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 co-morbidities. Patients may have suboptimal response to some analgesics or be at risk of drug interactions or adverse drug reactions 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 U.K. National Health Service (NHS) by GPs who were at risk of suboptimal analgesic response or adverse drug reactions due to CYP2D6 inhibition through polypharmacy. This was achieved by reviewing clinical prescribing information provided by GPs at time of referral.

Methods

A review of information provided in GP letters from 250 patients referred to a NHS hospital pain service over a 3 month period. 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. There was no information about non-pain concomitant medication for 54 (23.5%) of the 230 patients with information about current pain medication. Fifty two (29.5%) of 176 patients with information about non-pain concomitant medication were prescribed at least one CYP2D6 inhibitor. Thirty five (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 National Health Service hospital pain clinics. There is a need to consider of 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.

Key words

Pain Management, Analgesic Drugs, General Practitioner, CYP2D6, Polypharmacy

INTRODUCTION

Chronic pain is a complex condition affecting 1 in 5 adults with increasing prevalence through the lifespan[1,2,3]. Co-morbidities include diabetes, hypertension and cardiovascular disease[4]. Management is difficult and patients are often prescribed a variety of analgesics and drugs not typically prescribed as analgesics but are beneficial in pain management (i.e. pain adjuvants such as tricyclic antidepressants)[4,5,6]. 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]. General practitioners 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 metaboliser (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 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%[22]. A strong CYP2D6 inhibitor would change an EM phenotype to a PM phenotype and a moderate/weak CYP2D6 inhibitor would change an EM 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 six year study of 65,526 hospitalised patients found that one in five patients were co-prescribed a CYP2D6 inhibitor with the potential to prevent prodrug activation[11]. The aim of the service improvement project was to determine the proportion of patients referred to a specialist pain service in the U.K. National Health Service (NHS) by GPs who may be at risk of suboptimal analgesic response or adverse drug reactions 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 UK (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 ten 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 (HR), two pain research nurses and a clinical trial administrator. Data was 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 defined by the British National Formulary (BNF)[12] and the British Pain Society Opioid Guidelines[13]. Analgesic drugs reliant on CYP2D6 activity to obtain analgesic efficacy were identified using prescribing guidelines for CYP2D6 phenotypes produced by Clinical Pharmacogenetics Implementation Consortium[14,15] and the Dutch Pharmacogenetics Working Group[14,16]. 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[17].

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)[18] and the UK Medicines and Healthcare Products Regulatory Agency (MHRA)[19] (Table 1). Drugs were categorised as weak inhibitors if they were named in the literature by Flockhart[20] and Baxter[21] 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 Flockhart[20] 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.

[Insert Table 1 here]

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.[22]. 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[14,15] and the Dutch Pharmacogenetics Working Group[14,16].

RESULTS

There were 260 referrals over the three month period (Figure 1). Ten referrals were not from the patient's GP and were excluded from the analysis. 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 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.

[Insert Figure 1 here]

Analysis of prescribed analgesics and adjuvants

Current medication consisted of 532 GP prescriptions of 40 different analgesic or pain adjuvant drugs (Table 2). The most frequently prescribed class of drugs was non-opioid analgesics (i.e. paracetamol and NSAID = 150/532 (28.2%) prescriptions for 150/230 (65.2%) patients) followed by strong opioids (134/532 (25.1%) prescriptions for 134/230 (58.3%) patients) and weak opioids (86/532 (16.1%) prescriptions for 86/230 (37.4%) patients). The most common analgesic drug prescribed was paracetamol (81/532 (15.2%) prescriptions for 81/230 (35.2%) patients) followed by tramadol (58/532 (10.9%) prescriptions for 58/230 (25.2%) patients) and co-codamol (56/532 (10.5%) prescriptions for 56/230 (24.3%) patients). Pain adjuvant drugs were readily prescribed with similar numbers of prescriptions for tricyclic antidepressants (64/532 (12.0%) prescriptions for 64/230 (27.8%) patients) and anticonvulsants (78/532 (14.6%) prescriptions for 78/230 (33.9%) patients). The most frequently prescribed tricyclic antidepressant (TCA) was amitriptyline (59/532 (11%) prescriptions for 59/230 (25.65%) patients) and the most frequently prescribed anticonvulsant was gabapentin (39/532 (7.3%) prescriptions for 39/230 (17.0%) patients) and pregabalin (38/532 (7.1%) prescriptions for 38/230 (16.5%) patients).

