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Patient perspectives of dabigatran: Analysis of on-line discussion forums

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Abstract

Background—In 2010 the US Food and Drug Administration approved dabigatran, the first new anticoagulant for stroke prevention in non-valvular atrial fibrillation (AF) since 1954. To date there is little data that reflects the experiences and perceptions of real-world patients with dabigatran. The abundance of internet-based discussion forums and support groups related to AF or anticoagulation may provide a low-cost resource for assessing patient experiences.

Objective—Determine patient experiences and perceptions regarding dabigatran through qualitative thematic content analysis of comments posted on publicly accessible virtual discussion forums and internet support groups.

Measurements—Comments posted between January 2011 and September 2012 were downloaded from websites focusing on support of patients with AF or on anticoagulation therapy. Comments were analyzed for thematic content.

Results—Five broad thematic categories emerged from the posted comments: general concerns about safety and efficacy, questions about indications and contra-indications, questions about proper use and storage, questions about diet and drug restrictions, and experiences with perceived side effects. Our data revealed that a primary concern for patients taking dabigatran is the lack of antidote to reverse the effects of dabigatran if bleeding occurs. Several questions pertaining to the use of dabigatran with other medications or medical conditions were noted, and multiple patients expressed confusion about instructions for using dabigatran before and after medical procedures. An unexpected finding included several criticisms of the medication packaging, which many patients found inconvenient or difficult to open. Finally, several perceived side effects were noted, including some not reported in clinical trials.

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Conclusions—Online communities may provide information about topics that are a concern to patients and that may not be discernible in clinical trials, such as medication side effects, proper use, and safety. Our data also highlighted potential topics that may not be a priority to researchers but are nevertheless important to patients (e.g., medication convenience or packaging). Despite the growing use of online health-related communities, very little research makes use of this low-cost resource for identifying patient interests regarding therapeutic treatments to guide patient-oriented research.

INTRODUCTION

Within the US, approximately two-thirds of the adult population uses the internet and 81% of these users seek health information online[1]. Moreover, a growing number of websites provide a forum for patients with specific chronic conditions to interact with one another to share experiences, ask questions, and provide emotional support. The growing use of online resources for sharing stakeholder experiences may lead to an abundant amount of patient-generated online information reflecting stakeholder interests regarding therapeutic treatments.

Atrial fibrillation (AF) is a common cardiac arrhythmia with a lifetime risk of 25% in United States (US) adults[2]. AF puts patients at risk for stroke and accounts for up to 25% of all ischemic strokes in the US[3] Appropriate use of anticoagulation therapy significantly reduces the risk of stroke for patients with AF. Until recently, warfarin has been the only anticoagulant available for stroke prevention in AF.[4] Warfarin acts by inhibiting the synthesis of Vitamin K-dependent clotting factors. It has a relatively long half life (36 hours), and a somewhat delayed anticoagulation effect, reaching peak effect in 3 to 5 days. [5] Important drawbacks to warfarin are its narrow therapeutic window, sensitivity to genetic factors in individual patients, and multiple food and drug interactions. Because of these factors, warfarin dosing must be individualized for each patient and patients taking warfarin must undergo regular blood monitoring of the Internal Normalized Ratio (INR) to ensure therapeutic anticoagulation is maintained.

In 2010 the US Food and Drug Administration approved dabigatran (Pradaxa®), the first new anticoagulant for stroke prevention in AF since 1954.[6] Unlike warfarin, dabigatran acts by directly inhibiting the activity of thrombin, a key protein involved in blood clotting. It is a relatively fast acting drug, reaching peak anticoagulation effect in less than 2 hours with a half-life of 12 hours in healthy patients.[5] Dabigatran offers several advantages over warfarin, including more consistent anticoagulation, fewer drug and food interactions and no need in regular INR monitoring.[6, 7] However, several adverse effects were reported in clinical trials, including dyspepsia and increased risk of gastrointestinal bleeding compared to warfarin.[6, 7] Moreover, in contrast to warfarin, dabigatran must be taken twice daily and requires special storage and handling procedures to limit loss of potency over time.[8] In addition, because dabigatran is metabolized almost entirely through the kidneys it is not recommended for patients with severe renal disease. Finally, while the anticoagulation activity of warfarin may be reversed with doses of Vitamin K or prothrombin complex concentrate, there is currently no effective way to reverse the anticoagulant effects of dabigatran in the event of unwanted bleeding.[9] However, the short half-life of dabigatran is

