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ORIGINAL ARTICLE

Impact of Pharmacogenomic Information on Values of Care and Quality of Life Associated with Codeine and Tramadol-Related Adverse Drug Events

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Abstract

Objective: To assess the potential impact of Pharmacogenomic (PGx) variation in cytochrome P450 2D6 (CYP2D6) enzyme function, using loss in quality-adjusted life years (QALYs) associated with treatment problems, and the willingness to pay to avoid treatment problems from patients' and payers' perspectives.
Patients and Methods: The study included patients prescribed tramadol or codeine, or both, between January 1, 2005, and December 31, 2017. Demographic information and adverse drug events, including adverse drug events and poor pain control, were collected from the electronic health records using natural language processing techniques and review by trained abstractors. Patients' willingness to pay and QALY estimates were based on comprehensive literature review. The CYP2D6 phenotypes were divided into 4 groups: ultra-rapid metabolizers, normal metabolizers, intermediate metabolizers, and poor metabolizers.
Results: Among the 2860 identified patients, 63 (2%) were ultrarapid metabolizers, 1449 (50%) were normal metabolizers, 1155 (40%) were intermediate metabolizers, and 193 (7%) were poor metabolizers. The patients' average estimated willingness-to-pay value to avoid treatment problems was $23 per month; poor metabolizers developed problems with the highest estimated willingness-to-pay value ($32 per month). The mean QALY loss among all patients was 0.024 QALYs (8.8 healthy days); poor metabolizers had the highest loss (0.027 QALYs, 9.9 healthy days).
Conclusion: Patients with various phenotypes developed different treatment problem profiles. Poor CYP2D6 metabolizers developed problems with highest willingness to pay, and they might potentially benefit most from PGx-guided treatment and problem prevention.

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Opioid analgesics are frequently used for management of both acute and chronic pain.[1,2] Opioid prescriptions in the United States are common, with a rate of 59 per 100 persons in 2017.[3] Codeine and tramadol are two of the most commonly used opioids. Codeine yields adverse effects of gastrointestinal discomfort, vertigo, sleepiness, and rash[4]; tramadol has been reported to cause nausea, vomiting, fatigue, sedation, sweating, and serotonin toxicity.[5,6] Many of these treatment problems, including adverse drug events (ADEs) and poor pain control, are not life-threatening, and they can require limited management by health care providers. Therefore, the direct financial effects of these problems may be limited; however, these problems also affect quality of life, and information quantifying the effects of such outcomes on patient quality of life is lacking.

Cytochrome P450 2D6 (CYP2D6) is the primary enzyme that bioactivates codeine, and variation in CYP2D6 function has been associated with treatment problems related to use of tramadol and codeine.[7] At the genetic level, persons exposed to codeine and

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tramadol with the CYP2D6 poor metabolizer phenotype have lower levels of the active opioid metabolites, while patients with ultrarapid CYP2D6 phenotypes experience higher systemic levels of the metabolites.[8] Therefore, poor CYP2D6 metabolizers might have less pain control compared with normal metabolizers.[9] In contrast, ultrarapid CYP2D6 metabolizers require less pain medication to achieve pain control, but they may be at greater risk of other ADEs compared with normal metabolizers.[10-12]

Consideration of patient pharmacogenomics (PGx) information at the time of drug prescriptions holds the potential to avoid ADEs and to maximize drug effectiveness.[13-15] Ideally, access to CYP2D6 phenotype information at the time of drug prescription would enable genotype-guided drug and dose selection.[13-15] Such information could improve the patient experience and reduce health care costs. However, clinical guidelines regarding the implementation of PGx information into clinical practice were mainly established using data from pharmacokinetic studies. Data regarding value of care or improvements in quality of life owing to the implementation of PGx information for opioid prescriptions is currently limited.[16,17]

Therefore, the goal of our study was to understand to what extent PGx-guided treatment might decrease potential costs associated with treatment problems or improve the quality of life for patients who receive codeine and tramadol prescriptions. To accomplish this goal, we described the types of treatment problems experienced by patients who received codeine or tramadol prescriptions. Second, using existing literature, we assigned monetary values to the problems based on what patients have reported that they are willing to pay to avoid these events; we also assigned quality-adjusted life years (QALYs) to each ADE or case of poor pain control. QALY is a generic measure of disease burden that aggregates both health-related quality of life and length of life into a single measure.[18] QALYs are frequently used in cost-effectiveness analyses to measure health outcomes related to treatment effectiveness. One QALY reflects the treatment benefit of gaining the patient 1 full year of life with good health, and it was designed for interpersonal comparison.[19] Finally, we estimated health insurance's (payer's) willingness to pay to treat the problems. Together, our study provides an innovative approach to examine the monetary effects that PGx information could provide on treatment problems and loss in QALYs that patients might experience with codeine or tramadol prescriptions.

