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Original Article

A service improvement project to review prescribing information provided by general practitioners for new referrals to a UK National Health Service hospital pain clinic: potential implications of CYP2D6 enzyme inhibition

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Abstract

Introduction: Chronic pain is often managed using co-prescription of analgesics and adjuvants, with concomitant medication prescribed for comorbidities. Patients may have suboptimal response to some analgesics or be at risk of drug interactions or adverse drug reactions (ADRs) due to polypharmacy affecting CYP2D6 enzyme activity. The aim of the service improvement project was to determine the proportion of patients referred to a specialist pain service in the UK National Health Service (NHS) by general practitioners (GPs) who may be at risk of suboptimal analgesic response or ADRs due to CYP2D6 inhibition through polypharmacy. This was achieved by reviewing clinical prescribing information provided by GPs at time of referral. It was hoped that the findings could be used to aid clinical and prescribing decisions without conducting CYP2D6 genotyping or phenotyping.

Methods: A review of letters from 250 patients referred to an NHS hospital pain service from GPs over a 3-month period was undertaken. Information about current and concomitant medications was analysed to identify the potential for CYP2D6 inhibition and adverse events.

Results: Letters failed to provide information about current pain medication for 20 (8%) patients or non-pain concomitant medication for 54 (21.6%) patients. Of 176 patients, 52 (29.5%) patients with information about non-pain concomitant medication had been prescribed at least one known CYP2D6 inhibitor. A total of 35 (19.9%) patients were identified as being at risk of an adverse drug reaction and 33 (18.75%) patients at risk of suboptimal analgesic response due to co-administration of CYP2D6 inhibitors.

Conclusion: The review revealed the need for improved detail in GP referral letters used to transfer care to UK NHS hospital pain clinics. There is a need to consider an individual's CYP2D6 phenotype when prescribing analgesic prodrugs to manage persistent pain. Caution is needed when patients are co-prescribed codeine or tramadol with selective serotonin reuptake inhibitors (SSRIs).

Keywords

Pain management, analgesic drugs, general practitioner, CYP2D6, polypharmacy

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Introduction

Chronic pain is a complex condition affecting one in five adults with increasing prevalence through the lifespan.^{1–3} Comorbidities include diabetes, hypertension and cardiovascular disease.⁴ Management is difficult, and patients are often prescribed a variety of analgesics and also drugs not typically prescribed as analgesics but which are beneficial in pain management (i.e. pain adjuvants such as tricyclic antidepressants (TCA)).^{4–6} A trial and error approach is often used when prescribing. Inadequate pain relief can lead to sequelae such as depression, poor mobility and insomnia which may result in referral to a specialist secondary care pain service.^{4,7,8}

Achieving a pain treatment plan during general practitioner (GP) consultations is challenging because of time constraints.⁹ GPs need to assess how individuals respond to drugs. Polymorphic variations of genes affect the fate of many drugs, and this needs to be considered to optimise therapeutic drug response. Cytochrome P450 enzymes are responsible for the biotransformation of many drugs and cause variability in drug pharmacokinetics and response. There are 17 cytochrome P450 families in man that are encoded by 57 functional genes. Six cytochrome P450 enzymes have important roles in drug metabolism CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP2E1 and CYP3A4. It is estimated that the metabolism of 25–30% of prescribed drugs requires CYP2D6. The *CYP2D6* gene has polymorphic variability with over 100 known allelic variants resulting in four CYP2D6 phenotypic groups: poor metaboliser (PM) with no CYP2D6 activity, intermediate metaboliser (IM) with reduced activity, extensive metaboliser (EM) with normal activity and ultra-rapid metabolisers (UM) with greater than normal activity.¹⁰

The CYP2D6 enzyme is involved in the metabolism of analgesic prodrugs such as codeine and tramadol that are reliant on the activity of CYP2D6 for conversion to the active form. Individuals who are genetically PM, IM and UM phenotypes may experience suboptimal analgesic response due to low plasma concentrations of active metabolites. They may also experience adverse drug reactions (ADRs) to higher than expected plasma concentrations of the unmetabolised drug. Combining analgesic prodrugs reliant on CYP2D6 with pain adjuvants or non-pain concomitant medication that also induce CYP2D6 activity may cause toxicity due to elevated levels of the active form of the prodrug. Inhibition of CYP2D6 through co-prescribed pain adjuvants and non-pain medication can reduce CYP2D6 activity by 50–100%.¹¹ A strong CYP2D6 inhibitor would reduce an EM phenotype to a PM phenotype, and a moderate/weak CYP2D6 inhibitor

would reduce to an IM/EM phenotype. In both cases, suboptimal analgesic response and ADRs could occur if the individual was co-prescribed codeine or tramadol for persistent pain.