advantageous if bleeding should occur, and drug elimination can be hastened through renal dialysis.

Because experience with dabigatran is limited, to date there is no data that reflects the experiences of real-world patients with dabigatran. This study examines perceptions and experiences with dabigatran through thematic content analysis of comments posted by patients and their caregivers on virtual discussion forums and internet support groups related to anticoagulation and AF. Despite the growing use of online resources for sharing stakeholder experiences, very little research makes use of this low-cost resource for identifying stakeholder interests regarding therapeutic treatments.

METHODS

Setting and Participants

First, we used widely available internet search engines (i.e., Google, Bing) to identify online communities focusing on support of patients/families with AF and/or anticoagulation therapy. Search terms included “discussion forum”, “discussion board”, and “support group” combined with health-related words such as “medication”, “drugs”, “atrial fibrillation”, “dabigatran”, “pradaxa”, “stroke prevention”, or “heart disease”. Websites were then screened by two of the authors (MSVS and MW) according to name, content, and recent activity. Websites were excluded if the purpose of the discussion forum was not health related, if they did not allow input from patient and caregivers (e.g., ‘expert opinion’ sites only), and if there were no comments posted regarding dabigatran since January 2011. Most websites screened did not require registration to view participant posts. Only one website (yahoogroups/afib) required registration. Two of the study authors (MSVS and MW) received approval from the site administrator to register after indicating that the purpose for accessing the site was for research pertaining to patient experiences and perspectives on dabigatran. We did not interact with participants on any site.

Data Collection and Analysis

Data collection and analysis were conducted in an iterative process. Text posted between January 2011 and September 2012 was downloaded from each site and imported into a qualitative data management software (MaxQDA Plus 10) for thematic content analysis. Thematic content analysis is a data reduction and analysis strategy for qualitative data in which thematic categories are identified in transcripts or text, and subsequently used to rigorously code the content of the data.[10] Initially, posts were downloaded from a single site (www.drugs.com). Coding began by reviewing a sample of 100 individual posts which were coded by the author (MSVS) with assistance from an expert in qualitative research methods (HSR). Coding was limited to comments that reflected personal experience, questions, or judgments about dabigatran (i.e., posts reciting findings from scientific studies were not considered personal experience). A single post could represent multiple comments in different thematic categories. Most comments were anonymous and provided very few details about the patients. Nevertheless, it was usually possible to identify multiple comments by the same individual through user names. Multiple comments by the same individual about the same topic were collapsed into a single comment so that opinions and

experiences of dominant users were not overrepresented. User names were subsequently removed from our final database to preserve anonymity of participants. After generating an initial codebook based on the first 100 posts, additional posts from the other websites were extracted and coded. The codebook was periodically reviewed and revised as new themes emerged. Finally, using the codebook, a research assistant independently reviewed and coded a random sample of 100 postings to test the reliability and validity of the codes, and kappa scores indicating inter-rater agreement with the author's coded text was calculated.

This study was reviewed and considered exempt from human subjects research by the University of Iowa Institutional Review Board.

RESULTS

We identified 468 unique posts regarding dabigatran that were posted between January 2011 and September 2012 on 10 websites that met criteria for inclusion (See Appendix 1 for list of included websites). The vast majority of posts were by individuals commenting or inquiring about the use of dabigatran for themselves; 37 posts were by persons commenting or inquiring on behalf of another individual (e.g., "my 82 year old mother was put on Pradaxa..."). Coding agreement between the author and research assistant on a sample of 100 comments was 0.87 (95% CI, 0.85–0.90) based on the kappa score.

