Paroxetine-Induced Conversion of Cytochrome P450 2D6 Phenotype and Occurence of Adverse Effects

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Abstract. The paper is focused on a comparison of the distribution of side effects of treatment with paroxetine within a group of 30 patients genotyped and phenotyped for their CYP 2D6 metabolic status.

Genotyping procedure showed that the patient group did not include any individual with poor metabolizer (PM) genotype; on the other hand, most patients (24) were classified as PMs by virtue of their phenotype, which suggests that a conversion to the poor metabolic phenotype ("phenocopy") occurred, probably as a consequence of a long-term administration of the strong CYP 2D6 inhibitor paroxetine. As to the occurence of common adverse effects, no marked difference between subjects converted into the PM group and those who had no history of such conversion was found. A significantly higher incidence of sexual dysfunction ($p < 0.05$) was, nevertheless, recorded in patients with the PM phenotype.

The results of the study may provide evidence that it is the metabolic phenotype status, rather than the genetically given enzyme capacity (CYP 2D6 genotype), that is relevant for the actual toleration of treatment with CYP 2D6 inhibitors.

Key words: CYP 2D6 — Phenotype — Paroxetine — Depression — Adverse effects

Introduction

Metabolic conversion of drugs in the organism represents one of the important pharmacokinetic factors contributing to the therapeutic effect as well as the intensity and frequency of adverse effects. The rate and intensity of the drug metabolising processes are largely determined genetically. But, the effect of non-genetic factors like induction or inhibition of metabolizing enzymes induced by other drugs or environmental substances, dosage of drugs (A-type ADRs) or disease state may largely be important, too.

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Cytochrome P450 2D6 (CYP 2D6) is one of the oxidative enzymes most thoroughly examined, as it is involved in metabolism of numerous important drugs including psychotropics (phenothiazine and other neuroleptics, tricyclic antidepressants, selective serotonin reuptake inhibitors, beta-blockers etc.). CYP 2D6 activity is characterized by genetic polymorphism, which is monogenous in character; the inheritance of the enzyme deficit in poor metabolizers (PM phenotype) is autosomal and recessive. There are 5–10 % of PMs in European population (Alván et al. 1991; Hadašová et al. 1996).

Current genotyping methods provide considerably precise determination of the CYP 2D6 genotype. There have been identified 48 point mutations and 53 deficient alleles in the CYP 2D6 gene locus on the long *q* arm of the 22nd chromosome (Maréz et al. 1997). The patient's genotype and actual phenotype frequently show discrepancies, and a consensus about the role of genotype in the phenotype expression of the metabolic status in patients treated with substrate medication has not been reached yet (Daly et al. 1996). This is because the actual metabolic phenotype can be a mere phenocopy arisen from drug-drug interactions, mainly inhibition at the substrate level. PMs are then exposed to an increased risk of adverse or toxic effects and other complications due to extremely high concentrations of the non-metabolized parent substance in the organism.

Administration of drugs that are strong CYP 2D6 inhibitors may, mainly in a long-term therapy like psychopharmacotherapy, have clinical impact even in individuals with normal metabolic status, i.e. extensive metabolizers (EM), provided that phenotype conversion to the PM status occurred.

The possibility of enzyme inhibition and its consequences have long been under discussion (Spina et al. 1997; Llerena et al. 1993). The phenotype conversion from EM to PM has often been described in association with treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants (Kohler et al. 1997). Paroxetine and fluoxetine are referred to as the strongest CYP 2D6 inhibitors among SSRIs (Sindrup et al. 1992; Brosen et al. 1993; Preskorn and Magnus 1994). Above all, paroxetine therapy is associated with the risk of many drug-drug interactions or incidence of adverse effects due to the decreased metabolism of the drug.

Published data on temporary phenotype conversion as a consequence of administration of substrate drugs call for clinical studies that would clear up the relationship between the genetic code of an individual and metabolic conversion of psychotropic drugs with regard to their therapeutic efficacy and safety.

The aim of the present study was to determine the CYP 2D6 genotypes and phenotypes in patients who had undergone a long-term therapy with paroxetine, and compare the rate and intensity of the side effects of treatment within the patients subgrouped according to their PM or EM metabolic status. Another goal was to evaluate the distribution and intensity of adverse effects in patients with the EM genotype who had a history of paroxetine-induced phenotype conversion to PM, compared with EM patients without conversion of the metabolic phenotype.