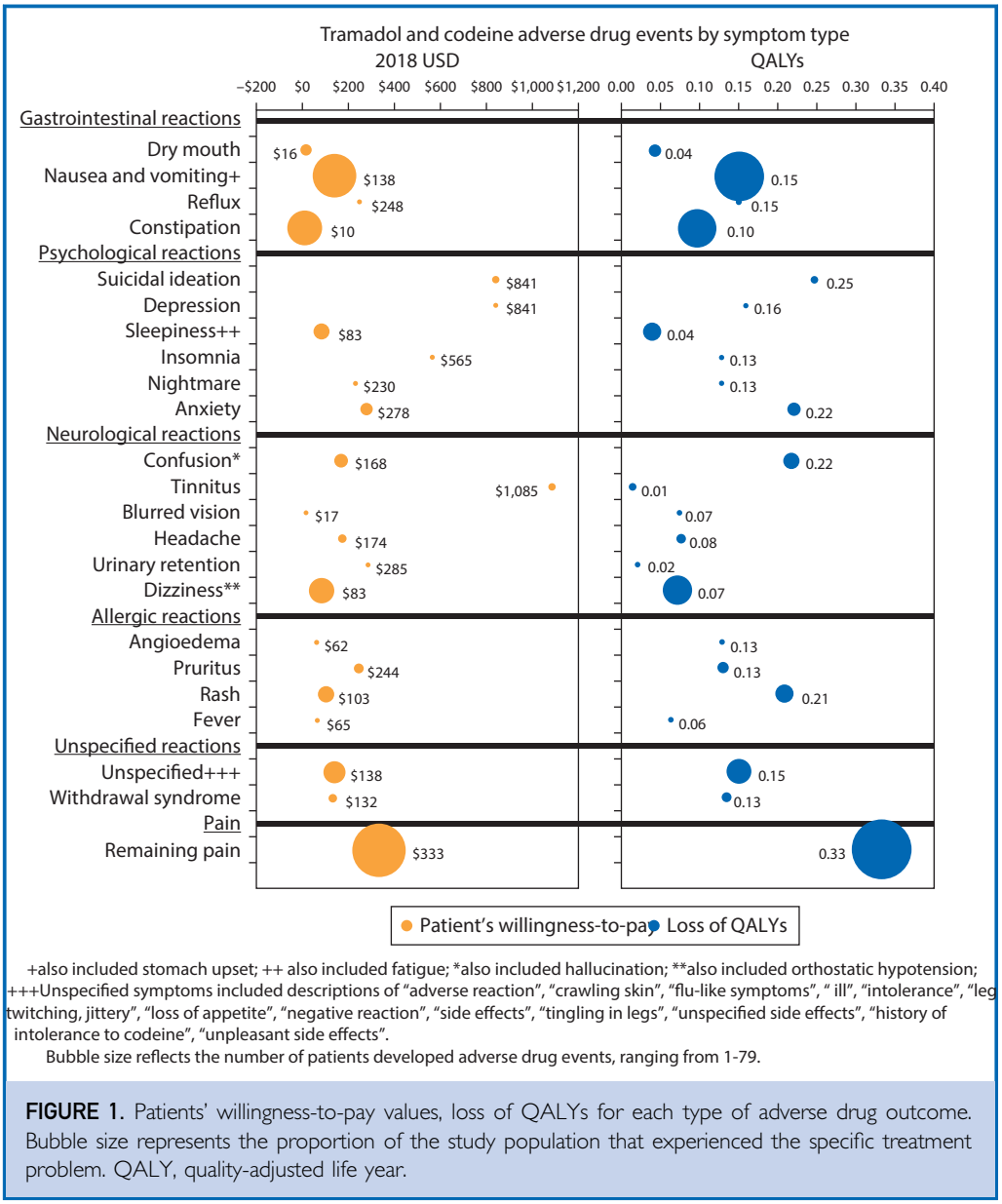
PATIENTS AND METHODS

Study Population

This study included patients who participated in the Right Drug, Right Dose, Right Time-Using Genomic Data to Individualize Treatment (RIGHT Study), and who were prescribed tramadol and codeine between January 1, 2005, and December 31, 2017.[20] In brief, the RIGHT study enrolled 10,074 participants with self-reported demographic information and blood samples sequenced for CYP2D6.[20] The initiation of tramadol and codeine treatment was captured using the Rochester Epidemiology Project (REP) research infrastructure, with the details reported previously.[21] Normalized names for clinical drugs provided by RxNorm were used to identify the ingredients that included tramadol or codeine.[22] We excluded persons who were found to have prior tramadol or codeine use between January 1, 2004, and December 31, 2004, and those who used codeine as a cough suppressant. We also excluded persons who were prescribed strong or moderately strong CYP2D6 inhibitors (Supplemental Table 1, available online at http://mcpiqojournal.org) during this period[23] to minimize the effect of phenoconversion, which is a change in apparent drug metabolism phenotype owing to drug−drug interaction rather than to genetic variation.[24] The study was approved by the Mayo Clinic Institutional Review Board (IRB# 16-000189), and all the study subjects gave informed consent.

