrillation were associated with equal numbers of days of hospitalization, similar complication rates, and similarly low rates of persistent atrial fibrillation 60 days after onset. Neither treatment strategy showed a net clinical advantage (Gillinov et al., 2016). Jennings & Baker, 2016 suggests that preoperative amiodarone exposure does not increase mortality in cardiac transplant recipients, questioning the usefulness of amiodarone. Diederichsen et al.,
(2016) looked explicitly at thyroid function. They found that amiodarone had a significant impact on thyroid function after only one month, but with a fast recovery of thyroid function after amiodarone discontinuation.

Literature Synthesis

The only conclusion common to each study is that monitoring side effects would be beneficial. There are no guidelines or gold standards for practitioners to follow. A significant amount of high-quality literature on the effects of amiodarone on each body system exists. Still, a comprehensive study on the totality of amiodarone’s side effects is missing from current literature. Protocols and guidelines will help providers prescribe amiodarone more safely. It is recommended that a protocol be developed for providers to follow for the safe, effective, and evidence-based use of amiodarone to treat atrial arrhythmias.

Project Implementation

Project Design

The project site is a Twin Cities cardiology and electrophysiology clinic. The target population was 20 MDs and 16 advanced practice providers. The project would be determined to be a success if at least 30% of providers report the protocol as useful, easy to use, and likely to accept as determined by Davis’s scale. The project would also be determined successful if the protocol was used at least 50% of the time amiodarone is ordered. The intervention was education provided via email covering the current evidence-based practice of therapeutic drug monitoring while on amiodarone, education on how to access the protocol in the EHR, and the usefulness of using the protocol when practicing evidence-based care. EHR reports on the protocol use were generated
pre- and post-implementation. The frequency of prescribing amiodarone were also compared against the frequency of protocol use. That data was gathered in an EHR report.

**Methods**

Perceived usefulness correlates strongly with user acceptance. Fred D. Davis's Perceived Usefulness, Perceived Ease of Use, and User Acceptance of Information Technology survey was adapted to measure predictive user acceptance. This tool is a valid measurement of usefulness with a reliability of .98 and ease with a reliability of .94 (Davis, 1989). Fred D. Davis permitted using the survey for this QI project via email.

Davis's survey has six statements on the perceived usefulness of information technology and six on ease of use to determine if the information technology will be adapted for future use. Two questions on his original survey do not pertain to the project and were omitted. Each of the remaining ten questions asked the participant to rate how they feel about each statement. The responses to choose from included: extremely likely, quite likely, slightly likely, neither, slightly unlikely, quite unlikely, and extremely unlikely. Each response was assigned a point: extremely likely=1, quite likely=2, slightly likely=3, neither=4, slightly unlikely=5, quite unlikely=6, extremely unlikely=7. Once averages were calculated, the protocol would be considered successful if the average score was less than four for both categories.

The project also measured if educating on evidence-based practice and protocol availability increases the use of the protocol. Protocol use pre- and post-implementation was compared. The frequency of amiodarone prescription use was also compared to
that of amiodarone protocol use. If the protocol was used 50% of the time, amiodarone is prescribed, the intervention would be considered successful.

The project site already had an amiodarone protocol built into the EHR. This protocol had many recommended monitoring tests that were no longer evidence-based. The last time this protocol was up to date was August 2004. Before any implementations for this QI project, an EHR report was run to see how often the amiodarone protocol had been used at the practice site. The report showed that no provider at the project site had ever used the amiodarone protocol.

Project implementation:

On March 15th, 2022, the 36 providers received an email explaining the purpose of this QI project. The communication provided education on evidence-based practice for therapeutic drug monitoring of patients on amiodarone and explained how to access the protocol in the EHR. It explained how the protocol could be used to deliver evidence-based care. The email also gave informed consent and explained that a follow-up email would contain a link to a survey asking the providers for their feedback on using the protocol. On April 12th, 2022, a reminder email with the same information was sent to the same 36 providers.

Seven weeks after the initial email, on May 4th, 2022, another email was sent explaining the project's purpose and containing a link to a survey. The survey was administered through a Google Form, and all responses were anonymous. With this survey was a reminder that the providers were still able to use the protocol. Nine weeks after the initial email, EHR reports were run to assess how often the amiodarone protocol was used. A second EHR report was run to determine how many amiodarone
prescriptions were written since the original implementation email. This second report allowed for a comparison between how often the protocol was used versus how often amiodarone was prescribed.

