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Research paper

Investigating the potential role of BDNF and PRL genotypes on antidepressant response in depression patients: A prospective inception cohort study in treatment-free patients

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ABSTRACT

Background: Brain-derived neurotrophic factor (BDNF) is associated with response to antidepressant drugs in mood and anxiety disorders. Prolactin (PRL) is a pituitary hormone with behavioural effects, acting as a neurotrophic factor within the brain and may be involved in antidepressant response.
Objectives: To investigate the relationship between *BDNF* and *PRL* genotypes with antidepressant drug response.
Methods: Prospective inception cohort of 186 Russian treatment-free participants (28 men and 158 women) between 18 and 70 years clinically diagnosed with depressive disorder who initiated antidepressant medication. DNA polymorphisms were genotyped for *PRL* rs1341239, *BDNF* rs6265 and rs7124442. Primary outcome was measured by differences in Hamilton Depression Rating Scale (ΔHAM-D) scores between baseline/week two, week two/week four, and baseline/week four. Linear regression and independent *t*-test determined the significance between polymorphisms and ΔHAM-D.
Results: Comparisons between genotypes did not reveal any significant differences in scores during the first two weeks of treatment. In the latter two weeks, *BDNF* rs7124442 homozygous C patients responded significantly worse in comparison to homozygous T patients during this period. Further analysis within women and in postmenopausal women found a similar comparison between alleles.
Limitations: Study lasted four weeks, which may be considered short to associate genuine antidepressant effects.
Conclusions: Patients taking tricylic antidepressants were noted to have a significant improvement in ΔHAM-D compared to patients taking SSRIs. Homozygous C *BDNF* rs712442 patients were found to respond significantly worse in the last two weeks of treatment.

1. Introduction

With a lifetime prevalence of ~15%, major depressive disorder (MDD) has become a prominent cause of disability in the Western world (Bromet et al., 2011). The high lifetime prevalence of MDD greatly exceeds figures for other mental disorders, such as schizophrenia,

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bipolar disorder and borderline personality disorder (American Psychiatric Association, 2013). This may be partially connected to a more heterogeneous symptom profile compared to other mental disorders.

Arguably, the underlying pathological processes are also more heterogeneous in MDD. This may explain why diagnostic manuals and instruments such as DSM-5 and ICD-10 (World Health Organization, 2016) appear incapable of predicting treatment response (Montgomery, 2016). As neither DSM-5 nor ICD-10 was designed to measure treatment outcome, the limits of categorical systems in validating biomarkers for treatment response are considered. In turn, the utilization of Hamilton Depression Rating Scale to study a patient's depressive state provides the capacity for monitoring treatment effectiveness throughout the study period.

Many patients with MDD do not respond optimally to their antidepressant medication. Even when prescribed first-line treatment (i.e. selective serotonin reuptake inhibitors), roughly 60% of patients were found to have an adequate response (Bauer et al., 2013, 2015). With multiple factors associated with the efficacy of antidepressants, investigating the effect of genetic factors promises to limit sub-optimal treatments (Laje and MacMahon, 2007). Genome-wide association studies (GWAS) have been carried out to investigate the effect of antidepressant response and the pharmacogenomics of depression (Fabbri and Serretti, 2015). However, focusing solely on GWAS leads to a limited understanding of a depressive episode and clarification on the mechanism of action for targeted treatment is required.

To improve the current situation, it is necessary to identify the pathological mechanisms underlying the symptoms of a depressive episode (Loonen and Ivanova, 2016a,b) to provide tailored antidepressant treatment. Therefore, our group studies the possible relationship between gene polymorphisms, related biomarkers and drug treatment response of depressive disorders within the context of our «Validation of biomarkers in depression» project.

Prolactin, also called the lactotrophin hormone, is a 199 amino-acid pituitary hormone. Apart from its role as a pituitary hormone, prolactin is also produced as a cytokine by immune cells, with its receptor belonging to the cytokine receptors type 1 family (Peeva et al., 2003). The gene encoding prolactin (*PRL*) has been mapped to chromosome 6p21 (Evans et al., 1989; Owerbach et al., 1981). In humans the *PRL* locus contains a specific promoter, driving the expression in non-pituitary tissues (Featherstone et al., 2012). Stevens et al. (2001) identified a functional polymorphism in the *PRL* gene, − 1149 G/T (rs1341239), demonstrating the G allele was associated with increased extra-pituitary promoter activity and increased levels of lymphocyte PRL mRNA.

Ivanova and colleagues revealed the existence of a significant association between the polymorphic variant rs1341239 and the development of hyperprolactinemia in patients with schizophrenia (Ivanova et al., 2017). Within the brain, prolactin acts as a neuropeptide to promote physiological responses related to reproduction, stress adaptation, neurogenesis, and neuroprotection (Torner, 2016). The action of prolactin on the nervous system contributes to the wide array of changes occurring in the female brain during pregnancy, resulting in the attenuation of the hypothalamic–pituitary–adrenal axis and regulating neurogenesis in both the subventricular zone and the hippocampus (Torner, 2016). Therefore, alterations in the prolactin system could contribute to the pathogenesis of mood and anxiety disorders.

