Published in final edited form as:
Pharmacogenomics J. 2009 August ; 9(4): 258–264. doi:10.1038/tpj.2009.14.

Cytochrome P450 2D6 Activity Predicts Discontinuation of Tamoxifen Therapy in Breast Cancer Patients

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Abstract

The selective estrogen receptor modulator tamoxifen is routinely used for treatment and prevention of estrogen receptor positive breast cancer. Studies of tamoxifen adherence suggest that over half of patients discontinue treatment before the recommended 5 years. We hypothesized that polymorphisms in *CYP2D6*, the enzyme responsible for tamoxifen activation, predict for tamoxifen discontinuation. Tamoxifen-treated women (n = 297) were genotyped for *CYP2D6* variants and assigned a “score” based on predicted allele activities from 0 (no activity) to 2 (high activity). Correlation between CYP2D6 score and discontinuation rates at 4 months were tested. We observed a strong non-linear correlation between higher CYP2D6 score and increased rates of discontinuation ($r^2 = 0.935$, $p = 0.018$). These data suggest that presence of active CYP2D6 alleles may predict for higher likelihood of tamoxifen discontinuation. Therefore, patients who may be most likely to benefit from tamoxifen may paradoxically be most likely to discontinue treatment prematurely.

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Conflicts of interest:

JMR has received research funding Pfizer and speaking honoraria for Roche Diagnostics.
TS has received speaking honoraria for Roche Diagnostics.
DAF is on the Scientific Advisory Board of Labcorp, Inc, is a consultant to Roche Molecular Diagnostics, and has received research funding from Pfizer and Novartis.
DFH has received research funding from AstraZeneca, Glaxo-Smith Kline, Pfizer, and Novartis.
VS has served as a consultant to Wyeth Pharmaceuticals, Concert Pharmaceuticals and JDS Pharmaceuticals, and has received research funding from Glaxo-Smith Kline, Pfizer, and Novartis.

Keywords

Tamoxifen; Cytochrome P450 2D6; pharmacogenetics; compliance; adherence

Introduction

Adherence to medication prescription regimens are universally recognized to be important contributors to variability in response across a wide spectrum of clinical therapeutics. Non-adherence may have significant clinical consequences that include increases in presumed drug resistance, inappropriate dosage increases and loss of therapeutic effect.[1] Virtually no data exist on genetic contributors to non-adherence or compliance.

Adjuvant use of the selective estrogen receptor modulator (SERM) tamoxifen decreases risks of breast cancer recurrence and death in women with estrogen receptor (ER)-positive, early stage disease.[2] Prospective randomized trials have suggested that the optimal duration of tamoxifen therapy is at least 5 years.[2-4] Although tamoxifen has been used for over 3 decades in the treatment of ER-positive breast cancer, the true extent to which patients adhere to therapy has not been established. Reports of controlled, prospective clinical trials designed to test the efficacy of tamoxifen suggest that fewer than 15% of women discontinue tamoxifen therapy prior to completing the recommended 5 years.[2,3,5-7] However, several recent studies of tamoxifen use either in clinical trials or in the community setting have demonstrated that up to 55% of women do not adhere to tamoxifen therapy, both in the prevention and adjuvant treatment settings.[8-15] Non-compliance with treatment reduces benefit for individual patients, and adds a level of uncertainty to the interpretation of clinical trial results.

The pharmacology and metabolism of tamoxifen are complex, with extensive biotransformation of the drug catalyzed by both Phase I and Phase II drug metabolizing enzymes. Although tamoxifen itself is a relatively weak anti-estrogen, its metabolites have varying tissue-specific estrogenic and anti-estrogenic properties.[16] We have previously demonstrated that the genetically polymorphic liver enzyme cytochrome P450 (CYP) 2D6 is responsible for the production of a key anti-estrogenic metabolite, 4-hydroxy-N-desmethyl tamoxifen, designated endoxifen.[17-20] Endoxifen is as equally potent as another anti-estrogenic metabolite, 4-hydroxy-tamoxifen,[21] but in patients with wild-type *CYP2D6*, endoxifen is present at ~10-fold higher concentrations than 4-hydroxy-tamoxifen. Compared to women with wild-type *CYP2D6*, women taking CYP2D6 inhibitors such as paroxetine or women who are homozygous for inactivating single nucleotide polymorphisms (SNPs) in *CYP2D6* have low circulating endoxifen serum concentrations while on tamoxifen therapy.[17,19,20]