Our analysis revealed five broad thematic categories to the posted comments. Comments within these broad categories were further classified to create a comprehensive typology representing patient and caregiver questions and opinions regarding dabigatran (Table 1).

1) General safety and efficacy of dabigatran

The first theme reflects general questions or observations about the safety, efficacy, and convenience of dabigatran, overall and relative to other anticoagulants. The largest number of comments questioned the safety and efficacy of dabigatran relative to other anticoagulants—most frequently warfarin; although aspirin and rivoraxaban were also mentioned, as well as other non-prescription alternatives such as garlic, taurine, vitamin E, olive leaf extract, and fish oil. Many comments favored the convenience of dabigatran over warfarin, noting that dabigatran does not require regular blood tests and does not have food restrictions. Interestingly, many individuals were perplexed by the lack of monitoring with dabigatran. The lack of an antidote when bleeding occurs was noted by several individuals as a particularly dangerous aspect of the drug and a reason for not taking dabigatran.

2) Indications and contra-indications for dabigatran

The second theme reflects conditions that indicate or contra-indicate dabigatran. Several comments questioned whether dabigatran could be used for treatment of conditions other than atrial fibrillation, including blood clots and coagulation disorders. Many individuals inquired whether specific comorbid conditions may contraindicate dabigatran, such as cardiac valve disease, history of acute myocardial infarction, renal disease, dementia, or prior gastrointestinal bleeding. Finally, several patients questioned the need for a blood thinner at all, especially when they were in normal sinus rhythm or had undergone a successful cardiac ablation. Many patients also knew their own CHADS2 score and

questioned why there were placed on dabigatran with a CHADS2 score of 0 or 1. (The CHADS2 score indicates a patient's risk of stroke by assigning one point each for a history of Cardiac failure, Hypertension, Age>75, and Diabetes, and two points for prior Stroke; most clinical guidelines recommend anticoagulants for patients with a CHADS2 score of 2 or greater).[11, 12]

Proper use and storage of dabigatran—The third theme reflects the proper use of dabigatran and included questions about dosing and frequency, the use of dabigatran around medical, surgical, and dental procedures, and storage and packaging.

Comments about dosing and frequency included questions about what to do in the event of missed doses or accidentally taking multiple doses too close together. Some patients questioned whether it is permissible to skip or reduce doses if side effects are problematic, or reported substituting another anticoagulant (e.g., aspirin, fish oil) on occasion. The strict guideline that dabigatran be taken 12 hours apart was also noted as a difficult regimen to maintain. Interestingly, four individuals noted that dabigatran has a faster onset of action compared to warfarin, and questioned whether dabigatran could be taken only when symptoms of AF are present.

The second subset of comments under *Proper Use* focused on the use of dabigatran prior to a dental or surgical procedure. Many patients expressed concern that interrupting dabigatran use prior to procedures might increase the risk of stroke. There appeared to be very different and sometimes conflicting experiences regarding instructions for using dabigatran and other anticoagulants in advance of dental or surgical procedures, particularly cardiac ablation, colonoscopy, and dental procedures. For example, many patients were instructed to discontinue dabigatran prior to cardiac ablation, although a small number of individuals reported that they were instructed *not* to discontinue dabigatran prior to ablation. There were also questions and conflicting information about the timing of dabigatran discontinuation before a procedure (reported range 1–7 days prior). Several other comments questioned the process for transitioning from one anticoagulant to another (e.g., aspirin to dabigatran), or ceasing an anticoagulant altogether.

