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Risk Phenotypes, Comorbidities, Pharmacotherapy, and Electroconvulsive Therapy (ECT) in a Cohort with Difficult-to-Treat Depression in Comparison to an Unmedicated Control Group

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ABSTRACT

Background Approximately 15–25 % of depressed patients suffer from difficult-to-treat depression (DTD). Patients with DTD require a thorough examination to avoid the oversight of treatable (psychiatric/somatic) comorbidities or (pseudo-)resistance to antidepressant drugs (ADs). Polymorphisms of the cytochrome P450 (CYP) enzymes 2D6 and 2C19, which play a major role in the metabolism of ADs, may contribute to resistance to ADs. Patients with DTD might benefit from electroconvulsive therapy (ECT).

Methods We enrolled 109 patients with DTD and 29 untreated depressed controls (UDC). We assessed risk phenotypes, comorbidities, and treatment, including ECT. We also performed pharmacokinetic analyses of CYP2D6 and CYP2C19.

Results DTD patients significantly more often suffered from comorbid psychiatric diseases, especially ICD-10: F40-F48 (DTD:40.4 %, UDC:17.2 %, OR 11.87, $p = 0.011$) than UDC patients. DTD patients receiving ECT were more likely to achieve remission (37.7 % vs. 11.8 %, OR = 3.96, $p = 0.023$). Treatment with ADs did not differ between remitters and non-remitters. No significant differences were observed in the distribution of *CYP2D6* and *CYP2C19* variants between both groups.

Conclusion Patients with DTD appear to experience comorbid neurotic stress and somatoform disorders (ICD-10: F40 – F48) more frequently. Therefore, a comprehensive differential diagnosis is crucial when patients do not respond sufficiently to antidepressant medication. Genotyping *CYP2D6* and *CYP2C19* should be considered.

Introduction

Major depressive disorder (MDD) is a strong contributor to the global burden of disease [1], accounting for an estimated economic loss of 118 billion Euros in 2004 [2]. Various treatment options are available, including antidepressant drugs (ADs), psychotherapy, and brain stimulation techniques[3]. Nevertheless, even after having undergone several therapeutic trials, roughly 30 % of patients do not achieve remission. Even if remission is achieved, there is a considerable risk of relapse, ranging from 35 % to 70 % within one year after remission and increasing with the number of previous acute treatment trials [4].

McAllister-Williams and colleagues proposed the term "difficult-to-treat-depression" (DTD), defined as "depression that continues to cause significant burden despite usual treatment efforts" [5]. This condition is estimated to affect 15–25 % of all patients with MDD [6]. In their international consensus statement, they discussed the difficulties in treating patients with DTD, including the need to identify additional underlying conditions such as hypothyroidism, diabetes mellitus, a deficiency in vitamin B12 or D, sleep apnea, and undiagnosed psychiatric comorbidities [5]. If an MDD occurs secondary to an organic pathology (e. g., dementia), it is likely to be difficult to treat, and both disorders need to be properly addressed [5].

The concept of "treatment resistance" represents a different approach that classifies patients solely based on their response to drugs. It is most commonly defined as a condition that occurs in patients who do not improve after two adequate pharmacotherapy trials, defined as two distinct ADs used in sufficient dosage and for an adequate duration. Treatment resistance can be caused by a variety of circumstances, including pseudoresistance (e. g., insufficient dosage, non-adherence, and no structured control of the treatment success) [7]. Patients with initial pseudoresistance are more prone to developing treatment resistance as their condition progresses: studies indicate that the probability of achieving remission decreases significantly to roughly 15 % if patients do not respond to antidepressant medication within the first two weeks. Response rates decline even lower to about 10 % when there is no response within the first three weeks [8].

Affecting 60–70 % of depressed patients, the prevalence of psychiatric comorbidities, especially anxiety and substance use disorders, is remarkably high. The presence of a comorbid anxiety disorder has been hypothesized to impact remission rates adversely [9]. The STAR*D study identified an anxious depression subtype in 50 % of participants, which exhibited a reduced likelihood of achieving remission across various treatment levels [10]. Nonetheless, the relative effectiveness of ADs does not appear to differ significantly compared to placebo in depressed patients with or without anxiety [9]. In contrast to anxiety disorders, individuals with substance use disorders are often excluded from randomized controlled trials. In the STAR*D study, approximately 20 % of patients experienced drug or alcohol abuse/dependence, and those with such disorders were less likely to achieve remission, particularly during monotherapy with citalopram [11]. Overall, there is evidence suggesting that comorbid substance use disorder contributes to the failure to attain remission [9, 12]. Moreover, comorbid psychiatric disorders, especially anxiety, substance use, and personality disorders, significantly contribute to the risk of suicide in depressed patients [13]. This evidence suggests that comorbid psychiatric disorders are a risk factor for developing DTD.

Electroconvulsive therapy (ECT) is one of the oldest treatments for mental disorders but still represents the most well-established and effective treatment option for DTD to date [14]. Consequently, guidelines recommend the utilization of ECT, specifically in cases characterized by DTD [15–17]. While alternative treatments for DTD, such as repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), or intranasal administration of esketamine, have been approved and are readily available, current research lacks sufficient trials directly comparing the efficacy of these interventions with ECT [14, 18–20]. One recent Swedish study conducted a register-based comparison between ECT and rTMS, revealing ECT's superior effectiveness over rTMS when patients underwent both interventions [21].

One approach to address the problem of treatment resistance or difficulty in the treatment of depression is the establishment of patient-tailored treatment options. Personalized medicine using pharmacogenetics is frequent in oncology, but it is still uncommon in psychiatry. Polymorphisms of cytochrome (CYP) enzymes are a significant source of variation in the pharmacokinetics, adverse drug reactions, and responsiveness of drugs. Only a handful of CYP enzymes are responsible for the biotransformation of the majority of foreign substances, including 70–80 % of all medications in clinical use [22]. The two isoenzymes, CYP2D6 and CYP2C19, are of particular importance for the metabolism of many AD. According to the Clinical Pharmacogenetics Implementation Consortium (CPIC), five primary phenotypes are caused by polymorphisms in the *CYP2D6* and *CYP2C19* genes [23]: poor metabolizer (PM), intermediate metabolizer (IM), normal (extensive) metabolizer (NM), rapid metabolizer (RM), and ultrarapid metabolizer (UM). Due to the possible induction and/ or inhibition of CYP enzymes, the clinically observed phenotype can differ from the genotype-inferred phenotype, a phenomenon known as phenoconversion (PC) [24]. CYP2D6 is involved in the metabolism of at least 30 psychotropic drugs [25]. The significance of *CYP2D6* and *CYP2C19* gene variations was just recently demonstrated for the two ADs venlafaxine (mainly substrate of CYP2D6) and amitriptyline (mainly substrate of CYP2C19) [26]. Underlining this finding, pharmacogenetic testing was able to increase response and remission rates for individuals with DTD in a significant patient- and rater-blinded trial [27]. The symptom relief was even more pronounced in 75 % of patients who, by chance, received treatment based on their pharmacogenetics status [27]. Furthermore, it has been suggested that *CYP2C19* polymorphisms significantly contribute to treatment response [28]. Thus, an understanding of pharmacogenetics and the pharmacokinetic properties of ADs is a prerequisite for the informed selection of drug treatment and may increase the likeliness of treatment response.

