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Effects of Pharmacogenetic Screening for CYP2D6 Among Elderly Starting Therapy With Nortriptyline or Venlafaxine

A Pragmatic Randomized Controlled Trial (CYSCE Trial)

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Abstract:

Purpose/Background: The duration of untreated depression is a predictor for poor future prognosis, making rapid dose finding essential. Genetic variation of the CYP2D6 isoenzyme can influence the optimal dosage needed for individual patients. The aim of this study was to determine the effectiveness of CYP2D6 pharmacogenetic screening to accelerate drug dosing in older patients with depression initiating nortriptyline or venlafaxine.

Methods/Procedures: In this randomized controlled trial, patients were randomly allocated to one of the study arms. In the intervention arm (DG-I), the specific genotype accompanied by a standardized dosing recommendation based on the patients' genotype and the prescribed drug was directly communicated to the physician of the participant. In both the deviating genotype control arm (DG-C) and the nonrandomized control arm, the physician of the participants was not informed about the genotype and the associated dosing advise. The primary outcome was the time needed to reach adequate drug levels: (1) blood levels within the therapeutic range and (2) no dose adjustments within the previous 3 weeks.

Findings/Results: No significant difference was observed in mean time to reach adequate dose or time to adequate dose between DG-I and DG-C. Compared with the nonrandomized control arm group, adequate drug levels were reached significantly faster in the DG-I group (log-rank test; $P = 0.004$), and there was a similar nonsignificant trend for the DG-C group (log-rank test; $P = 0.087$).

Implications/Conclusions: The results of this study do not support pharmacogenetic CYP2D6 screening to accelerate dose adjustment for nortriptyline and venlafaxine in older patients with depression.

Key Words: pharmacogenetic screening, CYP2D6 genotyping, nortriptyline, venlafaxine, elderly

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Major depressive disorder is a potential chronic disorder with an estimated prevalence rate around 4.7%,[1] and rates are highest in the older population (7.2% in more than 75 years).[2] The burden of major depressive disorder does not only affect mental health but also physical health and quality of life.[3]

Efficacies of different antidepressant drugs are comparable, but drugs have different adverse drug profiles. Because selective serotonin reuptake inhibitors (SSRIs) have a more favorable adverse effect profile, they are often recommended as first-choice treatment. If the SSRI is not effective or not tolerated, an alternative treatment can be considered.[4] Another SSRI, a tricyclic antidepressant, for example, nortriptyline, in older persons; a serotonin-norepinephrine reuptake inhibitor, mostly venlafaxine; and a monoamine oxidase inhibitor are all part of these alternative treatment options. Because the duration of untreated depression is a predictor for poor prognosis in the already fragile elderly population, rapid dose finding of the secondary treatment option with minimal adverse events is essential.[5]

Nortriptyline and venlafaxine are both metabolized by the highly polymorphic cytochrome P450 2D6 (CYP2D6) isoenzyme: nortiptyline to the active metabolite E-10-hydroxynortriptyline half as potent as nortriptyline, venlafaxine to the equipotent metabolite *O*-desmethylvenlafaxine. Most often, the genetic differences are classified into 4 different phenotype groups: poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultrarapid metabolizers (UMs).[6] The UM phenotype is associated with therapeutic inefficacy, whereas an increased risk of toxicity and adverse effects has been reported in the PM and IM

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groups.[7] In current clinical practice, therapeutic drug monitoring (TDM) helps to find optimal dosage for individual patients and to check adherence. Besides TDM, it has been put forward that information on the CYP2D6 genotype can further improve dose finding, but scientific evidence from rigorous trials is lacking.[8–10] We also showed this in a post hoc analysis of an earlier smaller clinical trial in elderly treated with nortriptyline and venlafaxine.[11] In the Netherlands, national guidelines are established based on systematic review of the literature, with therapeutic recommendations for nortriptyline and venlafaxine based on genotype information for CYP2D6.[10] These guidelines have been acknowledged by international initiatives such as the PharmGKB database. The influence of genotype at elderly patients treated with nortriptyline and venlafaxine in the Netherlands has been previously studied, indicating results from genotyping of elderly gives a good indication of a patient's phenotype if coadministered medication, and the "intermediate genotype" is taken into account.[11] This current trial aimed to investigate the clinical effects of implementation of the Dutch guideline for dose adaptations of nortriptyline and venlafaxine based on CYP2D6 genotype.

The primary objective of this pragmatic prospective randomized trial was to determine the effect of *CY*P2D6 *sc*reening among *e*lderly (CYSCE) on the time needed to obtain therapeutic drug levels as an accepted proxy for adequate treatment in depression.[12,13] The secondary objectives were to determine the effect of pharmacogenetics screening for CYP2D6 on adverse drug reactions, self-reported functional health status, and quality of life.

