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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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Polymorphic drug metabolism (CYP2D6) and utilisation of psychotropic drugs in hospitalised psychiatric patients: a retrospective study

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Abstract *Aim*: The aim of the current retrospective study was to assess the influence of polymorphic drug metabolism as assessed by genotyping, on the on the utilisation of psychotropic drugs in hospitalised psychiatric patients. The utilisation of psychotropic drugs was assessed using pharmacy records with emphasis on the number of prescriptions and prescriptions for possible side effects.
Methods: CYP2D6 genotype was assessed in 241 psychiatric patients by investigation for the five most common allelic variants (*CYP2D6*3, *4, *6, *7, *8*) and the presence of gene duplication using allele-specific polymerase chain reaction. Data concerning the pharmacotherapy of the patients were retrieved from the pharmacy information system. Data was analysed on differences observed in pharmacy records concerning the different metabolic classes: ultra rapid metabolisers (UMs), extensive metabolisers (EMs) and poor metabolisers (PMs).
Results: For CYP2D6, 2.5% was UM (95% CI: 0.5–4.5%, $n=6$) and 8.3% was PM (95% CI: 4.8–11.8%, $n=20$). Drugs metabolised by CYP2D6 were less frequently prescribed in PMs than EMs (21.1% vs 33.6%, $P=0.023$). The average duration of prescriptions was significantly lower in PMs than EMs (54 days vs 106 days, $P=0.010$). Between UMs and EMs, no significant differences were found, although a similar tendency was observed. With regard to dose, no consistent differences were observed between the CYP2D6 genotype classes. Drugs against Parkinsonian-like side effects were given twice as frequently in PMs as EMs (6.9% vs 3.4%, $P=0.045$).
Conclusions: Patients with impaired CYP2D6 metabolism received fewer CYP2D6 drugs. PMs were more prone to Parkinsonian-like side effects as evidenced by more prescriptions for drugs combating these side effects. Dose titrations were not often used to compensate for genetic polymorphisms. Pharmacy records might be a useful tool to detect differences related to polymorphic metabolism.

Keywords Polymorphic drug metabolism · Psychotropic drugs · Psychiatric patients

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Introduction

The cytochrome P_{450} enzyme CYP2D6 plays an important role in the metabolism of psychoactive drugs. It is estimated that it is involved in the metabolism of about 50% of all psychoactive drugs [1]. It is polymorphically expressed causing considerable variation between individuals [2, 3]. For CYP2D6, this variability is associated with about 50 mutations in the highly polymorphic *CYP2D6* gene locus [4]. In Caucasians, the

most common non-coding alleles are *CYP2D6*4* (about 75% of null alleles), *CYP2D6*5* (about 15% of null alleles) and *CYP2D6*3* (about 5% of null alleles), whereas all other non-coding alleles have a prevalence of 1% or lower [5].

The clinical consequences of impaired metabolism have been studied extensively during recent years [6]. It is well documented that 20–30% of patients do not respond to therapy with psychotropic medication [7]. Therapeutic drug monitoring (TDM) may decrease the proportion of non-responders to 10–20%, indicating a relationship between blood levels and clinical effect [8].

The metabolism of tricyclic antidepressants (TCAs), such as desipramine, amitriptyline, imipramine, clomipramine and nortriptyline, is clearly associated with CYP2D6 metabolism. Impaired metabolism may result in high plasma levels, long half-lives and increased excretion of the parent compound, accompanied by decreased plasma levels of metabolites. For many TCAs clear relationships between blood level and side effects have been shown [9]. Novel antidepressants (serotonin selective re-uptake inhibitors) such as paroxetine, fluoxetine, citalopram and fluvoxamine are also metabolised by CYP2D6. They have a wider therapeutic index than the TCAs, making them safer [10]. However, some of the novel antidepressants are potent inhibitors of CYP2D6-mediated metabolism, which may result in clinically relevant interactions [11].