Brain-derived neurotrophic factor (BDNF), discovered in 1982 (Barde et al., 1982), plays an important role in neural differentiation, the survival of nerve cells, neurite outgrowth, and synaptic plasticity (Binder and Scharfman, 2004; Cowansage et al., 2010; Zheleznyakova et al., 2016). Numerous genetic, pharmacological and behavioural studies have linked dysregulation of BDNF to major psychiatric and neurological disorders, including mood and anxiety disorders (Cowansage et al., 2010; Jentsch et al., 2015; Loonen and Ivanova, 2016b). The human *BDNF* gene, located on chromosome 11p14.1, has a complex structure and its expression is under sophisticated epigenetic control (Cowansage et al., 2010; Zheleznyakova et al., 2016). *BDNF* genotype and expression can be expected to modulate BDNF levels and its neuroplastic effects and, therefore, may affect the vulnerability to develop mood disorders.

BDNF rs6265 and rs7124442 were found to be associated with mental health disorders and antidepressant effects, albeit with mixed results. A recent review on the interaction between *BDNF* and depression did not associate rs6265 with MDD or hippocampal volume in all patients with MDD but was found to be associated in late-life depression (Kishi et al., 2018). On the other hand, *BDNF* rs6265 was found to be associated with antidepressant response in patients with MDD (Tsang et al., 2017). Building on previous pharmacogenetic studies on antidepressant response, our study aims to investigate the responses within the aforementioned *BDNF* single nucleotide polymorphisms (SNPs) and *PRL* rs1341239 in treatment-free Russian patients.

To investigate the effect of *PRL* and *BDNF* SNPs to antidepressant response, the Hamilton Depression Rating Scale (HAM-D) will be measured at baseline, after two weeks and after four weeks of treatment to determine the patient's level of depression. The overall decrease in HAM-D score between baseline and week four will determine the final antidepressant response. However, the first two weeks of antidepressant response has been studied to not vary between treatment and placebo (Stassen et al., 2007). Stassen's study compared seven different antidepressants and placebo, where differences between the treatments did not differ initially but a significant difference between the antidepressants and placebo was found after roughly two weeks. We hypothesize the specific antidepressant response has a lag time of roughly two weeks and treatment response in the first two weeks will be non-specific and similar throughout all tested genotypes.

In the first part of our study, we investigated the possible relationship between *PRL* and *BDNF* genotypes and protein levels in 186 treatment-free patients with a clinical diagnosis of a depressive disorder of at least moderate severity. Of note, more than half of the studied patients had never been treated with antidepressant medication during their entire life. We observed a significant association between *BDNF* gene variant rs6265 and the severity of depression (Losenkov et al., submitted). In the second part of our study, we explored the potential association between one *PRL* and two *BDNF* genotypes and antidepressant treatment response. Antidepressant treatment was initiated immediately after the first study and clinical conditions were assessed after two and four weeks of treatment. As this paper's aims to investigate the pharmacogenetic *PRL* and *BDNF* markers in antidepressant treatment response, we looked to build on the previous study's findings.

2. Materials and methods

2.1. Patients

The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki 1975, revised in Fortaleza, Brazil, 2013), and approved by the Institutional Medical Review Board (protocol 49 from 23.04.12). Participants were recruited from psychiatric departments of the Mental Health Research Institute, Tomsk National Research Medical Center and provided written informed consent.

Participants, aged 18–70 years old, were included based on a clinical diagnosis of single depressive episode (ICD: F32) or recurrent depressive disorder (ICD: F33) (World Health Organization, 2016). Patients were categorized to have a major depressive episode of at least moderate severity (Hamilton Depression Rating Scale score greater than 14) according to the Mini International Neuropsychiatric Interview (M.I.N.I., 5.0.0) (Sheehan et al., 1998). The patients had not been treated with antidepressant medication in the preceding six months before admission into the clinic. In addition, more than half the patients (54.5%) have not received antidepressant treatment in their life. The

Table 1
Antidepressant medication taken by patients.

Class	Antidepressant	Patients
SSRIs	**Total**	91
	Sertraline	24
	Paroxetine	21
	Escitalopram	16
	Fluoxetine	12
	Fluvoxamine	12
	Citalopram	4
	Trazodone	1
	Trazodone + Paroxetine	1
TCAs	**Total**	23
	Clomipramine	16
	Pipofezine	6
	Amitriptyline	1
SNRIs	**Total**	14
	Venlafaxine	10
	Duloxetine	4
Agomelatine	Agomelatine	11
NaSSa	**Total**	11
	Mirtazapine	7
	Mianserin	4
SSRIs + Agomelatine	Fluvoxamine + Agomelatine	1

Antidepressant taken over the course of the four weeks by patients. SSRIs: selective serotonin receptor inhibitors, TCAs: tricyclic antidepressants; SNRIs: serotonin–norepinephrine reuptake inhibitors; NaSSAs: noradrenergic and specific serotonergic antidepressants.

exclusion criteria considered the following status: non-Caucasian ethnicity, schizophrenia, decompensated personality disorders, pregnancy, or any relevant gynaecological or endocrine (thyroid) disorder, relevant pharmacological withdrawal symptoms, organic brain disorders (e.g., epilepsy, Parkinson's disease), or treatment with antidopaminergic drugs (antipsychotic or antiemetic drugs).