MATERIALS AND METHODS

Study Design

The trial protocol was published earlier.[14] In short, the trial was designed as a multicenter randomized controlled trial across multiple old age psychiatry and geriatric mental health care institutions across the Netherlands. Ethical approval was obtained by an independent ethics committee (RTPO-Leeuwarden-NL; file number: NL40925.099.12). Patients were recruited by their physician or a research nurse. The study was built up as a 2-part informed consent design in which patients had to give separate written informed consent for both parts. The first part of the study consisted of a basic genotype screening in which each eligible patient (see eligibility criteria in the Participants section hereinafter) starting with nortriptyline or venlafaxine was asked permission for genotyping. Patients with PM, IM, and UM genotypes and a selection of the patients with an EM genotype were selected for participation in the second (trial) part of the study and were asked for a second informed consent. From the patients with the EM genotype, a random selection of patients was allocated to an additional (external cohort) reference group. If selected for the trial part of the study, eligible patients were invited for a baseline visit in which baseline characteristics were determined (Table 1). At 2, 4, and 6 weeks after baseline, blood samples were collected to estimate the blood level of the drug by a "dried blood spot" (DBS) method. This method was validated for TDM by means of a liquid chromatography–mass spectrometry method.[12,13] In addition, questionnaires concerning adverse drug reactions, quality of life, severity of depression, and medication dose were administered. Patients, for whom a clinically acceptable dose was not established within 6 weeks, were followed up for an additional 2 weeks until dose finding was completed. These additional 2-week samples were collected only for those patients who had a dose change 3 weeks or less before the moment the sample was collected, because it can take up to 2 to 3 weeks for patients with a PM profile to reach steady-state concentration for nortriptyline.[15] This study is reported according to the CONSORT guidelines[16,17] for reporting randomized trials and was registered at ClinicalTrials.gov (Identifier: NCT01778907) before the start of the trial.

Participants

Patients were eligible for participation in this study if they were 60 years or older, diagnosed by the physician as having a major depression according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition–Text Revision) and criteria (code: 296.2x or 296.3x). Furthermore, only those patients initiating with either nortriptyline or venlafaxine were considered eligible, and the patient needed to be able to understand the informed consent procedures. Patients were excluded for trial participation if there was known liver cell damage, a proxy for a poor hepatic function (aspartate aminotransferase and alanine aminotransferase or γ-glutamyl transferase ≥ twice the maximal reference value), impaired renal function (estimated glomerular filtration rate <30 mL/min) in combination with venlafaxine use, or if patients were currently using interacting drugs that influence blood levels of nortriptyline or venlafaxine (ie, patients using terbinafine, ketoconazole, voriconazole, kinidine, propafenon, cimetidine, fluoxetine, paroxetine, bupropion, duloxetine, sertraline, abirateron, cinacalcet, rifampicine, or ritanovir). Drug interactions were based on pharmacy interaction monitoring software, summary of product characteristics, and Flockhart's interaction table (Flockhart D. Drug interactions: cytochrome P450 drug interaction table). The pharmacokinetic interaction of CYP2D6 in monotherapy with nortriptyline or venlafaxine was studied in this trial; therefore, the primary outcome was the time needed to reach adequate drug levels. As such, possible pharmacodynamic interactions with comedication were not taking into account.

CYP2D6 Genotyping

The first part of the study consisted of CYP2D6 genotyping using a DBS sample.[18] Single-nucleotide polymorphism were assessed for the *3, *4, *5, *6, *10, *17, and *41 alleles together with the duplications of the CYP2D6 gene. Based on the enzyme activity of the different alleles, a prediction was made for the phenotype after the Royal Dutch Pharmacists Association CYP2D6 guidelines and the Clinical Pharmacogenetics Implementation Consortium translation guidelines.[12,13]

Presence of 2 alleles lacking enzyme activity (*3, *4, *5, *6) is considered as a PM phenotype. One allele lacking enzyme activity paired with an allele with decreased enzyme activity (*10, *17, *41) results in an IM phenotype. In addition, the presence of only one allele lacking enzyme activity or 2 alleles with decreased enzyme activity also results in an IM phenotype. A duplication of the CYP2D6 gene results in an UM phenotype prediction, unless it is combined with any allele with reduced or lacking enzyme activity, an IM duplication. With this genotype, a prediction of the overall enzymatic activity and the subsequent dosing advice cannot be given, and therefore, these genotypes are excluded.