Materials and Methods

Patients were screened in the University Department of Psychiatry in Brno (Czech Republic). The group included patients with residual symptoms of a depressive disorder. They were 30 outpatients with the diagnose of a first episode of a depressive disorder ($n = 13$) and those with a recurrent depressive disorder ($n = 17$) with residual symptoms of depression (initial scores 7–12 on the 21-point Hamilton scale of depression (HAMD-21) (Hamilton 1997). All patients had a history of long-term treatment with paroxetine (average dose: 20.8 ± 5.6 mg daily, average period of administration: 131.4 ± 74.9 days). The sex distribution of patients was in line with that common in clinical practice: there were about two thirds of wo men ($n = 21$) and one third of men ($n = 9$, see Table 1). The study was undertaken in the period of January 2000 – May 2001. It was performed in accordance with the Helsinki declaration (1975), and approved by the appropriate ethical committee. All patients had given their written informed consent prior to the onset of any activities connected with the study.

Table 1. Characteristics of the group of patients treated with paroxetine

Number of patients	30	9 men, 21 women
Age	23–56 years	ø 38.3 years SD 9.4 years
Diagnosis: Depressive disorder Recurrent depressive disorder	13 17	
Drug doses	10–40 mg *per* day	ø 20.8 mg SD 5.6 mg
Duration of drug administration	42–300 days	ø 131.4 days SD 74.9 days
Total HAMD score	7–12	ø 9.3 SD 1.5

The patients included in the study were taking no other preparations known to affect CYP 2D6 metabolism; except for paroxetine, they were treated only with benzodiazepines: oxazepam, alprazolam and bromazepam. Scores on the HAMD-21 scale were estimated and incidence of adverse effects of treatment established on the UKU scale (Lingjaerde et al. 1987). The latter scale, based on a list of symptoms and their respective severities, was developed by a Scandinavian group of psychiatrists. It enables users to select individual items (not a total score) to be evaluated in individual patients.

CYP 2D6 genotyping was based on an allele-specific polymerase chain reaction (PCR) with detection of mutations in exons 3 (wt/mut ex 3), 4 (wt/mut ex 4),

5 (wt/mut ex 5) and deletion in exon 6 (Heim and Meyer 1990; Saxena et al. 1994; Vojtíšková and Hadašová 1997).

CYP 2D6 phenotyping was performed using dextromethorphane (DEM) as a test substance. DEM (25 mg) was taken orally in the morning before breakfast; urine was than collected for 8 hours after the DEM administration. The 0–8 h urine concentrations of DEM and its metabolite dextrorphane (DOR) formed *via* the CYP 2D6-mediated O-demethylation reaction were determined by high pressure liquid chromatography (HPLC) according to Park et al. (1984). The phenotype classification was based on calculation of a metabolic index $MR_{DEM/DOR}$. The antimode value distinguishing between EMs and PMs was set at MR = 0.3, in agreement with literature and the data available for the Czech population (Zelenková et al. 1997).

The statistical evaluation was performed using the CSS Statistica StatSoft programme (Tulsa, USA, 1993), the Mann-Whitney U test, and the χ^2 test. Value $p = 0.05$ was regarded as a statistically significant difference between the groups being compared.

Results

Determination of genotype and phenotype of patients treated with paroxetine

The results of this part are summarized in Tables 2 and 3. The group of 30 patients included no subject with a PM genotype. Eighteen patients (60%) had a normal homozygote genotype CYP 2D6 wt/wt, 12 patients (40%) had a heterozygote mutation in exons 4 or 5.

According to the actual metabolic phenotype, in 24 (80%) out of the 30 patients in the group a phenotype conversion to PMs occurred. The MR values for each individual patient after treatment with paroxetine are listed in Table 3.

There were found no marked differences in total HAMD scores between individuals with EM and PM metabolic status. The severity of depressive disorder and the therapeutic effect of paroxetine in those two groups did not differ, either (Mann-Whitney U test).