Pharmacogenetic testing (PGx) is not routinely recommended by (inter-)national treatment guidelines [15, 16, 29] due to the lack of standardization of the currently available tests and the need for a clearer therapeutic implication. However, a number of (international) professional organizations, including CPIC, the Dutch Pharmacogenetics Working Group (DPWG), and the US Food and Drug Administration (FDA), are making the first suggestions regarding the use of PGx in the treatment of patients with mental illnesses

[30]. Additionally, in a recent meta-analysis, Brown and colleagues were able to demonstrate that antidepressant medication that is administered in accordance with PGx is associated with a notable improvement in depressive symptoms [31].

To advance the understanding of the etiopathogenesis of DTD and its treatment options and use these implications to develop personalized therapy strategies, we first examined to what extent phenotypes and mental as well as somatic comorbidities contribute to DTD development. In the second step, we focused on the success of treatment interventions (i. e., ECT and pharmacotherapy). Finally, we investigated the occurrence of abnormal drug metabolism due to genetic variations in the pharmacokinetic genes *CYP2D6* and *CYP2C19*, which may further compromise treatment success in DTD.

Material and Methods

Study design and patients

This cross-sectional investigation includes a cohort of patients who participated in a difficult-to-treat depression registry study (NEKTOR, German: Therapieresistente Depression / Difficult-to-treat Depression – Registerstudie) at Hannover Medical School (MHH), Germany. A total of 109 patients with DTD (n = 67 received ECT after inclusion) and 29 patients with MDD who were not treated with ADs at the time of inclusion (unmedicated depressed controls, UDC) were included in the analysis. All participants, either in- or outpatients, were in treatment at the Department of Psychiatry, Social Psychiatry, and Psychotherapy at MHH. The MHH Ethics Committee (No. 2842–2015) approved the present study, which adheres to the 1964 Declaration of Helsinki and its later amendments. Each patient provided written informed consent prior to enrollment in the study.

Before their inclusion, experienced psychiatrists verified the diagnosis of MDD and psychiatric comorbidities in participants using criteria according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) utilizing the German adaptation of the Structured Clinical Interview for Diagnosis (SCID) and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Additionally, patients underwent cerebral imaging, and routine blood work was utilized to look for underlying somatic diseases such as hypothyroidism, vitamin B12 deficiency, or vitamin D deficiency, which were then treated accordingly.

The DTD group and UDC group were matched for sex and body mass index (BMI). The smoking status in DTD and UDC was comparable.

Definition for DTD and exclusion criteria

For inclusion in the DTD registry, DTD was defined based on the work of McAllister-Williams and colleagues [5], requiring (a) at least two adequate treatment trials with AD (i. e., adequate dosage and duration) in the current depressive episode and (b) at least moderate severity of MDD as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS > 20) and Beck Depression Inventory-II (BDI-II > 20). Exclusion criteria were organic psychiatric diseases (F0X), psychotic disorders apart from F3X.3, and substance abuse (F1X) with a present need for detoxification. At the time of study inclusion, patients in the UDC group were required not to have taken any AD for the duration of at least five half-lives of their last AD.

Definition of remission

In the DTD group, remission was defined as a MADRS score below 10 after 4 weeks in individuals with ECT (n = 67) or 8 weeks in patients without ECT (n = 42).

Blood sample collection and processing

For genotyping, blood samples were collected between 8 and 9 am after overnight fasting. Ethylenediaminetetraacetic acid (EDTA) monovettes containing the samples were stored at 4 °C for up to three hours following collection. Among the 138 collected samples, 68 were frozen at − 80 °C and shipped to the Therapeutic Drug Monitoring (TDM) Laboratory in Würzburg on dry ice. The remaining 70 samples were kept in their original EDTA collection tubes and sent to the TDM laboratory in cool packs within three days of collection without further processing.

Genotyping of CYP2D6 and CYP2C19 gene variants

A total of eleven *CYP2D6* and six *CYP2C19* gene variants were genotyped on a MassArray Analyzer 4 system (Agena Bioscience GmbH, Hamburg, Germany) using a self-designed panel that utilized Spectro-CHIP®-96 Arrays and iPLEX® Pro chemistry, following the manufacturer's instructions. Copy number variation (CNV) in *CYP2D6* was determined using the *CYP2D6* RealFast™ CNV Assay from ViennaLab Diagnostics GmbH (Vienna, Austria, 2021). Genotyping quality was proofed with PLINK v1.9 [32]. All 17 genotyped single nucleotide polymorphisms reached a minor allele frequency (MAF) of more than 0.01, a genotyping call rate above 99 %, and genotype distribution did not deviate from Hardy-Weinberg-Equilibrium (p > 0.01).

Haplotype and star allele coverage were determined using gene-specific haplotype tables from the PharmGKB homepage (https://www.pharmgkb.org/gene; accessed last on 05 May 2021). Phenotypes were determined according to the specifications of the CPIC (Clinical Pharmacogenetics Implementation Consortium. 2021. https://cpicpgx.org/; accessed last on 08 March 2022).

Assessment of CYP2D6 phenoconversion (PC)

PC was conducted as suggested by Cicali and colleagues [33]. In accordance with their approach, the CYP2D6 activity value for patients undergoing treatment with a moderate or strong CYP2D6 inhibitor was initially adjusted by multiplying it by 0.5 or 0, respectively. The resultant adjusted activity factor was then used to determine the adjusted phenotype (functional enzyme status; PhenotypePC) according to CPIC specifications [34]. Drugs causing PC by concomitantly inhibiting or inducing metabolism via CYP2D6 were identified based on information extracted from the Flockhart table [35]. While melperone and perazine are not explicitly listed in the Flockhart table, their clinically relevant CYP2D6 inhibitory effects have been previously reported [35–37], and thus, both drugs were classified as moderate inhibitors.

Statistical analysis

Statistical analyses were performed and figures were generated using R, v4.1.1 [38] and Excel 2016 (Microsoft Corp., Redmond, USA). For baseline demographic information, results are presented as mean ± standard deviation. The contribution of phenotypes, comorbidities, and CYP2D6 / CYP2C19 metabolizer status on the development of DTD was analyzed using logistic regression models (independent variable: DTD versus UDC group; dependent variables: phenotypes, comorbidities, and metabolizer status). For analysis of treatment (ECT and pharmacotherapy) and metabolizer status in regard to remission, logistic regressions were performed, modeling drug use, ECT, or metabolizer status on the outcome of remission. Drug-tobacco, drug-alcohol, or drug-gene interaction terms on the outcome of remission, were analyzed using multiple regression models. Each regression analysis was adjusted for age and sex. For all analyses, the nominal significance level ($p \leq 0.05$) was Bonferroni-adjusted for the number of tests in the corresponding group of results.