The third subset under *Proper Use* includes comments about procedures for storing dabigatran and a dislike of the packaging for the drug. Dabigatran is available either in a bottle or a blister package, and can break down and lose potency if not kept in the original packaging. Many patients expressed a preference for keeping pills in a weekly pill box and found the manufacturer packaging inconvenient, particularly if they planned to be away from home. Several individuals had devised their own method for storing the medication (using tin foil, plastic sandwich bags, or moisture absorbing pads). Others obtained the medication in blister packs, which they reported as easier to transport but difficult to open. Indeed, there were several comments expressing frustration at how difficult the foil blister packages were to open (“*completely adult proof*”), with one individual noting the irony of using a sharp knife to open a product that increases the risk of bleeding. Three individuals also noted the large size of the pill and questioned whether it was permissible to chew or open the capsule.

3) Drug and diet interactions

There was a wide breadth of medications questioned for possible drug and diet interactions with dabigatran. A large number of patients reported taking antacids or proton pump inhibitors, although only three individuals specifically questioned whether these medications interact with dabigatran. Multiple questions regarding permissible over-the-counter medications for pain relief were also noted. Possible interactions with antiarrhythmics were mentioned in multiple comments, with dronedarone being the most frequent. Several comments questioned whether dabigatran has food restrictions similar to warfarin.

4) Unpleasant Side Effects

The final thematic category includes unwanted side effects, which represent more than half of the total comments. Table 2 lists individual side effects noted as well as the number of comments reporting each side effect, in order to assess the relative frequency of each side effect. Gastrointestinal side effects were the most common with nearly 200 comments. Comments broadly categorized as general energy level were second most frequent (e.g., fatigue, dizziness). Other frequently noted side effects included pain or swelling of muscles and joints, major and minor bleeding episodes, mood and mental impairment (e.g., confusion, depression), fluid management problems (e.g., fluid retention, difficulty urinating), skin rash, change in blood sugar, blurred vision, chest pain, and shortness of breath.

DISCUSSION

This study used a novel low-cost method of extracting and synthesizing comments from widely available public internet forums to determine the experiences of real world patients regarding dabigatran. While many comments posted by patients or their caregivers were not unexpected given what is known about dabigatran from clinical trials, several areas of discussion reflected concerns not typically addressed in clinical trials (e.g., medication storage). Moreover, findings highlighted topics most central to patients' concerns, many of which have potential to impact medication compliance and ultimately outcomes. Five main areas of concern were identified that are likely of high priority to patient and caregivers.

First, patients liked the fact that dabigatran, in contrast to warfarin, does not require regular blood tests and has no diet restrictions. Nevertheless, they were generally puzzled by the lack of monitoring, and found the lack of antidote for uncontrolled bleeding particularly frightening. Indeed, while antidotes have been investigated (e.g., prothrombin complex concentrate, dialysis to remove dabigatran), an effective reversal agent has not been identified[13, 14]. Developing more effective protocols for reversing dabigatran when bleeding occurs and identifying the risk of mortality and morbidity when bleeding occurs while taking dabigatran appear to be high priority topics for many patients.

Second, given the number of questions regarding the schedule for dabigatran doses, physicians and pharmacists might pay closer attention to educating patients about dosing. Because online support groups are typically not monitored by health professionals, opportunities exist for patients to receive inaccurate, unconventional, or even dangerous

guidance about medication dosing from well-intended individuals. Notably, there was substantial discussion and some confusion regarding the proper dosing of dabigatran around the time of surgical procedures. Current recommendations call for ceasing dabigatran 2 to 4 days prior to high risk procedures, depending on renal function[15]. While some of the difference in the use of dabigatran peri-operatively may be attributed to differences in patient risk (e.g., renal function), practice variation across physicians and communication between patients and physicians also appear to be factors. Providers should also be aware that uncertainty around dosing- even if warranted based upon gaps in scientific knowledge- can be unsettling to patients.