Distribution of adverse effects of paroxetine treatment in EM and PM patients

When rated on the UKU scale, 29 of 30 patients reported some adverse effects; only one man (homozygote EM by his genotype, but PM by his phenotype) did

Table 2. Results of CYP 2D6 genotyping and phenotyping in 30 patients treated with paroxetine

Metabolic genotype	Homozygote wt/wt	18 EM
	Heterozygote wt/mut ex 4	9 EM
	Heterozygote wt/mut ex 5	3 EM
Metabolic phenotype	$MR_{DEM/DOR} < 0.3$	6 EM
	$MR_{DEM/DOR} \geq 0.3$	24 PM

Table 3. Individual characteristics of the CYP 2D6 genotypes and phenotypes in patients treated with paroxetine. MR, metabolic index = [DEM]/[DOR]

Pat. No.	Sex	MR	Phenotype	Genotype	Mutation
1	F	0.0054	EM	EM	wt/mut ex 4
2	M	0.0077	EM	EM	wt/mut ex 4
3	M	0.0570	EM	EM	wt/wt
4	F	0.0950	EM	EM	wt/wt
5	F	0.1160	EM	EM	wt/wt
6	F	0.2900	EM	EM	wt/wt
7	F	0.3210	PM	EM	wt/mut ex 5
8	F	0.3240	PM	EM	wt/mut ex 5
9	F	0.3930	PM	EM	wt/wt
10	F	0.4160	PM	EM	wt/mut ex 4
11	F	0.4520	PM	EM	wt/mut ex 4
12	F	0.4870	PM	EM	wt/mut ex 4
13	F	0.5600	PM	EM	wt/wt
14	M	0.6110	PM	EM	wt/mut ex 4
15	M	0.6360	PM	EM	wt/mutex 4
16	F	0.6370	PM	EM	wt/wt
17	F	0.6880	PM	EM	wt/wt
18	F	0.7270	PM	EM	wt/wt
19	F	0.9950	PM	EM	wt/mut ex 5
20	F	1.0360	PM	EM	wt/wt
21	M	1.0590	PM	EM	wt/mut ex 4
22	M	1.0690	PM	EM	wt/wt
23	F	1.1470	PM	EM	wt/wt
24	F	1.2170	PM	EM	wt/wt
25	M	1.3190	PM	EM	wt/wt
26	F	1.3920	PM	EM	wt/wt
27	M	1.5140	PM	EM	wt/wt
28	F	1.7640	PM	EM	wt/wt
29	M	2.0190	PM	EM	wt/mut ex 4
30	F	3.0420	PM	EM	wt/wt

not report any complaints related to his therapy. The frequencies of adverse effects were highest in those most commonly associated with the administration of SSRIs – tension, insomnia, tremor, excessive sweating, headache, sexual dysfunction. The complete list of side effects that occurred in investigated patients is shown in Figs 1 to 4. The differences in distribution of side effects between EMs and PMs did not

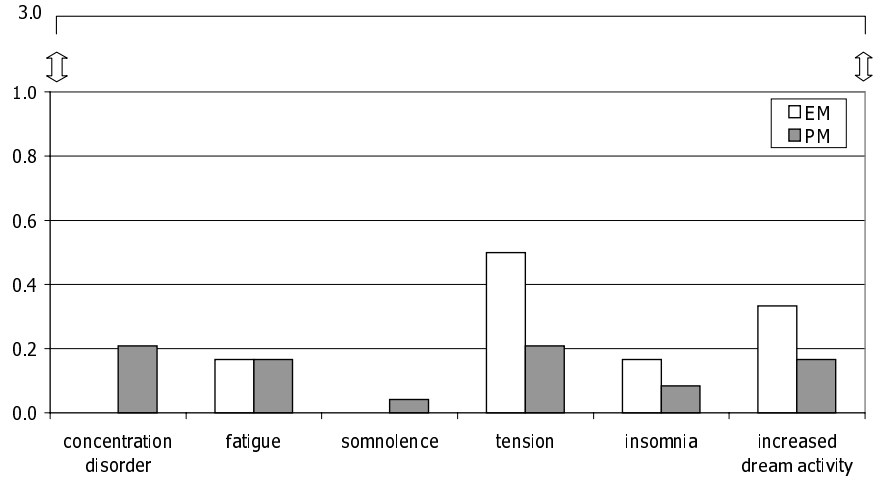

Figure 1. Average values for EMs and PMs on the UKU scale – psychic side effects in long-term paroxetine therapy.