Results

Risk phenotypes in DTD and UDC

We found that DTD patients were significantly older than those in the UDC group (OR = 1.05, $p = 0.001$, $p_{adjusted} = 0.012$), but the groups did not differ in age of first diagnosis ($p > 0.05$). Furthermore, patients in the DTD group were less likely to report acute suicidal thoughts (OR = 0.32, $p = 0.017$, $p_{adjusted} = 0.221$) and the initial manifestation of psychiatric abnormalities for the first time at baseline (OR = 0.24, p = 0.008, $p_{adjusted} = 0.104$) than patients of the UDC group at a nominal significance level. The MADRS score did not differ between the two groups, however, the BDI-II total score was higher in the DTD group than in the UDC group with nominal significance (OR = 1.06, p = 0.010, $p_{adjusted} = 0.130$). Additionally, patients in the DTD group suffered from a longer duration of their depressive episode on a nominal level (OR = 3.80, p = 0.021, $p_{adjusted} = 0.272$). There were no discernible differences regarding the smoker status, alcohol use, BMI, family predisposition, and psychotherapy before inclusion in the study ($p_{all} > 0.05$). An overview of these characteristics is shown in ▶ **Table 1**.

Comorbid mental and somatic disorders in DTD and UDC

To examine which comorbid diseases may be associated with the development of DTD, we examined all ICD-10 main groups present in at least three patients. The most pronounced difference between groups was found for neurotic stress and somatoform disorders more frequently represented in the DTD group on a nominal level (ICD10: F40-F48; OR = 4.21, $p = 0.011$, $p_{adjusted} = 0.086$). Subanalyses, restricted on comorbid phobic and other anxiety disorders (ICD10: F40-F41; OR = 2.9, $p = 0.114$, $p_{adjusted} = 0.910$) or PTSD (ICD10: F43; OR = 6.35, $p = 0.091$, $p_{adjusted} = 0.725$) showed however only a trend for significant differences between groups. The presence of comorbid diagnoses of mental and behavioral disorders caused by psychotropic substances (ICD-10: F10-F19), behavioral problems with physical disorders and factors (ICD-10: F50-F59) or comorbid personality and behavioral disorders (ICD-10: F60 – F69) did not vary between the two groups ($p > 0.05$). The results are summarized in ▶ **Table 2.**

In general, we also observed that patients in the DTD group were significantly more likely to suffer from somatic diseases (mainly endocrine and cardiovascular diseases, especially arterial hypertension, and diseases of the musculoskeletal system) compared to pa-

▶ **Table 1** Risk phenotypes in difficult-to-treat depression (DTD) compared to unmedicated depressed controls (UDC) . Significant differences (nominal and/ or adjusted) are written in bold. Bonferroni-adjusted p-values (x13 tests) are displayed in brackets. N, Number of patients; (%), percent; OR, odds ratio; SD, standard deviation; BMI, body mass index; MADRS, Montgomery–Åsberg Depression Rating Scale; BDI-II, Beck Depression Inventory – Second Edition.

	DTD N = 109		UDC N = 29		DTD *versus* UDC	
	N (%)	Mean ± SD	N (%)	Mean ± SD	OR	*p*-value ($p_{adjusted}$)
Sex (female/male)	63 (57.8) / 46 (42.2)		16 (55.2) / 13 (44.8)		0.90	0.800 (1)
Age (years)		52 ± 15.0		41 ± 13.0	1.05	**0.001 (0.013)**
Age at diagnosis (years)		33 ± 17.0		31 ± 13.0	1.01	0.725 (1)
Smoker	33 (39.8)		8 (27.6)		1.61	0.338 (1)
Alcohol use	6 (7.5)		2 (6.9)		1.27	0.791 (1)
BMI (kg/m²)		27.5 ± 6.1		25.6 ± 4.9	1.08	0.078 (1)
MADRS (score)		31 ± 8.0		30 ± 10.0	1.01	0.808 (1)
BDI-II (score)		37 ± 11.0		31 ± 11.0	1.06	**0.010 (0.130)**
Duration of current depressive episode (weeks)		129 ± 224.0		58 ± 104.0	3.80	**0.021 (0.272)**
Suicidality (yes)	42 (38.9)		21 (72.4)		0.32	**0.017 (0.221)**
Familiar predisposition (yes)	48 (76.2)		8 (72.7)		1.94	0.418 (1)
Initial manifestation of psychiatric abnormalities (yes)	9 (8.3)		8 (27.6)		0.24	**0.008 (0.104)**
Psychotherapy prior to inclusion (yes)	74 (67.8)		17 (58.6)		2.18	0.097 (1)

▶ **Table 2** Comorbid mental disorders in difficult-to-treat depression (DTD) compared to unmedicated depressed controls (UDC). Significant differences (nominal and/ or adjusted) are written in bold. Bonferroni-adjusted p-values (x7 tests) are displayed in brackets. ICD-10, International Classification of Diseases tenth revision; N, Number of patients; (%), percent; OR, odds ratio; SD, standard deviation.

	DTD N = 109	UDC N = 29	DTD *versus* UDC	
ICD-10 mental diagnoses	**N (%)**	**N (%)**	**OR**	***p*-value ($p_{adjusted}$)**
Mental and behavioral disorders caused by psychotropic substances (F10-F19)	22 (20.2)	3 (10.7)	2.01	0.310 (1)
Neurotic stress and somatoform disorders (F40-F48)	44 (40.4)	5 (17.9)	4.21	**0.011 (0.086)**
▪ Phobic and other anxiety disorders (F40-F41)	27 (24.8)	3 (10.7)	2.9	0.114 (0.910)
▪ Post-traumatic stress disorders (F43)	14 (12.8)	1 (3.6)	6.35	0.091 (0.725)
▪ Other neurotic, stress, and somatoform disorders (F42; F44-F48)	16 (14.7)	3 (10.7)	2.10	0.288 (1)
Behavioral problems with physical disorders and factors (F50-F59)	3 (2.8)	1 (3.6)	1.44	0.766 (1)
Personality and behavioral disorders (F60-F69)	21 (19.3)	5 (17.9)	2.16	0.202 (1)

tients in the UDC group (OR = 6.95; $p = 5.2^{*}10^{-5}$, $p_{adjusted} = 4.2^{*}10^{-4}$; data not shown).

ECT intervention

In the next step, we investigated changes in remission-rate in DTD patients depending on the respective treatment. Out of a total of 109 DTD patients, we had data on remission for 95 patients. Patients who were treated with ECT (N = 61) were significantly more likely to achieve remission (37.7 %) than patients who did not receive ECT (N = 34; 11.8 %; OR = 3.96; $p = 0.023$).

Drug use in DTD

During the current depressive episode, patients in the DTD group underwent at least two treatment trials with ADs. Patients were treated with selective serotonin reuptake inhibitors (SSRIs), serotonin modulators and stimulators, selective serotonin-norepinephrine reuptake inhibitors (SSNRIs), α2-receptor antagonists, tricyclic antidepressants (TCAs), monoamine oxidase (MAO) inhibitors, lithium, first-generation antipsychotic drugs (FGAs), second-generation antipsychotic drugs (SGAs), benzodiazepines/ Z-drugs, anticonvulsant drugs (▶ **Table 3**), or a combination of the above-mentioned drug classes. Apart from patients who were treated with benzodiazepines/ Z-drugs (OR = 4.01; $p = 0.006$, $p_{adjusted} = 0.080$), none of the other drug groups were associated with a higher remission-rate due to pharmacotherapy within the DTD group, not even at a level of nominal significance ($p_{all} > 0.05$; data not shown). Venlafaxine and mirtazapine were the most frequently used ADs followed by sertraline and (es-) citalopram. During their current depressive episode, 4.6 % of DTD patients were treated with amitriptyline and 3.7 % of patients with tranylcypromine.