In a retrospective analysis of patient genotypes from a trial of adjuvant tamoxifen therapy previously conducted by the North Central Cancer Treatment Group (NCCTG), we demonstrated that women homozygous for the common non-functional *CYP2D6* variant *4 were at higher risk of disease relapse compared to those with one or more wild-type *CYP2D6* alleles.[22] In the same patient cohort, subjects with variant *CYP2D6* genotype experienced fewer hot flashes than women with wild-type *CYP2D6*. These data suggest that tamoxifen-associated hot flashes may be a marker for metabolism of tamoxifen to the anti-estrogenic metabolite endoxifen. These results, as well as those from other large studies, suggest that women who are better able to metabolize tamoxifen, as determined by greater hot flash frequency, may derive greater benefit from therapy.[23,24]

Although the allelic frequency of *CYP2D6*4* in the NCCTG study described above (0.174) was consistent with that expected in a Caucasian population, we observed a higher than expected rate of patients with the homozygous *CYP2D6*4* genotype (6.8% in study versus 4.6% expected) which was not in Hardy-Weinberg equilibrium.[25] These data led us to hypothesize that CYP2D6 activity might influence patient adherence to therapy. Specifically, patients with reduced CYP2D6 activity would have lower concentrations of endoxifen, experience fewer side effects, and thus be more likely to complete the one year of tamoxifen therapy. We reviewed data from an open-label prospective observational trial of tamoxifen therapy in order to evaluate the potential association between *CYP2D6* genotype or phenotype and early discontinuation of tamoxifen therapy. We utilized the recently developed CYP2D6 activity scoring system by Blake et al. [26] to predict each patient's CYP2D6 metabolic phenotype, based on her CYP2D6 genotype, for correlation with tamoxifen discontinuation.

Results

Evaluable Patients and Characteristics

Of the 297 subjects enrolled in the trial, 280 had *CYP2D6* genotype available for analyses. The DNA from 17 patients was not of sufficient quality to allow *CYP2D6* genotype determination. Discontinuation of tamoxifen therapy was analyzed at 4 months following treatment initiation, as described in the Materials and Methods section. Overall, 41 of the 280 (14.6%) subjects discontinued participation in the trial, with 28 (10.0%) withdrawing due to tamoxifen-related side effects and 13 (4.6%) for non-tamoxifen associated reasons (Figure 1). Only subjects who withdrew for tamoxifen-related side effects were considered for further analyses. The patient characteristics and detailed trial design have been reported previously [27]. The reported side effects for patients that withdrew for tamoxifen-related reasons (n = 28) are shown in Table 2.

CYP2D6 Activity Score Correlation with Patient Discontinuation

In order to predict extent of tamoxifen metabolism by the CYP2D6 enzyme, CYP2D6 activity score was calculated for each subject as described in the Materials and Methods section. We tested whether high CYP2D6 activity scores were associated with higher likelihood of tamoxifen treatment discontinuation due to unacceptable side effects. All ten patients enrolled on the study who had two non-functioning CYP2D6 alleles remained on trial for at least 4 months. Patients who continued study participation for at least 4 months or who withdrew due to tamoxifen-related side effects within 4 months of treatment initiation were stratified by CYP2D6 score and results are shown in Table 3. Using a Michaelis-Menten model, we observed a significant correlation between increasing CYP2D6 score and drug discontinuation due to side effects ($r^2 = 0.935$, $p = 0.018$) (Figure 2A). Adjustment of scores for concomitant medications that alter CYP2D6 activity eliminated the relationship between CYP2D6 score and treatment discontinuation rates (Figure 2B).

Other Genetic Polymorphisms Do Not Correlate with Tamoxifen Discontinuation

We hypothesized that genetic polymorphisms in genes involved in tamoxifen metabolism but are not involved in the production of endoxifen would not be associated with tamoxifen discontinuation in our study. Therefore, common variants in *CYP2C19* (*2 and *17) and *CYP3A5* (*3) were correlated with drug discontinuation due to side effects. We did not observe statistically significant associations between genotype and study discontinuation rates and these polymorphisms (data not shown).