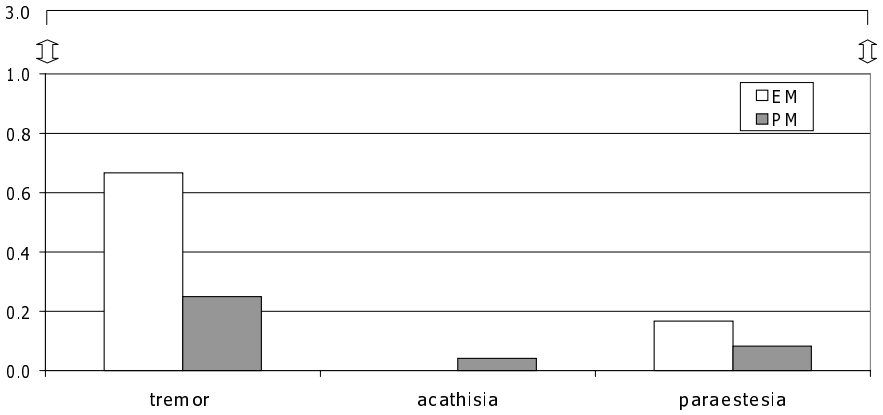

Figure 2. Average values for EMs and PMs on the UKU scale – neurologic side effects in long-term paroxetine therapy.

reach the level of statistical significance (Mann-Whitney U test) for any of the items under examination.

The number of patients reporting sexual dysfunction in all items covered by the UKU scale (decreased libido, impaired erectivity, impaired lubrication, impaired ejaculation, anorgasmy) was significantly higher within the group of patients with the PM phenotype (21 out of 24 subjects, i.e. 87.5 %) than in remaining 6 EMs. Only three PM patients (2 women and 1 man) reported no complaints regarding

