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SHORT COMMUNICATION

Prescribed Doses of CYP2D6-Metabolized Drugs and Hemodynamic Responses in Relation to CYP2D6 Genotype Among Older Patients Exposed to Polypharmacy

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Abstract

Background Many drugs with dose-dependent effects on hemodynamic variables are metabolized by cytochrome P450 2D6 (CYP2D6). The aim of this study was to compare prescribed dosages and hemodynamic responses of such drugs in relation to pharmacogenetic variability in CYP2D6 metabolism among patients aged ≥ 70 years exposed to polypharmacy.

Materials and Methods We included 173 patients with detailed information about drug use. The patients were retrospectively subjected to *CYP2D6* genotyping, which comprised the most common variant alleles encoding reduced, absent, or increased CYP2D6 metabolism. In order to compare dosages across different CYP2D6-metabolized drugs, all prescribed daily doses were harmonized to the 'percent of a daily defined dose' (DDD). The mean harmonized DDD was compared between genotype-predicted normal metabolizers (NMs) and patients with reduced or absent CYP2D6 enzyme activity, defined as intermediate or poor metabolizers (IMs/PMs). Blood pressure, pulse, and patient proportions with orthostatism and bradycardia were also compared between genotype subgroups.

Results The genotype-predicted phenotype subgroups comprised 79 NMs (45.7%), 75 IMs (43.4%), and 16 PMs (9.2%). There were no differences in dosing of CYP2D6 substrates between NMs and IMs/PMs ($p = 0.76$). A higher proportion of CYP2D6 IMs/PMs experienced orthostatism ($p = 0.03$), while there were no significant subgroup differences for the other hemodynamic variables.

Conclusion In this real-life clinical setting of patients aged ≥ 70 years, dosing of CYP2D6 substrates were not adjusted according to genotype-predicted CYP2D6 metabolism. The increased occurrence of orthostatism in patients with reduced/absent CYP2D6 metabolism may indicate that individualized dosing based on genotype has the potential to prevent adverse effects in these vulnerable patients.

Key Points

Pharmacogenetic variation in CYP2D6 metabolism can affect clinical effects as well as adverse effects of many drugs.

We found that patients aged ≥ 70 years with reduced or absent CYP2D6 metabolism received equal doses of CYP2D6-metabolized drugs as patients with normal CYP2D6 metabolism, and had an increased occurrence of orthostatism.

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1 Introduction

Individual variability in drug response depends on many factors in addition to the prescribed dosage, in particular, age, gender, organ functions, polypharmacy, drug–drug interactions, and pharmacogenetics. In recent years, increasing attention has been paid to the impact of pharmacogenetic differences on clinical and adverse effects of drug treatment [1], and in particular the role of genetic polymorphisms in drug-metabolizing enzymes [2].

Cytochrome P450 2D6 (CYP2D6) is one of the most well studied genetic polymorphic enzymes involved in drug metabolism. CYP2D6-metabolizing phenotype is closely related to genotype, and patients are generally divided into the following four phenotype subgroups based on genotype: 'poor metabolizers (PMs),' 'intermediate metabolizers (IMs),' 'normal metabolizers (NMs)', and 'ultrarapid metabolizers (UMs)' [3]. Population frequencies of the various CYP2D6 phenotype subgroups differ between ethnic groups due to environmentally driven selection of 'best-fit' genotypes. In Caucasian populations, the proportion of PMs is higher than in other ethnic groups, while the proportion of UMs is generally higher in southern versus northern world regions [4].

CYP2D6 is involved in the metabolism of about 25% of all clinically used drugs [5]. For drugs where CYP2D6-mediated metabolism is a major eliminating pathway, the systemic exposure (effective dose) is very dependent on *CYP2D6* genotype [4]. The relative effective dose may differ up to tenfold across different *CYP2D6* genotype subgroups. This implies a great potential for variability in therapeutic response for non-genotype-adjusted dosages [4]. For older people, where secondary eliminating pathways are often reduced (e.g., renal filtration or secretion), the genotype effect could be even more pronounced, making dosage adjustments critical in order to avoid overtreatment.