A 6-year study of 65,526 hospitalised patients found that one in five patients was co-prescribed a CYP2D6 inhibitor with the potential to prevent prodrug activation.¹² The aim of the service improvement project was to determine the proportion of patients referred to a specialist pain service in the UK National Health Service (NHS) by GPs who may be at risk of suboptimal analgesic response or ADRs due to CYP2D6 inhibition through polypharmacy. This was achieved by reviewing clinical prescribing information provided by GPs at time of referral. It was hoped that the findings could be used to aid clinical and prescribing decisions without conducting CYP2D6 genotyping or phenotyping.

Methods

A service improvement project was undertaken at the pain service of a large NHS teaching hospital at a major city in the United Kingdom (Leeds). A protocol was designed by the authors and peer reviewed by members of the pain service team which resulted in only minor typographical changes. The protocol was reviewed by the Leeds Teaching Hospitals NHS Trust Research and Innovation Research Governance Manager who confirmed it was not research and requested it to be recorded on the NHS Trust's Clinical Audit Database. The project involved reviewing GP referral letters for specialist pain management that were received by the pain service from 1 January 2013 to 31 March 2013. Referrals from other sources such as NHS consultants were excluded.

A data extraction sheet was devised and piloted using 10 GP referral letters with only minor amendments made to the design. The final data extraction sheet documented current pharmacological treatment prescribed by the GP at the time of referral and previous pharmacological treatment for the current episode of pain including analgesics, pain adjuvants and non-pain concomitant medication. Data extraction was performed by the principal investigator (H.R.), two pain research nurses and a clinical trial administrator. Data were transferred to a dedicated database by the clinical trials administrator and crossed checked for accuracy by a research nurse.

The characteristics of clinical prescribing information provided by the GP were assessed for completeness including current and recent analgesic prescription, pain adjuvants and non-pain concomitant medications. Information about non-drug pain management was not extracted. Drugs prescribed for each patient were categorised according to their pharmaceutical class as

Table 1. Drugs that are known to be CYP2D6 inhibitors that were used for identification of potential drug interactions in this review.

Strong CYP2D6 inhibitors ≥ 5 -fold increase in area under the curve or $>80\%$ decrease in clearance	Moderate CYP2D6 inhibitors ≥ 2 but <5 -fold increase in area under the curve or 50–80% decrease in clearance	Weak CYP2D6 inhibitors ≥ 1.25 but <2 -fold increase in area under the curve or 20–50% decrease in clearance	Known CYP2D6 inhibitors (classified as weak for the purpose of this audit)		
Bupropion ^{19–22} Fluoxetine ^{19–22} Paroxetine ^{19–22} Quinidine ^{19–22} Cinacalcet ²¹	Duloxetine ^{19,21,22} Cinacalcet ^{19,20} Terbinafine ^{19,22} Sertraline ²¹	Amiodarone ^{19,21,22} Celecoxib ^{19,21} Cimetidine ^{19,22} Desvenlafaxine ¹⁹ Diltiazem ¹⁹ Diphenhydramine ^{19,21,22} Echinacea ¹⁹ Escitalopram ^{19,21} Febuxostat ¹⁹ Gefitinib ¹⁹	Hydralazine ¹⁹ Hydroxychloroquine ¹⁹ Imatinib ¹⁹ Methadone ^{19,21} Oral Contraceptives ¹⁹ Propafenone ^{19,22} Ranitidine ^{19,21} Ritonavir ^{19,21,22} Sertraline ^{19,22} Telithromycin ¹⁹ Verapamil ¹⁹	Chlorpheniramine ²¹ Clomipramine ²¹ Chlorpromazine ²¹ Citalopram ²¹ Clemastine ²¹ Cocaine ²¹ Dextropropoxyphene ²² Doxepin ²¹ Doxorubicin ²¹ Halofantrine ²¹ Histamine H1 antagonist ²¹ Hydroxyzine ²¹ Levomopromazine ²¹	Metoclopramide ²¹ Mibefradil ²¹ Midodrine ²¹ Moclobemide ²¹ Perphenazine ²¹ Reduced haloperidol ²¹ SSRIs ²² Ticlopidine ²¹ Triptelenamine ²¹ Valdecoxib ²²

FDA: Food and Drug Administration; MHRA: Medicines and Healthcare Products Regulatory Agency.