Pharmacogenomic Phenotyping

The CYP2D6 phenotypes were divided into 4 groups according to the drug metabolism rates estimated from patients' genotypes: (1) ultrarapid metabolizers, including ultra-rapid and rapid metabolizers; (2) normal metabolizers, including normal and intermediate to normal metabolizers; (3) intermediate metabolizers,



+also included stomach upset; ++ also included fatigue; *also included hallucination; **also included orthostatic hypotension; +++Unspecified symptoms included descriptions of "adverse reaction", "crawling skin", "flu-like symptoms", " ill", "intolerance", "leg twitching, jittery", "loss of appetite", "negative reaction", "side effects", "tingling in legs", "unspecified side effects", "history of intolerance to codeine", "unpleasant side effects".

Bubble size reflects the number of patients developed adverse drug events, ranging from 1-79.

FIGURE 1. Patients' willingness-to-pay values, loss of QALYs for each type of adverse drug outcome. Bubble size represents the proportion of the study population that experienced the specific treatment problem. QALY, quality-adjusted life year.

including intermediate and poor to intermediate metabolizers; and (4) poor metabolizers. The processes of genotyping and phenotype prediction have been reported previously.[25]

Identifying Treatment Problems and Their Values

Treatment Problems. Treatment problems included ADEs and poor pain control. These data were captured from reviewing the electronic health records. The reviewing process included two steps. First, a natural language processing technique was applied in the initial screening for opioid-related adverse outcomes. This process captured all electronic health record sentences with normalized opioid names and key words related to treatment problems (eg, nausea, vomiting, constipation and poor-pain-control). Second, two abstractors (J.L.S. and a trained nurse abstractor) reviewed the screened sentences and recorded any adverse symptom or poor pain control event attributed to codeine or tramadol within 6 weeks after the first codeine or tramadol prescription.

Adverse symptoms were further grouped in 6 system categories (eg, nausea and vomiting were classified as "gastrointestinal symptoms"). Our final definition of treatment problems included the presence of either an adverse symptom attributed to codeine or tramadol or documentation of poor pain control (eg, "patient has been taking Ultram but continues to complain of severe neck pain") after prescription of these medications. If there was no mention of adverse symptoms or poor pain control in the medical record notes, the patient was classified as not having treatment problems. Figure 1 lists all treatment problem types and their system categories.

Patients' Willingness to Pay to Avoid Treatment Problems. We estimated patients' willingness to pay to avoid treatment problems resulting from a codeine or tramadol prescription. Willingness to pay provides a useful estimate of a patient's perceived value of care, because monetary value is a proxy for the trade-off and priority a person places on receiving a particular outcome.[26] To obtain willingness-to-pay monetary values for each problem, we conducted a comprehensive literature review across multiple databases from inception through October 11, 2019, and the inception varies by database. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Ovid PsycINFO, and Scopus. Controlled vocabulary supplemented with keywords was used to search for patients' willingness to pay in monetary values of opioid-induced symptoms from the patient's perspective, in the United States and Canada. We found 21 relevant studies (of 1294 possible studies) reporting the monetary values patients that were willing to pay to treat the problem types identified in our study. The literature review process and the search strategies are shown in the Supplemental Table 2 and Supplemental Figure 1 (available online at http://mcpiqojournal.org). All the monetary values were converted from the study year to 2018 US dollars using the gross domestic product price deflator from the Bureau of Economic Analysis.[27]

Health-Related Quality of Life Loss Owing to Treatment Problems. We also used loss in QALYs to quantitatively measure the effect of individual treatment problems on both length of life and health-related quality of life. The decrease in QALYs for each of the problem types was estimated using the available literature from the best possible similar patient populations within the most recent 20 years (1998-2018). If we were unable to find estimated QALYs for ADEs using studies from US or Canadian populations, we used results from European countries as close estimations.