Discussion

Our previous studies have shown that women with genetic variants in *CYP2D6* have lower circulating concentrations of the active tamoxifen metabolite endoxifen.[17-20] Preliminary data suggest that these women experience fewer drug-related hot flashes and exhibit higher rates of disease recurrence.[22] Interestingly, two recent studies have also reported an association between tamoxifen-related side effects with disease outcome in tamoxifen treated breast cancer patients.[23,24] In the current study, we demonstrate that *CYP2D6* genotype may also influence discontinuation of tamoxifen therapy. We observed that women with genetic variants in *CYP2D6* that confer low enzyme activity were more likely to continue participation in an observational clinical trial of tamoxifen during the first 4 months of prescription compared to women with intermediate or normal enzyme activity. Increasing CYP2D6 activity, as predicted by genotype, and rate of tamoxifen discontinuation were highly correlated. Taken together, our results suggest an intriguing hypothesis that the women most likely to benefit from tamoxifen therapy may be, paradoxically, least likely to adhere to therapy. However, confirmation of these studies in additional patient cohorts is required before any clinical implications can be drawn.

Although the majority of reports have suggested that there is a direct correlation between variant *CYP2D6* genotype and worse breast cancer outcomes, several recent retrospective analyses reported contradictory results.[22,28-37] Although there are a number of differences among these studies including number of subjects, patient characteristics, dosage and length of tamoxifen therapy, other breast cancer therapies, and consideration of concomitant medications, our results may also help explain, in part, this discrepancy. None of the studies conducted to date have considered differences in patient adherence to or discontinuation of therapy due to *CYP2D6* genotype. Our results suggest that, as compared to subjects with variant *CYP2D6* activity, patients with wild type *CYP2D6* may be more likely to both obtain benefit from tamoxifen therapy and discontinue the drug because of side effects. These results indicate that the apparent beneficial effects of metabolism of tamoxifen to the anti-estrogen endoxifen that have been noted in clinical trials may have been diluted by decreased adherence or persistence to therapy.

The tolerability of tamoxifen varies widely between published reports and may be under-reported.[38] Side effect reporting in initial clinical trials focused on life-threatening and serious adverse reactions, including thromboembolic events, stroke, and endometrial cancer.[12] It is these serious toxicities that have limited the use of tamoxifen, particularly in the chemoprevention setting. However, the impact of less severe but more frequent and troubling side effects, such as hot flashes, which are particularly bothersome to some patients and which may greatly impact quality of life, is frequently minimized in large prospective clinical trials.[38] Since these side effects substantially influence adherence, they potentially alter the overall perceived benefit of tamoxifen on risk of breast cancer recurrence and survival in large populations.[7]

Multiple factors related to adherence to therapy for chronic illness have been identified, including concomitant psychological issues, cost, complexity of therapy, and side effects.[39] Patient beliefs about both necessity of and concerns about medications can also directly impact adherence to therapy for chronic illness.[40] More recently, factors specific to adherence of breast cancer patients to adjuvant endocrine therapy have been identified, including patient age, race, prior mastectomy, and interaction with an oncologist. [41] It can be particularly difficult for patients to adhere to therapy for an asymptomatic disease, such as adjuvant therapy for early stage breast cancer, especially when the therapy causes side effects. However, despite being aware of the issues surrounding non-adherence to tamoxifen therapy, health care providers are frequently unable to correctly predict patient non-

adherence.[1] Although side effects account for only a portion of non-adherence to tamoxifen, one approach to improving adherence rates is through the use genetic predictors of adherence. These could potentially be used to identify patients who are most likely to discontinue tamoxifen due to toxicity, and who may benefit from early interventions to ameliorate the side effects.

