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Modern molecular study of weight gain related to antidepressant treatment: clinical implications of the pharmacogenetic testing

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Abstract

Antidepressant medication influences cellular lipogenesis, being associated with metabolic side effects including weight gain. Due to the increasing use of antidepressants in children and adolescents, their metabolic and endocrine adverse effects are of particular concern, especially within this pediatric population that appears to be at greater risk. Genetic factors with a possible influence on antidepressant's adverse effects include CYP [cytochrome P450 (CYP450)] polymorphisms. We target to evaluate the efficacy of the pharmacogenetic testing, when prescribing antidepressants, in correlation with the occurrence of adverse events and weight gain. Our research was performed between the years 2010 and 2016, in the University Clinic of Child and Adolescent Psychiatry, Timişoara, Romania. We recruited 80 patients, children and adolescents with depressive disorders. Our study sample was divided in two groups: G1 – 40 patients took treatment after pharmacogenetic testing, and G2 – 40 patients without pharmacogenetic testing before the treatment election. Our results show statistically significant differences concerning the weight gain for groups G1 (with pharmacogenetic testing) and G2 (without pharmacogenetic testing). The CYP genotype and the pharmacogenetic testing, for choosing the personalized antidepressant therapy in children and adolescents with depressive disorders, proved to be good predictors for the response to antidepressants and the side effects registered, especially for weight gain. The significant correlations between the CYP polymorphisms for group G2 (without pharmacogenetic testing) and the weight gain/body mass index (BMI) increase, as major side effects induced by antidepressants, proved the fact that the pharmacogenetic screening is needed in the future clinical practice, allowing for individualized, tailored treatment, especially for at-risk pediatric categories.

Keywords: antidepressants, pharmacogenetic testing, weight gain, CYP genotype, depressive disorders.

Introduction

Depressive disorder is a highly prevalent disease that is challenging to treat, often requiring medication and dose adjustments. Genetic factors play an important role in psychotropic medication responses. Antidepressant medication is a treatment of first choice in depressive disorders but also antipsychotics, anxiolytics and mood stabilizing medication can be used, in function of the clinical profile of the patient [1–4].

In general, psychopharmacological treatment in depressive disorders is characterized by long treatment courses, frequent drug changes, lack of compliance, numerous relapses, a high incidence of adverse events and marked interindividual differences in drug response [5–7].

The antidepressants but also the atypical antipsychotics involved in the treatment of depressive disorders, in particular some of them, influence cellular lipogenesis and are associated with weight gain, metabolic side effects and body mass index (BMI), as well as blood insulin levels increase [8–10]. Weight gain, poses the patients also to other significant risks, diabetes mellitus and metabolic syndrome. Due to the increasing use of antidepressant medication also in children and adolescents, their metabolic and endocrine adverse effects (weight gain, obesity, metabolic syndrome, increased levels of circulating insulin) are of particular concern especially within this pediatric population that appears to be at greater risk [10].

The new perspectives in the field of pharmacogenetics give us the opportunity to make some connections between the clinical features, the pharmacogenetic markers and the further clinical evolution and prognostic in depressive disorders [11]. Also, these pharmacogenetic markers are helpful in quantifying the medication response, the clinical evolution and avoiding the severe adverse events, also relevant weight gain in depressive disorders. The treatment of election in the management of depression should be chosen in correlation with the pharmacogenetic and clinical profile of the target patients. When choosing the suitable pharmacotherapy, the pharmacogenetic markers should be analyzed carefully [12–15].

In this frame, the pharmacogenetics of antidepressant-induced weight gain represents a promising perspective in tailoring the individualized treatment to the needs of the patient and avoiding the significant side effects. It is well known today, with the development of pharmacogenetics, that genetic variability can affect both pharmacokinetic and pharmacodynamic drug properties [8–10, 16, 17]. Because the drug safety issues are becoming more important, studying the underlying genetic mechanisms of adverse drug reactions can bring important benefits to patients by helping in the process of choosing the best drug with the least expected side effects [18–24]. Pharmacogenetic studies have shown a significant correlation between genotype and adverse effects associated with antidepressants [23, 25, 26]. So that it is necessary to assess the single nucleotide polymorphisms (SNPs) in patients treated with antidepressants.

The CYP [cytochrome P450 (CYP450)] system is involved in the metabolism of several classes of mental health medications, including antidepressant medication: selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and atypical antipsychotics. Consequently, variability of CYP enzyme activity can significantly differ between individuals. The activity of CYP enzymes may vary among individuals based on their classification as a poor, intermediate, extensive, or ultra-rapid metabolizer [27–29].

So that, the nucleotide polymorphisms within different genes can alter the metabolism, efficacy and adverse events of psychiatric drugs, including medication needed in treating depressive disorders. There are different metabolic phenotypes in function of those CYP polymorphisms [30–34].