Payer's Willingness to Pay for the Improvement of Health-Related Quality of Life. The widely accepted threshold for payers' willingness to cover the costs associated with decreases in quality of life is $50,000-10,000/QALY.[28] We estimated the payer's monthly willingness to pay by multiplying the QALYs by $50,000/QALY (Equation 1).[29,30] This threshold has been adopted by most of the recent cost-effectiveness studies for most countries.[31] Payers' willingness to pay was calculated using the following function:

$$Willingness\_to\_Pay_i \Big/ month = \frac{U_i\ years \times \$50000/year}{12\ months} \quad (Equation\ 1)$$

where U_i is the number of QALY lost for each adverse outcome.

Patients' and payers' willingness to pay estimates and decreases in QALYs associated with each of the ADEs are listed in Supplemental Table 3 (available online at http://mcpiqojournal.org).

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TABLE. Patient Characteristics for Full Study Sample and by CYP2D6 Phenotype[a]

Variable	Full sample	Ultra-rapid metabolizer	Normal metabolizer	Intermediate metabolizer	Poor metabolizer
Number of patients	2860	63 (2%)	1449 (51%)	1155 (40%)	193 (7%)
Mean BMI, kg/m^2 (SD)	29.74 (7.36)	29.27 (5.66)	29.53 (6.53)	30.02 (8.58)	29.68 (5.47)
Mean age, years (SD)	61.27 (13.58)	63.84 (11.33)	60.83 (13.94)	61.39 (13.22)	62.99 (13.49)
Sex, n (%)					
Female	1680 (59%)	37 (59%)	869 (60%)	666 (58%)	108 (56%)
Male	1180 (41%)	26 (41%)	580 (40%)	489 (42%)	85 (44%)
Race, n (%)					
White	2690 (94%)	56 (89%)	1354 (93%)	1101 (95%)	179 (93%)
African American	11 (0%)	0 (0%)	7 (0%)	4 (0%)	0 (0%)
Asian/Native	22 (1%)	0 (0%)	18 (1%)	4 (0%)	0 (0%)
Others[b]	137 (5%)	7 (11%)	70 (5%)	46 (4%)	14 (7%)
Ethnicity, n (%)					
Non-Hispanic	2823 (99%)	62 (98%)	1428 (99%)	1140 (99%)	193 (100%)
Hispanic	33 (1%)	1 (2%)	18 (1%)	14 (1%)	0 (0%)
Unknown	4 (0%)	0 (0%)	3 (0%)	1 (0%)	0 (0%)
Marital status, n (%)					
Married	2259 (79%)	55 (87%)	1131 (78%)	917 (79%)	156 (81%)
Previously married[c]	409 (14%)	6 (10%)	209 (14%)	172 (15%)	22 (11%)
Never married	191 (7%)	2 (3%)	108 (7%)	66 (6%)	15 (8%)
Unknown	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)
Education, n (%)					
≤High school	423 (15%)	7 (11%)	227 (16%)	154 (13%)	35 (18%)
College	1363 (48%)	28 (44%)	678 (47%)	570 (49%)	87 (45%)
Postgraduate	1070 (37%)	28 (44%)	542 (37%)	429 (37%)	71 (37%)
Unknown	4 (0%)	0 (0%)	2 (0%)	2 (0%)	0 (0%)
Prescription, n (%)[d]					
Codeine	785 (27.4%)	14 (22.2%)	394 (27.2%)	314 (27.2%)	63 (32.6%)
Tramadol	2384 (83.4%)	55 (87.3%)	1206 (83.2%)	969 (83.9%)	154 (79.8%)
Number of ADEs					
1 ADE type	241 (8.4%)	3 (4.8%)	118 (8.1%)	103 (8.9%)	17 (8.8%)
2 ADE types	44 (1.5%)	3 (4.8%)	27 (1.9%)	11 (1.0%)	3 (1.6%)
≥3 ADE types	8 (0.3%)	0 (0.0%)	5 (0.3%)	3 (0.3%)	0 (0.0%)
Any ADE	301 (10.5%)	6 (9.5%)	155 (10.7%)	120 (10.4%)	20 (10.4%)
No ADE	2567 (89.8%)	57 (90.5%)	1299 (89.6%)	1038 (89.9%)	173 (89.6%)

[a]ADE, adverse drug event; BMI, body mass index.
[b]Others including race reported by patients as "other," mixed, or unknown.
[c]Includes widowed or divorced but currently not married.
[d]A total of 311 (10.8%) patients were prescribed of both codeine and tramadol.