2.2. Study design and ratings

After admission and obtaining informed consent, patients were diagnosed and assessed within two full days. Antidepressant treatment was initiated immediately thereafter. Out of the studied 151 patients, 129 patients were treated with serotonin reuptake inhibitors (selective serotonin reuptake inhibitors (SSRIs)) – 91, tricyclic antidepressants (TCAs) – 23, serotonin and noradrenaline reuptake inhibitors (SNRIs) – 14), 22 patients were treated with serotonin type 2 receptor antagonists and one patient was treated with a combination of both (Table 1). Depressed patients were assessed with the 17-item Hamilton Depression Rating Scale (HAM-D 17) (Hamilton, 1960) and the Clinical Global Impression Scale, Severity (CGI-S) (Guy, 1976).

2.3. Blood sampling

Venous blood samples were drawn from the median antecubital vein after an 8-hour overnight fast and collected into evacuated tubes containing EDTA. Blood samples were stored in several aliquots at −20 °C, until the DNA was isolated.

2.4. Genotyping

The DNA was genotyped for the studied genes in the Laboratory of Genetics of the University of Groningen with the MassARRAY® System (Agena Bioscience™) and in the Laboratory of Molecular Genetics and Biochemistry of the Mental Health Research Institute with "StepOnePlus" (Applied Biosystems). rs1341239 (minor allele frequency (MAF): 0.38) was measured within the prolactin gene (ENSG00000272168) and rs6265 (MAF: 0.15) and rs7124442 (MAF: 0.27) was measured within the *BDNF* gene (ENSG00000176697).

2.5. Statistical analysis

After excluding patients with missing data on treatment response and/or genotype, outcomes were defined characterizing the difference in HAM-D 17 score between entry and two weeks of treatment (ΔHAM-D 0–2 weeks), after two and four weeks of treatment (ΔHAM-D 2–4 weeks) and entry and four weeks of treatment (ΔHAM-D 0–4 weeks), with a higher ΔHAM-D score denoting better clinical outcome. Normal distribution was tested utilising the P-P plot. Due to the small number *BDNF* rs6265 homozygous A subjects, the analysis was conducted by combining homozygous A and heterozygous GA.

Patient characteristics were determined using descriptive statistics (Supplementary Table 1). Multivariate linear regression was conducted to identify the independent factors associated with ΔHAM-D between the three time periods, including age, sex, type of antidepressant taken, *PRL* rs1341239, *BDNF* rs6265 and *BDNF* rs7124442 genotypes. Further investigation was conducted with paired-sample *t*-tests to determine the statistical significance between ΔHAM-D between the two time-points. Independent *t*-test determined the statistical significance between polymorphisms and ΔHAM-D in baseline and week two, and week two and week four. The cohort was analyzed between sexes and menopausal status. Levene's test was utilized to determine the variance within the independent *t*-test analysis. Statistical analysis was conducted with SPSS software (release 25.0). The significance level for all statistical tests was $p < 0.05$. Analysis with CGI-S scores was not conducted as the variables did not represent a normal distribution and outcomes were limited.

3. Results

A total of 186 depressed patients were eligible with 28 men and 158 women, aged 49.9 ± 10.8 (mean ± standard deviation). After excluding patients with missing genotype data and HAM-D scores, 151 patients were available for further analysis. Within the *BDNF* rs6265, only 3 patients were A homozygous and therefore they were combined with GA heterozygous patients. Demographic and clinical details of the selected patients are indicated in Supplementary Table 1.

Multivariate linear regression analyses for ΔHAM-D for the three time periods were conducted (Table 2, Supplementary Table 2). For the entirety of the study, no significance was found between the SNPs. A significant association for improved ΔHAM-D was noted in patients taking tricyclic antidepressants (ΔHAM-D 0–4 weeks: $B = 5.09$, $p = 0.004$; ΔHAM-D 0–2 weeks: $B = 3.71$, $p = 0.002$) compared to patients taking SSRIs. Agomelatine was found to be significant between baseline/two weeks and two/four weeks however as the associations were in opposite directions, significance in the overall study was not found. Due to the small number of males in our study, further analyses were conducted within female patients. The association for improved ΔHAM-D with patients taking tricyclic antidepressants continued (ΔHAM-D 0–4 weeks: $B = 4.54$, $p = 0.004$; ΔHAM-D 0–2 weeks: $B = 3.64$ $p = 0.004$). *BDNF* rs7124442 homozygous T was found to be associated with improved ΔHAM-D over homozygous C patients in the latter two weeks (ΔHAM-D 2–4 weeks: $B = 2.48$, $p = 0.035$). However, the *R*-squared values were low throughout each time period indicating a weak linear fit of the models. Therefore, independent analysis targeting each SNP was conducted (Supplementary Table 1).