The list was compiled using information from the following sources: FDA,¹⁹ MHRA,²⁰ Flockhart,²¹ Baxter.²²

defined by the British National Formulary (BNF)¹³ and the British Pain Society Opioid Guidelines.¹⁴ Analgesic drugs reliant on CYP2D6 activity to obtain analgesic efficacy were identified using prescribing guidelines for CYP2D6 phenotypes produced by the Clinical Pharmacogenetics Implementation Consortium^{15,16} and the Dutch Pharmacogenetics Working Group.^{15,17} Analgesic drugs that were identified were codeine (including codeine combinations such as co-codamol), tramadol and oxycodone, although there is an ongoing debate whether CYP2D6 phenotype for oxycodone affects analgesia or toxicity.¹⁸

Descriptive statistics were used to analyse the type and number of analgesics and pain adjuvants across the patient data set. The completeness of prescribing information was presented as ‘missing information’ from the referral letter. Prescribed analgesics, pain adjuvants and non-pain concomitant medications were categorised according to a list of CYP2D6 inhibitors and their strength of inhibition (i.e. strong, moderate and weak) compiled by the investigating team from information provided by the US Food and Drug Administration (FDA)¹⁹ and the UK Medicines and Healthcare Products Regulatory Agency (MHRA)²⁰ (Table 1). Drugs were categorised as weak inhibitors if they were named in the literature by Flockhart²¹ and Baxter²² as CYP2D6 inhibitors, but the extent of inhibition had not been confirmed by the FDA or the MHRA (Table 1). There were no inducers categorised by the FDA or MHRA, although Flockhart²¹ identified two inducers (rifampin and dexamethasone). The potential for drug interactions between analgesic prodrugs reliant on CYP2D6, and pain adjuvants or non-analgesic concomitant medications that inhibit or

induce CYP2D6 activity was inferred by matching the prescription of each patient against the list of inhibitors and inducers.

There was no information about the patients’ CYP2D6 genotype or phenotype. Therefore, it was not possible to infer the extent of suboptimal analgesic response or ADRs from GP prescribing of analgesic prodrugs reliant on CYP2D6 or from pain adjuvants or non-pain concomitant medications that inhibit or induce CYP2D6 activity either alone or in combination. Nevertheless, the magnitude of reduction of CYP2D6 activity for each inhibitor could be estimated using the CYP2D6 inhibition formulary by Borges et al.¹¹ Thus, strong inhibitors were classified as having 100% reduction of CYP2D6 activity and moderate or weak inhibitors classified as having 50% reduction of CYP2D6 activity. This information was used to explore the magnitude of potential drug interactions. Clinical implications of drug interactions were assembled using prescribing guidelines for CYP2D6 phenotypes produced by Clinical Pharmacogenetics Implementation Consortium^{15,16} and the Dutch Pharmacogenetics Working Group.^{15,17}

Results

There were 260 patient referrals over the 3-month period (Figure 1). Ten referrals were not from the patient’s GP and were excluded from the analysis. The referral letters of 20 of the 250 patients (8%) did not include information about current pain medication and could not be used in subsequent analyses. Information about current pain medication was available for 230 patients (127 females (55.2%) and 103

Figure 1. Flow of data gathered from general practitioner (GP) referral letters.

males (44.8%). There was no information about analgesics and pain adjuvants that had been tried previously for 111 (48.3%) of the 230 patients and no information about non-pain concomitant medication for 54 (23.5%) of patients.

Analysis of prescribed analgesics and adjuvants

There were 532 GP prescriptions of 40 different analgesic drugs or pain adjuvant drugs for current medication (Table 2). The most frequently prescribed class of drugs was non-opioid analgesics (i.e. paracetamol and nonsteroidal anti-inflammatory drugs (NSAID) = 150/532 (28.2%) prescriptions to 150/230 (65.2%) of patients) followed by strong opioids (134/532 (25.1%) prescriptions to 134/230 (58.3%) of patients) and weak opioids (86/532 (16.1%) prescriptions to 86/230 (37.4%) of patients). The most common analgesic drug prescribed was paracetamol (81/532 (15.2%) prescriptions to 81/230 (35.2%) of patients) followed by tramadol (58/532 (10.9%) prescriptions to 58/230 (25.2%) of patients) and co-codamol (56/532 (10.5%) prescriptions to 56/230 (24.3%) of patients). Pain adjuvant drugs were readily prescribed with similar numbers of prescriptions for TCA (64/532 (12.0%) prescriptions to 64/230 (27.8%) of patients) and anticonvulsants (78/532 (14.6%) prescriptions to 78/230 (33.9%) of patients). The most frequently prescribed TCA was amitriptyline (59/532 (11%) prescriptions to 59/230 (25.65%) of patients) and the most frequently prescribed anticonvulsant was gabapentin (39/532 (7.3%) prescriptions to 39/230

(17.0%) of patients) and pregabalin (38/532 (7.1%) prescriptions to 38/230 (16.5%) of patients).