Since the efficacy of a drug can be impaired by other substances, we additionally investigated whether interactions with tobacco or alcohol had an influence on the remission-rate. However, no significant interactions between any of the listed drugs/ drug classes and tobacco or alcohol consumption were detected ($p_{all} > 0.05$, data not shown).

Further, we found a trend pointing towards a higher utilization of drugs indicated for the treatment of other somatic illnesses in patients with DTD in comparison to the UDC group (OR = 2.62; $p = 0.054$; ▶ **Table 4**). The most common somatic drugs used in the DTD group were antihypertensive drugs (37.6 %), followed by L-thyroxine (22.9 %). In particular, antihypertensive drugs were used more frequently with nominal significance in patients with DTD than in those from the UDC group (OR = 5.19; $p = 0.036$, $p_{adjusted} = 0.109$).

Pharmacogenetic metabolizer status of CYP2D6 and CYP2C19 in DTD and UDC

In order to analyze whether a non-normal drug metabolism is generally more common in patients with DTD and whether this complicates successful treatment with psychotropic drugs, we compared the metabolism status of the two pharmacokinetic genes *CYP2C19* and *CYP2D6* between the DTD and UDC group. We initially separated both groups into normal and non-normal metabolizers but found neither a significant difference for *CYP2D6* nor *CYP2C19* ($p_{all} > 0.05$). Additionally, we compared the proportion of normal metabolizer (i. e., NM) and subgroups of non-normal metabolizer (i. e., PM, IM, NM, RM, and UM) for each gene, but again did not observe any differences among the groups ($p_{all} > 0.05$). To analyze potential drug-gene interactions, we determined the PC of CYP2D6 considering the correction factors for the concomitant medication. In so, we found that CYP2D6 poor metabolizers after PC were more frequent in DTD than in UDC patients, although this was only a nominal significance level (OR = 16.23; $p = 0.016$, $p_{adjusted} = 0.082$). Results are summarized in ▶ **Table 5**; an overview on metabolizer distribution for both genes, is shown in ▶ **Fig. 1**.

Pharmacogenetic impact of CYP2D6 and CYP2C19 metabolizer status on remission

To further clarify the role of the metabolizer status of the pharmacokinetic genes *CYP2D6* and *CYP2C19* play in remission, we compared the distribution of normal and non-normal metabolizers in regard to the remission rate. For *CYP2C19,* we found only a trend indicating a higher proportion of IM in the non-remission group (OR = 021; $p = 0.067$, $p_{adjusted} = 0.332$). Consistent with these observations, we also detected a trend towards a higher proportion of abnormal metabolizers of CYP2D6 in non-remitters (OR = 0.39; $p = 0.060$, $p_{adjusted} = 0.302$) after PC. This trend reached a nominal significance in the subgroup of PMs (OR = 0.12; $p = 0.013$, $p_{adjusted} = 0.064$). More detailed information is given in ▶ **Table 6**; an overview of the distribution of metabolizer status is shown in ▶ **Fig. 2**.

▶ **Table 3** Antidepressant drugs used in difficult-to-treat depression (DTD). The medication was not divided into the history of antidepressants taken during the present depressive episode and the actual medication taken at the time of inclusion into the study. (*) Sertraline is predominantly metabolized via the CYP2B6 pathway, alongside CYP2C19 [34]. *Other CYP enzymes may have a greater and more significant impact on metabolism;**Information modified according to [68]. N, Number of patients; (%), percent; ATC-Codes, Anatomical therapeutic chemical-codes; OR, odds ratio; MAO, monoaminoxidase.

Drugs	ATC-Codes	Metabolization via CYP2D6 or CYP2C19**	DTD N = 109
			N (%)
Serotonin reuptake inhibitors (SSRI)			54 (53.2)
Citalopram / Escitalopram	N06AB04 / N06AB10	Citalopram: main metabolization via CYP2C19, minor metabolization via CYP2D6; active metabolites: desmethylcitalopram and didesmethylcitalopram;	24 (22.0)
		Escitalopram: main metabolization CYP2C19, minor metabolization CYP2D6; weakly active metabolites: demethylescitalopram, didemethylescitalopram	
Fluoxetine	N06AB03	CYP2D6 and CYP2C19; active metabolites: norfluoxetine; autoinhibition of metabolism	7 (6.4)
Paroxetine	N06AB05	CYP2D6; no active metabolites	2 (1.8)
Sertraline (*)	N06AB06	main metabolization via CYP2C19; main metabolite: N-desmethylsertraline	31 (28.4)
Serotonin modulators and stimulators			1 (0.9)
Vortioxetine	N06AX26	CYP2D6; main metabolite is pharmacologically inactive,	1 (0.9)
Selective Serotonin-Noradrenalin-Reuptake-Inhibitor (SSNRI)			48 (44.0)
Venlafaxine	N06AX16	CYP2D6: active metabolite O-desmethylvenlafaxine CYP2C19: inactive metabolite N-desmethylvenlafaxine	34 (31.2)
Duloxetine*	N06AX21	minor metabolization CYP2D6; inactive metabolites	11 (10.1)
Milnacipran	N06AX17	no metabolization via CYP	9 (8.3)
α_2-receptor antagonists			34 (31.2)
Mirtazapine*	N06AX11	CYP2D6 (demethylation), weakly active metabolite	34 (31.2)
Tricyclic antidepressants			17 (15.6)
Amitryptiline	N06AA09	main metabolization via CYP2C19 (N-demethylation): main metabolite nortriptyline minor metabolization via CYP2D6 (hydroxylation)	5 (4.6)
Clomipramine	N06AA04	CYP2C19: active metabolite desmethylclomipramine CYP2D6: hydroxymetabolites	1 (0.9)
Doxepin	N06AA12	CYP2C19: active metabolite desmethyldoxepin CYP2D6: hydroxylation	2 (1.8)
Maprotiline	N06AA21	CYP2D6: N-desmethylmaprotiline	1 (0.9)
Nortryptiline	N06AA10	CYP2D6: 10-hydroxynortriptyline	1 (0.9)
Trimipramine	N06AA06	CYP2C19 and CYP2D6: N-desmethyltrimipramine, 2-hydroxytrimipramine and trimipramine N-oxide	4 (3.7)
Opipramol	N06AA05	CYP2D6: inactive metabolite dehydroxyethylopipramol	7 (6.4)
MAO-Inhibitors			7 (6.4)
Moclobemid	N06AG02	CYP2C19; no active metabolites	4 (3.7)
Tranylcypromine	N06AF04	no metabolization via CYP	4 (3.7)
Other antidepressants			57 (53.3)
Agomelatine*	N06AX22	minor metabolism via CYP2C19; no active metabolites	14 (12.8)
Tianeptine	N06AX14	no metabolization via CYP	5 (4.6)
Bupropion*	N06AX12	minor metabolism via CYP2D6	28 (25.7)
Trazodone*	N06AX05	minor metabolization via CYP2D6; active metabolite	9 (8.3)
Lithium	N05AN01	no metabolization via CYP	24 (22.0)
First-generation antipsychotic drugs (FGAs)			42 (38.5)
Pipamperone	N05AD05	no metabolization via CYP	26 (23.9)
Melperone	N05AD03	unknown involvement of hepatic enzymes; inhibition of CYP2D6	7 (6.4)
Haloperidol*	N05AD01	CYP2D6	1 (0.9)
Chlorprothixene	N05AF03	CYP2D6	2 (1.8)
Prothipendyl	N05AX07	unknown	1 (0.9)
Promethazine	R06AD02	CYP2D6; no active metabolites	9 (8.3)
Second-generation antipsychotic drugs (SGAs)			63 (57.8)
Quetiapine*	N05AH04	no metabolization via CYP2D6 or CYP2C19	35 (32.1)
Aripiprazole*	N05AX12	minor metabolization via CYP2D6; main metabolite dehydroaripiprazole	12 (11.0)
Clozapine*	N05AH02	CYP2C19 and minor metabolization via CYP2D6; main metabolites N-desmethylclozapine and clozapine-N-oxide	1 (0.9)
Olanzapine*	N05AH03	minor metabolization via CYP2D6	17 (15.6)
Risperidone	N05AX08	CYP2D6; active metabolite: 9-hydroxy-risperidone	11 (10.6)
Amisulpride	N05AL05	no metabolization via CYP	1 (0.9)
Others			59 (54.1)
Benzodiazepine/ Z-drugs	N05BA / N05CF	different metabolism depending on the substance	47 (43.1)
Anticonvulsant drugs	N03AX	different metabolism depending on the substance	20 (18.3)