To study the potential associations between the pharmacogenetic markers and ΔHAM-D scores, further analyses were conducted with independent *t*-tests for baseline/two weeks and two/four weeks for each SNP, stratified for sex and menopause state. Stratification for type antidepressant treatment was not investigated further as the number of patients per group limited statistical power. For each subgroup of patients, the frequency distribution of ΔHAM-D 17 (between 0–2 weeks and 2–4 weeks of treatment) were plotted and verified for normality utilising P-P plots. Within each subgroup and genotype, patients significantly improved during the first two weeks, as well as the last two

Table 2
Linear regression of covariates (age, gender, *PRL* and *BDNF* genotypes, type of antidepressant) for baseline/week four and week two/four.

All patients (n = 139)

HAM-D (0–4 weeks)					HAM-D (2–4 weeks)				
Baseline Predictors	*B*	95% CI	*p*-value	R^2	Baseline Predictors	*B*	95% CI	*p*-value	R^2
Age	−0.03	−0.12; 0.05	0.43	0.156□	Age	−0.01	−0.07; 0.06	0.84	0.211□
Gender	−1.67	−4.51; 1.18	0.25		Gender	−2.63	−4.88; −0.36	0.023*	
rs1341239 T	1.41	−1.52; 4.35	0.34		rs1341239 T	0.47	−1.86; 2.81	0.69	
rs1341239 GT	1.82	−0.16; 3.79	0.07		rs1341239 GT	1.43	−0.14; 3.01	0.08	
rs6265 AAG	0.00	−2.42; 2.42	0.99		rs6265 AAG	0.12	−1.8; 2.05	0.90	
rs7124442 T	0.98	−2.09; 4.05	0.53		rs7124442 T	2.17	−0.28; 4.61	0.08	
rs7124442 CT	0.13	−2.98; 3.23	0.94		rs7124442 CT	1.39	−1.08; 3.86	0.27	
TCAs	5.09	2.41; 7.77	0.004**		TCAs	1.91	−0.22; 4.04	0.08	
SNRIs	0.60	−2.61; 3.79	0.71		SNRIs	0.78	−1.76; 3.32	0.54	
NaSSAs	−1.69	−5.21; 1.83	0.34		NaSSAs	−2.79	−5.58; 0.01	0.05	
Agomelatine	−1.00	−4.36; 2.37	0.56		Agomelatine	−4.01	−6.68; −1.32	0.004**	

Female patients only (n = 124)

HAM-D (0–4 weeks)					HAM-D (2–4 weeks)				
Baseline Predictors	B	95% CI	*p*-value	R^2	Baseline Predictors	B	95% CI	*p*-value	R^2
Age	−0.03	−0.10; 0.04	0.45	0.160□	Age	−0.01	−0.07; 0.04	0.67	0.154□
rs1341239 T	1.05	−1.69; 3.78	0.45		rs1341239 T	0.12	−2.07; 2.30	0.92	
rs1341239 GT	1.75	−0.11; 3.61	0.07		rs1341239 GT	1.34	−0.15; 2.82	0.08	
rs6265 AAG	0.49	−1.76; 2.75	0.67		rs6265 AAG	0.39	−1.41; 2.19	0.67	
rs7124442 T	1.46	−1.40; 4.33	0.32		rs7124442 T	2.48	0.18; 4.76	0.035*	
rs7124442 CT	0.73	−2.19; 3.66	0.62		rs7124442 CT	2.24	−0.09; 4.57	0.06	
TCAs	4.54	2.04; 7.03	0.004**		TCAs	1.49	−0.50; 3.48	0.14	
SNRIs	1.04	−1.96; 4.04	0.50		SNRIs	0.71	−1.69; 3.11	0.56	
NaSSAs	−1.20	−4.50; 2.09	0.47		NaSSAs	−2.18	−4.81; 0.45	0.10	
Agomelatine	1.22	−2.10; 4.55	0.47		Agomelatine	−1.90	−4.55; 0.75	0.16	

Data are presented as regression coefficients (*B*), 95% confidence intervals (CI) and total explained variance (R^2); *$p < 0.05$; **$p < 0.01$; □$p < 0.05$ (ANOVA); TCAs: tricyclic antidepressants; SNRIs: serotonin–norepinephrine reuptake inhibitors; NaSSAs: noradrenergic and specific serotonergic antidepressants.

weeks of treatment. In nearly all subgroups and genotypes, improvement during the first two weeks was significantly greater ($p < 0.05$) than the last two weeks.