A total of 135 referrals (58.7%) had been prescribed at least one analgesic that was reliant on CYP2D6 to obtain analgesic efficacy. Only 22 (9.6%) patients had been prescribed a single analgesic drug without any other medication (i.e. on its own without a pain adjuvant or a non-pain concomitant drug). Of these patients, 10 had been prescribed a strong opioid, 1 a weak opioid, 3 a non-opioid and 8 a pain adjuvant. Three patients had been prescribed an analgesic drug reliant on CYP2D6 without a non-pain concomitant drug, and the analgesic efficacy for these three patients would be solely dependent on their phenotype (which was not known).

In all, 208 (90.4%) patients had been prescribed more than one drug (i.e. any combination of analgesic, pain adjuvant and non-pain medication). The most common prescription was two drugs from a combination of analgesic and/or pain adjuvant (80 (34.8%) patients). Two patients (0.9%) had been prescribed seven analgesic and/or adjuvant drugs (Table 3, Figure 1). A total of 167 (72.6%) patients had been prescribed more than one pain medication (i.e. any combination of analgesic and/or pain adjuvant).

Analysis of potential CYP2D6 inhibition by polypharmacy

Information about non-pain concomitant medication was available for 176 patients and was used in the subsequent analyses. No patients had been prescribed a CYP2D6 inducer (i.e. rifampin or dexamethasone). Of

Table 2. Analgesics, pain adjuvants and concomitant medication identified from referral letters from general practitioners with associated CYP2D6 inhibitor strength and risk of drug interactions (DIs) and adverse drug reactions (ADRs).

Drug	Analgesic efficacy dependent on CYP2D6	Strength of CYP2D6 inhibition	Risk of DIs and ADRs due to CYP2D6 inhibition	Current medication (no. of prescriptions)
Opioid analgesics				
Strong opioids				134
• Morphine		N/A		28
• Transdermal buprenorphine (Butrans)		N/A		10
• Transdermal buprenorphine (Transtec)		N/A		13
• Fentanyl		N/A		13
• Tramadol	Y	N/A	Y	58
• Oxycodone	Y	N/A	Y	12
Weak opioids				86
• Co-codamol	Y	N/A	Y	56
• Codeine	Y	N/A	Y	9
• DF118		N/A		17
• Co-dydramol		N/A		2
• Co-proxamol		Weak ^b		2
Non-opioid analgesics				
Paracetamol				81
Nonsteroidal anti-inflammatory				69
• Diclofenac		N/A		23
• Ibuprofen		N/A		15
• Naproxen		N/A		16
• Piroxicam		N/A		4
• Meloxicam		N/A		4
• Celecoxib		Weak ^a		3
• Etoricoxib		N/A		2
• Ketoprofen		N/A		2
Pain adjuvants				
TCA				64
• Amitriptyline		N/A	Y	59
• Nortriptyline		N/A	Y	3
• Trazodone		N/A		2
Anticonvulsants				78
• Pregabalin		N/A		38
• Gabapentin		N/A		39
• Carbamazepine				1
Other				20
• Tizanidine (muscle relaxant)		N/A		1
• Duloxetine		Moderate ^a		6
• Ketamine		N/A		1
• Baclofen		N/A		4
• Lidocaine patch		N/A		4
• Capsaicin cream		N/A		3
• Methocarbamol		N/A		1
Concomitant medication				
• Fluoxetine		Strong ^a		6
• Paroxetine		Strong ^a		3
• Sertraline		Moderate ^b /weak ^a		7
• Citalopram		Weak ^b		9
• Oral contraceptives		Weak ^a		4
• Ranitidine		Weak ^b		5
• Diltiazem		Weak ^a		6
• Metoclopramide		Weak ^b		3
• Terbinafine		Moderate ^a		2
• Escitalopram		Moderate ^a		1
• Hydroxychloroquine		Weak ^a		1
• Clomipramine		Weak ^b		1
• Tamoxifen		N/A		1
• Aripiprazole		N/A	Y	1

Note: a= confirmed by FDA/MHRA, b= confirmed through the literature. Y=Yes.

Table 3. Number of prescriptions of analgesic and pain adjuvant drugs from the 230 referrals that had information about current pain medication.