The usual situation is that PMs are at risk of over-exposure and side effects at standard dosages, but in UMs the potential clinical outcome is the opposite. For psychotropic agents and β-blockers, for instance, increased risk of side effects has been reported in PMs and insufficient clinical response in UMs [6, 7]. However, for some opioid analgesics being defined as prodrugs activated by CYP2D6 (e.g., codeine and tramadol), the potential clinical consequences are the opposite. In the case of codeine, PMs have been reported to obtain insufficient analgesia [8], while several case reports have been published showing respiratory depression in UMs due to increased CYP2D6-mediated bioactivation of codeine to morphine [9, 10].

Older people exposed to polypharmacy have a high risk of adverse drug reactions (ADRs) [11]. Many CYP2D6-metabolized drugs commonly used by older people exhibit hemodynamic effects, including cardiovascular and psychotropic drugs [4, 12]. It could be hypothesized that older IMs and PMs are at higher risk for ADRs, such as orthostatic hypotension or bradycardia, if dosages are not adequately adjusted. Genotyping is rarely used in clinical practice, and it may be argued that knowledge of the genotype is of limited relevance, since physicians will nevertheless adjust dosages according to the clinical response. It is, however, uncertain if the underlying genotypes are actually reflected by the prescribed dosages when physicians are unaware of the patients' ability to metabolize CYP2D6 substrate drugs.

The aim of this study was therefore to examine the prescribed dosages of CYP2D6 substrates in relation to genotype in home-dwelling patients aged ≥ 70 years exposed to polypharmacy. Secondarily, we assessed the impact of *CYP2D6* genotype on blood pressure and heart rate.

2 Methods

2.1 Study Population and Data Collection

Data were taken from baseline assessments of participants in a recently published cluster randomized clinical trial (RCT) investigating drug-related issues in elderly people receiving polypharmacy [13]. In accordance with the inclusion criteria of the RCT, the present observational study comprised home-dwelling patients aged ≥ 70 years, using at least seven daily medications administered by the home nursing service. The rationale for including these patients was based on the hypothesis that they would benefit most of the geriatric intervention studied in the RCT.

Measurements of blood pressure and pulse rate were carried out by a research assistant during a home visit, using a validated, automated blood pressure monitor (UA-767 Plus 30, A&D Medical, San Jose, CA, USA). Supine blood pressure and pulse rate were measured twice, after a minimum of 5 minutes' rest, and the mean value was used for the analyses. The patient then stood up, and measurements were repeated after 1 min. Comorbidity was assessed by the Cumulative Illness Rating Scale (CIRS) [14], based on a retrospective review of the patients' medical records. Dementia severity was assessed by the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) [15, 16].

Inclusion of patients was based upon informed consent. Patients unable to give a valid consent due to dementia were included based on informed consent from a close relative, in combination with assent from the patient. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Norway and by the Data Protection Official at Oslo University Hospital, and was carried out in accordance with the Declaration of Helsinki [17].

2.2 Identification of CYP2D6 Substrates

Medication charts were obtained from the patients' family physician (FP), and actual drug use was confirmed by patients and/or caregivers. Drugs were registered according to the Anatomical Therapeutic Chemical (ATC) classification system [18]. In order to define a major relevance of CYP2D6 in the metabolism of the various drugs used by the patients, descriptions of metabolic pathways available from the website http://www.pharmgkb.org were applied. We also reviewed summaries of product characteristics (SPCs) to obtain information about the relevance of CYP2D6 in the respective drugs' metabolism. Co-administration of CYP2D6 inhibitors was also registered.