Neuroleptics show no clear relationship between concentration and side effects and, therefore, the clinical relevance of polymorphism has been less well studied [11]. Perphenazine metabolism has been shown to be strongly dependent on CYP2D6 [12]. CYP2D6 is also involved in the metabolism of zuclopentixol, haloperidol, thioridazine and risperidone [11, 13].

A prospective study to assess the relationship between adverse events (AEs) (extrapyramidal) and CYP2D6 polymorphism showed that the prevalence of PMs in the AE group was significantly higher (45%) than in the non-AE group (14%) [14]. It was concluded that CYP2D6-impaired metabolism was a contributing factor in extrapyramidal side effects.

Retrospective studies have been published indicating genotyping as a clinically relevant and cost-effective tool [15, 16, 17]. These studies have tried to establish the efficacy of the utilisation of psychotropic drugs mainly by including drug-related AEs.

Pharmacy records are known to be reliable indicators of drug exposure, to provide objective therapeutic parameters, and are easily available [18]. They might be helpful in designing practical and cost-effective prospective studies in which sample sizes of up to 2000 patients are needed [17].

The aim of the current retrospective study was to assess the influence of polymorphic drug metabolism (CYP2D6) on the utilisation of psychotropic drugs of hospitalised psychiatric patients using pharmacy records.

Materials and methods

Patients

Patients were taken from a population of psychiatric inpatients of the psychiatric hospital Dennenoord (Zuidlaren, The Netherlands). Blood samples were obtained from samples taken for routine clinical chemistry during the first 6 months of 1998. Genotyping on CYP2D6 was performed as part of the pharmacotherapy. The results were unknown to the treating psychiatrist. Subjects were anonymous to the investigators. An independent medical ethics committee approved the study and the procedure for inclusion of the subjects. Only hospitalised patients were included for evaluation because the pharmacy records of outpatients were not available. Patients were hospitalised for psychotic conditions (mainly schizophrenia and schizoaffective disorders), mood disorders, anxiety states, some forms of epilepsy and severe personality disorders. In total, 241 patients (131 females and 110 males) were included.

Genotyping procedures

Genotyping was performed on *CYP2D6*, using DNA from whole blood samples. DNA was isolated using the QIAamp DNA mini kit (Westburg BV, Leusden, The Netherlands). *CYP2D6* was investigated for the five most common allelic variants using a long-range polymerase chain reaction (PCR) amplifying the whole *CYP2D6* gene followed by a multiplex allele-specific PCR [19]. The following allelic variants were investigated: *CYP2D6*3* (A), *CYP2D6*4* (B), *CYP2D6*6* (T), *CYP2D6*7* (E), *CYP2D6*8* (G). In addition, the presence of gene duplication that may lead to ultra metabolism was analysed using an allele-specific PCR [20] and was performed as described elsewhere [21]. In case of homozygous mutant genotypes, the subject was considered a poor metaboliser (PM). A subject was designated as ultra rapid metaboliser (UM) if gene duplication was detected. In all other cases, the subject was assumed to have a normal CYP2D6 activity (extensive metaboliser; EM).

Pharmacy records

Data concerning the utilisation of psychotropic drugs of the patients were retrieved from the pharmacy information system of the psychiatric hospital. All data from September 1989 to December 1999 have been used for evaluation. For all drugs acting on the nervous system [N class of the Anatomical Therapeutic Chemical (ATC) classification index], information on the metabolism and on defined daily doses (DDDs) were added. Metabolism was classified based on data from the primary source if applicable and was checked with two other sources for the validity [1, 22]. The DDDs were according to the World Health Organization (WHO) guidelines [23]. The database was constructed in Microsoft Access 2000 (Microsoft, Redmond, WA, USA).

Statistical analysis

The observed genotype prevalence was compared with data from healthy volunteers [24] (non-coding mutations) and psychiatric patients [21] (CYP2D6 ultra-rapid metabolism) using the Chi-Square test (χ^2 test).