▶ **Table 4** Concomitant drugs used in difficult-to-treat depression (DTD) in comparison to unmedicated depressed controls (UDC). Significant differences (nominal and/ or adjusted) are written in bold. Bonferroni-adjusted *p*-values (x3 tests) are displayed in brackets. N, Number of patients; (%), percent; OR, odds ratio

	DTD N = 109	UDC N = 29	DTD *versus* UDC	
	N (%)	N (%)	OR	*p*-value ($p_{adjusted}$)
Somatic Drugs	60 (55.0)	7 (24.1)	2.62	0.054 (0.163)
▪ Antihypertensive drugs	41 (37.6)	2 (6.9)	5.19	**0.036 (0.109)**
▪ L-Thyroxine	25 (22.9)	1 (3.4)	7.71	0.053 (0.159)

To assess whether remission is also affected by drug-gene interactions, we calculated interaction terms for both genes with each drug listed in ▶ **Table 3**. However, none of the calculated interactions reached significance ($p_{all} > 0.05$, data not shown).

Discussion

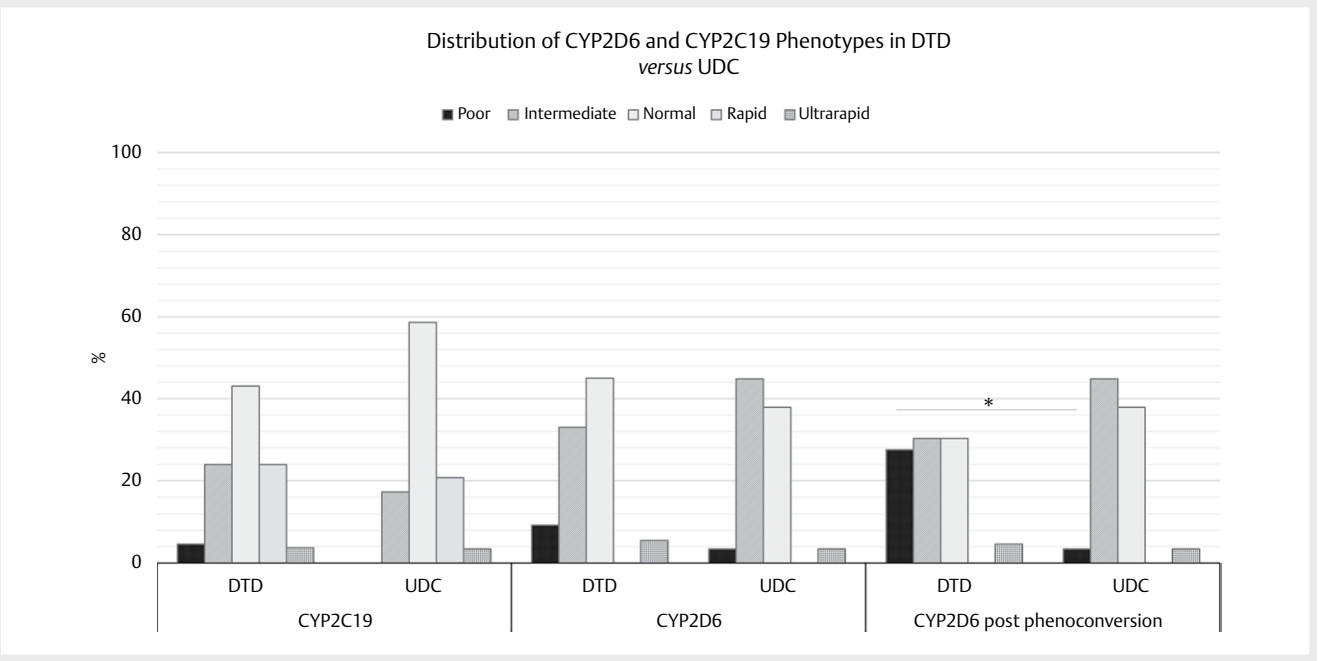
In our naturalistic cross-sectional study, we were able to demonstrate that patients with DTD are more likely to suffer from comorbid psychiatric disorders such as neurotic stress and somatoform disorders. Additionally, patients with DTD more frequently use drugs for somatic diseases. Patients receiving ECT were more likely to achieve remission compared to patients receiving treatment as usual (e. g. optimization of pharmacotherapy, psychotherapeutic interventions, occupational therapy). With regard to CYP 2D6 and 2C19, we found no significant difference in PGx between DTD patients and UDC. However, when PC of CYP2D6 was considered, DTD patients were more likely to have PM status compared to UDC. As far as remission in the DTD group was concerned, there was no difference in PGx of CYP enzymes, but after PC in CYP2D6 with subsequent PM status, it was more often in non- remitters than remitters.

Patients suffering from DTD were significantly older compared to those in the UDC group, whereas the two groups did not differ in age at the time of initial diagnosis. Older age is recognized as a patient-related factor contributing to DTD. Additionally, factors such as an early (< 18 years) or late onset (> 60 years) and a prolonged duration of illness are considered illness-related contributors to DTD [5]. Furthermore, in our study, patients in the UDC group more frequently reported the initial manifestation of their illness at the time of inclusion compared to the DTD group. Underlining this, the DTD group had a longer duration of illness. It is noteworthy, as we did not conduct follow-ups on the UDC group, we cannot ascertain whether patients in the UDC group developed DTD over the course of their illness.