2.3 Genotyping and Phenotype Classification

Venous blood samples collected on tubes with ethylenediaminetetraacetic acid (EDTA) as anticoagulant were used for determination of *CYP2D6* genotype, and the analyses were performed at the Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway. Briefly, extracted DNA samples were analysed for targeted *CYP2D6* variant alleles known to encode absent, reduced, or increased CYP2D6 metabolism using Taqman-based real-time PCR assays. The *CYP2D6* genotyping comprised the *non-coding* variants *CYP2D6*3* (*rs35742686*), *CYP2D6*4* (*rs3892097*), *CYP2D6*5* (whole gene deletion), and *CYP2D6*6* (*rs5030655*), the reduced-function variants *CYP2D6*9* (*rs5030656*), *CYP2D6*10* (*rs1065852*), and *CYP2D6*41* (*rs28371725*), as well as copy number analysis to identify multiplication of functional alleles giving rise to ultrarapid metabolism.

The patients were categorized into CYP2D6 metabolizer subgroups based on genotype. PMs were defined as homozygous carriers of non-coding alleles (*CYP2D6*3, *4, *5,* and **6*). IMs were defined as heterozygous carriers of non-coding alleles, homozygous carriers of reduced-function alleles (*CYP2D6*9, *10,* and **41*), or carriers of genotypes with combined reduced-function and non-coding alleles. NMs were defined as homozygous carriers of two fully functional (wild-type) alleles (*CYP2D6*1*) or carriers of one reduced-function allele combined with a wild-type allele. UMs were defined as carriers of multiple (> 2) copies of alleles encoding normal metabolic activity. This categorization of CYP2D6 metabolizer subgroups for statistical analyses is in accordance with standard practice at the time when the study was conducted, while a modification of the phenotype classification was recently published by members of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group [19].

2.4 Outcome Measures

2.4.1 Dosages

Our first aim was to examine the prescribed dosages of CYP2D6-dependent drugs in relation to genotype. As defined by WHO, "the defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults" [20]. In order to examine the prescribed daily dosages across a variety of drugs, prescribed dosages for all substrates were calculated as percent of DDD. The average percent of DDD was calculated for each patient for comparisons between CYP2D6 metabolizer subgroups. As differences in CYP2D6 metabolism will affect the response of drugs administered in pharmacologically active forms or prodrugs (e.g., codeine and tramadol) differently, separate comparisons were performed for these two situations.

2.4.2 Hemodynamic Variables

Our second aim was to examine the impact of CYP2D6 genotype on hemodynamic variables. The outcome measures used for these analyses were systolic (SBP) and diastolic blood pressure (DBP) measured in the supine position, change in SBP after 1 min in standing position, pulse rate, orthostatic hypotension, and bradycardia. Orthostatic hypotension was defined as a fall in SBP of at least 20 mmHg or a fall in DBP of at least 10 mmHg after 1 min in standing position, while bradycardia was defined as a pulse rate < 60/min.

2.5 Statistical Analyses

In the study population, UMs using a CYP2D6 substrate only comprised two patients, and this phenotype subgroup was therefore excluded from the statistical analyses. The patients were divided into two CYP2D6 metabolizer subgroups for outcome comparisons, NMs versus IMs and PMs merged into one group.

Since several non-CYP2D6 drugs can affect blood pressure, the use of such drugs from ATC group C01DA (nitrates), C02 (antihypertensives), C03 (diuretics), C07 (β-blocking agents), C08 (calcium channel blockers), C09 (agents acting on the renin-angiotensin system), G04CA (α-adrenoreceptor antagonists), N02A (opioids), N03 (antiepileptics), N04 (anti-parkinson drugs), N05 (psycholeptics), and N06A (antidepressants) was compared between the CYP2D6 metabolizer subgroups. Likewise, to account for non-CYP2D6 drugs that could contribute to bradycardia, the use of such drugs from ATC group C01AA (digitalis glycosides), C01B (antiarrhythmics, class I and III), C07 (β-blocking agents), and C08D (selective calcium channel blockers with direct cardiac effects) were assessed between

the genotype subgroups. However, the prescribed DDDs of the non-CYP2D6 drugs were not reviewed, prohibiting quantification of the potential modulation effect of these agents on the hemodynamic variables between the two CYP2D6 metabolizer subgroups.