For the evaluation of the data on differences caused by abnormal metabolism two analysis strategies were used. The first approach (drug approach) is a panel study in which records were selected of drugs known to be substrates for CYP2D6. Per compound, the mean dose, relative mean dose (dose related to the defined daily dose), mean prescriptions per patient per 100 days of hospitalisation and the mean duration of prescriptions per com-

Table 1 Patient characteristics classified per genotype. *PD* drug acting on the nervous system (ATC classification N), *NR* not relevant, *N* nervous system, *A* alimentary tract and metabolism, *J* general antiinfectives for systemic use, *R* respiratory system, *C* cardiovascular system

Characteristics	CYP2D6 predicted		
	Ultra rapid	Extensive	Poor
Demography			
Patients (prevalence)	6 (2.5%)	215 (89.2%)	20(8.3%)
Expected prevalence[1]	3.5%	88.5%	8.0%
Male/female	3/3	100/115	7/13
Mean age (years; min–max)	55 (26–80)	50 (18–89)	52 (24–90)
Pharmacotherapy			
Prescriptions of PD (min–max)	43 (6–140)	45 (1–305)	54 (5–221)
Duration (days; min–max)	937 (69–3091)	1252 (0–3698)	1478 (30–381)
Patient using drugs of N class	6 (100%)	202 (95%)	20 (100%)
Patient using drugs of A class	5 (85%)	149 (70%)	13 (65%)
Patient using drugs of J class	4 (67%)	126 (59%)	14 (70%)
Patient using drugs of R class	4 (67%)	127 (60%)	14 (70%)
Patient using drugs of C class	4 (67%)	75 (35%)	9 (45%)
Metabolism[2]			
Substrates for 2D6	18.8%	17.9%	16.9%
No substrates for 2D6	35.0%	45.3%	43.8%
Unknown	46.2%	36.8%	39.3%
Inhibition of 2D6 or 2C19	16.2%	18.7%	19.3%

[1]Expected prevalences based on other studies for UM patients [21] and EM and PM in healthy volunteers [22]

[2]The number of drugs for all ATC classes per patient as percentage of total number of drugs within the genotypic class