The studies and guides mention the SSRIs antidepressant treatment as first line treatment in depressive disorders. The genotypes CYP2D6 and CYP2C19 are strongest correlated with the response to the antidepressant medication, especially from the SSRI category. This prominent enzyme, CYP2D6, is involved in the metabolism of multiple antidepressants/antipsychotics and in the metabolism of approximately 25% of all medications metabolized by CYP [34–37]. So that, poor CYP450 activity could increase serum levels of antidepressants, leading to increased weight gain [38–40].

In our present research, we approach the theme of implementing the pharmacogenetic testing, in the management of depressive disorders in children and adolescents, in order to avoid the relevant weight gain, correlated with antidepressants or other chosen treatments [41–44].

In our study, a theme of high clinical interest is approached through the genetic information linked to the clinical issues related to the patient's side effects – antidepressants-induced weight gain.

The main objectives of our study were: the evaluation of the clinical utility of the pharmacogenetic testing, in order to avoid the weight gain in the treatment of depressive disorders; the efficacy and safety of the different pharmacological interventions with or without pharmacogenetic testing in the child and adolescent depressive disorders; the dynamic evaluation of the clinical evolution of the adverse events in depressive disorders, correlated with the pharmacogenetic testing, captured especially through weight gain and blood insulin levels' modifications. Also, the evaluation of the weight gain, in correlation with the chosen pharmacotherapy, after and without pharmacogenetic testing.

Patients, Materials and Methods

The present research was performed between the years 2010 and 2016, in the University Clinic for Child and Adolescent Psychiatry, "Louis Țurcanu" Emergency Hospital for Children, Timișoara, Romania. We recruited patients, children and adolescents with depressive disorders.

The diagnoses of the studied patients were put according to *Diagnostic and Statistical Manual* (DSM) IV and in the last two years through DSM-5 and reconfirmed by a child and adolescent psychiatrist through the *Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime version* (K-SADS-PL) application.

The study samples consisted of 80 patients, children and adolescents with depressive disorders. The patients included in the study were aged between 9 and 20 years old (median age 15.78±4 years old). Our patients were following an antidepressant treatment.

We obtained for each patient the informed assent and the informed consent from the parents/legal guardians. Our study was done in accordance with the Ethical Committee regulations of the "Victor Babeș" University of Medicine and Pharmacy, Timișoara, with the *International Conference on Harmonisation–Good Clinical Practice* (ICH–GCP) regulations and guidelines.

Our study sample was divided in two groups: 40 patients took treatment after pharmacogenetic testing (G1) and 40 patients without pharmacogenetic testing before the treatment election (G2).

Clinical evaluation of the patients

The patients in the study group had a diagnosis of depressive disorder, reconfirmed through the K-SADS-PL at baseline. Also, the *Child Depression Rating Scale* (CDRS) was applied by an authorized rater, in order to offer an objective measure for the psychiatric symptoms.

Because the children were still developing at the time of exposure to the antidepressants, in the context of physiological changes in hormonal and endocrine level and body composition, all the values were adjusted for gender, age and growth charts.

All the patients were receiving one of the chosen antidepressants, in function of their clinical profile with or without pharmacogenetic testing before. It must be mentioned that in their psychiatric history, some of the patients have changed their treatment through switching between those antidepressants, sometimes because of lack of efficacy or because of adverse events.

The compulsory evaluations included the phase evaluation of the clinical, neurobiological markers, and reevaluations applying the standardized procedures. We measured for each patient their body weight, their height and calculated their BMI for different time points – at baseline, three months, six months, one year, and 18 months.

Blood was also withdrawn, in order to dose their insulin levels at different time points. We evaluated the BMI and the blood insulin variations for these patients in different time points during the treatment with antidepressants.

Pharmacogenetic testing

The pharmacogenetic testing was done through the SNPs genotyping, using reverse transcription polymerase chain reaction (RT-PCR), after the DNA prelevation. The SNPs, the "star-alleles"/haplotypes and the sum of "star-alleles", inherited from the parents, were identified.

The genotypes of the CYP* allelic variants have been determined through the specific allelic fluorescence measurement, using the software for allelic discrimination. The identification of the alleles CYP2D6 *3, *4, *5, *41, responsible for the medication metabolizing types, was significant. Also, the panel including CYP2C19 *2, *3, *4 as major metabolic pathway is relevant. Genomic DNA was extracted from ethylenediaminetetraacetic acid (EDTA) blood using QIAamp DNA Mini Kit (Qiagen, Germany). DNA samples were stored at -80^{0}C. The CYP genotyping was performed, so that the laboratory staff was blinded to the patients' data.