Randomization and Allocation

Patients participating in the main study with a PM, IM, or UM genotype were selected and randomly allocated by computer (1:1) to either the "deviating genotype intervention" arm (DG-I) or the "deviating genotype control" arm (DG-C). An additional sample of patients with the EM genotype was allocated to a third "normal genotype control" arm (NG-C) to be able to compare prognosis with a natural course patient group and to control for potential information bias. Because it was expected that patients with the EM genotype are more prevalent than patients with a deviating genotype,[6] and to prevent any potential time-dependent

TABLE 1. Overview of the Baseline Characteristics of the Different Intervention Groups in Trial

	Randomized Trial				Nonrandomized Trial		
	Informed (DG-I; n = 27)		Not informed (DG-C; n = 22		External Control (NG-C; n = 57)		
	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	*P*
Sex (female)	14 (51.9)		14 (63.6)		38 (66.7)		0.420*
Age, y		70.2 (7.3)		68.5 (5.1)		71.8 (7.2)	0.137†
Setting							
Ambulant	14 (51.9)		13 (59.1)		28 (49.1)		0.729*
Clinical	13 (48.1)		9 (40.9)		29 (50.9)		
Depression							
296.2x	11 (40.7)		10 (45.5)		20 (35.1)		0.676*
296.3x	16 (59.3)		12 (54.5)		37 (64.9)		
MADRS score		29.4 (8.6)		28.9 (7.8)		29.5 (9.2)	0.958†
Medication							
Nortriptyline	18 (66.7)		13 (59.1)		36 (63.2)		0.861*
Venlafaxine	9 (33.3)		9 (40.9)		21 (36.8)		
Starting dose, mg							
Nortriptyline		18.1 (10.9)		18.1 (7.8)		22.6 (14.7)	0.547†
Venlafaxine		62.5 (18.8)		45.8 (16.5)		46.4 (16.4)	0.444†
Other medication (yes)	26 (96.3)		19 (86.4)		49 (86.0)		0.351*
Comorbidity (yes)	26 (96.3)		19 (86.4)		42 (73.7)		0.035*
Comorbidities (frequency)		2.6 (1.6)		1.9 (1.5)		2.4 (2.5)	0.151†
Genotype							
EM					*1/*1	37 (64.9%)	
					*1/*41	8 (14.0%)	
					*1/*10	3 (5.3%)	
IM	*1/*3	1 (3.7%)	*1/*4	6 (27.2%)	*1/*4	5 (8.8%)	
	*1/*4	9 (33.3%)	*1/*5	1 (4.5%)	*1/*6	2 (3.5%)	
	*1/*5	3 (11.1%)	*1/*6	2 (9.1%)	*1/*5	1 (1.8%)	
	*4/*10	1 (3.7%)	*4/*10	1 (4.5%)	*1/*3	1 (1.8%)	
	*4/*41	1 (3.7%)	*4/*41	3 (13.6%)			
	*10/*41	1 (3.7%)					
UM	*1/*41 DUP	1 (3.7%)	*1/*1 DUP	1 (4.5%)			
	*1/*1 DUP	1 (3.7%)					
PM	*3/*3	2 (7.4%)	*3/*4	1 (4.5%)			
	*4/*4	5 (18.5%)	*4/*4	7 (31.8%)			
	*3/*4	1 (2.7%)					
	*4/*5	1 (3.7%)					

*Pearson χ^2 test of all 3 groups.

†One-way analysis of variance.

MADRS indicates Montgomery-Åsberg Depression Rating Scale.[15]

bias, the selection of patients with an EM genotype allocated to the NG-C arm was dependent on the number of patients in the other trial arms. During the trial, patients were not informed about their genotype or trial status. After completion of the trial, the genotypic information of the control groups was communicated to the physician.

DG-I Arm

The DG-I arm included patients with a PM, IM, or UM genotype. The specific genotype accompanied by dosing advice was directly communicated to the physician approximately 14 days after inclusion, which coincides with the first visit after the start of treatment. The advice contained a standardized dosing recommendation of the Royal Dutch Pharmacists Association based on the patients' genotype and the prescribed drug (nortriptyline/venlafaxine).[12,13] For nortriptyline, the advice was given to adjust to 50% (PM), 75% (IM), 100% (EM), and 150% (UM) of the standard dose. Within the venlafaxine users, the advice of adjustment to 75% (PM), 100% (EM), and 150% (UM) of the standard dose was given to the physician. Based on the literature, no advice could be given to the IM venlafaxine users, and therefore, TDM was advised to their physician. The genotype-based recommendation was given on top of care and monitoring of drug use as usual, for example, TDM.