Further, we observed that comorbid neurotic stress and somatoform disorders were rather frequent in our cohort. Comorbid phobic and other anxiety disorders were considerably more common in the DTD group than in the UDC group (24.8 % vs. 10.7 %) but probably did not reach the significance level due to the small sample size in the subgroup. The significance of comorbid anxiety disorders – especially generalized anxiety disorder (GAD) – in pa-

▲ **Table 5** Metabolizer status of pharmacokinetic genes CYP2D6 and CYP2C19 in difficult-to-treat depression (DTD) compared to unmedicated depressed controls (UDC). Significant differences (nominal and/ or adjusted) are written in bold. Bonferroni-adjusted p-values (x5 tests) are displayed in brackets. N, number of patients; (%), percent; OR, odds ratio; PC, phenoconversion.

	CYP2C19				*CYP2D6*				*CYP2D6_PC*			
	DTD	UDC	DTD *versus* UDC		DTD	UDC	DTD *versus* UDC		DTD	UDC	DTD *versus* UDC	
	N = 109	N = 29			N = 109	N = 29			N = 109	N = 29		
Metabolizer status	N (%)	N (%)	OR	*p*-value ($p_{adjusted}$)	N (%)	N (%)	OR	*p*-value ($p_{adjusted}$)	N (%)	N (%)	OR	*p*-value ($p_{adjusted}$)
Normal	47 (43.1)	17 (58.6)			49 (45.0)	11 (37.9)			33 (30.3)	11 (37.9)		
Non-Normal	61 (56.0)	12 (41.4)	1.70	0.232 (1)	52 (47.7)	15 (51.7)	0.90	0.821 (1)	68 (62.4)	15 (51.7)	1.77	0.233 (1)
Normal	47 (43.1)	17 (58.6)			49 (45.0)	11 (37.9)			33 (30.3)	11 (37.9)		
Poor	5 (4.6)	0 (0)	1.01	0.992 (1)	10 (9.2)	1 (3.4)	2.84	0.361 (1)	30 (27.5)	1 (3.4)	16.23	**0.016 (0.082)**
Intermediate	26 (23.9)	5 (17.2)	1.73	0.351 (1)	36 (33.0)	13 (44.8)	0.76	0.568 (1)	33 (30.3)	13 (44.8)	1.06	0.915 (1)
Rapid	26 (23.9)	6 (20.7)	1.45	0.501 (1)	0 (0)	0 (0)			0 (0)	0 (0)		
Ultrarapid	4 (3.7)	1 (3.4)	0.77	0.830 (1)	6 (5.5)	1 (3.4)	0.73	0.793 (1)	5 (4.6)	1 (3.4)	0.71	0.781 (1)
Not determined	1 (0.9)	0 (0)			8 (7.3)	3 (10.3)			8 (7.3)	3 (10.3)		



▶ **Fig. 1** Distribution of CYP2D6 and CYP2C19 phenotypes in difficult-to-treat depression compared with unmedicated depressed controls. DTD, difficult-to-treat-Depression; UDC, unmedicated depressed controls; *p < 0.05; **padjusted < 0.05.

tients with DTD is well-established. GAD increased the risk for treatment resistance by a 1.7-fold in a cohort consisting of over 1400 patients with TRD [39]. It appears that, in particular, an early onset of GAD may further contribute to treatment resistance of depression [40]. Results from the STAR*D trial suggest that patients with the anxious subtype of MDD are more likely to suffer from treatment resistance than those without [10]. This finding is underlined by a recent study looking at drug-specific antidepressant treatment responses in anxious vs non-anxious depressed MDD patients [41]. Anxiety and depressive disorders appear to interact in a complex manner making their co-occurrence frequent: 90 % of individuals with anxiety disorders also have MDD and 85 % of patients with MDD suffer from an anxiety disorder [42]. Patients with both disorders suffer from more severe anxiety and MDD, require more intensive care, are at a higher risk of attempting suicide [43], and are more prone to experience severe work-related impairment [42] than those with only one disorder.

PTSD was also a frequent comorbid disorder in our cohort affecting 12.8 % with DTD. Comorbid MDD is present in approximately 50 % of patients with PTSD and can be easily overlooked due to many overlapping symptoms [44–46]. A meta-analytical estimate of PTSD and MDD in war veterans suggested that worldwide, in 2015, about 354 million people suffered from PTSD and 117 million suffered from both conditions [47]. The co-occurrence of both disorders might be particularly prevalent in those patients with high levels of neuroticism and low extraversion. These traits may impair appropriate help-seeking behavior and could contribute to the risk of both diseases becoming chronic [45]. Whether or not PTSD and MDD are "two distinct constructs with overlapping distress components" or whether their common co-occurrence is the result of imprecision within the diagnostic criteria has not been fully elucidated [45]. However, an oversight and non-treatment of comorbid PTSD might contribute to DTD; therefore, a comprehensive differential diagnosis, including a PTSD-specific interview, is of utmost importance.

It is also possible that due to the small sample size, we did not find significant differences in comorbid personality and behavioral disorders between both groups. However, the results from a 2006 meta-analysis suggest that a comorbid personality disorder doubled the risk for an unfavorable outcome of depression treatment compared to depressed patients without this comorbidity. They also investigated different treatment modalities (i. e., pharmacotherapy, psychotherapy, ECT) and were unable to identify a significant superiority of any treatment option, which may have been due to the fact that the included studies were mostly underpowered [48]. Interestingly, authors found very small – but statistically significant – benefit of ECT for the treatment of severe depression and comorbid personality disorder [48]. One of the most relevant personality disorders in patients with MDD is borderline personality disorder (BPD) [49]. Patients with MDD and BPD might particularly benefit from a combination of SSRIs and specialized psychotherapy. ECT, on the other hand, was not suggested as a promising treatment option for patients with BPD and MDD; rather, it should be considered for carefully selected patients with BPD and MDD [49, 50]. As for patients with PTSD, high neuroticism scores were also found to predict non-response in BPD comorbid with MDD. Interestingly, comorbid BPD significantly worsens the outcome of MDD but not vice versa [51].

Our findings and published data underline the importance of differentiating between MDD with and without comorbid psychiatric disorders and vice versa in order to provide the best possible treatment. Due to their often-overlapping symptoms, common

▲ **Table 6** Metabolizer status of pharmacokinetic genes CYP2D6 and CYP2C19 in difficult-to-treat depression (DTD). Remitted patients were compared with non-remitted patients according to pharmacotherapy. Significant differences (nominal and/ or adjusted) are written in bold. Bonferroni-adjusted p-values (x5 tests) are displayed in brackets. N, number of patients; R, Remission; NR, Non-remission; (%), percent of patients; OR, odds ratio; PC, phenoconversion.