[Insert Table 2 here]

One hundred and thirty five referrals (58.7%) were prescribed at least one analgesic that was reliant on CYP2D6 to obtain analgesic efficacy. Only 22 (9.6%) patients were 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 were prescribed a strong opioid, one a weak opioid, three a non-opioid and eight a pain adjuvant. Three patients were 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 CYP2D6 phenotype (which was not known).

Two hundred and eight (90.4%) patients were 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). One hundred and sixty seven (72.6%) patients were prescribed more than one pain medication (i.e. any combination of analgesic and/or pain adjuvant).

[Insert Table 3 here]

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 were prescribed a CYP2D6 inducer (i.e. rifampin or dexamethasone). Fifty two (29.5%) of these 176 patients were prescribed at least one known CYP2D6 inhibitor (Figure 2). Nine (5.1%) of the 176 patients were prescribed a strong inhibitor that would produce complete inhibition of CYP2D6 and 43 (24.4%) were prescribed an inhibitor that would reduce CYP2D6 activity by 50% (moderate inhibitor n = 8, weak inhibitor n = 35). Four (2.3%) patients were prescribed two or more inhibitors concurrently (i.e. strong + weak; moderate + weak; weak + weak; weak + weak + weak + weak). Seven (4.0%) patients were 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 were prescribed tramadol and codeine (both reliant on CYP2D6 activity) with duloxetine which is a pain adjuvant known to inhibit CYP2D6. Twenty six (14.8%) patients were 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 were prescribed an analgesic drug reliant on CYP2D6 combined with both pain adjuvants and non-pain concomitant drugs with the potential to inhibit CYP2D6.

[Insert Figure 2 here]

Thirty five (19.9%) of the 176 patients were at risk of clinically significant drug interactions (Figure 3) and 33 patients (18.75%) were at risk of suboptimal analgesic response due to co-administration of CYP2D6 inhibitors. At risk patients may have included 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 toxicity from high levels of aripiprazole (antipsychotic) and clomipramine (TCA) due to a lack of elimination by CYP2D6 inhibition[23]. Published prescribing guidelines for aripiprazole and clomipramine recommend reducing the standard dose by up to 67% in PMs to prevent ADRs[14,15]. Seventeen (9.7%) patients were at risk of moderate to weak CYP2D6 inhibition from non-selective serotonin reuptake inhibitors 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 at risk of breast cancer relapse due to CYP2D6 inhibition and lack of biotransformation of tamoxifen, an anti-oestrogen prodrug[14,16,19,22]. Sixteen patients (9.1%) were at risk of drug interactions due to co-prescription of a selective serotonin reuptake inhibitor (SSRI). Seven (4%) patients were prescribed fluoxetine or paroxetine which are strong CYP2D6 inhibitors producing complete inhibition of CYP2D6 activity. A further seven patients (4%) were prescribed sertraline or citalopram which are moderate/weak CYP2D6 inhibitors producing 50% reduction of CYP2D6 activity. Examples of prescribing resulting in limited analgesic efficacy and/or risk of ADRs included:

- 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.

[Insert Figure 3 here]

DISCUSSION

Statement of principal findings

This review of 230 referrals by GPs to a NHS hospital pain clinic over the three 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. 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. 58.7% of patients had been prescribed at least one analgesic that was reliant on CYP2D6 to obtain analgesic efficacy. 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 176 patients with referral letters that contained relevant 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.

Meaning of the study and implications for clinicians

Prescriptions for codeine, co-codamol and tramadol have risen over the last decade yet CYP2D6 phenotype of patients is not available to most GPs at the point of prescribing.. Up to 25% of the Caucasian population may be PMs, IMs or Ums with no or reduced CYP2D6 activity and at risk of suboptimal analgesic response and/or ADRs from toxicity[24,25]. 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. We estimated that there was a risk of clinically significant drug interactions for 19.9% of patients in our sample and a risk of suboptimal analgesia for 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 tamoxifen. There remains an ongoing debate as to whether CYP2D6 activity is crucial to tamoxifen metabolism and breast cancer relapse[19,26,27]. 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[14,15,16] . 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[20,28]. 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[29,30,31]. Poor communication of medication history and prescribing not carefully thought through is costly to patient well-being and the NHS[11,32,33,34,35,36].