Third, an unexpected finding in this study was the problems patients experience with dabigatran storage. Failure to store the medication in original containers may subject the medication to loss of potency, making it significantly less effective at reducing stroke.[8] Many patients found the storage requirements inconvenient – a finding that was not apparent in clinical trials and that may be overlooked in physician-patient communications. Prior research on the implications of medication packaging appears to be limited to the use of reminder packages to encourage adherence.[16] Additional topics for research include the prevalence of improper medication storage and the resulting loss of medication effectiveness, the potential for reduced medication adherence due to inconvenient medication storage criteria, and possible solutions to address storage preferences.

Fourth, interactions questioned most frequently reflected drugs to treat the side effects of dabigatran-- particularly gastrointestinal discomfort. Some research has already demonstrated that co-administration of dabigatran with agents that elevate gastric pH (i.e., antacids, and proton pump inhibitors) may reduce dabigatran exposure, although reductions are not considered clinically significant.[15, 17] Despite this previous research, many patients taking dabigatran are still unclear about recommendations for the use of antacids with the drug. Given the high rate of gastrointestinal side effects with dabigatran which often leads to discontinuing the drug, disseminating information on the most effective and safe medications to relieve the gastrointestinal and other symptoms associated with dabigatran may be particularly beneficial. It is also important to note that patients may initiate the use of over-the-counter medications to relieve side effects of dabigatran only after they start their regimen, making it less likely that they have discussed these medications with their health care provider. Processes to ensuring that this information is disseminated and understood at the time of dabigatran initiation are also important.

Fifth, the largest category of comments reflected adverse side effects. Many of the side effects reported by internet participants were also noted in the original clinical trial that compared dabigatran to warfarin for stroke prevention in AFs.[6, 7] Nevertheless, our data also demonstrate side effects not mentioned in published studies on dabigatran. For example, many internet users reported a change in blood sugar levels, blurry vision, and mental and mood effects. Fluid retention and difficulty urinating were also found in our data – side effects that may be a particular concern for patients with chronic heart failure. While these side effects may not be due to dabigatran, patients nevertheless perceive an association between these physical symptoms and dabigatran use that may warrant attention. Other medications such as cyclo-oxygenase (COX-2) inhibitors have initially looked promising in

efficacy trials but later found to have unacceptable side effects that were identified only after introduction into clinical practice.[18, 19] We believe there may be potential for internet-based support groups to assist with early identification of unexpected adverse events for newly approved drugs.

In recent years, multiple investigators have begun to explore the potential for the internet to provide information reflecting health care trends, activities, and outcomes. For example, analysis of internet search logs has been used to predict influenza outbreaks,[20, 21] measure the use of natural remedies to treat illness,[22] and provide information regarding drug interactions and adverse events not detected in clinical trials.[23, 24] While the current study is similar in that it uses data obtained through the internet, these prior studies focused on internet search activity as a tool for surveillance or epidemiologic analysis and typically identified relationships of interest in advance of analysis. In contrast, the current study uses internet-based *support groups or communities* to provide insight into patients' priorities, and the data are derived from conversation-based language often denoting emotions, fears, and confusion associated with their experiences. Moreover, as with a lot of qualitative research, the analysis of open ended text allowed concepts and relationships of importance to participants to be revealed, including those that researchers may not recognize as important prior to analysis. An example of this is the frustration many patients expressed with the packaging of dabigatran, which was an unexpected finding. Within the context of online support groups, prior studies have focused on processes that take place in online support groups and the impact that participation has on patient well-being.[25–29] We are not aware of previous research synthesizing comments from these groups to determine patient experiences and priorities as stakeholders in patient-oriented research.

This study has limitations. First, the comments analyzed were posted anonymously with few details about patients, and it is possible that internet users reflected in our data do not represent typical users of dabigatran. However, given current rates of internet use we find little reason to suspect that bias[1]. Moreover, within the US, the population of individuals who use the internet is similar in racial and ethnic composition to the overall US population, [30] suggesting that most segments of the population are represented. Even elderly patients, who use the internet less than younger counterparts, are well represented due to the active use of the internet by younger caretakers. Second, it was also often not possible to determine whether dabigatran was prescribed for stroke prevention in AF or for other purposes that are considered 'off-label'. Notably, the use of dabigatran for off-label purposes increased 4-fold over its first year of availability in the US.[31] Nevertheless, this distinction is relevant only if instructions, dosing, and side effects of the drug differ by clinical indication.

