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Nationwide drug-dispensing data reveal important differences in adherence to drug label recommendations on CYP2D6-dependent drug interactions

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Drug–drug interactions (DDIs) may have a profound impact on the individual drug response, for instance by reducing the clearance of involved drugs and thereby causing adverse drug reactions at supratherapeutic drug exposure.
- In specific cases, such a risk with specific drug combinations is stated in the drug label, including specific recommendations on the choice of drug and/or dose.
- Less frequently, DDIs that reduce the drug effectiveness may have been recognized as well.
- The clinical adherence to these recommendations is today unknown.

WHAT THIS ADDS

- The results from this study on specific drug combinations related to cytochrome P450-dependent drug metabolism indicate that Swedish doctors avoid prescribing strong inhibitors of drug metabolism together with drugs at risk of accumulation and exposure-dependent adverse drug reactions.
- However, 'silent' DDIs that impact on effectiveness appear to be neglected, pointing out an area for continued medical education of drug prescribers about such DDIs.

AIMS

The study aimed to investigate the clinical adherence to drug label recommendations on important drug–drug interactions (DDIs). Dispensing data on drug combinations involving selective serotonin reuptake inhibitor (SSRI) antidepressants could help to identify areas for intensified medical education.

METHODS

This was a retrospective, cross-sectional analysis of individual dispensing data regarding all individuals ≥15 years old in Sweden. The study analysed the prescribing and dispensing of CYP2D6 drugs (metoprolol, donepezil, galantamine, codeine, tamoxifen) together with CYP2D6-blocking SSRIs (paroxetine/fluoxetine) or SSRIs without significant CYP2D6 inhibition (citalopram/escitalopram/sertraline), and the related prescribing of CYP2D6-independent comparator drugs (atenolol, rivastigmine, propoxyphene, anastrozole). Odds were calculated between each CYP2D6 drug and the corresponding comparator drug in patients on fluoxetine/paroxetine and citalopram/escitalopram/sertraline, respectively. The odds ratio (OR) was calculated by dividing the obtained odds in patients on fluoxetine/paroxetine by the corresponding odds in patients on citalopram/escitalopram/sertraline.

RESULTS

Compared with patients that were dispensed citalopram/escitalopram/sertraline, patients dispensed fluoxetine/paroxetine had lower prescribing rates of metoprolol (adjusted OR 0.80; 95% confidence interval 0.76, 0.85), donepezil (0.65; 0.49, 0.86) and galantamine (0.58; 0.41, 0.81). In contrast, the use of prodrugs codeine (compared woth propoxyphene) or tamoxifen (compared with anastrozole) was similar among patients on fluoxetine/paroxetine and citalopram/escitalopram/sertraline (adjusted OR 1.03; 0.94, 1.12 and 1.29; 0.96, 1.73, respectively).

CONCLUSIONS

Clinically important DDIs that are associated with impaired bioactivation of prodrugs might be more easily neglected in clinical practice compared with DDIs that cause drug accumulation and symptomatic adverse drug reactions.

Introduction

Pharmacotherapeutic problems arising from drug–drug interactions (DDIs) contribute to a significant health burden and are judged to cause between 0.6% and 4.8% of hospitalizations [1, 2]. Consequently, it is important to improve the understanding of how and when prescribers adhere to drug label information about concerns with inadequate efficacy or critical drug interactions with certain combinations. In this study, we addressed this issue by looking at the dispensing patterns of drugs with a large potential for DDI and compared these with patterns of pharmacotherapeutic alternatives.

Many drugs such as antidepressants, antipsychotics and analgesics are specific substrates and/or inhibitors of the hepatic cytochrome P450 enzyme (CYP) 2D6 [3, 4]. When used in combination, which is common, for example, in cases of polypharmacy in the elderly population, unfavourable DDIs may occur. Interactions associated with selective serotonin reuptake inhibitor (SSRI) antidepressants dominate due to their widespread use and ability to inhibit the CYP2D6 enzyme [5–8]. However, the different SSRIs exhibit significant differences regarding the impact on CYP2D6-dependent drug metabolism. Paroxetine and fluoxetine have been shown to increase plasma concentrations of CYP2D6 drug substrates several-fold by pronounced inhibition of CYP2D6-dependent metabolism and clearance. In contrast, sertraline, citalopram and escitalopram do not have a marked impact on the activity of this enzyme [9], a difference also reflected in the drug labels [10].