Many non-hormonal therapies are available for treatment of tamoxifen-induced side effects.[42] In particular, the SSRIs (selective serotonin re-uptake inhibitors) and SNRIs (serotonin-norepinephrine re-uptake inhibitors) are effective for reduction of hot flash frequency and severity, as well as for treatment of depression and anxiety.[43] Better management of these symptoms can also lead to improvements in insomnia and fatigue. However, caution is necessary when using these drugs in the treatment of side effects since some, including paroxetine and fluoxetine, are potent or moderate inhibitors of the CYP2D6 enzyme, and therefore may render tamoxifen therapy less effective [17,19]. In our study, we observed that when patient CYP2D6 activity score was modified to account for the concomitant use of medications that inhibit CYP2D6, the relationship between CYP2D6 activity score and non-adherence was lost. This suggests that treatment with CYP2D6 inhibitors that ameliorate some tamoxifen-related side effects may enable more women with active CYP2D6 enzyme to continue to take the medication. However, the relationship between CYP2D6 score and side effect-related prescription rate could not be determined in this cohort, as compounds that inhibit CYP2D6 are prescribed for varying reasons and are not exclusively for hot flashes. While these observations require further study, they suggest that CYP2D6 metabolism may play a predictive role for development of tamoxifen-related side effects.

Our results, suggesting that there may be an association between tamoxifen pharmacogenetics and discontinuation of therapy, were derived from a single observational cohort study of predominantly Caucasian women and therefore must be considered exploratory and hypothesis-generating. One potential significant limitation of our study is a patient could have discontinued therapy for both tamoxifen-related and –unrelated reasons, yet only one of the reasons may have been recorded. This would result in under-reporting of tamoxifen-related side effects leading to discontinuation. The frequencies of *CYP2D6* variant alleles were consistent with those expected in this patient population and were in Hardy-Weinberg equilibrium at baseline. However, due to the small number of patients with a homozygous variant genotypes and the limited number of patients who discontinued therapy due to tamoxifen-related side effects, our data require confirmation in additional patient cohorts.

This current study suggests that *CYP2D6* genotype may predict discontinuation of, and possibly adherence to tamoxifen. Not only does *CYP2D6* genotyping potentially identify patients that will not respond to tamoxifen therapy, it may also identify patients likely not to adhere to the full 5 years of tamoxifen therapy and who could benefit from early educational or therapeutic interventions. To our knowledge, this study is the first to evaluate the predictive role of genetic variants in drug metabolizing enzymes and adherence to an important therapeutic agent, tamoxifen. In the future, it is possible that genetic testing may be used to identify patients less likely to comply with treatment recommendations and represents an important potential new area of investigation: the pharmacogenetics of therapeutic compliance.

Materials and Methods

Patients

Women were recruited into a multi-center, open-label prospective observational trial designed to test associations between genetic polymorphisms of candidate genes and tamoxifen-related phenotypes, including adverse effects and estrogenic and anti-estrogenic phenotypes. The clinical trial inclusion and exclusion criteria have been described previously.[19,20] Briefly, women with a diagnosis of ER-positive early stage breast cancer or ductal carcinoma in situ or women at high risk for breast cancer who were initiating therapy with tamoxifen were enrolled. The women were prescribed tamoxifen 20 mg orally per day for a planned 5 years. Subjects were followed on study only during the first year of tamoxifen therapy, and underwent evaluation for toxicity at baseline and 1, 4, 8, and 12 months after initiation of tamoxifen. Data regarding concomitant medications were collected at each time point. The protocol was approved by the institutional review boards at the three participating sites (Lombardi Comprehensive Cancer Center at Georgetown University Medical Center, Indiana University Medical Center, and the University of Michigan Comprehensive Cancer Center), and all subjects provided informed consent.[19,20]

Genotype Analysis

CYP2D6 genotype was determined as described previously.[19,20] In brief, genomic DNA was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA) according to the manufacturer's instructions. Two hundred eighty patients were genotyped for 33 CYP2D6 alleles using the AmpliChip® CYP450 Test (Roche Diagnostics, Basel, Switzerland) according the manufacturer's instructions. *CYP2C19*2* and CYP2C19*17 genotypes were determined using the Applied Biosystems' Taqman® Allelic Discrimination Assay (Foster City, CA) according to the manufacturer's instructions. Briefly, 10 ng DNA was added to a 5 μl reaction containing forward and reverse primers along with 2 allele specific labeled probes (one wild-type and one variant allele specific). The PCR and fluorescence measurements were performed using the ABI Prism 7700 sequence detection system. *CYP3A5*3* genotyping was performed by allele specific PCR. Primers for *CYP3A5*3* were described by LeCorre et al.[44] The PCR was performed on 30ng of genomic DNA using iQ SYBR Green Supermix (Bio-Rad Laboratories, Hercules, CA) with the final concentration of all primers at 200nM. The plates were cycled at 95°C for 3 minutes, followed by 45 cycles of 95°C for 10s then 60°C for 35s. The alleles were differentiated by the Ct values obtained from the real-time PCR reaction.