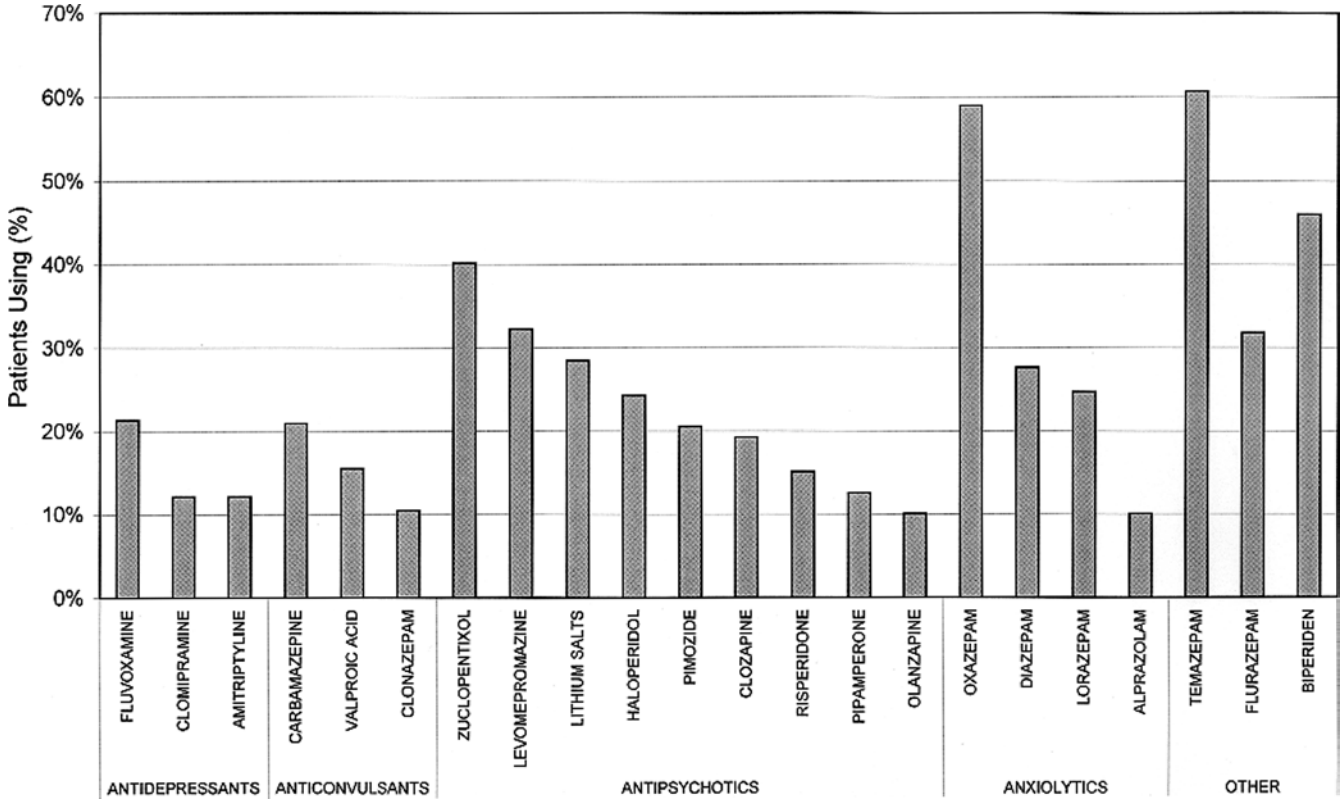

Fig. 1 Overview of most commonly used psychoactive drugs classified per class

pound were calculated. Patients were separated into panels based on the CYP2D6 genotype—UM, EM and PM—and were compared using one-way analysis of variance (ANOVA).

The second approach (patient approach) is an index-control group strategy in which abnormal patients (UM and PM) versus a control group (EMs matching with regard to age and sex) were selected in a proportion of 1:4. The following parameters were calculated per patient: number of psychotropic substrates for CYP2D6, compound and dose switches per time, prescriptions per time per metabolism class (e.g. CYP2D6, no CYP2D6 and unknown), number of prescriptions of drugs against Parkinsonian-like side effects (drug within ATC-class N04A). A compound switch was defined as a switch to a compound within the same group (within ATC code third level, e.g. antidepressants, neuroleptics, hypnotic/sedative and/or anxiety drugs).

For analysis, a subset analysis on the data of the first 180 days of pharmacotherapy per patient was used. Within this period, optimal pharmacotherapy in psychiatric patients is assumed to be established. Data was compared using one-way ANOVA. All statistics were performed with SPSS release 9.0.0 (SPSS Inc., Chicago, IL, USA).

Table 2 Pharmacotherapeutic characteristics of nine frequently prescribed psychoactive drugs known to be metabolised by CYP2D6 classified per genotype