We investigated the combined use of SSRI antidepressants and common drugs in chronic cardiovascular disease, Alzheimer's disease, pain disorders, and adjuvant treatment of breast cancer with access to individual drug-dispensing data in the unique Swedish Prescribed Drug Register [11]. The prescribing of combinations of different SSRIs and drugs that depend on CYP2D6 metabolism for their clearance or pharmacological bioactivation (hereafter referred to as CYP2D6 drugs) was compared with the prescribing and dispensing of similar drugs without CYP2D6-dependent activity (i.e. used for an identical or similar therapeutic indication and hereafter referred to as comparator drugs). For three of the CYP2D6 drugs (metoprolol, donepezil, galantamine), reduced elimination by CYP2D6 may lead to symptomatic adverse drug reactions (ADRs). In the case of the β-blocker metoprolol, reduced elimination of CYP2D6 may primarily cause bradycardia and hypotension. Gastrointestinal problems such as diarrhoea are more frequent at high exposure to the acetylcholine esterase inhibitors galantamine or donepezil. For the other two CYP2D6 drugs (codeine, tamoxifen), inhibition of CYP2D6-dependent metabolism may cause insufficient pharmacological effect, leading in the case of tamoxifen to earlier relapses [12–21].

Methods

Objectives

We hypothesized that doctors in Sweden would avoid the combined use of CYP2D6 drugs and specific SSRIs that block the activity of CYP2D6. Consequently, we hypothesized that the ratio between the frequencies of CYP2D6 drug users and those of comparator drug users would be lower among patients co-prescribed a CYP2D6-blocking SSRI than among patients prescribed other SSRIs. Thus, the outcome measures were odds ratios (ORs) of each of the five CYP2D6 drugs to respective comparator drugs in patients exposed to potent CYP2D6 inhibitor (fluoxetine or paroxetine) *vs.* patients being unexposed (instead prescribed citalopram, escitalopram or sertraline). Fluvoxamine was the only SSRI excluded from the analysis due to its negligible use (<0.2% of all SSRI users in Sweden, 2008). Data on the use of escitalopram were included in citalopram data in all analyses and Discussion below. In addition to these ORs, the period prevalence figures of the specific drug combinations under study were estimated for the Swedish population as a whole.

Study design

The study design was a retrospective, cross-sectional analysis of patients being dispensed prescription drugs in Sweden during the period from 1 January to 30 April 2008. The choice of a 4-month study period was based on the Swedish regulation and experience that most patients on long-term/chronic treatment repeat their drug-dispensing every third month. We selected all individuals, ≥15 years old, that were dispensed any of the drugs presented in Table 1. The cohort was established on data obtained from the Swedish Prescribed Drug Register [11].

Ethics approval

The study was approved by the Regional Ethics Committee in Karolinska Institutet (Stockholm, Sweden).

Data source

The Swedish Prescribed Drug Register contains data with unique patient identifiers for all dispensed prescriptions to the whole population of Sweden. The data collection is administered by the National Corporation of Swedish Pharmacies, a state-owned company responsible for the provision of pharmaceutical services at a nationwide level. Data on all dispensed prescriptions are transferred monthly to the National Board of Health and Welfare. The drugs were classified according to the Anatomical Therapeutic Chemical classification system [25]. The volume of dispensed drugs was estimated as defined daily doses (DDD) [22]. The period prevalence was assessed as the proportion of subjects in the Swedish population that were