Number of prescriptions per patient	One	Two	Three	Four	Five	Six	Seven
Number of patients (% of n=230)	63 (27.4%)	79 (34.3%)	54 (23.5%)	27 (11.7%)	3 (1.3%)	2 (0.9%)	2 (0.9%)
Number of prescriptions	63	158	162	108	15	12	14
Number of opioid prescriptions							
Strong opioids	20 (31.7%)	37 (23.4%)	38 (23.5%)	29 (26.8%)	1 (6.7%)	4 (33.3%)	5 (35.7%)
Weak opioids	13 (20.6%)	27 (17.0%)	27 (16.7%)	15 (13.9%)	3 (20.0%)	1 (8.3%)	0 (0%)
Number of non-opioid prescriptions							
Paracetamol	4 (6.3%)	25 (15.8%)	26 (16.0%)	21 (19.4%)	1 (6.7%)	2 (16.7%)	2 (14.3%)
Nonsteroidal anti-inflammatory	8 (12.7%)	24 (15.1%)	21 (13.0%)	10 (9.3%)	4 (26.6%)	1 (8.3%)	2 (14.3%)
Number of pain adjuvant prescriptions							
Tricyclic antidepressant	8 (12.7%)	14 (8.9%)	26 (16.0%)	10 (9.3%)	3 (20.0%)	2 (16.7%)	1 (7.1%)
Anticonvulsant	9 (14.4%)	26 (16.6%)	21 (13.0%)	15 (13.9%)	3 (20.0%)	2 (16.7%)	2 (14.3%)
Other	1 (1.6%)	5 (3.2%)	3 (1.8%)	8 (7.4%)	0 (0%)	0 (0%)	2 (14.3%)

Unless otherwise stated, percentages represent number of prescriptions (numerator) compared with the total number of prescriptions per column (number of prescriptions for each patient (denominator)).

Figure 2. Analysis of CYP2D6 inhibition from information provided in 176 GP referral letters. DIs: drug interactions; ADRs: adverse drug reactions; SSRIs: selective serotonin reuptake inhibitors.

these 176 patients, 52 (29.5%) had been prescribed at least one known CYP2D6 inhibitor (Figure 2). Of the 176 patients, 9 (5.1%) had been prescribed a strong

inhibitor that would produce complete inhibition of CYP2D6 and 43 (24.4%) had been prescribed an inhibitor that would reduce CYP2D6 activity by 50%

Figure 3. Potential clinically significant adverse drug reactions due to CYP2D6 inhibition. ADRs: adverse drug reactions; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants.

(moderate inhibitor $n=8$, weak inhibitor $n=35$). Four (2.3%) patients had been prescribed two or more inhibitors concurrently (i.e. strong+weak; moderate+weak; weak+weak; weak+weak+weak+weak). Seven (4.0%) patients had been prescribed at least one analgesic that was reliant on CYP2D6 in combination with at least one pain adjuvant that had the potential to inhibit CYP2D6 activity. Two (1.1%) patients had been prescribed tramadol and codeine (both reliant on CYP2D6 activity) with duloxetine which is a pain adjuvant known to inhibit CYP2D6. A total of 26 (14.8%) patients had been prescribed at least one analgesic that was reliant on CYP2D6 in combination with at least one non-pain concomitant drug that had the potential to inhibit CYP2D6. There were no patients that had been prescribed an analgesic drug reliant on CYP2D6 combined with both pain adjuvants and non-pain concomitant drugs with the potential to inhibit CYP2D6 activity.

Of the 176 patients, 35 (19.9%) were identified at risk of clinically significant drug interactions (Figure 3) and 33 patients (18.75%) were identified at risk of suboptimal analgesic response due to co-administration of CYP2D6 inhibitors. Patients 'at risk' may include an unknown number of UMs where suboptimal response would not occur if co-prescribed a moderate/weak CYP2D6 inhibitor. Two patients (1.1%) were at risk of ADRs from toxicity of high levels of aripiprazole (antipsychotic) and clomipramine (TCA) due to lack of elimination by CYP2D6.²³ Published prescribing guidelines for aripiprazole and clomipramine recommend reducing the standard dose by up

to 67% in PMs to prevent ADRs.^{15,16} A total of 17 (9.7%) patients were at risk of moderate-to-weak CYP2D6 inhibition from non-selective serotonin reuptake inhibitors (SSRIs) such as duloxetine (pain adjuvant), diltiazem (antihypertensive) and oral contraceptives that cause up to a 50% reduction in CYP2D6 activity. Four patients (2.3%) were at risk of ADRs from higher than expected plasma concentrations of amitriptyline which is eliminated via metabolism catalysed by CYP2D6. One patient was potentially at risk of breast cancer relapse due to CYP2D6 inhibition and lack of biotransformation of the anti-oestrogen prodrug tamoxifen.^{11,15,17,20} A total of 16 patients (9.1%) were at risk of drug interactions due to co-prescription with selective SSRIs. Seven (4%) were prescribed fluoxetine or paroxetine which are strong CYP2D6 inhibitors producing complete inhibition in CYP2D6 activity. A further seven patients (4%) were prescribed sertraline or citalopram which are moderate/weak CYP2D6 inhibitors producing 50% reduction in CYP2D6 activity. Examples of prescribing resulting in limited analgesic efficacy and/or risk of ADRs included the following:

- Co-codamol + strong CYP2D6 inhibitor with no other analgesia prescribed ($n=1$): no pain relief;
- Tramadol + moderate or weak CYP2D6 inhibitor with no other analgesia prescribed ($n=3$): at risk of limited pain relief;
- Co-codamol + tramadol + moderate or weak CYP2D6 inhibitor with no other analgesia prescribed ($n=1$): at risk of limited pain relief;

- Co-codamol + strong SSRI CYP2D6 inhibitor + other analgesics (n=4): at risk of limited pain relief;
- Tramadol + strong or moderate SSRI CYP2D6 inhibitor (n=11): at risk of serotonin syndrome.

Some patients were prescribed nortriptyline, but none of them were co-prescribed CYP2D6 inhibitors.

Discussion

Statement of principal findings

This review of 230 patient referrals by GPs to an NHS hospital pain clinic over the 3-month period found that 40 different analgesics or pain adjuvants were prescribed reflecting a population of patients refractive to treatment and requiring specialist pain management. In all, 58.7% of patients had been prescribed at least one analgesic that was reliant on CYP2D6 to obtain analgesic efficacy, and over 90% of these patients had been prescribed more than one drug. Co-administration of at least one CYP2D6 inhibitor was identified in 29.5% of the 176 patients where referral letters had sufficient information. There was a risk of a drug interaction resulting in an adverse drug reaction for 19.9% of these patients and a suboptimal analgesic response for 18.75% of patients. Interestingly, referral letters contained no information about current pain medication for 8% of patients. No information about non-pain concomitant medication was provided for 23.5% of patients where current pain medication was known.

Meaning of the study and implications for clinicians

Prescriptions for codeine, co-codamol and tramadol have risen over the last decade. It has been estimated that up to 25% of the Caucasian population are PMs or IMs with no or reduced CYP2D6 activity and at risk of suboptimal analgesic response. The prevalence of UMs in Caucasian populations is estimated to be 3–5% with a high risk of ADRs from toxicity.^{24,25} However, the patient's CYP2D6 phenotype is not available to most GPs at the point of prescribing. Polypharmacy confounds the problem, and our finding that over half of patients had been prescribed at least one analgesic reliant on CYP2D6 is of concern as we estimated that the potential risk of clinically significant drug interactions to be 19.9% of patients and suboptimal analgesia in 18.7% of patients.

The risk of ADRs resulting from co-prescription of SSRIs, predominantly sertraline, citalopram and fluoxetine, was of particular concern with 6.25% of patients at risk of serotonin syndrome. GPs need to be aware

that the risk of serotonin syndrome increases with the co-prescription of SSRIs with tramadol and fentanyl. There was also risk of toxicity from amitriptyline, aripiprazole and clomipramine, and a risk of suboptimal response to the CYP2D6 prodrug tamoxifen. There remains an ongoing debate as to whether CYP2D6 activity is crucial to tamoxifen metabolism and breast cancer relapse.^{20,26,27} When cases of CYP2D6 inhibition through polypharmacy or genetic polymorphisms present at clinic, drug doses should be lowered in line with prescribing guidelines to reduce the potential for ADRs.^{15–17} The risk of drug interactions and ADRs from CYP2D6 induction is generally low as dexamethasone and rifampin are the only drugs with potential for induction.^{21,28} Neither had been prescribed in our sample population.