CONCLUSIONS

Our data highlighted potential side effects not detected in the previous clinical trial on dabigatran (e.g., increased blood sugar, fluid retention, mood disorders), as well as issues that are important to patients but may not be addressed adequately in prior research (e.g., medication convenience). Despite the growing use of online health-related communities, very little research makes use of this low-cost resource as a tool for identifying patient interests regarding therapeutic treatments and for guiding patient-oriented research.

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APPENDIX 1. Websites

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- www.drugs.com
 - www.webmd.com
 - www.medhelp.org
 - www.healthboards.com
 - www.dailystrength.org
 - www.patientsville.com
 - Health.groups.yahoo.com/group/AFIBsupport
 - www.mdjunction.com/
 - www.afibbers.net
 - www.mdjunction.com/forums/atrial-fibrillation-discussions
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Key points for decision-makers

- 1.** Online health-related communities such as discussion forums and support groups may be a low-cost resource for identifying patient priorities to guide patient-oriented research.
- 2.** Based on patient online comments, primary concerns for patients taking dabigatran include the lack of antidote to reverse the effects of dabigatran if bleeding occurs, and perceived ambiguity regarding the use of dabigatran before and after medical procedures.
- 3.** Medication convenience and packaging are important to patients but may be overlooked by researchers.

Table 1

Example comments within each category and sub-category

I. General safety and efficacy of dabigatran	
a.	<p><u>Comparative effectiveness of dabigatran relative to other anticoagulants</u></p> <p>Have any comparative studies on efficiency [sic] of dabigatran vs use of vitamin E and buffered aspirin?</p>
b.	<p><u>Convenience</u></p> <p>It's great not to have to go get blood test anymore</p> <p>So glad to not have to worry about the foods that I eat – especially greens.</p>
c.	<p><u>Concern about lack of monitoring</u></p> <p>What about INR testing? No tests required even during the onset? How do you know if its working? Everyone is on the same dosage? How can that be?</p>
d.	<p><u>Concern about lack of antidote to reverse anticoagulation effect</u></p> <p>I understand that if you're bleeding internally you're a goner – they have no way to stop the bleeding.... so far!</p>
II. Indications and contra-indications for dabigatran	
a.	<p><u>For treatment of conditions other than atrial fibrillation</u></p> <p>I have a DVT in my leg and have had two PE's. on 10mg Coumadin. Could I switch to dabigatran? How effective is dabigatran at treating factor V leiden mutation?</p>
b.	<p><u>Medical histories that may contraindicate dabigatran</u></p> <p>I am suffering of coronary insufficiency and atrial fibrillation. I had a myocardial infarction before 6 years. I take amiodarone and atenolol. Can I use pradaxa??</p>
c.	<p><u>Indications for oral anticoagulation</u></p> <p>I had an ablation two months ago and have been Afib free since. My doc wants me to stay on Pradaxa for 3 months - even though there were no blood clots at the time of the ablation.... My question is, do I need to stay on Pradaxa even though I should be clot free (no Afib = no clots, correct?)</p>
III. Proper use and storage of dabigatran	
a.	<p><u>Dosing and Frequency</u></p> <p>If dabigatran causes mild nosebleeds is it okay to skip one one of the 150 mg. doses for a day once in a while?</p> <p>I was thinking to ask for a small prescription of Pradaxa to carry with me just in case I should go into afib. A security blanket, I suppose. Is anybody using it in that manner -- just anti-coagulating when you actually go into afib?</p> <p>what if I took my daily dose at 9:30 am and then forgot and took it again at 11:30 am?</p>
b.	<p><u>Undergoing medical, surgical, and dental procedures</u></p> <p>Should pradaxa be stopped before a dental visit to have your teeth cleaned? If so, how long before?</p> <p>I am switching off of it [dabigatran] right now in preparation for an ablation.... They want me on warfarin because they do not yet have a protocol for doing the ablation with people on pradaxa. The interesting thing is the EPs office said stop pradaxa, wait two full days, start coumadin again and do an INR 3 days later. My regular cardiologist's office said that was wrong, take full dose of coumadin along with pradaxa until INR is up to 1.7, then stop pradaxa. These are really different approaches!</p> <p>At first he [gastroenterologist] wanted me to stay off Pradaxa for only 5 days after the procedure [colonoscopy], but because I had flat polyps removed he changed it to 12 days...My electrophysiologist (EP) said 3 days before and 2–3 days after would usually be enough for Pradaxa with a colonoscopy even if polyps are removed.</p>
c.	<p><u>Storage and packaging</u></p> <p>Can you put dabigatran in a weekly pill box or should it be kept in bottle?</p>