Table 1
Rational for the choice of study drugs

Study drugs (ATC)	Rationale	Labelling according to the Swedish summary of product characteristics with regard to CYP2D6 inhibition [10]
CYP2D6 drugs		
Metoprolol (C07AB02)	Beta-adrenergic receptor antagonist. To a large extent metabolized by CYP2D6. The plasma concentration of metoprolol is elevated in patients that receive CYP2D6 inhibitors, which may result in exaggerated reduction of heart frequency and systemic blood pressure [14]	The combining of metoprolol with inhibitors of CYP2D6 may need to be accompanied by decrease in dose
Donepezil (N06DA02)	Acetylcholine esterase inhibitor. Metabolized by CYP2D6. Exposure-dependent adverse drug reactions, for instance gastrointestinal symptoms, are considered dose-limiting [17, 18]	Inhibitors of CYP2D6 may slow the metabolism of donepezil
Galantamine (N06DA04)	Acetylcholine esterase inhibitor. Metabolized by CYP2D6. Exposure-dependent adverse drug reactions, for instance gastrointestinal symptoms, are considered dose-limiting [16, 18]	Co-medication with paroxetine increases the bioavailability of galantamine by 40%. A decrease in dosing may be warranted
Codeine (R05DA04)	Opioid analgesic. Codeine is a prodrug for which the pharmacological effect is dependent on O-demethylation to morphine, a reaction catalysed by CYP2D6. Individuals who are co-administered drugs that inhibit this enzyme remain essentially unexposed for morphine, which results in a reduced or absent analgesic effect [19–21]	Studies have provided evidence that co-medication with inhibitors of CYP2D6 are clinically important and should therefore be avoided
Tamoxifen (L02BA01)	Used as an adjuvant treatment in oestrogen receptor positive breast cancer. The therapeutic efficacy is dependent on CYP2D6 bioactivation [13, 22, 23]	The clinical relevance is not known
Comparator drugs		
Atenolol (C07AB03)	Beta-adrenergic receptor antagonist. Similar cardiovascular indications compared with metoprolol. Eliminated in unchanged form by the kidneys without any significant CYP2D6-dependent metabolism [15]	No information regarding pharmacokinetic drug–drug interactions
Rivastigmine (N06DA03)	Acetylcholine esterase inhibitor. Similar indications compared with donepezil and galantamine, but not metabolized by CYP2D6, renal elimination [18]	Metabolic drug–drug interactions appear to be unlikely
Propoxyphene (N02AC04)	Opioid analgesic. Similar to codeine, preferentially used for treatment of mild to moderate pain. Propoxyphene does not require bioactivation and is metabolized primarily by CYP3A4 [24]	CYP3A4 and CYP2D6 may be involved in the metabolism of propoxyphene
Anastrozole (L02BG03)	Used as an adjuvant treatment in oestrogen receptor-positive breast cancer. Anastrozole is not a prodrug, but works by direct inhibition of CYP19-dependent steroid aromatization [12]	No information regarding drugs that interact with anastrozole

dispensed the different drugs during the period [26]. We selected all individuals, ≥15 years old, on any of the drugs presented in Table 1.

Statistics

To study associations between the different types of SSRI (fluoxetine/paroxetine *vs.* citalopram/sertraline) and the CYP2D6 drugs (metoprolol, donepezil, galantamine, codeine or tamoxifen) we used unconditional logistic regression. To minimize the possible bias of patients who changed CYP2D6 drugs, comparator drugs and/or SSRI within the 4-month study period, we included only patients who had been dispensed no more than one of the drugs in each therapeutic area and/or one type of SSRI (e.g. those who had been dispensed both a CYP2D6 drug and a comparator drug were excluded).

For each therapeutic area comparison, the odds were calculated between each CYP2D6 drug and the corresponding comparator drug in patients that were co-dispensed fluoxetine/paroxetine and citalopram/sertraline, respectively. The unadjusted OR was calculated by dividing the obtained odds in patients on fluoxetine/paroxetine by the corresponding odds in patients on citalopram/sertraline (Table 3). To adjust subsequently for differences in gender and age between the subgroups under comparison, multivariable models were used. The associations are presented as odds and ORs with 95% confidence intervals (CI). The departure from 1 (no association) is statistically significant at the 5% level, two-tailed, if the 95% CI does not include 1. An OR of <1 means that co-dispensing of CYP2D6 drug, in relation to the comparator drug, is lower among patients using fluoxetine/paroxetine compared with patients using citalopram/sertraline (see Table 3). It follows that an OR of > 1 means co-dispensing with the CYP2D6 drug is higher (more frequent) among patients dispensed fluoxetine/paroxetine than co-dispensing with citalopram/sertraline (Table 3). All statistical calculations were performed in SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