Comparisons between genotypes did not reveal any significant differences for improvement during the first 2 weeks of treatment (Supplementary Table 2). For the latter two weeks of treatment, differences in ΔHAM-D between genotypes became noticeable within *BDNF*. No statistical significance between *PRL* rs1341239 genotypes were identified. Homozygous A combined with heterozygous AG *BDNF* rs6265 did not show significance to homozygous G during the last two weeks (ΔHAM-D: 9.27 ± 4.26 vs. 7.62 ± 4.49, $p = 0.053$). *BDNF* rs7124442 homozygous C responded significantly worse in comparison to homozygous T during this period (ΔHAM-D: 5.60 ± 3.64 vs. 8.51 ± 4.26, $p = 0.016$). Comparison between the other rs7124442 genotypes did not denote any significance (Fig. 1).

Analysis within all women revealed little notable differences between genotypes of *PRL* rs13411239, *BDNF* rs6265 and *BDNF* rs7124442. Further stratification between pre-menopausal (<50 years of age) and post-menopausal (≥50 years) women was conducted to investigate the effect of menopause and genotype to HAM-D 17 score difference (Supplementary Table 3). Significant improvement was observed in HAM-D 17 score in *BDNF* rs6265 homozygous A combined with heterozygous AG patients compared to homozygous G patients (ΔHAM-D: 10.20 ± 3.76 vs. 7.55 ± 3.25; $p = 0.028$) in pre-menopausal women. Further significant improvement was not noted in *BDNF* rs6265 women only ($p = 0.110$) and post-menopausal women ($p = 0.658$).

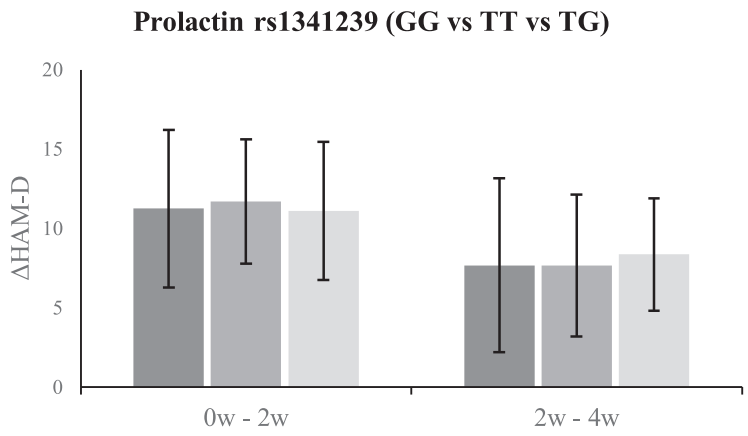
Additional analyses in the latter two weeks of treatment response in *BDNF* rs7124442 found significant decrease in ΔHAM-D in homozygous C genotype when compared to homozygous T genotype in all patients (ΔHAM-D: 5.60 ± 3.64 vs. 8.51 ± 4.26, $p = 0.016$), in all women (ΔHAM-D: 5.57 ± 3.77 vs. 8.64 ± 4.22, $p = 0.014$) and in post-menopausal women (ΔHAM-D: 4.77 ± 4.29 vs. 9.15 ± 4.23, $p = 0.008$) but not in pre-menopausal women (ΔHAM-D: 7.00 ± 2.34 vs. 7.88 ± 4.16, $p = 0.649$). Furthermore, homozygous C *BDNF* rs7124442 significantly responded worse to treatment during the latter two weeks of treatment than heterozygous CT in all women (ΔHAM-D: 5.57 ± 3.77 vs. 8.46 ± 2.94, $p = 0.004$) and in post-menopausal women (ΔHAM-D: 4.90 ± 4.06 vs. 8.21 ± 3.16, $p = 0.017$).

4. Discussion

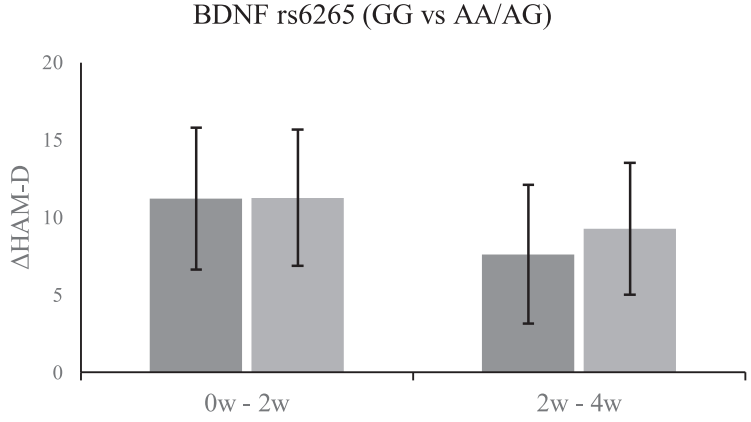
The aim of the study was to investigate the effect of antidepressant medication over the course of four weeks by calculating the difference in HAM-D 17 scores (ΔHAM-D 17). Categorizing ΔHAM-D 17between the first two weeks, the last two weeks and the total four weeks, the effect of *PRL* and *BDNF* genotypes were examined on the effect of antidepressant medication in patients with MDD.