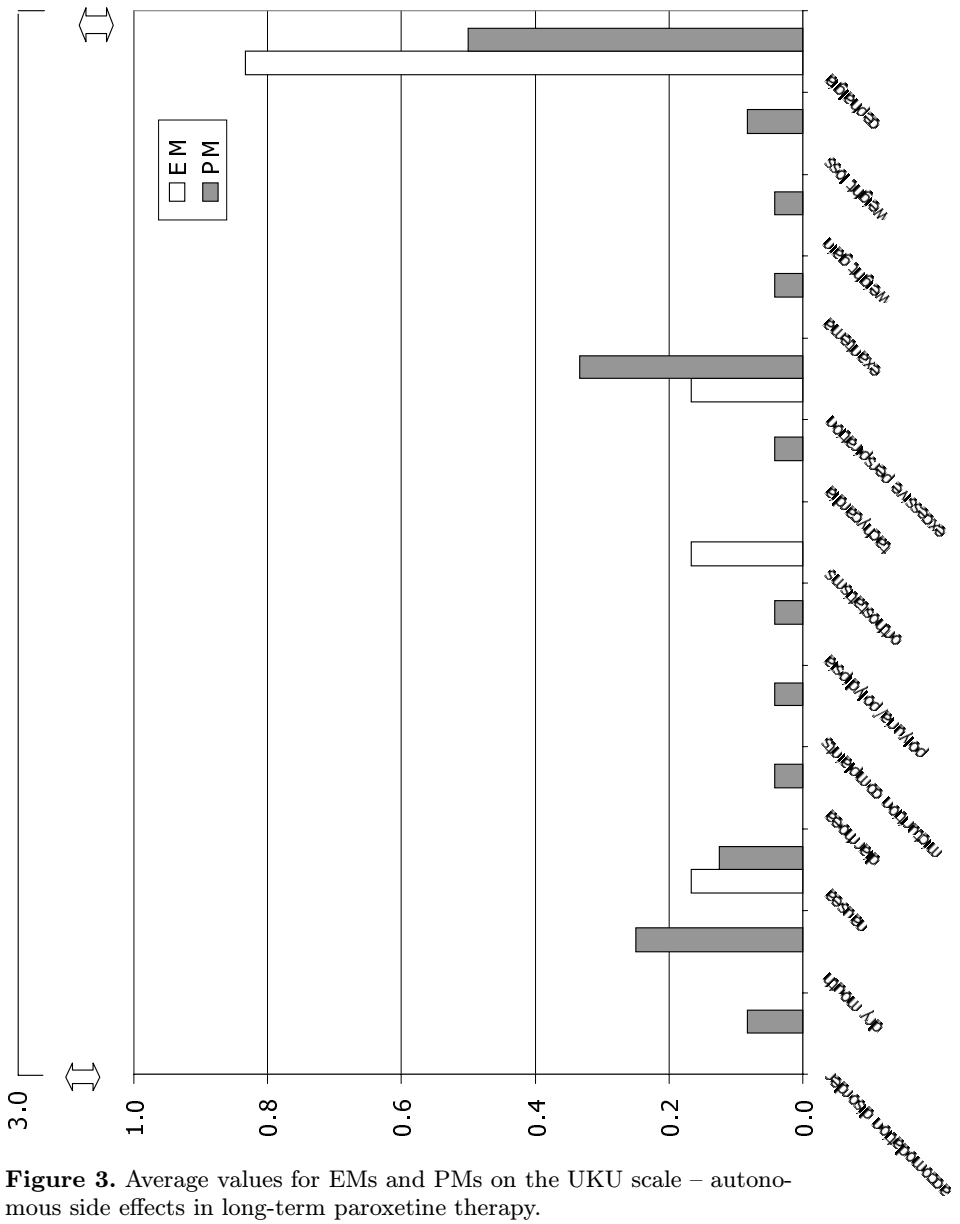

Figure 3. Average values for EMs and PMs on the UKU scale – autonomous side effects in long-term paroxetine therapy.

their sex functions. In contrast, among the six individuals with the EM metabolic status, there were three (2 women, 1 man), i.e. 50%, without sexual dysfunction. The difference in occurence of sexual dysfunction between EMs and PMs (Table 4) was statistically significant ($\chi^2 = 4.219$, $p \leq 0.05$).

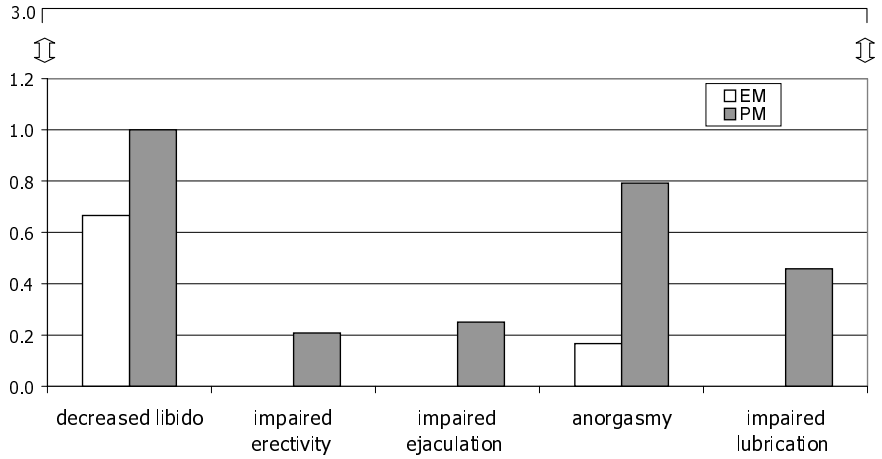

Figure 4. Average values for EMs and PMs on the UKU scale – sexual side effects in long-term paroxetine therapy.

Table 4. Relationship between EM or PM phenotype and occurence of sexual dysfunction as rated on the UKU scale

Patients	EM	PM	χ^2(significance)
without sexual dysfunction	3	3	–
with sexual dysfunction	3	21	4.219 ($p < 0.05$)

Discussion

The fact that the group of 30 patients included no individual with a homozygous mutation in the CYP 2D6 locus (PM genotype) may be due to the small size of the group. It can be supposed that a higher incidence of the PM genotype would be detected in larger numbers of patients.

The pilot study by de Leon et al. (1998), who examined 87 psychiatric patients, reported the PM genotype to be found in 12 subjects. In his study, 7 out of 10 patients with a PM genotype who were taking drugs affecting CYP 2D6 had side effects of medium severity measured on the UKU scale. Administration of a strong CYP 2D6 inhibitor can lead to phenotype conversion from the extensive to the poor metabolisation type (Sindrup et al. 1992; Ereshefsky 1996). Strong CYP 2D6 inhibitors include mainly SSRI antidepressants paroxetine and fluoxetine (Sindrup et al. 1992; Brosen et al. 1993; Preskorn and Magnus 1994).