For non-normally distributed variables, the Mann-Whitney *U* test was used to test for differences between the CYP2D6 metabolizer subgroups. For normally distributed variables, comparisons were performed using the independent samples *t*-test. Group differences for categorical variables were tested by Pearson's chi-square test or Fischer's exact test, as appropriate. In the case of statistically significant findings by univariate analysis, multivariate logistic regression was performed to account for potential confounders.

All statistical analyses were performed using IBM SPSS Statistics version 25.

3 Results

A blood sample for *CYP2D6* genotyping was obtained from 173 Caucasian patients. The genotype-predicted phenotype subgroups comprised 3 UMs (1.7%), 79 NMs (45.7%), 75 IMs (43.4%), and 16 PMs (9.2%). Characteristics of the respective metabolizer subgroups are presented in Table 1. The use of CYP2D6 inhibitors did not differ between metabolizer subgroups. Only weak CYP2D6 inhibitors were in use (i.e., escitalopram, mirabegron, and amiodarone). Although the CYP2D6 inhibitors were all detected in the NM or IM subgroups, both with functional metabolism, drug–drug–genotype interactions and phenoconversion was considered as unlikely due the limited inhibitory potency of the mentioned agents. Thus, the genotype-predicted CYP2D6-metabolizing phenotype was not adjusted for by any co-medications.

3.1 Dosages of CYP2D6 Substrates in Relation to Genotype

In the included patient population, a total of 19 different CYP2D6 substrates were in use, including three prodrugs. Their mean prescribed daily dosages and the respective percentage of DDD are presented in the various genotype subgroups in Table 2. Metoprolol was by far the most frequently used CYP2D6 substrate drug, being prescribed to 76 (43.9%) of the patients (Table 2).

The mean harmonized dosage of CY2D6-metabolized drugs administered in the pharmacologically active form was 58% of DDD for NMs, 59% of DDD for IMs, and 63% of DDD for PMs (Table 3). There was no statistically significant difference in drug dosages of active CY2D6 substrates between NMs and IMs/PMs ($p = 0.76$).

For CYP2D6 prodrugs, the mean dosage was 49% of DDD for NMs, 43% of DDD for IMs, and 43% of DDD for PMs (Table 3). There was no statistically significant difference in dosages of the prodrugs between NMs and IMs/PMs ($p = 0.74$).

3.2 Hemodynamic Effects in Users of CYP2D6 Substrates in Relation to Genotype

Table 4 provides an overview of hemodynamic variables in users of CYP2D6 substrates, except from prodrugs, in the various genotype subgroups. There was no statistically significant difference between NMs and IMs/PMs in SBP ($p = 0.79$), DBP ($p = 0.58$), or pulse rate ($p = 0.34$) measured in the supine position. SBP dropped in all groups after 1 min in the standing position, but there was no statistically significant difference between groups ($p = 0.15$). Nine patients had no measurements of standing blood pressure, and could not be examined for orthostatic hypotension.

The patient proportions with orthostatic hypotension (OH) was significantly higher for merged IMs (OH 44%)/PMs (OH 50%) than for NMs (OH 24%), $p = 0.03$. All patients with valid measurements of orthostatic hypotension

Table 1 Characteristics of participants in different CYP2D6 genotype subgroups

Characteristics	UM ($n = 3$)	NM ($n = 79$)	IM ($n = 75$)	PM ($n = 16$)
Age, mean (SD)	79.7 (9.0)	84.1 (7.8)	82.9 (7.0)	81.9 (6.5)
Female gender, *n* (%)	3 (100)	55 (70)	48 (64)	11 (69)
Number of CYP2D6 substrate drugs in use, mean (SD)	1.3 (1.2)	0.9 (0.9)	1.0 (0.7)	0.9 (0.9)
Total number of drugs used regularly, mean (SD)	11.0 (2.7)	9.4 (2.6)	10.0 (2.8)	10.0 (2.8)
CIRS sum, mean (SD)	18.3 (2.1)	16.6 (4.6)	16.8 (4.0)	16.4 (4.0)
CDR sum of boxes, mean (SD)	5.0 (5.0)	2.4 (3.3)	2.0 (3.3)	2.8 (3.6)