From the regression analyses, tricyclic antidepressants were found to be associated with greater improvement in ΔHAM-D score over four weeks compared to patients taking SSRIs. On the other hand, no significant association was found between the SNPs and ΔHAM-D score. Focusing on the latter two weeks of the study, we found an association between ΔHAM-D score improvement between *BDNF* rs7124442 homozygous T compared to homozygous C. Within the SNP analyses, homozygous A with heterozygous GA *BDNF* rs6265 was associated with a better response to antidepressant treatment compared to homozygous G during the last two weeks in premenopausal women only (age < 50) ($p = 0.023$). Furthermore, patients who were homozygous C *BDNF* rs7124442 responded significantly worse to antidepressants during the last two weeks of treatment in all patients ($p = 0.016$), in female patients ($p = 0.014$) and in post-menopausal patients (≥50 years) ($p = 0.012$). As baseline HAM-D score for homozygous C patients is lower than homozygous T patients, the differences may stem from this fact. Significance between ΔHAM-D over the entire study was not found between the two *BDNF* genotypes but warrants further investigation in the future. With respect to *PRL* rs1341239, no association between antidepressant response and genotypes was established within the patients, including within pre-menopausal and post-menopausal women.

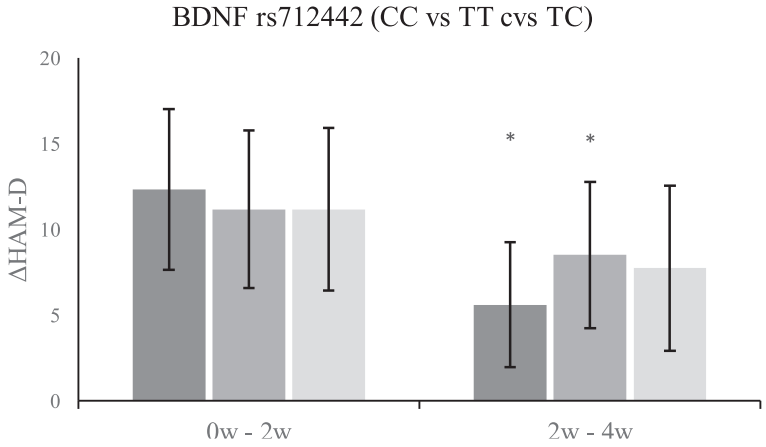
Prolactin is well known to play a role in regulating the behavior of



Comparison of ΔHAM-D between rs1341239 homozygous G, homozygous T and heterozygous TG patients over the first two weeks and second two weeks.



Comparison of ΔHAM-D between rs6265 homozygous G, homozygous A + heterozygous AG patients over the first two weeks and second two weeks.



Comparison of ΔHAM-D between rs7124442 homozygous C, homozygous T and heterozygous TC patients over the first two weeks and second two weeks.

Fig. 1. ΔHAM-D 17 scores between baseline and two weeks, and two weeks and four weeks in *PRL* rs1341239, *BDNF* rs6265 *and* rs7124442
Comparison of ΔHAM-D between rs1341239 homozygous G, homozygous T and heterozygous TG patients over the first two weeks and second two weeks.
Comparison of ΔHAM-D between rs6265 homozygous G, homozygous A + heterozygous AG patients over the first two weeks and second two weeks.
Comparison of ΔHAM-D between rs7124442 homozygous C, homozygous T and heterozygous TC patients over the first two weeks and second two weeks.

female mammals by regulating lactation and secretion of steroidal gonadal hormones. As prolactin is secreted within the central nervous system, its regulation may play a role in mood disorders. However, our study does not support a specific role for the regulation of extra-pituitary prolactin secretion in this respect. At entry, we did not find an association of pre-treatment prolactin levels with depression (Losenkov et al., submitted). Continuing the trend, we did not find an association between *PRL* genotypes with a response to antidepressant treatment.

Although the overall study investigated 186 depression patients, only 28 men participated, reducing the statistical power and size estimation on the effects of gender. From the 186 patients HAM-D 17 score and genotype data was not complete for all patients ($n = 33$ for *PRL* rs1341239 and *BDNF* rs6265; $n = 45$ for *BDNF* rs712442), decreasing the number of patients included in the regression analysis and *t*-tests. As the loss of genotype data was estimated to occur at random, no selection bias was identified from the missing data.

4.1. Menopausal status on depression and antidepressant effect

To account for the difference in estrogen levels in women, we split our cohort by menopausal status for further analyses. We assumed women between 18 and 50 years were pre-menopausal and women of age 50 years and older were post-menopausal. The effect of menopausal loss of estrogen and its contribution to post-menopausal depression is debated, although estrogen is noted to have an antidepressant effect (Graziottin and Serafini, 2009; Estrada-Camarena et al., 2010). Estrogen's role in the brain and strong neurotrophic effect has been studied, signifying its importance on the effect on neurotransmitter activity (Brann et al., 2007). To ascertain whether estrogen plays a role in treating depression, investigations looked to determine its antidepressant effects in post-menopausal women. In conjunction with serotogenic antidepressants, studies are suggestive of the combined treatment to be effective in reducing depressive symptoms in depressed post-menopausal women, compared to each treatment separately (Schneider et al., 1997; Westlund Tam and Parry, 2003).