DG-C Arm and NG-C Arm

The DG-C arm included patients with a deviating genotype, PM, IM, or UM genotype, and the NG-C arm included patients with a normal (EM) genotype. In contrast to patients in the

intervention arm (DG-I), the physician was not informed about the genotype and the associated dosing advise of patients in both control arms. In addition, the physician was blinded for the difference between both control arms to ensure representation of all the genotypes in the control group and prevent dose adjustment based on the participation in this study. During the trial, the genotyping method had to be transferred to a different laboratory and location, due to an unforeseen end of service of the primary laboratory. Although a continuity of the same genotyping method was established, this caused a temporarily delay in the genotyping of the *5 allele and duplications. Because this delay in *5 genotyping and duplications, only the prediction of the IM phenotype and the subsequent dosing advise was hindered. To maintain continuity at the recruiting sites, a second external control group (n = 10) was added to the study halfway through the trial: the IM control arm (IM-C). The addition of this extra control arm kept the randomization of the trial arms (DG-I and DG-C) intact, and therefore, the delay in advice did not affect the study randomization or the outcome. Results of genotype testing and dosing advice of the IM-C arm were not communicated to the physician. Both external control groups were combined and labeled as NG-C for the treating physician.

Outcomes

Primary Outcome

The primary outcome was the time in days needed to reach an adequate drug level of nortriptyline or venlafaxine. Adequate drug levels were defined as (1) blood levels within the therapeutic range as determined by a DBS and (2) no dose adjustments within the previous 3 weeks. Therapeutic ranges according to the current Dutch Clinical Pharmacy guidelines (NVZA) were followed, suggesting nortriptyline levels between 50 and 150 μg/L and venlafaxine + *O*-desmethylvenlafaxine levels between 250 and 750 μg/L (during the trial, the reference value of the guideline was adjusted to 100–400 μg/L after an update of literature[19] and used as further reference value of the therapeutic range in this study).

Secondary Outcomes

Secondary outcomes were the frequency, severity (ie, mild, moderate, and serious), and total sum of adverse effects measured by a shorter and modified version of the Antidepressant Side-Effect Checklist,[20] and quality of life measured by the EuroQol 5D-3L (EQ5D-3L; Dutch score range, −0.329 to 1.000) and the EuroQol visual analog scale (EQ-Vas; score range, 1–100).[21] Severity of depression was measured by the Quick Inventory of Depressive Symptomatology Self-Reported Questionnaire (QIDS-SR; score range, 0–27), to determine possible differences in treatment between groups related to the severity of depression instead of the genotype-based intervention.[22] All secondary outcomes, except for the adverse effects, were measured by a telephone interview from visit 2 till end point, every 2 weeks. Adverse effects were assessed by the physician before start of the treatment and during the trial every 2 weeks. In this way, we were able to correct for symptoms of depression, age-related physical symptoms, or other underlying physical diseases, which are often perceived by the patient as adverse effects of the antidepressant.[20] Because genotype information was available at visit 2, we expected the largest impact on secondary outcomes to be at visit 3. Therefore, we also assessed the difference between trial groups in frequency and severity of adverse effects between baseline and visit 3. In addition, we determined the differences in self-reported functional health status and general and disease-specific quality of life (EQ5D-3L; EQ-VAS) and severity of depression (QIDS-SR) between visit 2 and visit 3.

Statistical Analysis and Report

Baseline characteristics were presented using descriptive statistics including means for continuous variables and percentages for categorical variables. Analytical statistics to estimate differences between the groups of patients who were lost to follow-up versus patients who completed the trial as well as between the different study arms were determined by *t* tests for continuous variables and χ^2 tests for categorical variables.

The primary analysis assessed the mean time (in days) needed to obtain adequate drug levels. Because a part of the study population did not reach adequate drug levels, we also performed a Kaplan-Meier analysis with a log-rank test to analyze the survival rate of adequate drug levels between the different trial groups (survival = nonadequate drug level). A cutoff value of 70 days was used for each participant as being the end of the observation period to prevent crossing of the different survival curves (Fig. 2). Sensitivity analyses were performed to account for the robustness of our results, in which the cutoff value was changed to 80 and 100 days, the primary outcome was stratified into the different medication groups (nortriptyline and venlafaxine), and a separation was made between the clinical and ambulant patients. To determine the effect of dose of nortriptyline or venlafaxine on the time to reach adequate drug levels, we compared the different dosing levels at the end point for each patient, that is, the visit during which adequate dosing was reached, or when no adequate dosing was reached the last visit was taken as end point, by Kruskal-Wallis test. In addition, we performed a Kaplan-Meier analysis to analyze the effect of the different genotype groups (EM, IM, PM, and UM) on time to reach adequate drug levels. Analysis of variance or Kruskal-Wallis test was applied to test for potential differences of secondary outcome measures between the trial groups and the external reference group. A *P* value of 0.05 was considered statistically significant. The statistical analyses were performed using SPSS statistical software, version 24 (IBM SPSS Inc, Chicago, Illinois).