CDR Clinical Dementia Rating Scale, *CIRS* Cumulative Illness Rating Scale, *CYP2D6* cytochrome P450 2D6, *IM* intermediate metabolizer, *NM* normal metabolizer, *PM* poor metabolizer, *SD* standard deviation, *UM* ultrarapid metabolizer

Table 2 Number of prescribed CYP2D6 substrate drugs (decreasing order of frequency), dose mean, and average dosage in percent of DDD by CYP2D6 genotype subgroup

CYP2D6 substrate	UM ($n=3$)			NM ($n=79$)			IM ($n=75$)			PM ($n=16$)		
	n	Dose Mean (SD)	Average % of DDD	*n*	Dose Mean (SD)	Average % of DDD	*n*	Dose Mean (SD)	Average % of DDD	*n*	Dose Mean (SD)	Average % of DDD
Metoprolol	1	100.0 mg	67	34	71.0 mg (47.4)	47	34	60.3 mg (43.9)	40	7	94.6 mg (80.3)	63
Tamsulosin				5	0.4 mg (0.0)	100	7	0.5 mg (0.2)	114	2	0.4 mg (0.0)	100
Mirtazapine				7	23.6 mg (8.0)	79	4	26.3 mg (7.5)	88			
Oxycodone[a]				6	25.8 mg (36.7)	34	2	22.5 mg (24.8)	30	2	15.0 mg (7.1)	20
Codeine[a]	1	90.0 mg	90	3	60.0 mg (30.0)	60	4	30.0 mg (0.0)	30	1	90.0 mg	90
Tramadol[a]				1	300.0 mg	100	7	164.3 mg (69.0)	55			
Donepezil				1	10.0 mg	133	5	9.0 mg (2.2)	120			
Amitriptyline				3	25.0 mg (0.0)	33	2	37.5 mg (17.7)	50			
Venlafaxine	1	150.0 mg	150	2	93.8 mg (79.6)	94	2	75.0 mg (0.0)	75			
Fesoterodine				2	6.0 mg (2.8)	150				2	4.0 mg (0.0)	100
Mianserin				1	30.0 mg	50	2	25.0 mg (7.1)	42	1	20.0 mg	33
Carvedilol				1	12.5 mg	33	2	37.5 mg (17.7)	100			
Propranolol							3	46.7 mg (30.6)	29			
Amiodarone				1	100.0 mg	50	1	100.0 mg	50			
Risperidone				1	1.0 mg	20	1	1.0 mg	20			
Aripiprazole	1	10.0 mg	67									
Doxepin				1	20.0 mg	20						
Paroxetine				1	10.0 mg	50						
Tolterodine				1	4.0 mg	100						

Entire material ($N=173$)

CYP2D6 cytochrome P450 2D6, *DDD* defined daily dose, *IM* intermediate metabolizer, *NM* normal metabolizer, *PM* poor metabolizer, *SD* standard deviation, *UM* ultrarapid metabolizer

[a]Prodrug

Table 3 Average dosage in percent of DDD for users of CYP2D6 substrates ($N=121$) by CYP2D6 genotype subgroups

CYP2D6 substrate	UM ($n=2$)		NM ($n=50$)		IM ($n=59$)		PM ($n=10$)		p value[a]
	n	Average % of DDD	n	Average % of DDD	n	Average % of DDD	n	Average % of DDD	
Treatment intensity for users of CYP2D6 substrates (non-prodrugs)	2	88	46	58	51	59	9	63	0.76
Treatment intensity for users of CYP2D6 prodrugs	1	90	10	49	13	43	3	43	0.74

CYP2D6 cytochrome P450 2D6, *DDD* defined daily dose, *IM* intermediate metabolizer, *NM* normal metabolizer, *PM* poor metabolizer, *UM* ultrarapid metabolizer

[a]The p value is based on comparisons between two groups: NMs versus IMs/PMs (UMs excluded)

Table 4 Hemodynamic variables for users of drugs inactivated by CYP2D6 ($N=108$) by CYP2D6 genotype subgroup