Drug	Characteristics (average)	CYP2D6 genotype		
		Ultra rapid	Extensive	Poor
Amitriptyline	Dose (mg)	75	94	81
	Relative dose	1.00	1.26	1.08
	Prescriptions per 100 days	0.76	0.43	0.33
	Duration of prescription (days)	11	94	26
		$n^*=2$	$n=23$	$n=4$
Clomipramine	Dose (mg)	63	94	98
	Relative dose	0.63	0.94	0.98
	Prescriptions per 100 days	0.06	1.26	0.33
	Duration of prescription (days)	56	277	42
		$n=1$	$n=26$	$n=3$
Desipramine	Dose (mg)	–	74	66
	Relative dose	–	0.74	0.66
	Prescriptions per 100 days	–	0.73	0.41
	Duration of prescription (days)	–	27	38
		$n=0$	$n=15$	$n=2$
Fluvoxamine	Dose (mg)	100	111	113
	Relative dose	1.00	1.11	1.13
	Prescriptions per 100 days	0.12	1.69	0.34
	Duration of prescription (days)	147	40	52
		$n=2$	$n=46$	$n=5$
Haloperidol	Dose (mg)	4.9	5.7	6.9
	Relative dose	0.61	0.71	0.86
	Prescriptions per 100 days	0.33	2.09	1.18
	Duration of prescription (days)	58	187	83
		$n=2$	$n=51$	$n=7$
Perphenazine	Dose (mg)	–	18	17
	Relative dose	–	0.59	0.55
	Prescriptions per 100 days	–	0.60	0.29
	Duration of prescription (days)	–	308	38
		$n=0$	$n=21$	$n=3$
Risperidone	Dose (mg)	2.0	3.5	2.3
	Relative dose	0.33	0.59	0.38
	Prescriptions per 100 days	0.33	4.5	0.37
	Duration of prescription (days)	11	37	31
		$n=1$	$n=32$	$n=4$
Zuclopentixol	Dose (mg)	32	36	34
	Relative dose	1.07	1.19	1.14
	Prescriptions per 100 days	3.90	1.65	1.16
	Duration of prescription (days)	81	70	26
		$n=3$	$n=87$	$n=8$
Total[a]	Dose (mg)	52	68	60
	Relative dose	0.77	0.87	0.86
	Prescriptions per 100 days	1.23	1.72	0.59[b]
	Duration of prescription (days)	84	106	54[b]
		$n^c=16$	$n=519$	$n=52$

*n concerns number of patients treated (for each patient the mean of all records was calculated)
[a]Total based on all known CYP2D6 substrates (31 drugs including the nine tabulated drugs)
[b]Significant difference ($P<0.05$) with EM group by application of students t-test
[c]n concerns the total number of observations matching the criteria

Results

Patient characteristics and pharmacotherapy

Patient characteristics classified per genotype are presented in Table 1. It was observed that 2.5% (95% CI: 0.5–4.5%) were UMs and 8.3% (95% CI: 4.8–11.8%) were PMs. The observed prevalences did not differ from the expected prevalences (χ^2 test, $P=0.74$). The majority of the patients were females (54%) and the mean age was 50 years (range 18–90 years). The mean number of prescriptions of psychoactive drugs was 46 per patients during an overall average duration of about 3.5 years (1263 days). Almost all patients received psychoactive drugs (>95%). No statistically significant differences were observed between the genotype classes and pharmacotherapy and metabolism characteristics and, therefore, these factors were assumed to be randomly distributed in this patient population.

Antipsychotics were the most prescribed drugs (84% of all patients), anxiolytics/hypnotics (benzodiazepines) were prescribed in 79% of the patients and antidepressants (fluvoxamine, clomipramine, amitriptyline and others) in 52% (Fig. 1). The most frequently prescribed CYP2D6 substrates were zuclopentixol (40%), haloperidol (24.3%), fluvoxamine (21.3%) and risperidone (15.1%).

Drug approach

In Table 2 the pharmacotherapeutic characteristics of eight frequently prescribed substrates for CYP2D6 in