RESULTS

Baseline

In total, 199 of 202 patients gave informed consent for the first phase of the trial and offered CYP2D6 genotyping. Eighteen patients did not proceed in the study because they did not meet the inclusion criteria or had one or more exclusion items. Overall, 23 (12.6%) of the patients were labeled to be PM, 68 (37.2%) IM, 87 (47.5%) EM, 3 (1.6%) UM, and 2 (1.1%) IM with duplications. The 2 IMs with duplications were also excluded from the study based on their genotype.

Inclusion of the study took place between February 2013 and February 2017. The last follow-up visit was held in May 2017. Figure 1 shows the flowchart of the entire CYSCE trial and included patients followed up to 7 visits.

In total, 181 adults were considered for inclusion in the study. Table 1 gives an overview of the baseline characteristics of the different intervention groups of patients who finished the trial (N = 106). No significant differences were observed between the different trial groups except for difference in the presence of comorbidities (DG-I, n = 26/27 [96.3%]; DG-C, n = 19/22 [84.4%]; NG-I, n = 52/57 [73.7%]; *P* = 0.035). In a similar secondary analysis, we compared the patients who finished the trial (n = 106) with patients who did not participate in the complete trial (n = 75) because of being lost to follow-up, not being selected for the trial, or not signing the second informed consent form. We only found a significant difference (*P* = 0.006) in mean age between the finished trial group (mean [SD] age, 70.7 [6.9] years' n = 106) and the not

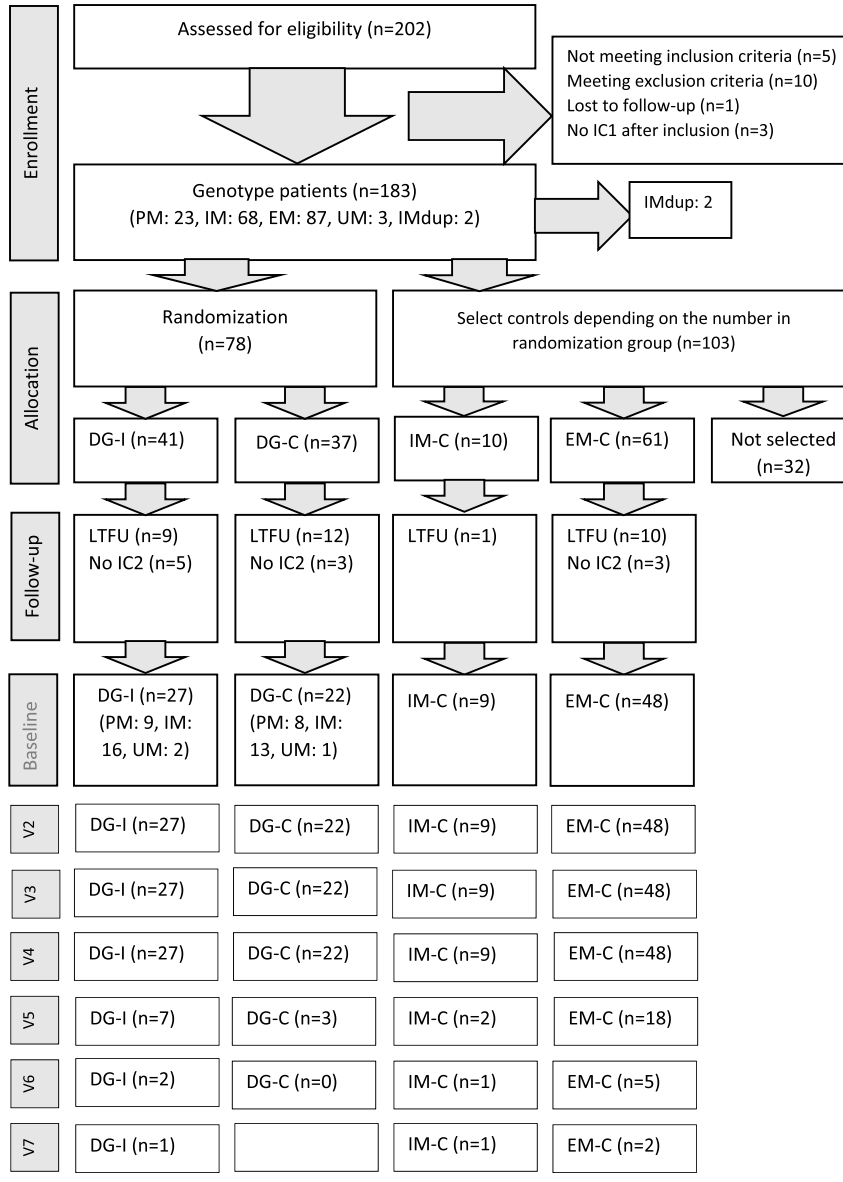

FIGURE 1. Flowchart of the CYSCE trial. IC, informed consent; IM-C/EM-C, IM/EM control arm = NG-C; IMdup, IMs with duplications; LTFU, lost to follow-up.