Analysis

This study examined the baseline patient characteristics for the overall sample and by the 4 CYP2D6 phenotypes. Average values of patients' willingness to pay, QALYs, and payers' willingness to pay were calculated for the overall sample and by phenotypes. The timeframe for QALYs and willingness to pay was calculated by month, because the opioid can be used as postoperational pain control, which is relatively short period. *P* for trend values were calculated from ordered logistic regression, and $P < .05$ were considered statistically significant. The study results were achieved under multiple assumptions (Supplemental Table 4, available online at http://mcpiqojournal.org).

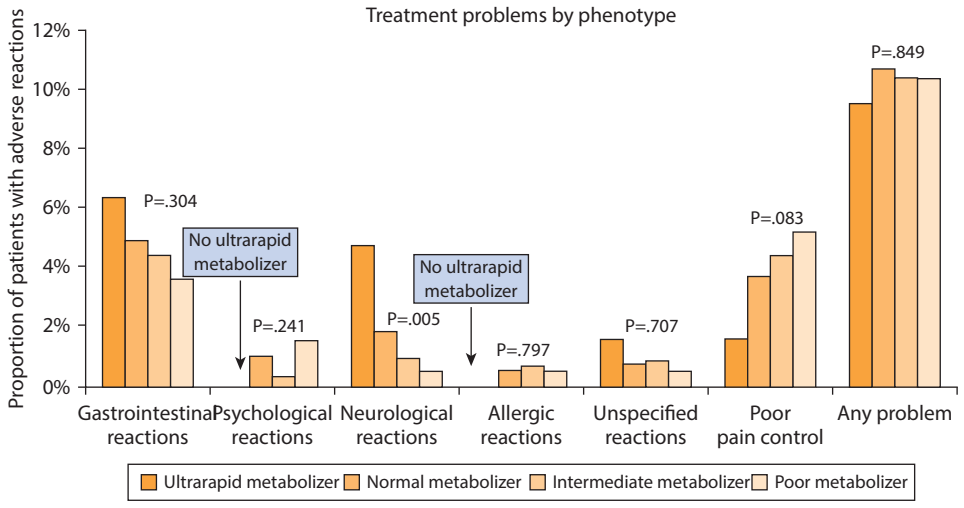

FIGURE 2. Differences in types of treatment problems (including drug adverse effects and poor pain control) due to codeine and tramadol prescriptions by CYP2D6 phenotype. *P* values were from logistic regressions of genetic groups on adverse events.

RESULTS

This study included 2877 patients with new tramadol and codeine prescriptions from January 1, 2005, to December 31, 2017. Characteristics of the study population are shown in Table. Overall, 792 patients (28%) were prescribed codeine, 2396 patients (83%) were prescribed tramadol, and 311 patients (11%) were prescribed both of the medications. Overall, 61 patients (2%) were CYP2D6 ultrarapid metabolizers, 1448 patients (50%) were normal metabolizers, 1175 patients (41%) were intermediate metabolizers, and 193 patients (7%) were poor metabolizers.

Two hundred forty-three patients (8.4%) had 1 type of ADE, 44 patients (1.5%) had 2 types, and 8 patients (0.3%) experienced 3 or more types of ADEs recorded in their medical records (Table). Type of ADE did not differ significantly by CYP2D6 phenotype, with the exception of neurologic reactions (Figure 2). Neurologic reactions were most frequent among ultra-rapid metabolizers and least frequent among poor metabolizers ($P = .006$). However, when ADEs were combined, the proportion of persons experiencing at least one ADE did not differ significantly by phenotype. Poor pain control was highest in poor metabolizers and lowest among ultrarapid metabolizers.

Figure 1 illustrates the patients' estimated willingness to pay to avoid individual treatment problems and the estimated QALYs for each problem. Bubble size represents the proportion of the study population that experienced the problem. For example, tinnitus was rare in our study population (n = 2; small bubble), but it had the highest estimated patient willingness-to-pay value ($1084 per month; Figure 1). Pain, nausea, and vomiting were more common problems (n = 117 and 79, respectively), but the corresponding estimated willingness to pay was lower ($333 and $138 per month, respectively). Pain had the highest QALY value, with an estimated loss of 0.33 QALYs owing to pain (Figure 1, right panel).