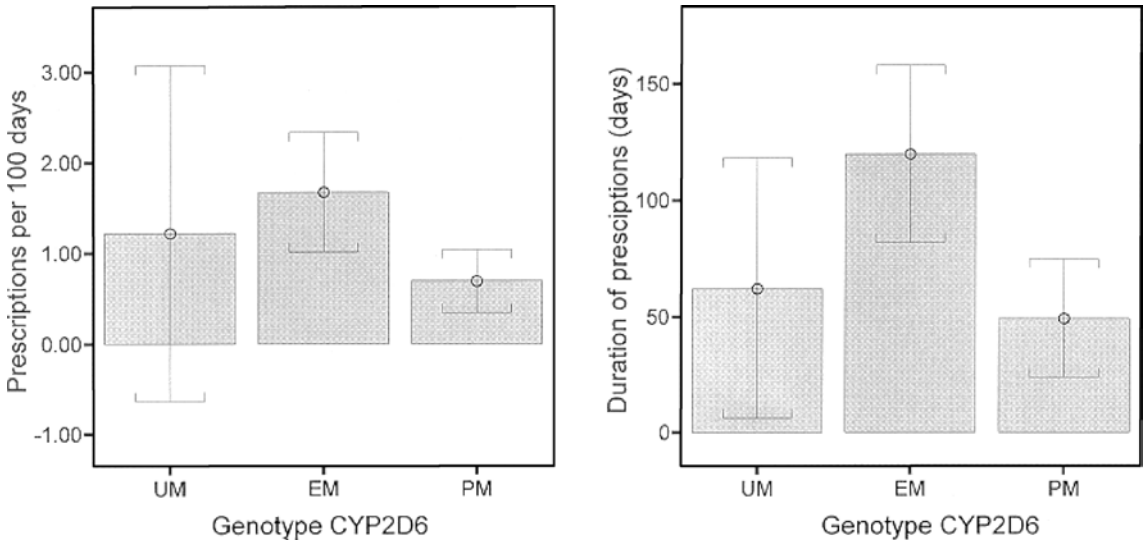

Fig. 2 Prescriptions per 100 days of hospitalisation and the average duration per prescription of a selection of drugs known to be metabolised by CYP2D6 classified in normal (EM) and abnormal (UM and PM) genotype for CYP2D6

this study are summarised, together with the characteristics of all known CYP2D6 substrates. With regard to dose, no consistent differences were observed between the CYP2D6 genotype classes. For some drugs, mean doses were lower in PMs (amitriptyline, desipramine, perphenazine, risperidone and zuclopentixol) than EMs; but, for other drugs, higher doses were observed (clomipramine, fluvoxamine, haloperidol). Comparison between EM and UM showed a lower dose in UMs for all drugs. The overall effect for CYP2D6 substrates showed a lower dose (both absolute and relative) in PMs than in EMs, but this effect was not statistically significant as calculated by ANOVA (dose $P=0.60$; relative dose $P=0.76$). For all CYP2D6 drugs, the number of prescriptions per 100 days was lower in PMs than EMs. Furthermore the prescriptions were generally prescribed for a shorter period to PMs than EMs. Figure 2 shows the results on these two parameters classified for abnormal (UM or PM) and normal (EM) subjects. The number of prescriptions per 100 days was significantly lower in PMs (0.59) than EMs (1.72) as shown using the students *t*-test ($P=0.035$; equal variances not assumed). In addition. the average duration was significantly lower ($P=0.010$) in PMs (54 days) than EMs (106 days). Between UMs and EMs, no significant differences were observed.

Patient approach

Table 3 shows the results of the ''patient approach'' analysis, in which two index groups (PM or UM) were compared with a four times larger control group of patients without indications for impaired metabolism (genotypic EMs). These groups were matched with respect to sex and age. In addition, the duration and the number of prescriptions of the individual utilisation of psychotropic drugs were comparable between the index group and control groups for both PMs and UMs. Between PMs and EMs, significant differences were observed for the prescriptions of drug metabolised by CYP2D6 and for the prescriptions for Parkinsonian-like side effects. In PMs, drugs metabolised by CYP2D6 were less frequently prescribed than in EMs (21.1% vs 33.6%, $P=0.023$). Drugs for Parkinsonian-like side effects, e.g. biperiden (Fig. 1), dexetimide, orphenadrine and trihexyphenidyl, were given twice as frequently in PMs as EMs (6.9% vs 3.4%, $P=0.045$). Switching of drugs tended to be more frequent in PMs than EMs (10.6% vs 8.7%) but this was not significant ($P=0.36$) and seemed not to be related to CYP2D6 switches, because the drug switches not affecting the route of metabolism were most frequently observed (about 60% of all switches). Dose decreases and increases were comparable between PMs and EMs ($P=0.73$ and $P=0.85$, respectively).