A lack of estrogen has been found to play an important role in inducing post-menopausal mood disorders and interaction between the neurotrophic effects of estrogens and BDNF may explain part of the lack of antidepressant effects in premenopausal women (Begliuomini et al., 2007). BDNF synthesizing neurons were found to be co-localized with estrogen receptors in the forebrain, which suggests the regulation of *BDNF* may be driven by a gonadal hormone (Sohrabji and Lewis, 2006; Scharfman et al., 2013). Chhibber et al. found in knockout mice with estrogen receptor subtype ERβ -/- to exert a downregulation effect on *BDNF*, with a 40% decrease in BDNF protein expression found in the hippocampus, while not significant in the cortex and hypothalamus. The downregulation effect was not found in subtype ERα -/- mice (Chhibber et al., 2017). The increased effect of antidepressants in post-menopausal women in our study further suggests the relationship between BDNF, estrogen and its antidepressant effect. However, as BDNF levels were not measured outside of baseline and no estrogen levels were measured, further investigation is needed.

4.2. Varied effects of antidepressant treatment

In the decades after the discovery of tricyclic antidepressant (TCA) drugs and monoamine oxidase (MAO) inhibitors in the 1950s, patients were found to have a lagged response time of two to three weeks to treatment after initiation (Klein et al., 1980). Evidence for the existence of a lag time to initial antidepressants activity was attained by Quitkin et al. (1984a, 1987), however, the validity of their findings has been challenged in multiple recent studies (Stassen et al., 2007; Taylor, 2007; Lam, 2012). In our study, we focused on investigating the specific and non-specific antidepressant effects by studying the differences in HAM-D 17 score between baseline and week two, and week two and week four. As HAM-D 17 score differences in the first two weeks were found to be similar across all patients, we stipulate the latter two weeks to signify true antidepressant effects. In our opinion, the initiation of the resilience-like mechanism could biologically be represented by a switch in the function of the habenuloid complex, which regulates the activity of ascending monoaminergic pathways from the midbrain (Loonen and Ivanova, 2019, 2018a,b).

4.3. Changing the description of depression

After the introduction of selective serotonin reuptake inhibitors (SSRIs) and other antidepressants in the 1980s, the category of depressive disorders which may be treated with antidepressants widened to include major depressive disorder (according to DSM-IV and DSM-5). This may contribute to why the effect size of treatment with an antidepressant versus placebo was substantially larger (2.17 vs. 1.42) and the number needed to treat fewer (3.1 vs. 8.0) in old (1959–1965) studies on imipramine in comparison to newer (1980–2010) antidepressant trials (Undurraga et al., 2013).

The characteristics of the current disease category 'major depression' are likely different from the original 'endogenomorphic depression' (Klein et al., 1980). This corresponds to the finding that current major depression is not an episodic disease but takes a more chronic course in most patients (Verduijn et al., 2017; Verhoeven et al., 2018). However, this may be attributed to a selection bias caused by exposure to prior antidepressant treatments in a patient's life. In our study more than half our patient population has never been treated with antidepressants, therefore limiting this exposure effect. We suggest the nonspecific reduction of the activity in the central motor system, which regulates the intensity of stress-avoiding (misery-fleeing, happiness regulating) behavior by serotonin enhancing drugs, makes a large contribution to the 'antidepressant' treatment effects (Loonen and Ivanova, 2016a, 2019, 2018a).

4.4. Comparison to previous pharmacogenetic studies investigating BDNF genotypes

Prior pharmacogenetic studies investigating the effect of *BDNF* genotypes to antidepressant treatment concluded with mixed results. Yoshida and colleagues investigated the effect of *BDNF* rs6265 in patients taking antidepressant medication, milnacipran ($n = 80$) and fluvoxamine ($n = 54$) for six weeks, with assessments at week one, two, four and six. Within the study population, heterozygous AG patients were noted for greater reduction in the assessment for severity of depression, with significance achieved throughout the study for milnacipran/fluvoxamine compared to homozygous G and homozygous A patients ($p = 0.0004$; $p = 0.0034$ respectively) (Yoshida et al., 2007). More recently, El-Hage and colleagues followed 187 patients on the effects of escitalopram, with 153 completing the six-week study. The effect of treatment after three weeks was significantly different in homozygous A patients in ($p = 0.015$) compared to homozygous G patients (El-Hage et al., 2015). While the trend continued in the last three weeks, the result was not found to be significant ($p = 0.150$). The two studies utilized the Montgomery and Åsberg Depression Rating Scale rather than the Hamilton Depression Rating Scale, therefore whether the results are comparable to our study may be argued.