	CYP2C19				*CYP2D6*				*CYP2D6_PC*			
	Remission (R)	Non-remission (NR)	R *versus* NR		R	NR	R *versus* NR		R	NR	R *versus* NR	
	N = 27	N = 68			N = 27	N = 68			N = 27	N = 68		
Metabolizer status	**N (%)**	**N (%)**	**OR**	***p*-value ($p_{adjusted}$)**	**N (%)**	**N (%)**	**OR**	***p*-value ($p_{adjusted}$)**	**N (%)**	**N (%)**	**OR**	***p*-value ($p_{adjusted}$)**
Normal	13 (48.1)	29 (42.6)			13 (48.1)	32 (47.1)			13 (48.1)	16 (23.5)		
Non-Normal	14 (51.9)	38 (55.9)	0.76	0.579 (1)	13 (48.1)	30 (44.1)	1.32	0.579 (1)	13 (48.1)	46 (67.6)	0.39	0.060 (0.302)
Normal	13 (48.1)	29 (42.6)			13 (48.1)	32 (47.1)			13 (48.1)	16 (23.5)		
Poor	2 (7.4)	2 (2.9)	2.40	0.446 (1)	2 (7.4)	6 (8.8)	177	0.562 (1)	2 (7.4)	26 (38.2)	0.12	**0.013 (0.064)**
Intermediate	2 (7.4)	18 (26.5)	0.21	0.067 (0.332)	7 (25.9)	22 (32.4)	0.93	0.897 (1)	7 (25.9)	19 (27.9)	0.51	0.259 (1)
Rapid	8 (29.6)	16 (23.5)	0.90	0.854 (1)	0 (0)	0 (0)			0 (0)	0 (0)		
Ultrarapid	2 (7.4)	2 (2.9)	1.50	0.712 (1)	4 (14.8)	2 (2.9)	4.73	0.108 (0.540)	4 (14.8)	1 (1.5)	4.18	0.256 (1)
Not determined	0 (0)	1 (1.5)			1 (3.7)	6 (8.8)			1 (3.7)	6 (8.8)		

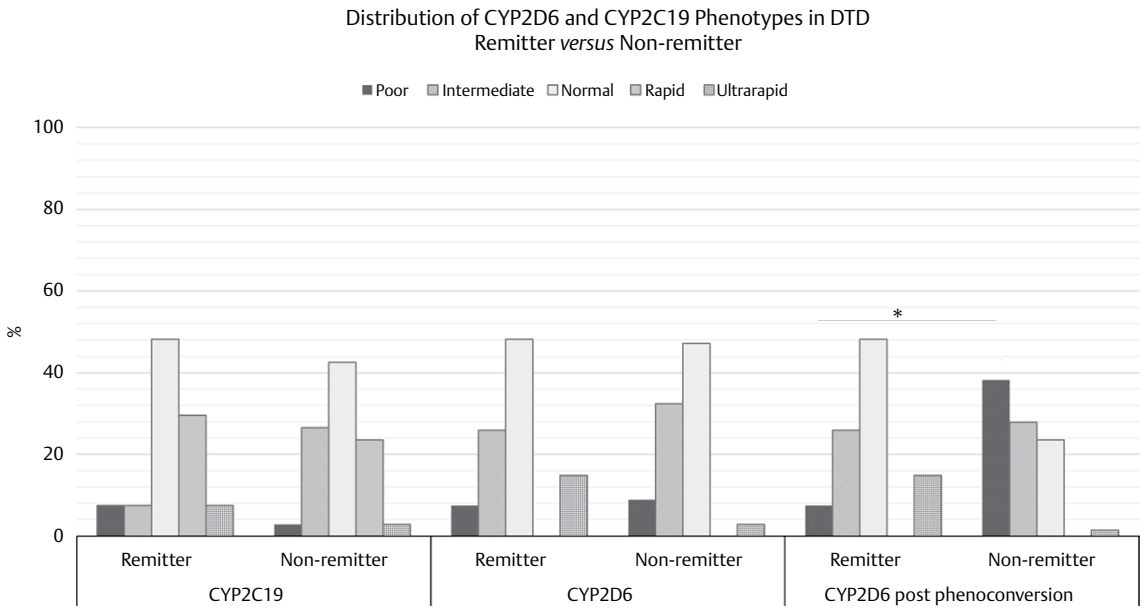
comorbidities such as anxiety disorders, PTSD, or personality disorders – especially BPD – often pose a challenge in making accurate diagnoses. Because these comorbidities may require a distinct treatment of their own, their identification is of utmost importance. Without proper treatment for each diagnosis, patients are more likely to experience a chronic course of their diseases. Tailored and specialized care is necessary to prevent the emergence of treatment resistance in either condition.

Patients receiving ECT in our cohort were more likely to achieve remission compared to those undergoing treatment as usual (i. e., pharmaco- and psychotherapy). This outcome is not surprising, considering that patients with DTD most likely underwent multiple treatment trials with ADs. Notably, our observed remission rates under ECT (37.7 %) were lower than rates reported in the literature, where remission rates of up to 75 % have been reported [52, 53]. The lower remission rates in our study could be attributed to the high prevalence of comorbidities. Further, we solely focused on remission and did not consider treatment response, which could also be a valid outcome criterion for patients enduring long-term illness. Nevertheless, our data unmistakably illustrates the advantages of utilizing ECT in the treatment of patients with DTD compared to conventional treatment methods.

Among patients in the DTD group, we did not observe any significant differences in drug use between patients in remission and those who did not achieve remission. Patients in remission were more likely to be treated with benzodiazepines / Z-drugs than unremitted patients. A recent Cochrane review suggested that the combination of ADs with benzodiazepines was superior to monotherapy with ADs in an early phase of the disease [54]. However, as patients in our DTD sample were not in the early phase of their illness, whether this consideration holds true for this subgroup of patients remains unclear. Patients with anxiety symptoms might particularly benefit from the short-term use of benzodiazepines, potentially improving adherence to ADs and lowering dropout rates due to adverse events [54]. However, the efficacy of benzodiazepines must be carefully weighed, especially against their well-known risk of dependence, mandating their use as only temporary [55].

Previous reports suggest that about two thirds of patients with MDD suffer from comorbid somatic illnesses [9, 56]. On the other hand, patients with multimorbidity — defined as having two or more chronic diseases — experience MDD twice as often as those without multimorbidity and three times more frequently than those without any chronic disorder at all [56]. While multimorbidity generally increases with age, it has been found to affect 7–35 % of individuals aged 18 to 65. Regardless of age, patients with additional chronic medical conditions have a 45 % higher risk of developing MDD than those without any further chronic medical conditions [56]. As with comorbid psychiatric disorders, the safe and effective treatment of somatic illnesses is imperative to provide effective care for patients with MDD.