	UM ($n=2$)		NM ($n=46$)		IM ($n=51$)		PM ($n=9$)		p value[a]
	n		n		n		n		
Supine SBP, mean (SD)	2	132 (4)	46	135 (22)	51	138 (22)	9	127 (15)	0.79
Supine DBP, mean (SD)	2	85 (7)	46	74 (12)	51	72 (13)	9	75 (18)	0.58
Change in SBP after 1 min standing, mean (SD)	2	−20 (10)	42	−7 (19)	48	−14 (22)	8	−12 (19)	0.15
Orthostatic hypotension, *n* (%)	2	1 (50)	42	10 (24)	48	21 (44)	8	4 (50)	0.03
Pulse rate, mean (SD)	2	73 (9)	46	70 (12)	51	67 (13)	9	67 (17)	0.34
Bradycardia, *n* (%)	2	0 (0)	46	9 (20)	51	15 (29)	9	3 (33)	0.22
Number of non-CYP2D6 drugs potentially affecting the risk of orthostatism[b], mean (SD)	2	5.0 (1.4)	42	3.9 (1.7)	48	4.1 (1.4)	8	3.9 (1.4)	0.53
Number of non-CYP2D6 drugs potentially affecting pulse rate[c], mean (SD)	2	0.5 (0.7)	46	0.9 (0.5)	51	1.0 (0.6)	9	0.9 (0.6)	0.43
Co-administration of CYP2D6 inhibitors, *n* (%)[d]	2	0	46	4 (9)	51	7 (14)	9	0 (0)	0.75

Patients using only CYP2D6 prodrugs are excluded

CYP2D6 cytochrome P450 2D6, *DBP* diastolic blood pressure, *IM* intermediate metabolizer, *NM* normal metabolizer, *PM* poor metabolizer, *SBP* systolic blood pressure, *SD* standard deviation, *UM* ultrarapid metabolizer

[a]The p value is based on comparisons between two groups: NMs versus IMs/PMs (UMs excluded)

[b]Comprising drugs from ATC groups C01DA, C02, C03, C07, C08, C09, G04CA, N02A, N03, N04, N05, and N06. Counts are included only for patients having valid measurements of orthostatism

[c]Comprising drugs from ATC groups C01AA, C01B, C07, and C08D

[d]Amiodarone, mirabegron, escitalopram

used at least one non-CYP2D6 drug (range 1–8) that could potentially increase the occurrence of orthostatism, but the mean number of such drugs did not differ between the genotype subgroups ($p=0.53$). The observed higher occurrence of orthostatism for IMs/PMs was further examined by logistic regression, showing that the difference versus NMs was unaffected by total numbers of drug use and comorbidity (adjusted odds ratio (OR) 2.6, 95% CI 1.1–6.3; $p=0.04$) [Table S1 in the electronic supplementary material (ESM)]. Data on renal and hepatic function were not systematically available for the included patients.

The calculated proportion of patients with bradycardia was also higher for IMs (29%) and PMs (33%) than for NMs (20%), but the association between metabolizer subgroup and bradycardia was not statistically significant ($p=0.22$). The mean number of non-CYP2D6 drugs potentially affecting pulse rate did not differ between the genotype subgroups ($p=0.43$).

Metoprolol was the most frequently used CYP2D6 substrate ($n=76$), which made it interesting to perform subgroup analyses for these patients (Table 5). There were no statistically significant differences between NMs and IMs/PMs for any of the hemodynamic variables in metoprolol-treated patients, but we observed a trend towards higher occurrence of orthostatic hypotension for IMs/PMs compared with NMs ($p=0.07$). As above, this finding was further examined by logistic regression (Table S2 in the ESM). The trend towards increased occurrence of orthostatism for IMs/PMs was unaffected by total drug use and comorbidity also for the metoprolol users (adjusted OR 2.8, 95% CI 0.9–8.4).