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 of the risk CYP2D6 inhibition 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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FIGURE LEGENDS

Figure 1

Flow of data gathered from General Practitioner (GP) referral letters

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

Figure 3

Potential clinically significant adverse drug reactions due to CYP2D6 inhibition

Key: ADRs = Adverse Drug Reactions; SSRIs = Selective Serotonin Reuptake Inhibitors; TCAs = Tricyclic Antidepressants

Figure 1

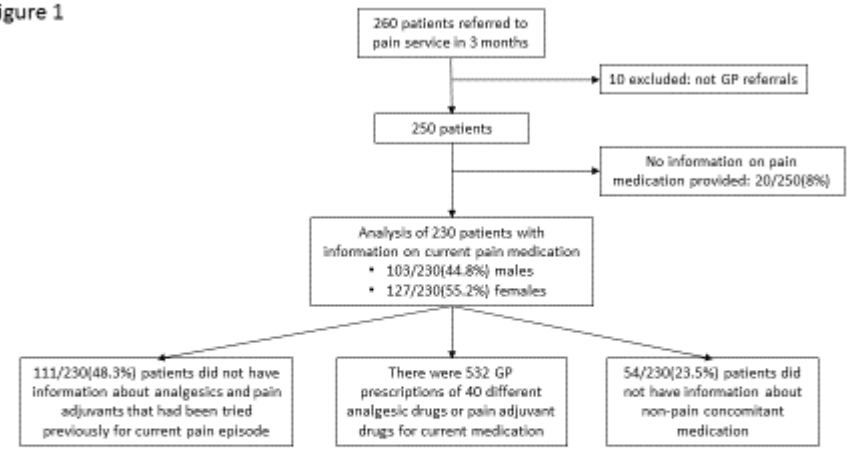

Figure 2

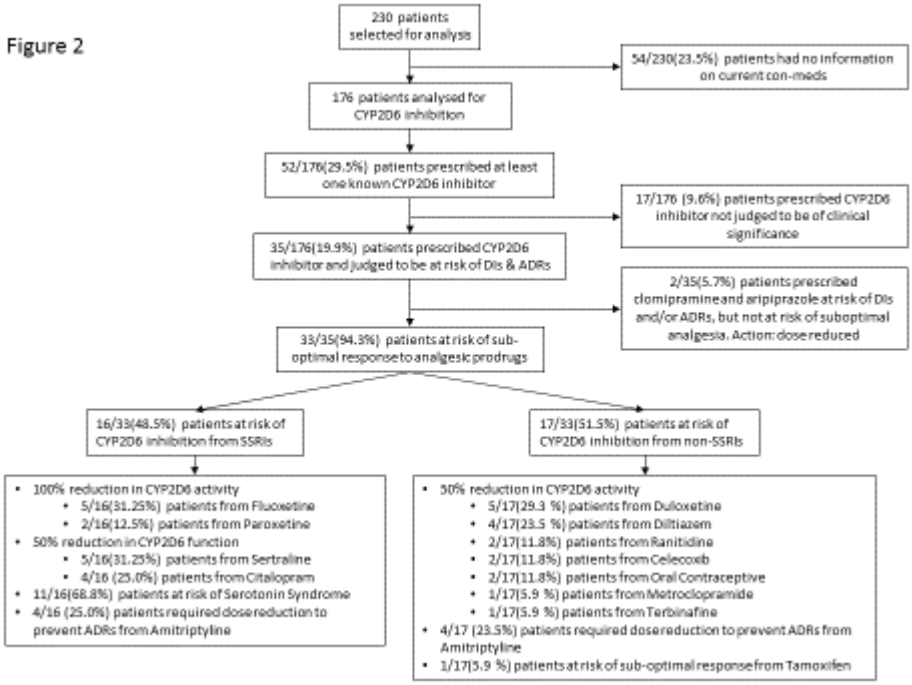

Figure 3

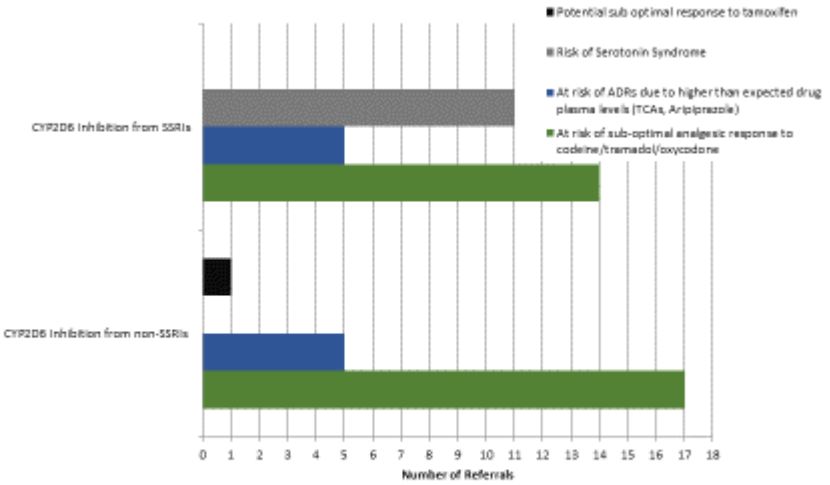

Table 1

Drugs that are known to be CYP2D6 inhibitors that were used for identification of potential drug interactions in this review. The list was compiled using information from the following sources: FDA[18], MHRA[19], Flockhart[20], Baxter[21]

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 *(classed as weak for the purpose of this audit)***	
Bupropion[18,19,20,21] Fluoxetine[18,19,20,21] Paroxetine[18,19,20,21] Quinidine[18,19,20,21] Cinacalcet[20]	Duloxetine[18,20,21] Cinacalcet[18,19] Terbinafine[18,21] Sertraline[20]	Amiodarone[18,20,21] Celecoxib[18,20] Cimetidine[18,21] Desvenlafaxine[18] Diltiazem[18] Diphenhydramine[18,20,21] Echinacea[18] Escitalopram[18.20] Febuxostat[18] Gefitinib[18]	Hydralazine[18] Hydroxychloroquine[18] Imatinib[18] Methadone[18,20] Oral Contraceptives[18] Propafenone[18,21] Ranitidine[18,20] Ritonavir[18,20,21] Sertraline[18,21] Telithromycin[18] Verapamil[18]	