CYP2D6 Activity Score

We assigned CYP2D6 “activity score” to patients based on their *CYP2D6* genotype, using the method described by Blake *et al*. [26] with minor modifications (*CYP2D6*9* allele was assigned a value 0.5 instead of 0.75, *1×N/*2×N were not assigned values above 1). These scoring changes were made due to the small number of patients on study with *9 and *1×N/*2×N alleles. As shown in Table 1, each *CYP2D6* allele was assigned a value from 0 (for nonfunctional alleles) to 1 (for fully functioning alleles) based on its relative activity for dextromethorphan *O*-demethylation.[26] Each patient's activity score represents the sum total of their individual *CYP2D6* alleles (ranging from 0 to 2) with a score of 0 representing the CYP2D6 poor metabolizer, 0.5 and 1 representing intermediate metabolizer, and 1.5 and 2 representing extensive metabolizer phenotypes. Gaedigk *et al* have developed, validated and extensively characterized the CYP2D6 activity score as an approach to most accurately predict a patient's particular CYP2D6 metabolic phenotype based on their genotype.[45]

We prospectively collected detailed concomitant medication usage for patients included in this cohort. We were therefore able to further refine the patients' CYP2D6 activity scores

based on each drug's documented ability to inhibit the enzymatic activity of CYP2D6 [19] (www.drug-interactions.com). Concomitant medications were categorized for strong, moderate, or weak/no inhibition of CYP2D6. Patients were considered to have taken inhibitor drugs if prescription/use of the drug was recorded at either 0 or 4 month visits. In patients taking more than one drug, only the strongest CYP2D6 inhibitor was factored into the CYP2D6 scoring (drugs were not considered additive for scoring purposes). Paroxetine, fluoxetine, and bupropion were considered strong inhibitors, and have been shown to completely inhibit CYP2D6 metabolism at clinically relevant doses; patients taking these drugs have CYP2D6 activity levels similar to patients homozygous for non-functional *CYP2D6* alleles.[46,47] Duloxetine, diphenydramine, and cimetidine were considered moderate inhibitors and demonstrate partial inhibition of CYP2D6 activity.[48-50]. Previously, we have demonstrated that venlafaxine has negligible effects on CYP2D6 activity or endoxifen serum concentration, so it was not considered an inhibitor of CYP2D6.[19] Based on these designations, 2 points were deducted from each patient's CYP2D6 metabolism score for strong inhibitors, 1 point for moderate inhibitors, and 0 points for the weak inhibitor no inhibitors. Adjusted scores less than zero were assigned a value of 0 (Table 1).

Tamoxifen Discontinuation

Patients who discontinued study participation prior to completion of 4 months of therapy were considered to have prematurely discontinued treatment for the purposes of this analysis. The 4 month time point was selected because tamoxifen serum concentrations reach steady state by 4 months.[17] Furthermore, in the quality of life Arimidex, Tamoxifen, Alone or Combination (ATAC) sub-study, tamoxifen-associated side effects plateaued at 3 months; therefore, we used the 4 month visit in our study as our cutoff for withdrawal due to side effects.[51] Treatment discontinuation was based on patient request to a trained clinical research nurse, including the self-reported reason for discontinuing therapy early. Subjects were categorized either as withdrawing due to tamoxifen-related or –unrelated reasons using prospectively recorded data on study case report forms and retrospectively obtained data from medical record chart review by study investigators without knowledge of patient genotype. Tamoxifen-unrelated reasons included: geographical (eg moving out of the area), insurance issues, inability to have research study blood drawn, non-compliance with clinical trial procedures, and discontinuation of medication for reasons other than side effects (such as switching to an aromatase inhibitor because of newly available clinical data or progression of disease). Tamoxifen-related reasons included unacceptable side effects that were definitely, probably, or possibly related to the drug, including depression, insomnia, emotional liability, hot flashes, vaginal bleeding, and headache.[14,38]