When I will be away from home at the time I take Pradaxa (8 am & 8 pm), I put the pill in a snack size Ziplock bag and press as much air out as possible while closing. I have assumed that keeping it that way for 1–2 hours is not damaging to the pill.

I have tried every way that I can think of and cannot get those blister packs open without using scissors or a knife. Now that does not make sense to me. Why in the world would a pharmaceutical company package a medication so that it would require a patient who is on blood thinner to use a sharp tool to open it.

IV. Drug and diet interactions

a. Drug interactions

I'm on both dabigatran and multaq (dronedarone). Is it safe to take Tylenol for back pain?

I am experiencing severe heartburn. May I take tums?

What about taking Pradaxa and Multaq - seems to be contraindicated? Cardiologist sent me to Electrophysiologist for evaluation and he prescribed Multaq. Pharmacist and internet indicate there can be a major reaction in patients also taking Pradaxa.

b. Diet restrictions

I'm eating lots of spinach, broccoli rabe, parsley, etc., now. Are you sure there are no conflicts with pradaxa?

Table 2

Unpleasant Side Effects (463 comments)

<u>Gastrointestinal/Indigestion</u>	<u>208</u>
Stomach discomfort (nausea, vomiting, upset stomach, stomach pain)	68
Upper GI Discomfort (Acid reflux, heartburn)	50
Lower GI Discomfort (constipation, gas, bloating, diarrhea)	48
Esophagus Discomfort (Lump in throat, esophageal pain, difficulty swallowing)	23
Hemorrhoids (new or worsening)	7
Loss of appetite, weight loss	6
Metallic taste in mouth	6
<u>General, energy level</u>	<u>76</u>
Fatigue	31
Headaches	14
Dizziness	13
Excessive Sweating	4
Feeling unusually cold or warm	4
Change in blood pressure	4
Weight Gain	2
Blood rushing to head	2
<u>Joint or Muscle Pain</u>	<u>37</u>
Muscle or joint pain	29
Swelling of feet, limbs	8
<u>Bleeding</u>	<u>38</u>
Major or serious bleed	13
Minor bleeding	25
<u>Fluid management</u>	<u>16</u>
Fluid Retention	9
Difficulty Urinating	5
Kidney Damage	2
<u>Mental and Mood</u>	<u>17</u>
Confusion, Disorientation	7
Mood (Depression, anxiety, mood swings)	5
Insomnia	5
<u>Other symptoms mentioned multiple times</u>	
Skin rash/itching	19
Change in blood sugar level	7
Eye problems (blurry vision)	7
Chest pain/angina	6
Abnormal Liver tests	3
Dry Mouth	3
Stroke/TIA	3
Shortness of breath; difficulty breathing	3

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Congestion and Coughing	3
Hair Loss	2
Repeated Falls	2
Tinnitus	2