selected or lost-to-follow-up group (mean [SD] age, 74.6 [7.4] years, n = 32).

Primary Outcome

The results of the primary outcome per trial group are presented in Figure 2. Actual plasma concentration values are presented in Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/JCP/A624. In total, 24 (88.9%) of the DG-I group reached an adequate drug level of nortriptyline or venlafaxine in 39.3 (12.3) days on average, compared with 16 (72.7%) of the DG-C group (mean [SD] days, 39.6 [10.5]) and 39 (68.4%) of the NG-C group (mean [SD] days, 48.1 [11.5]). No difference ($P = 0.663$) was observed between the DG-I group and the DG-C group in mean time to reach adequate dosing; however, a difference ($P = 0.003$) was observed between the 2 deviating genotype groups and the NG-C group (mean [SD] days: DG-I, 42.7 [15.2], n = 27; DG-C, 44.5 [13.0], n = 22; NG-C, 52.8 [13.0], n = 57). The Kaplan-Meier survival curve estimated that there was a significant difference (log-rank test; $P = 0.013$) between the 3 trial groups (DG-I, n = 27; DG-C, n = 22; NG-I, n = 57; Fig. 2). When comparing the survival curves of the DG-C group and the DG-I group, no significant difference was observed (log-rank test; $P = 0.425$). Compared with the NG-C group, the DG-I group was significantly faster in reaching adequate drug levels, as assessed by the Kaplan-Meier survival curve estimate (log-rank test; $P = 0.004$), whereas the DG-C did not show a significant difference compared with the NG-C group (log-rank test; $P = 0.087$). These results did not change when increasing the cutoff value of 70 to 80 or 100 days, stratifying the outcome per medication group or separating the clinical and ambulant patients.

A significant difference was observed in the dosing of nortriptyline between the 3 groups (median [interquartile range] dosing per day at end point: DG-I [n = 18], 50.0 [50.0–75.0] mg;

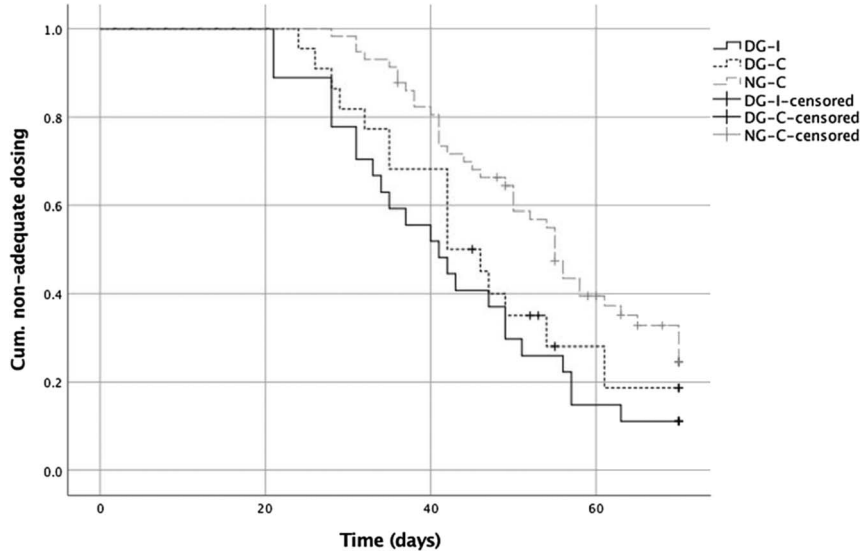

FIGURE 2. Survival curve of time to reach adequate drug levels of nortriptyline or venlafaxine per trial group.