Results

All individuals in the Swedish population ≥15 years old (n = 7 713 945) were included in the study. The mean age

Table 2

Prevalence of study drugs used in the adult Swedish population (>15 years of age), January to April 2008

CYP2D6 drug	*n*	*n*/1000 individuals
Metoprolol	406 369	53
Donepezil	15 475	2.0
Galantamine	6 602	0.9
Codeine	121 102	16
Tamoxifen	11 734	1.5
Comparator drug		
Atenolol	233 505	30
Rivastigmine	5 190	0.7
Propoxyphene	73 781	9.6
Anastrozole	8 140	1.1
SSRI antidepressant		
Fluoxetine	30 673	4.0
Paroxetine	27 228	3.5
Citalopram/incl. escitalopram	229 355	30
Sertraline	103 652	13

was 47 years, and 51% were women. The prevalence of the use of study drugs in the Swedish study population is given in Table 2, where it is evident that > 5% of the Swedish adult population were dispensed an SSRI antidepressant during the study period. Among these, citalopram (including escitalopram) or sertraline were most common (Table 2).

Table 3 shows the prevalence of study drug combinations including the associations between fluoxetine/paroxetine or citalopram/sertraline, and specific CYP2D6 drugs (i.e. subject to CYP2D6-dependent clearance or bioactivation) or a similar comparator drug. The numbers of individual patients in the whole population that were dispensed fluoxetine/paroxetine together with metoprolol, donepezil, galantamine, codeine and tamoxifen were 3164, 158, 61, 2322 and 131, respectively. Compared with patients who where dispensed citalopram/sertraline, patients dispensed fluoxetine/paroxetine had lower dispensing of metoprolol (adjusted OR 0.80; 95% CI 0.76, 0.85), donepezil (0.65; 0.49, 0.86) and galantamine (0.58; 0.41, 0.81). In contrast, the risk of being dispensed codeine (instead of propoxyphene) was similar among patients dispensed fluoxetine/paroxetine to those dispensed citalopram/sertraline (adjusted OR 1.03; 95% CI 0.94, 1.12). The same was true for tamoxifen (adjusted OR 1.29; 95% CI 0.96, 1.73), but as discussed below, the likely priority order in drug prescription makes the following phrasing more appropriate – the risk of being prescribed fluoxetine/paroxetine or citalopram/sertraline was similar among patients using tamoxifen compared with patients on anastrozole. The volumes of dispensed DDDs of all study drugs were similar in patients on the different SSRIs (see Table 3, footnotes).

Discussion

The results demonstrated variable dispensing of specific drug combinations related to CYP2D6-dependent drug

Table 3

Associations between the CYP2D6 drugs and respective comparator drugs in patients dispensed SSRIs with (fluoxetine/paroxetine) or without (citalopram/sertraline) a pronounced inhibitory effect on CYP2D6

SSRI	CYP2D6-drugs	Comparator drugs	Odds, CYP2D6 drugs (vs. comparator)	Odds ratios unadjusted (95% CI)	*P*-values	Odds ratios — adjusted for gender and age (95% CI)	*P*-values
	Metoprolol	**Atenolol**					
Fluoxetine/paroxetine	3 164[a]	2 392	1.32	0.73 (0.69, 0.78)	<0.001	0.80 (0.76, 0.85)	<0.001
Citalopram*/sertraline	29 058[b]	16 101	1.80				
	Donepezil	**Rivastigmine**					
Fluoxetine/paroxetine	158[c]	82	1.93	0.62 (0.47, 0.82)	<0.001	0.65 (0.49, 0.86)	0.003
Citalopram/sertraline	4 546[d]	1 463	3.11				
	Galantamine	**Rivastigmine**					
Fluoxetine/paroxetine	61[e]	82	0.74	0.60 (0.43, 0.84)	0.003	0.58 (0.41, 0.81)	0.002
Citalopram/sertraline	1 823[f]	1 463	1.25				
	Codeine	**Propoxyphene**					
Fluoxetine/paroxetine	2 322[g]	1 084	2.14	1.67 (1.54, 1.80)	<0.001	1.03 (0.94, 1.12)	0.559
Citalopram/sertraline	10 714[h]	8 326	1.29				
	Tamoxifen	**Anastrozole**					
Fluoxetine/paroxetine	131[i]	86	1.52	1.22 (0.92, 1.63)	0.168	1.29 (0.96, 1.73)	0.089
Citalopram/sertraline	1 017[j]	817	1.24				