Table 5 Hemodynamic variables for users of metoprolol ($N=76$) by CYP2D6 genotype subgroup

	UM ($n=1$)		NM ($n=34$)		IM ($n=34$)		PM ($n=7$)		p value[a]
	n		*n*		*n*		*n*		
Supine SBP, mean (SD)	1	135	34	135 (23)	34	137 (23)	7	129 (16)	0.93
Supine DBP, mean (SD)	1	80	34	74 (12)	34	71 (14)	7	71 (19)	0.35
Change in SBP after 1 min standing, mean (SD)	1	−13	31	−5 (17)	32	−12 (19)	6	−11 (22)	0.17
Orthostatic hypotension, *n* (%)	1	0	31	6 (19)	32	13 (41)	6	2 (33)	0.07
Pulse rate, mean (SD)	1	67	34	68 (11)	34	66 (13)	7	63 (18)	0.42
Bradycardia, *n* (%)	1	0	34	8 (24)	34	11 (32)	7	3 (43)	0.32
Number of non-CYP2D6 drugs in addition to metoprolol potentially affecting the risk of orthostatism[b], mean (SD)	1	3	34	3.1 (1.6)	34	3.2 (1.5)	7	2.9 (1.5)	0.59
Number of non-CYP2D6 drugs in addition to metoprolol potentially affecting pulse rate[c], mean (SD)	1	0	34	0.1 (0.2)	34	0.2 (0.5)	7	0.1 (0.4)	0.22
Co-administration of CYP2D6 inhibitors, *n* (%)[d]	1	0	34	4 (12)	34	7 (21)	7	0	0.75

CYP2D6 cytochrome P450 2D6, *DBP* diastolic blood pressure, *IM* intermediate metabolizer, *NM* normal metabolizer, *PM* poor metabolizer, *SBP* systolic blood pressure, *SD* standard deviation, *UM* ultrarapid metabolizer

[a]The *p*-value is based on comparisons between two groups; NMs versus IMs/PMs (UMs excluded)

[b]Comprising drugs from ATC groups C01DA, C02, C03, C07, C08, C09, G04CA, N02A, N03, N04, N05, and N06

[c]Comprising drugs from ATC groups C01AA, C01B, C07, and C08D

[d]Amiodarone, mirabegron, escitalopram

4 Discussion

There was no difference in the mean prescribed dosage of CYP2D6 substrates between the various CYP2D6-metabolizer subgroups, either for drugs inactivated by CYP2D6 or those activated by CYP2D6 (prodrugs). As *CYP2D6* genotype is known to be a major determinant of the exposure of the studied drugs, this may indicate that the physicians' clinical judgement is insufficient when the aim is to optimize dosages for older patients and avoid ADRs. This is supported by the significant difference in orthostatism between CYP2D6 slow and normal metabolizers. It would have been favorable to study IMs and PMs as separate subgroups, but the limited power did not allow for reasonable statistical comparisons of three CYP2D6 subgroups. However, it was interesting to observe an increased occurrence of orthostatism by a stepwise reduction in CYP2D6 metabolizer phenotype, where 24% of NMs, 44% of IMs, and 50% of PMs had this symptom. As the present study is based on a post-hoc analysis of a limited population size, the potential increased risk of ADRs in older CYP2D6 IMs/PMs should be further investigated prospectively in larger patient populations.

The patients included in our study were aged 70 years or older, multimorbid, and exposed to extensive polypharmacy, and therefore especially vulnerable to ADRs [21]. The fact that all metabolizer subgroups were prescribed lower doses of CYP2D6 substrate drugs than generally recommended, as indicated by the calculated percentage of DDD, could reflect a reduced drug tolerability in the included patient population, or precautious physicians. Other factors than variability in CYP2D6 metabolism may therefore be of similar or greater importance for dose requirements of the identified CYP2D6 substrates. However, taking into account the therapeutic heterogeneity of the CYP2D6 substrates and the significant impact on risk of orthostatism, we consider it likely that older patients with reduced or absent CYP2D6 metabolism should be dosed lower than those with normal metabolism. In line with this, use of *CYP2D6* genotyping should be considered as a tool for optimized dosing in older patients receiving complex treatment with multiple drugs.