**Social Justice Considerations**

Race is embedded into the decisions made by many healthcare providers, especially in cardiology (Vyas et al., 2020). “By embedding race into the basic data and decisions of health care, these algorithms propagate race-based medicine. Many of these race-adjusted algorithms guide decisions in ways that may direct more attention or resources to white patients than to members of racial and ethnic minorities” (Vyas et al., 2020). The American Heart Association (AHA) Get with the Guidelines–Heart Failure Risk Score (Peterson et al., 2010) and The Society of Thoracic Surgeons both use race-based guidelines that steer resources away from non-Hispanic blacks without giving any evidence as to why this is built into the risk-algorithm (Researchers at Massachusetts General Hospital Target Cardiac Surgery, 2018).

Although race is not built into algorithms used in electrophysiology, racial disparities persist. Rodriguez et al., (2019) found that minority patients with cardiovascular implantable electronic device infections (CIEDIs) experienced more procedural complications during extraction and had a significantly longer index hospitalization length than Caucasian patients. "Our minority cohort of patients was on average five years younger and had infections associated with typically less virulent organisms than our Caucasian cohort, yet despite these findings, their total hospitalization length of stay was approximately two days longer on average" (Rodriguez et al., 2019). Sridhar et al., (2016) looked at the Nationwide Inpatient
Sample database to identify all patients with cardiac resynchronization therapy (CRT) implantation from 2002 to 2010. They found that significant and persistent gender and racial disparities favoring men (71.4%) and white (79.6%), respectively, were noted in all years.

The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Clinical Practice Guidelines state:

The ACC/AHA Task Force on Clinical Practice Guidelines strives to ensure that the guideline writing committee includes requisite expertise and is representative of the broader medical community by selecting experts from a broad array of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, and scopes of clinical practice. The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence.

(Arnett et al., 2019)

The studies mentioned above demonstrate that the standards set by ACC/AHA are not always upheld. There are plenty of cardiac screening tools that propagate race-based medicine. With the known disparities minorities face when receiving cardiac care, the amiodarone monitoring protocol will help to equalize screening for all patients. Race will not be factored into the protocol as there is no evidence that people of different ethnicities need different monitoring.
Evaluation

Analysis

The purpose of this project was to determine if providers reported a protocol for prescribing and refilling amiodarone was useful and easy to use and if providing education on evidence-based practice increased the use of the protocols. The data collected included frequency in protocol use pre-and post-education/email implementation. The frequency of amiodarone orders was compared to determine how often the protocol was being used versus how often amiodarone was being prescribed. This was to assure that the protocol was not being used due to a lack of amiodarone orders.

An EHR report run before the education showed that the previous amiodarone protocol was never used at any of the outpatient clinics. From March 15th, 2022, the date of the first email, to May 17th, 2022, the day the survey closed, amiodarone was prescribed 209 times within the practice site’s cardiology and electrophysiology group. A second EHR report was run after the survey ended and showed that between March 15th to May 17th, the amiodarone protocol was used five times. These EHR reports reflect that even though there was an increase in the use of the amiodarone protocol after implementation, the percentage of amiodarone orders where the protocol was being used was very small, 2.39% of the time.

Nine providers responded to the Google form survey. Of those that responded, seven were NP/PAs and two were MD/DOs. Seven of the respondents reported greater than 10 years of practice and cardiology. One of the respondents reported having over five years but less than 10 years, and another reported having between one and five
years of experience. Out of the nine responders, seven were female, and two were male.

Participants were asked to give a score that reflected their level of agreement using a scale of 1 to 7, with 1 for extremely agree and 7 for extremely disagree:

1. Extremely agree (2) Quite agree (3) Slightly agree (4) Neither (5) Slightly disagree (6) Quite disagree (7) Extremely disagree. At this practice site, protocols in the EHR are called SmartSets. When asked if using the SmartSet enabled them to accomplish tasks more quickly, the average response was 3.55.
When asked if the amiodarone SmartSet improved job performance the average response was 3.55.

When asked if using the SmartSet increased their productivity, the average response was 3.55.
When asked if using the SmartSet made their job easier to do, the average response was 3.55.

When asked if the amiodarone SmartSet was useful, the average response was 3.67.
When asked if it was easy to get the SmartSet to do what they want, the average response was 3.22.

When asked if interacting with the SmartSet was clear and understandable, the average answer was 3.0.
When asked if interacting with the SmartSet was flexible, the average answer was 3.375.

When asked if it was easy to become skillful at using the SmartSet, the average answer was 3.22.
When asked if the SmartSet was easy to use, the average answer was 3.0.

The second half of the survey included free text questions about the protocol. The first question asked participants to state what they liked most about using the protocol. Feedback in this section included responses stating they never used it, it was easy to use, a good idea for streamlining amiodarone tapering, automated ordering routine labs, and “it’s quick.” The second free text question asks participants what they liked least about the amiodarone protocol. Responses here included comments that they did not use it, that there were too many automatic orders results (X-ray etc.) for which they did not want the results, wanted to know more about the process of following up with abnormal results, need to add it to the favorites list, opening it at another site, and not routinely prescribing amiodarone.