The review demonstrates that GPs should be diligent when co-prescribing drugs dependent on CYP2D6 activity. It also revealed the need for improved detail in referral letters in line with new national standards when care is transferred across the 'care boundaries' of primary to secondary care.^{29–31} Poor communication of medication history and prescribing not carefully thought through is costly to patient well-being and the NHS.^{12,32–36}

Implementation of improvements to service

GP referrals that were identified at risk of suboptimal analgesic response and/or ADRs through inhibition of CYP2D6 from polypharmacy were notified to the consultant pain specialist for review. The pain consultant conveyed the findings of the initial clinical assessment in the pain clinic to the GP with an appropriate treatment plan (e.g. change analgesic, change in non-pain concomitant medication or other clinically relevant action). The patient was followed up in the pain clinic as per standard care. In addition, the service has been improved, so that the consultant pain specialist reviewing the patient undertakes a medication review for CYP2D6 inhibition at the clinic visit to identify individuals who are at risk of their phenotype changing because they are prescribed a CYP2D6 substrate in combination with a CYP2D6 inhibitory drug (i.e. phenocopying). For example, an EM may appear to be an IM or a PM due to CYP2D6 inhibition by the confounding drug. The use of online tools such as SuperCYP (<http://bioinformatics.charite.de/supercyp/>) can aid identification of inhibition of CYP enzymes from polypharmacy. Our findings suggest that GPs prescribing codeine and tramadol may lack knowledge about the impact of CYP2D6 polymorphisms on patient care, suggesting a need for continuing professional development on CYP2D6 and pain pharmacology.

Limitations of the project

It was necessary to exclude 23.5% patients from the analysis of CYP2D6 inhibition as no information was provided on co-prescribed medication. The review was limited to clinical prescribing information provided by the GP at the time of referral and did not gather information about prescribing rationale, including drug titration. Referral letters did not contain specific information about supplementary 'over the counter' medication, dietary intake and herbal supplements that had the potential to inhibit CYP2D6. It is important that prescribers undertake a complete medication review, so that patients disclose this information and it is disclosed in referral letters.

Future research

Prescribers may engage more fully with CYP2D6 prescribing guidelines if CYP2D6 screening could be conducted in a reliable, easily executed and cost effective manner. As CYP2D6 genotyping is not readily available in the NHS, the ability to infer an individual's phenotype at the point of care would be a valuable tool for healthcare professionals. There is a need to develop a cost-effective method of inferring phenotype that is easily utilised in a clinical setting, and therefore, we have undertaken a follow-up study investigating the prevalence, genetic profile and phenotype frequencies of participants with persistent pain who do not respond to oral codeine.

In conclusion, prescribers need to be aware of the potential impact of polymorphic variability of the CYP2D6 gene on the analgesic response to common analgesics such as codeine and tramadol. To reduce the incidence of serious drug interactions and ADRs such as serotonin syndrome, prescribers also need to be aware the risk of inhibition of CYP2D6 from polypharmacy, especially when patients are co-prescribed tramadol. It is critical that GP referral letters contain sufficient detail about current and past medication to guide pain practitioners in future decisions about treatment.

Take home message. Referring a patient to a specialist pain service is a crucial point in their management. Many GP referral letters did not provide sufficient detail about current and past medication to aid specialist pain clinicians. This project demonstrated the potential impact of CYP2D6 inhibition in patients referred for specialist pain management. Analysis of prescribing information in referral letters found a potential suboptimal analgesia and adverse events due to polypharmacy causing inhibition of the CYP2D6 enzyme. Clinicians need to be more aware of the impact of CYP2D6 inhibition on response to analgesics.

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References

1. Elzahaf RA, Tashani OA, Unsworth BA, et al. The prevalence of chronic pain with an analysis of countries with a Human Development Index less than 0.9: a systematic review without meta-analysis. *Curr Med Res Opin* 2012; 28(7): 1221–1229.
2. Bras M, Loncar Z and Fingler M. The relief of pain as a human right. *Psychiatr Danub* 2006; 18(1–2): 108–110.
3. Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006; 10(4): 287–333.
4. Fine PG. Long-term consequences of chronic pain: mounting evidence for pain as a neurological disease and parallels with other chronic disease states. *Pain Med* 2011; 12(7): 996–1004.
5. Smith HS. Opioid metabolism. *Mayo Clin Proc* 2009; 84(7): 613–624.
6. Singh A. Pharmacogenomics-the potential of genetically guided prescribing. *Aust Fam Physician* 2007; 36(10): 820–824.
7. Dysvik E, Natvig GK, Eikeland OJ, et al. Coping with chronic pain. *Int J Nurs Stud* 2005; 42(3): 297–305.
8. Jensen MP, Turner JA, Romano JM, et al. Coping with chronic pain: a critical review of the literature. *Pain* 1991; 47(3): 249–283.
9. Health & Social Care Information (HSCi). *GP workload survey report*. London: HSCiC, 2007, <http://www.hscic.gov.uk/article/2021/Website-search?productid=713&q=GP+workload+survey&sort=Relevance&size=10&page=1&area=both#top> (accessed 13 October 2013).
10. CYP2D6 allele nomenclature, 2013, <http://www.cypalleles.ki.se/cyp2d6.htm> (accessed 18 October 2013).
11. Borges S, Desta Z, Jin Y, et al. Composite functional genetic and comedication CYP2D6 activity score in predicting tamoxifen drug exposure among breast cancer patients. *J Clin Pharm* 2010; 50(4): 450–458.
12. Tirkkonen T and Laine K. Drug interactions with the potential to prevent prodrug activation as a common