Data are based on drug dispensing in the Swedish population (≥ 15 years of age), January to April 2008. [a]Mean defined daily dose (DDD) metoprolol (SD): 63 (48). [b]Mean DDD metoprolol (SD): 61 (46). [c]Mean DDD donepezil (SD): 118 (60). [d]Mean DDD donepezil (SD): 122 (60). [e]Mean DDD galantamine (SD): 128 (69). [f]Mean DDD galantamine (SD): 124 (60). [g]Mean DDD codeine (SD): 96 (128). [h]Mean DDD codeine (SD): 93 (117). [i]Mean DDD tamoxifen (SD): 123 (55). [j]Mean DDD tamoxifen (SD): 127 (51).

metabolism. Patients treated with an SSRI that blocked CYP2D6 activity had a significantly lower risk to be co-dispensed a CYP2D6 substrate for which the accumulation may lead to symptomatic ADRs (metoprolol, donepezil and galantamine). However, Swedish physicians appeared to be less concerned when considering co-dispensing of SSRIs for drugs that require CYP2D6-dependent bioactivation (tamoxifen and codeine).

We acknowledge that findings from register studies are often hampered by confounders. However, we have attempted to address this in the present study by controlling for age and gender in the statistical analysis, and also the use of comparator drugs in the two different SSRI groups enabled us to control for confounding by indication. This strengthened our conclusions, but the approach to control for indication biases relies on the assumption that CYP2D6 drugs and corresponding comparator drugs, as well as the different SSRIs, are used on similar/identical clinical indications [27]. However, some differences may exist, such as the listed contraindications between codeine and propoxyphene, which may account for differences in prescribing practices. In addition, the recent attention to serious adverse reactions to propoxyphene may contribute to a shift in prescribing that favours codeine rather than propoxyphene regardless of what kind of SSRI is co-administered. Another known difference in prescribing relates to the use of breast cancer adjuvants in treatment of oestrogen receptor-positive tumours. Aromatase inhibitors are not used in premenopausal women, while both aromatase inhibitors and tamoxifen may be used in women beyond menopause. According to the Swedish national guidelines [28], tamoxifen is regarded as first-line treatment also in postmenopausal women with low risk of recurrence, i.e. without nodal spread, but then aromatase inhibitors represents a therapeutic alternative. The slightly better adjuvant effect of aromatase inhibitors is outweighed by its worse adverse reaction profile in terms of an increased risk of osteoporosis, joint tenderness and hypercholesterolaemia. Among women co-medicating with potent inhibitors of CYP2D6, aromatase inhibitors would certainly still be an option in postmenopausal women. Age is therefore one obvious factor that may potentially confound the results, but fortunately we were able to adjust for this. However, there may additional confounders. A way to evaluate the risk of residual confounding by indication would have been to scrutinize the different individual indications behind the use of CYP2D6 drug and comparator drug, respectively. Unfortunately, this information was not retrievable in the register database.

Literature data indicate that sertraline, in a dose-dependent manner, may inhibit CYP2D6 to some extent and increase the plasma level of typical CYP2D6 drugs such as tricyclic antidepressants by ~40% [29, 30]. However, this should be compared with a far more pronounced inhibition or block of CYP2D6 activity by fluoxetine and paroxetine, which in different studies cause a corresponding increase in plasma concentrations by 100–300% and 327–421%, respectively [9, 31]. The clinical significance of partial CYP2D6 inhibition at high doses of sertraline remains to be clarified. In conclusion, it seems rational in the present investigation to compare the potent CYP2D6 inhibitors fluoxetine and paroxetine together, *vs.* sertraline together with citalopram and escitalopram.