Participants were then encouraged to make a statement on what they would like to see changed about the protocol. Feedback here included fewer preset imaging labs and allowing providers to select their preferences. Another participant stated they would like to know what was learned from it, they needed to use it more and get more comfortable using it. Another participant stated they would like to see an elimination of
the options that raise costs without benefits. The last question on the survey asked if there were any other thoughts for the amiodarone protocol. Feedback here includes that it is a good idea that needs some perfecting and that it would have been very helpful had it been needed.

**Interpretation of results.**

The survey had a 25% participation rate given that nine out of the 36 providers responded. On average, the providers that responded were in favor of the protocol, given they deemed it to be useful and easy to use. However, from March 10th to May 17th, out of the 209 amiodarone orders prescribed, the protocol was only used five times. The infrequency of the use of the amiodarone protocol could bring into question the validity of the results. Even though providers were provided education on the benefit of an automated protocol, information on the most recent evidence-based practice, and screenshot images on how to access the protocol, a vast majority of providers, when given the opportunity to use the protocol, did not use it.

**Discussion**

The survey results indicate that providers thought a useful and easy-to-use protocol for monitoring outpatients on amiodarone would be an asset to their practice. All the average scores were positive (left of the neutral point). The feedback given in the free text questions reflected that many providers thought they did not have the opportunity to use the protocol. The EHR report showed that between March 15 to 2022 and May 17th, 2022, amiodarone was prescribed in an outpatient encounter 209 times. There appears to be a disconnect between perceived frequency and actual frequency of amiodarone orders. In the free text section, providers believed there were too many
orders in the protocol and that providers did not necessarily want the results of those tests. This could reflect the overburden of providers with test results in managing patients outside of clinic visits. This may indicate a need for further education on the importance of why therapeutic drug monitoring tests.

**Limitation of Project**

One major limitation to the project is that very few providers used the amiodarone protocol when prescribing. The project aim was to determine whether providers think an amiodarone protocol is useful and easy to use. Because so few providers used the protocol, it is difficult to determine if the aim was met. It is difficult to generalize with such a low rate of use. There was a 25% response to the survey. However, several of the comments at the end of the survey stated that the responder never used the protocol. The second major limitation to the project was that only 25% of possible responders answered the questions in the survey. Data was to be considered valid if at least 30% of providers responded. With a low turnout of responses, it is difficult to determine whether the data collected can be generalized to the entire group. A third limitation to the project is distinguishing if there is a difference between general cardiology and electrophysiology providers. This question was not asked in the demographic data of the survey.

**Conclusion**

Theoretically, people believe useful tools and easy-to-use shortcuts make their jobs easier. This tool was introduced, but very few providers used it even though amiodarone was often prescribed. One variable that could have potentially played a role and could not be controlled for is that during the same period, there was a major EHR
update affecting how providers review results. Traditionally, providers do not favor EHR updates, and they may have been too overburdened with learning the new update to incorporate a new protocol into their practice.

It was also the time of year that this health organization completed its annual employee engagement survey. Employees received frequent emails encouraging them to complete the employee engagement survey during the same time as this study. Perhaps the over-communication about the employee engagement survey led to this QI survey being lost in the provider’s emails.

These conclusions call into question the usefulness of updating protocols with the most recent evidence-based recommendations if these protocols are not being used.

**Recommendations**

If the study were to be repeated, the implementation should occur when there are no planned EHR updates. It would also be wise to ask for survey participation outside of a planned annual survey. Perhaps another method of educating providers on the benefit of using automated protocols built into the EHR would have been more effective than an email. Another recommendation is to have an EHR super user teach a class on using the protocol, and providers could have hands-on practice using the technology before needing it in a clinical setting.

Providers are already overburdened with extra work outside of their direct patient care hours, such as responding to telephone encounters and medical messages, providing a plan of care after test results are in, and ensuring that all their documentation is up to compliance standards. Any sort of QI project will only add to
their workload. Providers also often feel that EHR updates and EHR shortcuts are not beneficial to their practice.

Especially during COVID, the importance of QI projects has faded into the background of most health care organizations. Without any evidence that it saves money and without anyone who can bridge between direct patient care and QI projects, it is difficult to prioritize QI projects in healthcare organizations. One way to combat this would be to identify a QI champion. This could be a Doctor of Nursing Practice (DNP) to lead QI initiatives. Some healthcare organizations employ a QI champion who works with providers to identify needs within the patient care departments and bridges the gap between the administration and infrastructure systems. This is a challenging and often impossible gap to close without someone uniquely identified to facilitate QI projects that will be useful to those providing direct care. Not involving those providing the care would be a missed opportunity to improve patient care.
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