Discussion

The prevalences of impaired metabolism observed in the subjects in the present study were, as expected, not different from that in the general population [21, 24]. In 18% of all drugs used in this study, metabolism was mediated by CYP2D6. This enzyme was more prominently involved in the metabolism of the prescribed psychoactive drugs (about 35%) which is in line with other observations [1, 17]. The large majority (91%) of all patients used at least one CYP2D6-sensitive drug during pharmacotherapy.

No dose-related differences were observed for the three subgroups. The mean average dose did not significantly differ between EMs and PMs nor between EMs and UMs (Table 2). Also, the frequencies of dose switches were equal between PM or UM and the EMs (Table 3). It is important to note that the treating psychiatrist was

Table 3 Pharmacotherapeutic characteristics of patients known to be poor or ultra rapid metabolisers for CYP2D6 (index) relative to a control panel of CYP2D6 extensive metabolisers

	Characteristics (average)	CYP2D6 genotype	
		Index	Control
Demography/ pharmacotherapy		Poor	Extensive
	Males	$n=7$ (35%)	$n=28$ (35%)
	Females	$n=13$ (65%)	$n=52$ (65%)
	Age (years; min–max)	52 (24–90)	52 (23–89)
	Duration of therapy (days ± SEM)	1478 (± 239)	1350 (± 129)
	Number of prescriptions (± SEM)	54 (± 13)	43 (± 5)
		$n=20$	$n=80$
Fraction of total prescriptions during first 180 days	Prescriptions of CYP2D6 drugs (%; ± SEM)	21.1% (± 3.7%)#	33.6% (± 2.5%)
	Prescriptions of non-CYP2D6 drugs (%; ± SEM)	62.7% (± 5.1%)	55.3% (± 2.5%)
	Total switches (%; ± SEM)	10.6% (± 1.8%)	8.7% (± 1.0)
	Switches without implication*(%; ± SEM)	7.2% (± 1.5%)	5.2% (± 0.7%)
	Switches to CYP2D6 drug** (%; ± SEM)	2.1% (± 0.8%)	1.6% (± 0.3%)
	Switch from CYP2D6 drug*** (%; ± SEM)	1.3% (± 0.5%)	1.8% (± 0.4%)
	Switch to lower dose (%; ± SEM)	8.3% (± 1.6%)	9.1% (± 1.0%)
	Switch to higher dose (%; ± SEM)	9.8% (± 1.8%)	9.4% (± 0.8%)
	Prescriptions against Parkinsonian-like side effects (%; ± SEM)	6.9% (± 2.3%)#	3.4% (± 0.6%)
Demography/ pharmacotherapy		Ultra rapid	Extensive
	Males	$n=3$ (50%)	$n=12$ (50%)
	Females	$n=3$ (50%)	$n=12$ (50%)
	Age (years; min–max)	55 (26–80)	55 (24–81)
	Duration of therapy (days ± SEM)	937 (± 458)	1581 (± 256)
	Number of prescriptions (± SEM)	43 (± 21)	43 (± 7)
		$n=6$	$n=24$
Fraction of total prescriptions during first 180 days	Prescriptions of CYP2D6 drugs (%; ± SEM)	30.2% (± 2.6%)	38.5% (± 4.7%)
	Prescriptions of non-CYP2D6 drugs (%; ± SEM)	56.9% (± 7.6%)	48.7% (± 4.0%)
	Total switches (%; ± SEM)	6.1% (± 2.4%)	10.9% (± 2.0)
	Switches without implication (%; ± SEM)	2.7% (± 1.5%)	7.5% (± 1.7%)
	Switches to CYP2D6 drug (%; ± SEM)	1.9% (± 1.5%)	2.2% (± 0.6%)
	Switch from CYP2D6 drug (%; ± SEM)	1.5% (± 0.7%)	1.2% (± 0.4%)
	Switch to lower dose (%; ± SEM)	6.5% (± 2.9%)	8.4% (± 1.7%)
	Switch to higher dose (%; ± SEM)	8.7% (± 2.5%)	9.9% (± 1.2%)
	Prescriptions against cholinergic AEs (%; ± SEM)	2.7% (± 2.2%)	5.3% (± 1.0%)