The phenotype conversion to the poor metabolic phenotype in 24 out of 30 patients treated with paroxetine in the present study corresponds well with the data reported in literature (e.g., Kohler et al. 1997). In the study by de Leon et al. (1998) referred to above, 28 (i.e. 46%) out of 61 genotypically EMs reported side effects of treatment during administration of substances affecting CYP 2D6

metabolism. The author speculates that these subjects might have experienced a phenotype conversion to the poor metabolizer phenotype. There was, nevertheless, only a single subject in his group treated with paroxetine. Thus, the lower incidence of side effects in his group could be explained by the fact that other medicaments used were not as strong CYP 2D6 inhibitors as paroxetine. Spina et al. (1997) described a correlation between plasmatic levels of desiramine and the metabolic phenotype in a group of 31 patients. The group included two patients with PM phenotype whose high plasmatic levels of desipramine correlated with occurence of numerous side effects of treatment demanding the dosage reduction.

In our group of patients, the occurrence of side effects of paroxetine treatment did not correlate with the patients' classification as either EM or PM. There were even items (mainly headache, tremor and tension) in which the occurrence of side effects was, though insignificantly, higher in the EM than within the PM subgroup (see Figs. 1–4). Likewise, Vandel et al. (1992) found no correlation between phenotype conversion and severity of side effects in his group of 25 patients treated with combination of fluoxetine with tricyclic antidepressants. The plasmatic levels of tricyclics varied considerably in the study, too, and did not correlate with clinical severity of side effects of treatment. Similarly, in the study of Kaye et al. (1989) the plasma concentrations of paroxetine had no close correlation with the effect of treatment and tolerability.

The overall incidence of adverse effects during paroxetine therapy in our group of 30 patients did not substantially differ in any item from data obtained by metaanalysis of controlled studies using large patient groups. More than 4,000 patients treated with paroxetine (Edwards and Anderson 1999) reported most frequently sweating (21%), somnolence (17%), headache (15%), nausea (15%), insomnia (14%), constipation (12%), sexual dysfunction (9%), dry mouth (7%), vertigo (7%), tremor (5%), diarrhoea (3%). The low incidence of sexual dysfunction in this study (9%) is probably due to the methods of data collection; patients tend not to report these complaints spontaneously and have to be asked explicitly about them.

In our study, adverse effects of the sexual dysfunction type occurred mainly in patients with the PM phenotype and, unlike with EM subjects, reached the level of statistical significance. A significantly higher incidence of sexual dysfunctions in individuals with history of a phenotypic conversion to poor metabolisers after administration of a strong CYP 2D6 inhibitor paroxetine is a new finding which has not been, to our knowledge, described yet. Explanation of this phenomenon remains, though, on the level of hypotheses and the finding calls for verification in a study with larger numbers of patients.

It is known that the decrease in dopamine transmission in the central nervous system may lead to a higher incidence of sexual disorders (Seagraves 1989). CYP 2D6 distribution in the brain correlates with the distribution of a dopamine transporter (Niznik et al. 1990, Kalow and Tyndale 1992). One can suggest that the increased incidence of sexual dysfunctions might be in coherence with a paroxetine-induced dysbalance in the dopaminergic system as well as alteration of CYP 2D6-mediated metabolism in the brain.

Except for a sexual dysfunction, our study did not prove a clinical impact even of the profound CYP 2D6 inhibition into the efficacy of or toleration to treatment in homozygous or heterozygous EM patients. Although inhibition of CYP 2D6 metabolic activity is likely to occur during the long-term paroxetine therapy, it need not be, mainly in monotherapy, a reason for an especial disquiet, mainly owing to the relatively low toxicity of the preparation itself.

Combinations of paroxetine with other psychotropic and non-psychotropic drugs are considerably common in clinical practice, whether in treatment of psychiatric disorders coinciding with internal diseases or in treatment of acute states that occur during long-term therapy of psychic disorders. If several drugs metabolized by CYP 2D6 are given concomitantly, the risk associated with the potential enzyme inhibition increases and dosages of the co-administered drugs have to be adjusted after a necessary initial dose to prevent undesirable complications. In these cases, determining the CYP 2D6 metabolic phenotype is highly desirable in order to predict the efficacy of further therapy and incidence of undesirable drug effects.

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