BDNF rs7124442 genotypes were not been studied as extensively as rs6265, however, findings by Domschke et al. in German patients ($n = 268$) found significantly worse treatment outcome over six weeks in homozygous T patients ($p = 0.01$) (Domschke et al., 2010). Our study found contrary treatment results for rs7124442, with homozygous C patients responding significantly worse compared to homozygous T patients (ΔHAM-D: 5.60 ± 3.64 vs. 8.51 ± 4.26). The antidepressants taken in Domschke's study were mainly serotonin-norepinephrine reuptake inhibitors (SNRIs) and noradrenergic and specific serotoninergic antidepressants (NaSSAs). For our study, the

majority were prescribed SSRIs, which may cause the difference in findings.

4.5. Strengths and limitations

All patients in our study are treatment-free with more than half the patient population not treated with antidepressant drugs throughout their life, limiting previous exposure effects of SSRIs. In addition, the majority of the patients were seriously depressed (HAM-D 17 score ≥ 24), according to the criteria of Zimmerman et al. (2013). A limitation of our study was that it lasted only four weeks, which may be considered short for the occurrence of genuine antidepressant effects (Quitkin et al., 1984b). Furthermore, some genotype groups consisted of a small number of patients, limiting the strength of the analysis and compounding the effect of varied pharmacological treatment across patients.

Nonetheless, differences in treatment effect were identified between genotype zygosity and warrants further investigation. The number of SSRIs and SNRIs utilized within the cohort requires further pharmacogenetic investigation to determine whether specific polymorphisms in serotonin receptor genes play a role in antidepressant response. Due to the limited number of male patients, further analysis was not conducted to determine the effect of genotype in antidepressant treatment effects within the sub-population.

5. Conclusions

Linear regression for ΔHAM-D between entry and four weeks showed no significance for *PRL* and *BDNF* SNPs in antidepressant treatment response within the patient cohort. Tricyclic antidepressants were found to be associated with greater ΔHAM-D over four weeks compared to SSRIs. *PRL* rs1341239 genotype did not affect antidepressant effect in patients throughout the study. *BDNF* rs6265 genotype difference was not significant in all but one patient subgroup throughout the study. Premenopausal women with *BDNF* rs6265 homozygous A and heterozygous GA genotype were associated with a better response to antidepressant treatment during the last two weeks compared to homozygous G. *BDNF* rs712442 homozygous C patients were found to respond significantly worse in the last two weeks of treatment compared to homozygous T patients, but not in pre-menopausal women. Homozygous C patients were also found to respond significantly worse when compared to heterozygous CT patients in all women and in post-menopausal women but not in pre-menopausal women.

Author's contribution

Taichi Ochi (TO) and Natalya M. Vyalova (NMV) share first authorship. Anton J.M. Loonen (AJML), Fokko J. Bosker (FJB) and Svetlana A. Ivanova (SAI) instigated and designed the study. AJML and SAI coordinated and supervised the study. TO, NMV and Innokentiy S. Losenkov (ISL) designed and performed the statistical analysis and contributed to writing the paper. SAI wrote the study protocol and selected the SNPs. ISL and Lyudmila A. Levchuk (LAL) monitored the study. GGS collected clinical data. ISL, LAL, NMV, Diana Z. Osmanova (DZO) and Ekaterina V. Mikhalitskaya (EVM) isolated DNA, genotyped the samples and recorded all data in an Excel database. Nikolay A. Bokhan (NAB) supervised the clinical work. SAI, AJML and Bob Wilffert (BW) supervised the technical work. Ivan V. Pozhidaev only genotyped the DNA samples (together with DZA) within the laboratory of genetics of the University of Groningen and agrees not to be co-authors. TO and AJML wrote the manuscript. FJB, BW and SAI adapted the manuscript. All authors read the paper and agree with its content. Their role justifies their (co)-authorship to this paper.

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CRediT authorship contribution statement

Taichi Ochi: Formal analysis, Visualization, Writing - original draft. **Natalya M. Vyalova:** Formal analysis, Investigation. **Innokentiy S. Losenkov:** Data curation, Formal analysis, Investigation, Project administration, Validation. **Lyudmila A. Levchuk:** Investigation, Validation. **Diana Z. Osmanova:** Data curation, Investigation. **Ekaterina V. Mikhalitskaya:** Data curation, Investigation. **Anton J.M. Loonen:** Conceptualization, Funding acquisition, Project administration, Writing - original draft. **Fokko J. Bosker:** Conceptualization, Writing - review & editing. **German G. Simutkin:** Investigation. **Nikolay A. Bokhan:** Supervision. **Bob Wilffert:** Supervision, Writing - review & editing. **Svetlana A. Ivanova:** Conceptualization, Funding acquisition, Methodology, Project administration, Writing - review & editing.

Declaration of Competing Interest

The authors have no interest to declare in relationship to this study.

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Supplementary materials

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