CYP allele identification was performed by using TaqMan Drug Metabolism Genotyping Assay for Allelic Discrimination CYP2D6* and TaqMan® PCR Master Mix (Applied Biosystems), according to the protocol provided by the producer. Allelic discrimination was carried out on Applied Biosystems 7900HT Fast Real-Time PCR System in a reaction volume of 25 μL, containing TaqMan Drug Metabolism Genotyping Assay for Allelic Discrimination CYP and TaqMan® PCR Master Mix and DNA probe. Genotypes were determined by measuring allele-specific fluorescence using the software for allelic discrimination (Applied Biosystems). Based on the CYP genotype, three activity groups of metabolizers were identified: wild type (WT), SNP and the mixed type (WT/SNP).

Statistical analysis

All analyses were carried out using Statistical Package for the Social Sciences (SPSS) software (version 17.0, Chicago, IL, USA) and Microsoft Excel.

In order to correlate the CYP* genotype with the weight gain and insulin level at different time points we used the Friedman non-parametric test for pair values. For comparing the weight gain and insulin variation / increase between the groups – G1 (patients with depressive disorders who benefited of pharmacogenetic testing in choosing the proper medication) and G2 (without pharmacogenetic testing), we applied the Mann–Whitney non-parametric test. For comparing the median of BMI and the insulin level at two different timepoints, and in each two with two different timepoints, the Wilcoxon signed-rank non-parametric test was used.

Results

We obtained significant results through our present research. We identified for the group G1 (40 patients with depressive disorders, where the pharmacogenetic testing was applied) pharmacogenetic polymorphisms at the level of CYP450 enzymes. So, we observed in our studied samples the WT or normal type metabolizer, the patients who had SNP, who need in the clinical practice the adjustment of the doses of the administered pharmacotherapy, as well as careful choosing of the medication, and the WT/SNP (mixed type), who encounter also some difficulties in this area.

Therefore, the pharmacogenetic CYP testing permitted us to choose the proper medication in function of the patients' genotype and also to adjust the medication doses accordingly, in order to avoid significant adverse events.

In the group where the pharmacogenetic testing was not performed – G2 (40 patients also with depressive disorders) –, the medication has been assigned according to the clinical symptoms but not to the personalized, pharmacogenetic profile of the patients.

Therefore, when prescribing medication for pediatric depressive disorders, we must pay attention. So that, the major CYP metabolizing pathways for the principal antidepressant medication groups are for the SSRIs (CYP2D6 or/and CYP2C19), for the SNRIs also CYP2D6, and for Agomelatine CYP3A4.

The descriptive statistics for the study groups (G1+G2) is summarized in the Table 1.

In order to compare the BMI values for the five timepoints, for the sample of patients with depressive disorders, we applied the Friedman non-parametric test for pair values and we obtained statistically significant values (p<0.001). Comparing the timepoints each two with two, using the Wilcoxon signed-rank non-parametric test, we obtained in each of the 10 comparisons statistically significant differences (p<0.001). So that, the BMI increase from the start moment until 18 months is significant, with a significance threshold α=0.

We also took into account another very important value, the blood insulin, which is in direct correlation with the metabolic, hormonal state and the weight/BMI variations of depressive patients under treatment with antidepressants.

Insulin values for four different timepoints in the whole sample of patients were compared. We obtained for insulin statistically significant differences between the timepoints (p<0.001), the values of insulin being increased during the treatment with antidepressants. So that the insulin values increased from baseline to 18 months, with a significance threshold α=0.001.

For the comparison of the values between different timepoints for each group, we applied the Friedman non-parametric test for pair values. For the patients from group G2 (without pharmacogenetic testing chosen antidepressant treatment), the BMI values increased significantly since the baseline, because of the CYP polymorphisms of the patients (SNP and WT/SNP) (p<0.001, α=0.001). For insulin values, the differences between the timepoints were also statistically significant (α=0.001). The results are presented in Table 2.

For the patients from group G2, without pharmacogenetic testing, the increase of the insulin values from baseline until 18 months is statistically significant (α= 0.001), meaning that the patients in this group, because the antidepressant treatment was not adapted to their genotype, were most prone and exposed to the adverse effects of the antidepressants – increased insulin values or even hyperinsulinism, with high morbidity consequences.

The increase of the BMI values from baseline until 18 months is also statistically significant, with a threshold of significance α=0.001. The BMI increase was much higher than for the group G1, meaning that the patients from group G2 were much prone and exposed to adverse effects, expressed through weight gain and BMI increase.

Concerning the patients from group G1, the comparisons between the different timepoints are summarized in Table 3.

The increase of the BMI values from baseline until 18 months is not statistically significant. We obtained the threshold of significance α=0.05 for the comparison baseline – 18 months. The BMI increase was much lower than for patients from group G2, meaning that the patients from group G1 were not so prone and exposed to adverse effects, expressed through weight gain, because their antidepressant treatment has been chosen adapted to their pharmacogenetic profile.