#Significant differences between index and control $P<0.05$
*No metabolic change: a switch from one drug to another without changes in the metabolic route of the drug regarding CYP2D6
**Switch form non-CYP2D6 drug to a CYP2D6 drug
***Switch from a CYP2D6 drug to a non-CYP2D6 drug

unaware of the genotype of the patient. Hence, without knowledge of the genotype status, dose titrations based on the patients metabolising capacity could not be expected. Therefore, it seems reasonable to suppose that in case of problems with the utilisation of psychotropic drugs, alternative drugs would be used. The data presented were in agreement with such an assumption because the characteristics of drugs used in patients with a normal metabolising capacity was found to be different from that in patients with abnormal metabolising capacities. The number of prescriptions per 100 days for known CYP2D6 drugs was significantly lower in the CYP2D6 PM genotype and the duration for use in these prescriptions was significantly shorter (Fig. 2). The fraction of prescriptions of CYP2D6 drugs was significantly lower in the index group (PMs) than in EMs, which again indicates that CYP2D6 drugs were given less frequently to PM patients (Table 3). The lower number of CYP2D6 drugs prescribed in PMs may be caused by the higher incidence of AEs, which can easily be observed without knowledge of the genotype. Indications for a higher incidence of AEs in PMs were observed by the significantly higher number of prescriptions per 100 days of drugs for Parkinsonian-like side effects (Table 3). Other studies have also shown an increased incidence of PMs among those suffering from severe side effects [9, 14, 15, 16, 17, 25, 26, 27, 28, 29].

Surprisingly, the pharmacotherapy of the UM patients were generally comparable with EMs. These results suggest that the pharmacotherapy is less affected in UMs than in PMs. This may be explained since the UM and EM genotypic classes have a large overlap in metabolic ratios, whereas between EMs and PMs there is no overlap [5]. In addition, CYP2D6 metabolism for some psychoactive drugs results in an active metabolite and, therefore, ultra rapid metabolism may result in normal pharmacological activity. The above assumptions are in line with a study in which the failure to respond to typical antipsychotics could not be associated with the UM genotype [28].

So far, most studies have focused on AEs to measure the efficacy of pharmacotherapy, but in none of the studies have pharmacy records been used as a measure of the quality of the pharmacotherapy. Focusing on the "efficacy of the pharmacotherapy" as a clinical endpoint has not often been done; however, this endpoint is crucial for cost-efficacy studies. Though it should be noted that AEs and efficacy are only partly related to metabolic polymorphism and that other important polymorphisms, e.g. receptor and transporter polymorphisms, also play a role [30, 31]. In addition, it should be realised that CYP2D6 genotyping does not predict the actual phenotype with a 100% certainty, e.g. missing mutations may cause false negatives; comedication may cause CYP2D6 inhibition; etc. It is therefore unlikely that genotyping can fully replace therapeutic drug monitoring but information on the individual metabolising genotype might be helpful in optimising TDM procedures (sample frequency and scheduling) [32]. The same conclusion is drawn by Kirchheiner et al who reviewed dose recommendations for 32 antidepressants based on genotypes of cytochrome P_{450} enzymes [33]. They conclude that the existence of other partially unidentified variables should not detract us from considering known determinants.

In conclusion, this retrospective study showed that pharmacy records might be a useful tool to detect differences related to polymorphic metabolism. They revealed that psychoactive drugs metabolised by CYP2D6 were less frequently prescribed in PMs than EMs. Furthermore, PMs seemed to be more prone to Parkinsonian-like side effects, as evidenced by more prescriptions for drugs combating these side effects. Large prospective studies are needed to further document both the beneficial effect and cost effectiveness of genotyping.

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