DG-C [n = 13], 50.0 [50.0–62.5] mg; NG-C [n = 36], 75.0 [50.0–100.0] mg; Kruskal-Wallis test, $P = 0.035$) and between the DG-I group and the NG-C group (Kruskal-Wallis test, $P = 0.035$). The results were not affected after the exclusion of the UM group. No significant difference was observed in the dosing of venlafaxine between the 3 groups. The Kaplan-Meier survival curve estimated that there was a significant difference (log-rank test; $P < 0.001$) in time to reach adequate drug levels between the 4 genotype groups (EM [n = 48], IM [n = 38], PM [n = 17], UM [n = 3]; Supplementary Figure S1, Supplemental Digital Content 2, http://links.lww.com/JCP/A625). The UM and PM groups reached the adequate drug dose faster compared with the EM group (log-rank test, $P < 0.001$). When comparing the survival curves without the UM group, still an overall significant difference was observed (log-rank test, $P = 0.006$).

Secondary Outcomes

The differences between trial groups in overall frequency and overall severity scores of adverse effects in both nortriptyline and venlafaxine were all not statistically significant. Stratification into the different medication groups (nortriptyline and venlafaxine) did not yield a different result. Looking at the differences between visit 1 and visit 3 in frequency and severity of adverse effects stratified between trial groups, significant differences were observed in the frequency of adverse effects (mean [SD] difference: DG-I, 1.48 [4.92]; DG-C, 2.09 [4.85]; NG-C, −2.51 [5.22]; $P < 0.001$) and the frequency of serious adverse effects (mean [SD] difference: DG-I, 0.37 [1.08]; DG-C, 0.59 [1.37]; NG-C, −0.37 [1.29]; $P < 0.001$; Supplementary Figure S2, Supplemental Digital Content 2, http://links.lww.com/JCP/A625). In Table 2, the mean difference between visit 2 and visit 3 of the trial of self-reported quality of life per trial group is reported. No significant differences were observed. Table 2 also shows the mean difference between visit 2 and visit 3 of the trial of average severity score of depression per trial group. No significant difference was observed between the different trial groups.

DISCUSSION

Our study results revealed that there is no difference in the time needed to reach adequate drug levels when providing CYP2D6 genotype information, compared with no information, to the physician of patients with deviating genotype. No difference in dose at end point was observed between the 2 groups, which could indicate a lack of genotype-based dose prescription by the physicians. The DG-I arm differed significantly from the external control group (NG-C) in time needed to reach adequate drug levels, most likely caused by a lower dose needed to reach adequate dosing for deviating genotypes, dominated by the IM and PM genotypes. Alternatively, the difference between the DG-I arm and the external control group could have been caused by the CYP2D6 phenotype variability. The interindividual variability is low or absent for both IMs and PMs (DG-I, DG-C), whereas the variability in EMs (NG-C) is generally extensive due to additional sources of variability, for example, presence of rare 2D6 variants or nongenetic factors affecting CYP2D6 phenotype.[23] Because we wanted to investigate the clinical effects of implementation of the Dutch guideline, we did not analyze different phenotypes as a separate subgroup. The difference in frequency of adverse effects and frequency of serious adverse effects between baseline and visit 3 was significantly lower in the external control group compared with the deviating genotype groups (DG-I and DG-C). This would also match the interpretation that deviating genotypes (dominated by IM and PM genotypes) start with a dose closer to the effective dose than EM-genotypes, which leads to a higher drug blood level. When

TABLE 2. The Mean Difference in Self-Reported Quality of Life (EQ5D-3L; Dutch Score Range, −0.329 to 1.000; EQ-VAS, Score Range, 0–100) and Severity Score of Depression (QIDS-SR; Score Range, 0–27) Per Trial Group Between Visit 2 and Visit 3

	Trial Group	n	Mean Difference (SD)	P*
EQ5D-3L score	DG-I	19	0.09 (0.14)	0.747
	DG-C	20	0.04 (0.25)	
	NG-C	39	0.08 (0.25)	
EQ-VAS score	DG-I	18	9.72 (13.88)	0.231
	DG-C	20	1.25 (9.30)	
	NG-C	39	4.36 (18.00)	
QIDS-SR score	DG-I	18	−1.28 (4.00)	0.220
	DG-C	20	−1.75 (4.34)	
	NG-C	38	−3.03 (3.41)	

*One-way analysis of variance.

looking at quality of life and severity of depression as the outcome measure, no general effect of CYP2D6 genotyping information was seen on each of these secondary outcome measures. It could be questioned whether changes in quality of life and depressive symptom severity are detectable in such short period of time.

The analyses at baseline revealed that the different treatment groups were comparable for most of the measured baseline characteristics. The presence of somatic comorbidities was significantly more frequent in the deviating genotype groups than in the control group. A possible explanation could be that a deviating genotype is related to frailty, although this was not seen in other clinical treatment parameters, like severity of depression or medication use. The higher presence of comorbidities could also have confounded the difference between time to reach adequate drug levels between the external control group and the 2 deviating genotype arms. However, because of multiple testing of different variables between the different trial groups, the difference in the presence of comorbidities could also be based on chance. In addition, because there was by design no difference in baseline characteristics between the deviating genotype trial arms, this could not explain the absence of an effect of genotyping on time to reach adequate drug levels between these 2 randomized trial groups.