We have not found other studies evaluating the impact of *CYP2D6* polymorphisms on treatment intensities across various CYP2D6 substrates, but prescribed dosages in relation to *CYP2D6* genotype of single drugs has, to some extent, been investigated [22–27]. For example, in a large population-based cohort of elderly patients, Bijl et al. found significantly lower maintenance doses of antidepressants in PMs compared with NMs [22]. For metoprolol, which is extensively metabolized by CYP2D6, some studies have found that PMs were prescribed significantly lower doses than NMs [23–25], while others did not find such differences [26, 27].

Despite CYP2D6 PMs obtaining a fivefold higher exposure of metoprolol per dose, the reported findings of the impact of *CYP2D6* genotype on hemodynamic variables and side effects are conflicting [28, 29]. While some studies have found associations between *CYP2D6* genotype and clinical

effects [6, 23, 24, 30, 31], others have not [26, 32–34]. This may partly be explained by the fact that most studies were performed in a naturalistic setting without any controlled dosing protocol. In the present study, the metoprolol dosing was similar regardless of CYP2D6 genotype, with a non-significantly higher proportion of patients with orthostatism in CYP2D6 IMs/PMs versus NMs. Thus, in older CYP2D6 IMs/PMs, it seems rational to initiate metoprolol treatment with a lower dose than usually recommended.

There were relatively few patients using CYP2D6 substrates other than metoprolol with strong hemodynamic effects, such as tricyclic antidepressants (TCAs) [35]. We cannot rule out that patients with reduced or absent CYP2D6 metabolism have previously used more CYP2D6 substrates, but that ADRs caused these drugs to be stopped before the initiation of our study.

The most important weakness of our study is that relatively few patients were included, which reduces the statistical power of the comparisons. Further studies should therefore replicate our findings, preferably in larger populations of older patients. In addition, we did not have sufficient data for all participants to include renal or hepatic impairment as covariates in the analyses, and cannot rule out that this could have affected the observed findings. Another aspect is that more refined classification or subgrouping of *CYP2D6* genotype-predicted phenotypes by the use of the functional allele enzyme activity scores, which is currently advised to be applied by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG), may improve the clinical interpretation of the possible association between CYP2D6 metabolism and treatment outcomes. However, very limited clinical research is performed on the pharmacogenetic impact of drug effects and side effects in the increasing population of home-dwelling older patients. In this context, our findings are novel, and highlight the possible relevance of pharmacogenetic differences for drug response in older patients subjected to polypharmacy.

5 Conclusions

In a naturalistic clinical setting of older, home-dwelling patients, dosing of CYP2D6 substrates was not adjusted according to genotype-predicted CYP2D6 metabolism. The increased frequency of orthostatism in CYP2D6 IMs/PMs versus NMs may therefore reflect higher exposure of CYP2D6 substrates in the former subgroup, and in particular metoprolol, which was by far the most commonly used CYP2D6 substrate with hemodynamic effects. Further studies should therefore investigate if dose adjustments based on preemptive *CYP2D6* genotyping can improve clinical outcomes and reduce side effects in older patients subjected to polypharmacy.

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Author Contributions RR had full access to all data in the study and is responsible for the data integrity and accuracy of the data analysis. Study concept and design: all authors. Acquisition of data: RR. Analysis and interpretation of data: all authors. Statistical analysis: RR. Preparation of the manuscript: RR. Critical revision of the manuscript for important intellectual content: all authors. Funding acquisition: TBW. Supervision: TBW, EM. All authors read and approved the final manuscript.

Compliance with Ethical Standards

All procedures were in accordance with the ethical standards of the institutional and national research committee (the Regional Committee for Medical and Health Research Ethics in Norway) and with the 1964 Helsinki declaration and its later amendments.

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Conflict of interest RR, TBW, JS, HK, and EM declare that they have no conflict of interest.

Ethical approval The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Norway and by the Data Protection Official at Oslo University Hospital.

Data availability The datasets analyzed during the current study are not publicly available due to restrictions from the Norwegian Data Protection Officer, but are available from the corresponding author on reasonable request.

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