On average, patients' average willingness to pay for avoiding a problem associated with codeine or tramadol treatment was estimated at $23.16 per month (Figure 3A). The mean QALY loss owing to the treatment problems among all the patients was 0.024 QALYs (8.8 quality-adjusted days; Figure 3B). Finally, the overall estimated payers' willingness to pay was $100 per month (Figure 3C). Patients with a poor metabolizer phenotype had the

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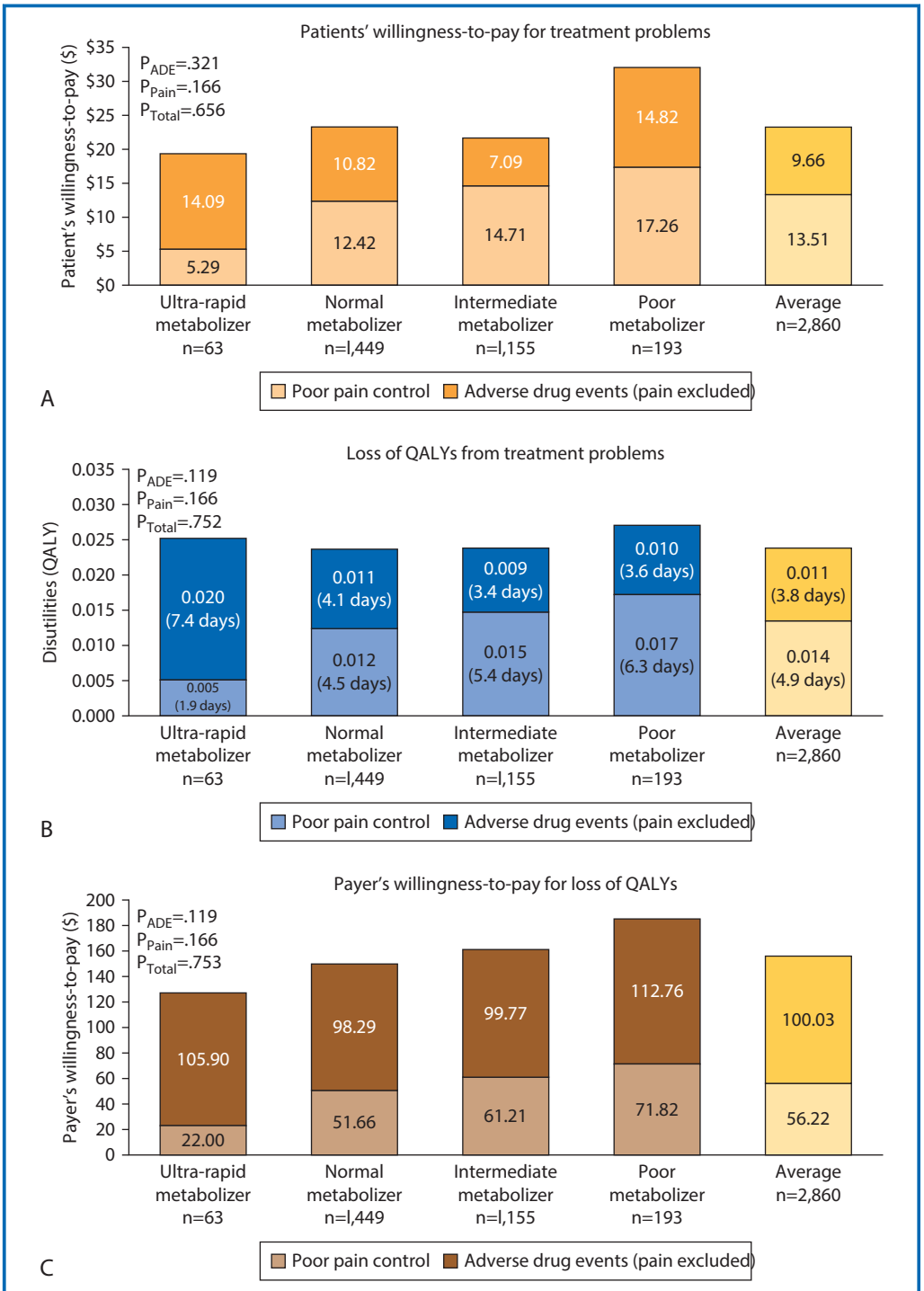

FIGURE 3. Estimated patient willingness to pay, QALYs, and payer willingness to pay overall and by CYP2D6 phenotype. (A) Estimated amount patients would be willing to pay to avoid treatment problems. (B) Estimated loss of QALYS owing to treatment problems. (C) Estimated willingness to pay from payer's perspective. *P* values are from logistic regressions of genetic groups on adverse events. ADE, adverse drug events; QALY, quality-adjusted life-years.

highest estimated willingness to pay to avoid their treatment problems ($32 per month), worst QALYs (10 quality-adjusted days), and the highest estimated payer willingness to pay ($113 per month). These results were not statistically significant (all *P* values >.05). We used the threshold of $100,000 per QALY to examine the cost-effectiveness of genetic testing. The results suggested that if the testing costs were less than $88.86 for each patient, it would be cost-effective for all the genetic groups. The testing value changed among genetic variant groups (Figure 4). We found that health care payers' willingness to pay was $75-$87 per month higher than patients' willingness to pay for each phenotype group. Figure 4 illustrates the differences in patients' willingness to pay versus payers' willingness to pay for treatment problems owing to codeine and tramadol prescriptions.