Statistical Considerations

Endoxifen exposure is proportional to CYP2D6 activity scores. An increase in CYP2D6 score correlates with an increase in CYP2D6 metabolic activity [26,45]. A pharmacodynamic relationship between a drug exposure and its effect profile is usually modeled by a Michaelis-Menten model. Hence, CYP2D6 score and off-study rate is described by this nonlinear model. A weighted Michaelis-Menten nonlinear regression model was employed to describe the relationship between off study rate versus CYP2D6 score using S-PLUS®7 software (Insightful Corp., Seattle, WA):

$$\text{drop out rate} = \frac{B_{\text{MAX}} \times \text{score}}{K_D + \text{score}},$$

where B_{max} represents the maximum drop-out rate when the score reaches maximum, K_D represents the score at 50% drop rate. Weighting was determined by the standard error of off study rate for each score. As the contribution of the other two genotypes (CYP2C19 and CYP3A5) to endoxifen concentration is negligible, they are not expected to correlate with the off-study rate. Their correlations with the off-study rate were analyzed through ANOVA and F-test, and served as the negative controls. Since CYP2D6 genotype is the only variable that we hypothesized to correlate with the off-study rate, the p-value provided is not corrected for multiple comparisons.

Acknowledgments

We are grateful to Drs. C. Kent Osborne and Michael D. Johnson for their valuable input.

This work was supported in part by Grants U-01 GM61373 and T-32 GM007767, Indiana University GCRC Grant M01RR00750, University of Michigan GCRC Grant M01-RR00042, and Georgetown University (NIH M01-RR13297), from the National Institute of General Medical Sciences (Bethesda, MD), Damon Runyon-Lilly Clinical Investigator award CI-3 from the Damon Runyon Cancer Research Foundation (VS), Fashion Footwear Charitable Foundation of New York/QVC Presents Shoes on Sale™ (DFH) and Breast Cancer Research Foundation grant N003173 (JMR), and by Grant Number M01-RR000042 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NCRR or NIH.

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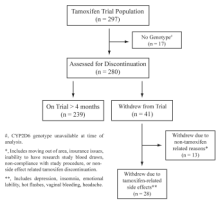

Figure 1.

Consort diagram of tamoxifen trial population. Patients who continued study participation for at least 4 months (n = 239) or discontinued study participation for tamoxifen-related side effects (n = 28) were analyzed for associations between *CYP2D6* genotype and treatment discontinuation (n = 267).

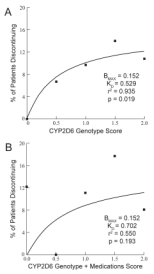

Figure 2.

CYP2D6 genotype is a predictor of tamoxifen discontinuation. Data shown as percentage of patients with CYP2D6 score that discontinued treatment due to tamoxifen-related side effects. Non-linear Michaelis-Menten modeling of CYP2D6 score based on genotype (A) or adjusted for concomitant medications (B).

Table 1

CYP2D6 Scoring System.

CYP2D6 Allele	Points Assigned/Allele
*1, *1×N, *2, *2×N, *35	1
*9, *10, *17, *41	0.5
*3, *4, *5, *6, *11	0
Medication	**Points Adjustment**
Paroxetine	-2
Fluoxetine	-2
Bupropion	-2
Duloxetine	-1
Diphenhydramine	-1
Cimetidine	-1

Table 2

Side Effects and Frequency among Patients Discontinuing Tamoxifen Therapy.

Side Effect	n (%)
Hot Flashes	13 (46.4)
Emotional Lability	7 (25)
Insomnia	5 (17.9)
Fatigue	5 (17.9)
Depression	3 (10.7)
Anxiety	3 (10.7)
Headache	2 (7.1)
Vaginal Bleeding	2 (7.1)
Weight Gain	2 (7.1)
Other*	12 (42.9)

*1*Including vision changes, nausea, liver toxicity, rash, night sweats, hair loss, leg swelling, arthralgia, myalgia, and other gynecological concerns

Table 3

Patients Discontinuing Tamoxifen Therapy (Off) vs. Remaining on Therapy (On) according to CYP2D6 Score.

CYP2D6 Score	Off - n (%)	On - n (%)
0	0 (0.0)	10 (4.2)
0.5	1 (3.6)	14 (5.9)
1	7 (25.0)	65 (27.2)
1.5	7 (25.0)	43 (18.0)
2	13 (46.4)	107 (44.8)
Total	28	239