Compared to patients in the UDC group, those in our DTD cohort were more likely to use somatic drugs, indicating a higher burden of somatic – and especially cardiovascular – comorbidities. However, patients in the DTD group were also significantly older than UDC. Patients with underlying somatic comorbidities such as hypothyroidism may respond poorly to treatment with ADs, where-



▶ **Fig. 2** Distribution of CYP2D6 and CYP2C19 phenotypes in remitter compared to non-remitter within the difficult-to-treat depression group. *p < 0.05; **padjusted < 0.05.

as sufficient treatment of hypothyroidism can improve their mood and potentially restore euthymia. Euthyroidism may even be a prerequisite for AD efficacy [57]. These considerations emphasize the particular value of determining thyroid function in patients with DTD. Patients with chronic somatic illnesses or comorbid mental illnesses are often excluded from participation in randomized-controlled effectiveness trials (RCT), therefore, 60–70 % of individuals with MDD do not meet the eligibility criteria for RCTs [9, 58]. Therefore, real-world data such as ours is of great value.

Detected in 41 to 56 % of patients, a non-normal metabolizer status of CYP2D6 or CYP2C19 was a common encounter in both patients in the DTD and the UDC group. However, we were unable to substantiate that PGx of *CYP2D6* and *CYP2C19* differed between DTD patients and the UDC group. While PC in CYP2D6 with subsequent PM status was more common in DTD patients (62 %) than in UDC (52 %), the significance of this finding did not survive correction for multiple testing. Of particular interest is that PC of CYP2D6 was prevalent in over 68 % of non-remitters with DTD (compared to 48 % in remitters with DTD). This is an intriguing discovery, given that the activity of CYP enzymes affects drug serum concentrations and thus may influence the effectiveness of drugs metabolized by these enzymes, as well as the incidence of side effects. Depending on the specific drug, metabolization via CYP enzymes converts drugs into either active or inactive metabolites. Consequently, a prodrug activated via metabolization may be more likely to cause side effects in individuals with a UM status, while a PM status could result in a higher burden of side effects for an active compound prior to metabolization. On the other hand, a drug in its active form before metabolization may be ineffective in individuals with an RM or UM status or result in a higher incidence of side effects in those with a PM status [59, 60].

We can only speculate about the lack of response to AD in our DTD cohort, as we did not assess the frequency of adverse drug reactions prior to presentation during our consulting hours. However, PGx and the subsequent tailoring of drug selection are recommended as beneficial adjuncts to the pharmacotherapy of MDD. When ADs are used in accordance with the results of PGx (e. g., dose adjustment, drug change), there is a greater likelihood of response, remission, and improvement of MDD severity [61]. This effect may potentially even prevent the occurrence of DTD due to a quicker and more effective treatment.

As many drugs used to treat somatic illnesses are likewise degraded by CYP2D6 and CYP2C19, PGx is helpful for psychiatry and also for other fields of medicine [60].

The activity of CYP enzymes is not only mandated by genetics but also by interactions with other substances, such as other drugs and tobacco smoke. The latter influences drug metabolism primarily via CYP1A2 due to polycyclic aromatic hydrocarbons in tobacco smoke [62]. However, the effects of smoking on CYP2D6 and CYP2C19 functionality are currently unclear. Only a few studies have investigated this issue; higher concentrations of the active metabolite of clopidogrel – a substrate of CYP2C19 and CYP3A4 among other CYP enzymes–, have been found in smokers compared to non-smokers, suggesting an induction of enzymes involved in the metabolism of clopidogrel through smoking [63]. The effects of smoking on plasma levels of TCAs are inconclusive as the available studies failed to account for CYP polymorphisms that may be responsible for the observed effects in some studies [64]. Alcohol can affect the activity of CYP2D6 and CYP2C19, but the effects seem to be small [65, 66].

Strengths and limitations

One advantage of our study is that we included individuals who had undergone adverse event-related therapy cessation as well as those with many failed prior drug trials due to a lack of AD efficacy. Additionally, we included study participants with MDD who were not treated with an AD at the time of inclusion. However, several limitations must also be considered. First, the sample sizes in both groups were comparatively small, thus reducing statistical power. This may have contributed to the lack of statistical significance of several of our findings, such as the effect of PGx. Moreover, we did not conduct a follow-up on the UDC cohort, so we cannot determine whether patients in that group developed DTD later on. Therefore, our findings should be validated in a larger, longitudinal sample. We also did not consider other mechanisms of drug degradation, such as glucuronidation, drug transport via p-glycoprotein [67], or additional variables and epigenetic factors that may impact the effects of the drug and the phenotype of the metabolizer [25].

Conclusion

Patients with DTD appear to more commonly suffer from comorbid psychiatric, such as anxiety and personality disorder, as well as somatic disorders. Therefore, when patients do not sufficiently respond to treatment with AD, a comprehensive differential diagnosis is crucial. However, perhaps due to the small sample size of the present study, we were unable to substantiate our theory that patients with DTD are more likely to have genetic polymorphisms of CYP2D6 and CYP2C19. To further investigate the effects of CYP polymorphisms in DTD, a replication study with a significantly bigger sample size is required.

Author Contributions

HBM: Supervision of patient recruitment. Data analysis and manuscript drafting. AB: Recruitment of patients under supervision and data management. Organizing analysis of the blood samples. Revision of the manuscript for important intellectual content. AN: Supervision of the study, essential contribution to the conception and design of the work. Revision of the manuscript for important intellectual content NM: Enormous support regarding organizing the blood samples and revising the manuscript for important intellectual content. RS: Revision of the statistical analysis and revision of the manuscript for important intellectual content. GLB: Support concerning statistical analysis and revision of the manuscript for important intellectual content. TF: Recruitment and treatment of patients. Revision of the manuscript for important intellectual content. AG: Recruitment of patients and data management. Revision of the manuscript for important intellectual content. JS: Revising of the manuscript for appropriate language and important intellectual content. SB: Substantial contribution to the conception of the work. Revising the study for important intellectual content. MSC: Conducted the pharmacogenetic analyses and revision of the manuscript for important intellectual content. SU: Supervised and conducted the pharmacogenetic analyses. Revision of the manuscript for important intellectual content. JD: Revising the manuscript for important intellectual content. HF: Essential contribution to the conception and design of the work, analysis and interpretation of the data. HW: Essential contribution to the analysis and the interpretation of the data. Revising the manuscript for important intellectual content. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Hannover Medical School (protocol code 2842–2015 and date of approval: 18.08.2015).

Informed Consent Statement

Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Study data can be made available upon reasonable request to the corresponding author.

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This investigation was undertaken in part for Anton Borchert's doctoral thesis. Pharmacopsychiatry has released an abstract for a poster presentation at the AGNP/DGBP Congress in Germany in 2022. In addition, we want to express our gratitude to all of the study participants.

Conflict of Interest

HBM took part in educational events sponsored by Livanova and Rovi. RS took part in an educational event sponsored by Livanova. HF received speaker‘s honararia and served as advisor for Recordati Pharma GmbH and Janssen-Cilag Gmbh. AN received lecture fees from Novartis and Merck. NM is currently working for SCENTS Health GmbH. JS has participated in two educational events sponsored by Otsuka/Lundbeck. JD was the co-recipient with BioVariance of a grant of the Bavarian Ministry of Economic Affairs, Regional Development and Energy (BayMED, MED-1604–0010) and an investigator in a European grant (Horizon 2020 SME programme of the European Union ref 696802) to P1Vital. AB, GLB, TF, AG, SB, MSC, SU, and HW declare that they have no conflicts of interest.

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