Based on the nortriptyline and venlafaxine genotype-based dose adjustment guidelines and the related research,[12,24,25] we expected that the implementation of pharmacogenetics in clinical practice would affect the adequate treatment for patients in a positive way. Although the effect of genotype on metabolic capacity of specific psychotropic drugs like nortriptyline and venlafaxine is well known, clinical effectiveness is dependent on more factors. Dose adjustments based on genotype may not be informative enough to make a clinical impact on, for example, drug efficacy and prevention of adverse drug events.[26] This is in line with previous research on the effect of genotyping on treatment efficacy in depressed patients.[27–29] However, the observation that the EM genotypes needed a longer time to reach an adequate drug level is an interesting finding, considering that most of the current pharmacogenetic guidelines aim at dose reduction among patients with a decreased metabolic activity. Therefore, the beneficial effects of genotyping in depressed patients might be in a faster titration among patients with an EM genotype, but research into the effect of supplying genotype information in the first weeks of the treatment for EM patients is required.

The mean age of the patients that finished our trial was on average 4 years lower compared with the nonselected normal genotype arm and those lost to follow-up. This could have affected the representativeness of the external control group (NG-C) for time to reach adequate drug levels, but cannot explain the absence of effect between the 2 deviating genotype arms and the absence of effect in adverse effects because there was no difference in mean age at baseline. It might, however, be speculated that present clinical practice in this elderly population seems to be based more on the patient characteristics of PM and IM genotypes, and that knowledge of the EM genotype would allow for a faster increase in dosing than usual and therefore lead to a more adequate treatment for EM genotype patients. This is corroborated by the significantly lower frequency of total and serious adverse effects on baseline compared with visit 3 in the EM genotype group. However, this should be investigated in a future clinical trial.

The percentage of patients with the PM genotype is relatively high, 12.6% (8% observed by Tamminga et al[30]), but because of the limited number of patients, interpretation can only be speculative.

Strengths

To our knowledge, this is the first and only pragmatic randomized clinical trial examining the effect of pharmacogenetic screening for CYP2D6 among elderly patients starting therapy with nortriptyline or venlafaxine. The pragmatic design of this study allows for greater external validity compared with usual randomized controlled trial designs and therefore better applicability to clinical practice.

Limitations

However, the results of this study should be considered in the context of a few possible limitations. First, patients who finished the trial were significantly younger compared with patients who did not finish the trial. Although genetic differences are not dependent on age, the relative effect of genotype information could be more substantial in the fragile older population, which would be underestimated in our younger elderly population. However, there is no scientific evidence that a difference of 4 years in age could clinically impact the effect of pharmacogenetic screening among elderly. Second, as mentioned previously, it is possible that physicians are already experienced in the dose finding of patients with IM and PM genotype in particular by means of TDM, possibly strengthened by clinical and scientific knowledge regarding adverse events in an already fragile population and the presence of genotypic diversity among these patients.[31] This may have caused the lacking effect of providing genotype information because clinical practice is already dosing the patients with IM and PM genotype correctly. However, the effect of genotype information on the EM genotype patients is missing in our trial, because this group was considered as a control group. Because the genotype advice was given to the treating physician after start of treatment, the effect of the genotype information could be limited. Genotype information is becoming more readily available, which could also improve the impact of genotyping. Another possibility of the lacking effect of genotype information could be the restriction of a faster dose adjustment in an ambulant setting due to logistical problems. However, based on our results, no difference was observed between clinical and ambulant patients. Lastly, we did not meet the required number of patients included according to the sample size calculation before the conduct of the study. Based on our primary power calculation, a minimum of 48 participants followed up until adequate drug dose was needed per treatment arm.[14] The primary hypothesis of the effect of genotyping was a reduction of 50% in time to reach adequate drug levels of nortriptyline or venlafaxine in weeks. Taking into account the current distribution of time in days to reach adequate dosing in days in the DG-C group and a reduction of 50% in the DG-I group, this resulted in an estimated post hoc power of 100%. This indicates that we could not reject the null hypothesis that there is no difference between the group of 50% or more with 100% certainty.

In conclusion, the addition of CYP2D6 genotype to optimize drug dosing in older persons with depression and who start with nortriptyline or venlafaxine does not affect the adequate treatment for this patient population. Because our trial was set in older patients, it is uncertain how results may be applicable to younger patients.

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