Another uncertainty about the dispensing data relates to the employment of a fixed time window to estimate the use of drug combinations. Although generally regarded valid, applying a time window may be associated with both under- and overestimation of exposure [32–34]. An alternative method that may be associated with less bias is the assessment of concomitantly used drugs at a fixed time point, based on the calculated duration of use of each dispensing. However, this involves a substantially more elaborate and time-consuming method and is associated with other types of bias [33, 34]. This led to the development of the current analysis plan, in which the large number of registered patients is a clear strength.

As discussed earlier, even though DDIs are regarded as a major healthcare problem, there are surprisingly very few published reports on how DDIs can affect subsequent drug prescribing and utilization in practice. A study on 2779 Veterans Affairs patients showed no difference in prescribing patterns for patients on paroxetine/fluoxetine compared with patients on sertraline [34]. However, the validity of these results is impaired by the small number of patients studied and by the lack of control drugs. This led to the development of the current study with the Swedish Prescribed Drug Register, giving us the opportunity to study the entire Swedish population. The calculated proportions were thus determined rather than estimated, adding to the robustness of our findings.

The common feature of all three drugs with lower dispensing to patients on CYP2D6 inhibitors was the risk of symptomatic ADRs at increased exposure, which have been discussed earlier. However we accept that whether or not these risks were considered prior to initiating treatment with the CYP2D6 drug or CYP2D6 inhibitor is unclear, as the temporal relationships between different drug treatments were not analysed in our cross-sectional approach. For example, the relative imbalance towards the dispensing of rivastigmine rather than donepezil in patients co-dispensed with CYP2D6 inhibitors might result from patients starting on donepezil but subsequently switched to rivastigmine with the development of gastrointestinal intolerance. However, it could also reflect clinical awareness of the risk of an unfavourable DDI prior to commencing treatment with the acetylcholine esterase inhibitor, and a resulting rational choice in drug prescription. A third possibility may be an intervention by the pharmacist responsible for dispensing of the inappropriate drug combination. Even though Swedish pharmacists occasionally do alert the prescribing physician, this is not done on a routine basis. Therefore, today, this latter

explanation is considered to be only a minor contributor to the observed results.

In contrast, the results from this study suggest that physicians largely ignore the potential impact of drugs with DDIs that lead to reduced pharmacological effect when prescribing drugs such as SSRIs in clinical practice. We hypothesized that physicians would preferentially prescribe sertraline, citalopram and escitalopram as opposed to fluoxetine and paroxetine in patients co-prescribed, for example, codeine. The risk of reduced or absent pain relief with codeine in this large cohort of patients (2322 individuals on combined treatment with fluoxetine or paroxetine, Table 3) appears to be overlooked. There are several possible reasons for this; (i) the lack of pain relief effectiveness is not properly evaluated in this population of depressed patients; (ii) sufficient analgesia may be achieved by other means, e.g. by additional use of other analgesics including paracetamol and/or cyclooxygenase inhibitors; (iii) poor compliance and reduced or irregular intake of the CYP2D6-blocking antidepressant reduces the impact on codeine; (iv) the clinical relevance of this interaction may be lower than presently believed. Indeed, it is warranted to elucidate this issue further. The risk of impaired therapeutic efficacy of tamoxifen with combined treatment with CYP2D6-blocking SSRIs is discussed in the paroxetine drug label, but not in the prescribing label for fluoxetine or tamoxifen. However, the impact of drug label changes to changing prescribing patterns is uncertain and perhaps the focus should be more on further pharmacological education of practising doctors.

The use of computerized decision support is another way to reduce inappropriate prescribing and dispensing. In Sweden there are a few systems available that alert for DDIs, but it is unclear to what extent they are actually used at present [35, 36]. A major problem with decision supports has been the generation of too many warnings that may be considered clinically irrelevant and thereby carry a risk for alert fatigue [36–38].

In conclusion, the present data from the Swedish population suggests that 'silent' DDIs related to reduced bioactivation of prodrugs appear to be more neglected in clinical practice compared with DDIs that cause drug accumulation and overt ADRs. This indicates a need for improved compliance with drug label recommendations as well as a need for continuous medical education about the basic pharmacology of commonly used drugs. This is especially important in high-volume prescribing areas, and will help improve the subsequent quality of care, benefiting all key stakeholders

Competing interests

None to declare.

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