DISCUSSION

This study provided important information that the number of problems from treatment does not provide enough information in evaluating the adverse effects. When weighted by patients' values in either monetary values or QALYs, differences appeared among groups of patients with different PGx backgrounds.

Overall, estimated amounts that patients would be willing to pay to avoid treatment problems, and the estimated QALYs lost owing to these problems, were modest. However, estimated payer willingness to pay to improve QALYs was nearly 5 times greater than patient willingness to pay, suggesting the substantially large benefit that PGx information could bring to both stakeholders. Finally, patients with poor CYP2D6 metabolizer phenotypes had the highest willingness to pay and the worst QALY estimates, suggesting that this population is the most likely to benefit from PGx-directed prescribing.

The significance of this study is that we estimated the amount patients would be willing to pay to avoid specific problems, which was captured from previous studies in similar populations. This study provided information that could facilitate clinical communication on treatment outcomes, based on the theory that people use the subjective value of the treatment outcome to generate expectations for the treatment.[32] Overall, we found that patients would be willing to pay modest amounts ($23 per month) to avoid treatment problems and that the number of QALYs lost owing to codeine and tramadol were also modest (9 quality-adjusted days). These figures reflect the relatively limited proportion of persons who had treatment problem information documented in their medical records, and the fact that most effects of codeine and tramadol are relatively short term. One important reason is that only 10% of the patients in our study had documentation in their medical record indicating a treatment problem resulting from codeine or tramadol, which is consistent with other studies on tramadol and codeine.[4,6] Similar to other studies, the ADEs observed in our study could reflect the real-world nature of our study, as patients are not routinely asked about medication responses. We expect that some patients who were prescribed these medications experienced treatment problems, coped with the problems at home, and did not report problems to their health care providers. Therefore, our estimates are likely to be an underestimate of both the true proportion of persons who experienced

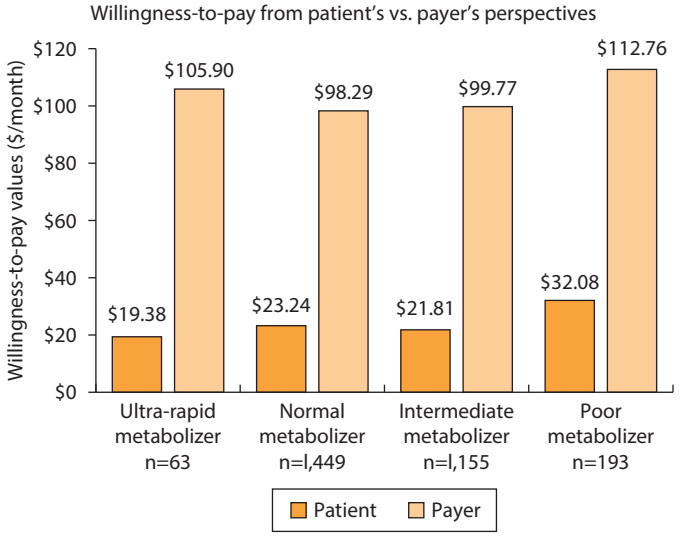

FIGURE 4. Estimated patient willingness to pay and payer willingness to pay overall and by CYP2D6 phenotype with patients' total values for opioid treatments, including all adverse symptoms and poor pain control. Payers' willingness to pay was calculated from $50,000 per QALY multiplied by the QALYs lost owing to treatment problems. All the values were converted to 2018 US dollars using the gross domestic product price deflator.

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treatment problems following codeine and tramadol use, and an underestimate of the costs of these problem. Another important phenomenon discovered by this study was that tramadol was predominantly used in clinical practice than codeine (80% vs. 20%), and the problem profiles were similar to what developed from tramadol use (Supplemental Figure 2, available online at http://mcpiqojournal.org).

We also found that persons with poor metabolizer CYP2D6 phenotypes had the highest estimated values of willingness to pay owing to codeine and tramadol. For example, the average estimated willingness to pay for a poor metabolizer to avoid a treatment problem was $32 per month compared with an estimated $19 per month for an ultrarapid metabolizer. We also found that treatment problems can decrease patients' health-related quality of life by approximately 8-10 days during 1 healthy year. If these could be avoided, poor metabolizers would receive the biggest benefit (gaining 9.9 healthy days) compared with normal metabolizer patients (gaining 8.6 healthy days). We also compared this benefit to health care payers' willingness to pay and found that the threshold was $113 per month for poor metabolizer patients and $98 per month for normal metabolizer patients, which suggests that the costs below this threshold would be cost-effective from the health care payers' perspective. In summary, although cost differences among metabolizer phenotypes were not statistically significant, our results suggest that poor metabolizer patients could benefit more from PGx-guided prescribing compared with normal metabolizers.