Chlorpheniramine[20] Clomipramine[20] Chlorpromazine[20] Citalopram[20] Clemastine[20] Clomipramine[20] Cocaine[20] Dextropropoxyphene[21] Doxepin[20] Doxorubicin[20] Halofantrine[20] Histamine H1 antagonist[20] Hydroxyzine[20] Levomepromazine[20]	Metroclopramide[20] Mibefradil[20] Midodrine[20] Moclobemide[20] Perphenazine[20] Reduced haloperidol[20] SSRIs[21] Ticlopidine[20] Tripelen-namine[20] Valdecoxib[21]

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 & ADRs due to CYP2D6 inhibition**	**Current medication (n=prescriptions)**
Opioid Analgesics				
a) 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
b) 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				
a) Paracetamol				81
b) Non-steroidal 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				
a) TCA				64
• Amitriptyline		N/A	Y	59
• Nortriptyline		N/A	Y	3
• Trazadone		N/A		2
b) Anti-convulsants				**78**
• Pregabalin		N/A		38
• Gabapentin		N/A		39
• Carbamazepine				1
c) 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
• Methcarbamol		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

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

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							
a) Strong opioids	20(31.7%)	37(23.4%)	38(23.5%)	29(26.8%)	1(6.7%)	4(33.3%)	5(35.7%)
b) 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							
a) Paracetamol	4(6.3%)	25(15.8%)	26(16.0%)	21(19.4%)	1(6.7%)	2(16.7%)	2(14.3%)
b) Non-steroidal 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							
a) Tricyclic antidepressant	8(12.7%)	14(8.9%)	26(16.0%)	10(9.3%)	3(20.0%)	2(16.7%)	1(7.1%)
b) Anticonvulsant	9(14.4%)	26(16.6%)	21(13.0%)	15(13.9%)	3(20.0%)	2(16.7%)	2(14.3%)
c) Other	1(1.6%)	5(3.2%)	3(1.8%)	8(7.4%)	0(0%)	0(0%)	2(14.3%)