- source of irrational prescribing in hospital inpatients. *Clin Pharm Ther* 2004; 76(6): 639–647.
13. British National Formulary (BNF), <http://www.bnf.org/bnf/index.htm> (accessed 31 January 2013).
 14. British Pain Society (BPS). Opioids for persistent pain: good practice, London: BPS 2010, https://www.britishpainsociety.org/static/uploads/resources/files/book_opioids_recommendations_short.pdf (accessed 31 June 2013).
 15. PharmaGKB. CYP2D6 dosing guidelines, <http://www.pharmgkb.org/gene/PA128> (assessed 26 September 2013).
 16. Hicks JK, Swen JJ, Thorn CF, et al. Clinical pharmacogenetics implementation consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. *Clin Pharm Ther* 2013; 93(5): 402–408.
 17. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte—an update of guidelines. *Clin Pharm Ther* 2011; 89(5): 662–673.
 18. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharm Ther* 2014; 95(4): 376–382.
 19. Food & Drug Administration (FDA). CYP2D6 inhibitors. Silver Spring, MD: FDA, (last updated 2011), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#4> (accessed 4 February 2013).
 20. Medicines and Healthcare products Regulatory Agency (MHRA) UK Public Assessment Report. *Tamoxifen: reduced effectiveness when used with CYP2D6 inhibitors*. London: MHRA, 2011, <http://www.mhra.gov.uk/home/groups/s-par/documents/websiteresources/con129101.pdf> (accessed 18 October 2013).
 21. Flockhart DA. *Drug interactions: cytochrome P450 drug interaction table*. Indiana University School of Medicine, 2007, <http://medicine.iupui.edu/clinpharm/ddis/clinical-table/> (accessed 4 February 2013).
 22. Baxter K. *Stockley's drug interactions: a source book of interactions, their mechanisms, clinical importance, and management*. London: Pharmaceutical Press, 2008, p. 6.
 23. Food & Drug Administration (FDA). Aripiprazole pharmacogenomic information. Silver Spring, MD: FDA, <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm236063.htm> (accessed 21 February 2014).
 24. Neafsey P, Ginsberg G, Hattis D, et al. Genetic polymorphism in cytochrome P450 2D6 (CYP2D6): population distribution of CYP2D6 activity. *J Toxicol Environ Health B Crit Rev* 2009; 12(5–6): 334–361.
 25. Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. *Pharmacogenomics* 2002; 3(2): 229–243.
 26. Brauch H, Schroth W, Goetz MP, et al. Tamoxifen use in postmenopausal breast cancer: CYP2D6 Matters. *J Clin Oncol* 2013; 31(2): 176–180.
 27. Lum DWK, Perel P, Hingorani AD, et al. CYP2D6 genotype and tamoxifen response for breast cancer: a systematic review and meta-analysis. *PLoS One* 2013; 8(10): e76648.
 28. Preissner S, Kroll K, Dunkel M, et al. SuperCYP: a comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. *Nucleic Acids Res* 2010; 38: D237–D243.
 29. Frances Report, 2013, <http://www.midstaffspublicinquiry.com/report> (accessed 12 January 2014).
 30. Health and Social Care Information Centre (HSCIC) and Academy of Medical Royal Colleges. *Standards for the clinical structure and content of patient records*. London: HSCIC, 2013.
 31. Fitzgerald RJ. Medication errors: the importance of an accurate drug history. *Brit J Clin Pharm* 2009; 67(6): 671–675.
 32. Brennan MJ. The clinical implications of Cytochrome P450 interactions with opioids and strategies for pain management. *J Pain Symptom Manage* 2012; 44(6): S15–S22.
 33. McCance-Katz EF, Sullivan LE and Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. *Am J Addict* 2010; 19(1): 4–16.
 34. Bertilsson L, Dahl MLL, Dalén P, et al. Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. *Brit J Clin Pharm* 2002; 53(2): 111–122.
 35. Meyer UA. Pharmacogenetics and adverse drug reactions. *Lancet* 2000; 356(9242): 1667–1671.
 36. National Patient Safety Agency. *Safety in doses (NPSA): medication safety incidents in the NHS*. London: The Stationery Office, 2007.