Strengths of our study include our adoption of innovative methods of conducting cost-effectiveness analysis by assigning each problem value captured from a literature review. This method is advantageous because it can increase study generalizability to inform decision making in a wide range of the population.[33] The values assigned to treatment problems were previously reported by patient populations who actually developed the symptoms, and were from the US patients' perspective. Therefore, these values theoretically provide a practical and accurate view of the treatment experience and treatment burden following opioid prescriptions in the United States.

An additional strength of our study included our examination of willingness to pay from both patients' and payers' perspectives. We followed the recommendation from the Second Panel on Cost-effectiveness in Health and Medicine that more studies are needed to investigate the health care costs from societal, patient's and payer's perspectives.[34] In comparing both perspectives, we are able to identify potential benefits that PGx information would bring to both of the stakeholders. In particular, the health care payers had 5-fold higher willingness to pay than patients did; therefore, avoiding ADEs could potentially bring a much greater benefit from health care payers' perspective than from patients' perspective. However, we suggest that PGx implementation needs to be evaluated at both levels separately. In addition, we note that the health care payers' willingness-to-pay threshold used in this study ($50,000 per QALY) was relatively low compared with the threshold of $100,000 per QALY that has been used recently in other cost-effectiveness analyses in developed countries.[31] Therefore, the differences between patients perceived value of care and payers' willingness to pay may be underestimated.

Our study results were limited by the scarce results from the current literature. We adopted the best possible evidence from the available literature, but some values could still be an underestimation or overestimation of true costs. For example, the value we assigned to tinnitus was $1085 per month. This value was adopted from a survey study in which the patient population was self-registered for a "Tinnitus Update" email listserv. Therefore, the responders could be patients with relatively severe tinnitus that impaired their social functions, who tend to look for more treatment information.[35] Although we adopted the values reported from patients with the mildest tinnitus level, and only 2 of the patients in our population reported tinnitus in our study, this value of tinnitus could overestimate the average patient's experience of tinnitus, and it might overestimate the average treatment value for tinnitus.

This study is also limited by the treatment problems captured through medical record

review. As such, the problem needed to be shared with the health care provider and documented in the medical record. We therefore expect that our capture of treatment problems is likely an underestimate of the true number of problems that occur in patients after using tramadol or codeine. Fewer outcomes results in more limited power and a reduced ability to detect associations should they actually exist. Our results are therefore conservative, and we might have missed weaker associations. We also note that the patient is the best source of information for treatment problems, and future studies that collect treatment problem information at the time of treatment are needed to obtain complete information. Despite these limitations, we note that when compared with other studies of tramadol and codeine, our ADE rates are comparable. For example, the study by Nossol et al[6] found that patients received tramadol developed nausea (3.4%), dizziness (1.5%), and vomiting (1.1%).

Finally, we conducted multiple tests of association, and considering associations as significant at $P < .05$ may be too permissive; however, P values are completely dependent on sample size, and they should be used only as a guide to highlight potentially interesting patterns.

CONCLUSION

We estimated willingness to pay related to treatment problems resulting from treatment with codeine and tramadol from both the patient and the payer perspective. Although overall costs were modest, we found that patients with a poor metabolizer CYP2D6 phenotype are likely to benefit most from PGx-guided prescribing designed to reduce treatment problems resulting from these prescription medications.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ADE** = adverse drug event; **CYP2D6** = Cytochrome P450 2D6; **PGx** = pharmacogenomics; **QALY** = quality-adjusted life year; **RIGHT** = Right Drug; **Right Dose** = Right Time-Using Genomic Data to Individualize Treatment; **REP** = Rochester Epidemiology Project

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Potential Competing Interests: Drs. Wang and Weinshilboum are cofounders and stockholders of OneOme, LLC, a pharmacogenomic decision support company.

All authors made substantial contributions to this study. Y.Z. and J.L.S. conceptualized and designed the study; Y.Z. performed the analysis, and drafted the manuscript; Y.Z., G.S.L., and J.L.S. finalized the results, interpretation of the data and the first draft of the manuscript; S.J.B., B.J.B., N.B.L., A.M.M., J.E.O., L.W., and R.W. provided critical comments for significant intellectual content; J.L.S. provided acquisition, supervision and funding support for this study, and acts as the study guarantor. All authors read and approved the manuscript for publication.

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