For the patients from group G1, the increase of the insulin values from baseline until 18 months is not statistically significant, proving the fact that the patients in this group are not so exposed to the side effects of the antidepressants.

We compared the differences between group G2 and group G1, as regard the evolution of the BMI and insulin level, the results being summarized in Table 4.

Table 1 – ***Comparisons between the different timepoints for the total groups of patients with depressive disorders (G1+G2) descriptive statistics***

Timepoint	No. of patients	BMI [kg/m^2]				Insulin values [µU/mL]			
		Mean	*SD*	*Min.*	*Max.*	*Mean*	*SD*	*Min.*	*Max.*
Baseline	80	19.82	2.54	15	29	9.61	3.46	4.4	17.7
Three months	80	20.47	2.3	16.7	29.3	11.23	5.21	4.6	21.43
Six months	80	22.33	2.91	17.7	29.9	13.35	4.04	4.8	24.9
One year	80	24.53	3.37	17.5	32	18.27	10.3	4.9	81.1
18 months	80	25.59	4.22	17.3	36	19.26	10.01	4.9	34.7

BMI: Body mass index; SD: Standard deviation; Min.: Minimum; Max.: Maximum.

Table 2 – ***Comparisons between the different timepoints for the group G2, without pharmacogenetic testing***

Timepoint	No. of patients	BMI [kg/m^2]				Insulin values [µU/mL]			
		Mean	*SD*	*Min.*	*Max.*	*Mean*	*SD*	*Min.*	*Max.*
Baseline	40	21.28	2.92	16	28	6.4	2.11	4.4	12.6
Three months	40	22.41	2.78	17.4	28.7	11.26	1.42	5.6	17.8
Six months	40	25.35	1.99	21.5	29.9	15.55	3.76	7.9	24.9
One year	40	27.41	1.93	23.8	32	26.69	1.2	24.9	28.9
18 months	40	28.23	2.14	24.5	35	28.18	1.78	25.3	30.7

BMI: Body mass index; SD: Standard deviation; Min.: Minimum; Max.: Maximum.

Table 3 – ***Comparisons between the different timepoints for patients from group G1, with pharmacogenetic testing***

Timepoint	No. of patients	BMI [kg/m^2]				Insulin values [µU/mL]			
		Mean	*SD*	*Min.*	*Max.*	*Mean*	*SD*	*Min.*	*Max.*
Baseline	40	20.43	2.44	16	29	6.8	3.53	4.4	17.7
Three months	40	21.26	2.58	16.3	29.3	7.99	4.12	4.9	18.3
Six months	40	22.49	2.67	17	29.9	11.21	3.76	4.8	20.5
One year	40	22.69	2.75	17.1	30.9	12.27	10.26	4.9	81.4
18 months	40	22.89	3.13	17.3	36	12.44	3.94	4.9	19.9

BMI: Body mass index; SD: Standard deviation; Min.: Minimum; Max.: Maximum.

Table 4 – ***Statistical differences through Wilcoxon signed-rank test, between group G1 and group G2, regarding the BMI and insulin levels***

Timepoint	BMI mean [kg/m^2]		BMI		Insulin mean [μU/mL]		Insulin	
			$p^{significance}$	α level of significance			$p^{significance}$	α level of significance
Baseline	Group G2	21.28	0.696^{ns}	0.05	Group G2	6.40	0.696^{ns}	0.01
	Group G1	20.43			Group G1	6.80		
Three months	Group G2	22.41	0.114^{ns}	0.05	Group G2	11.26	0.001^{s}	0.01
	Group G1	21.26			Group G1	7.99		
Six months	Group G2	25.35	<0.001^{s}	0.001	Group G2	15.55	0.001^{s}	0.01
	Group G1	22.49			Group G1	11.21		
One year	Group G2	27.41	<0.001^{s}	0.001	Group G2	26.69	<0.001^{s}	0.001
	Group G1	22.69			Group G1	12.27		
18 months	Group G2	28.23	<0.001^{s}	0.001	Group G2	28.18	<0.001^{s}	0.001
	Group G1	22.89			Group G1	12.44		

BMI: Body mass index; ns: Not significant; s: Significant.

It is important to note that at moment of treatment initiation, there were no statistically significant differences between the BMI of patients from group G2 and group G1. We found that the differences of BMI are statistically significant (p<0.001). It was observed that patients from group G2 present higher BMI as compared with patients from group G1. Also, for insulin values, statistically significant differences were found for each timepoint and from baseline until 18 months. Comparisons of BMI between groups G1 and G2 in the different timepoints – BMI BSL (baseline), after three months, six months, one year (12 months), and 18 months –, are presented in Figure 1.

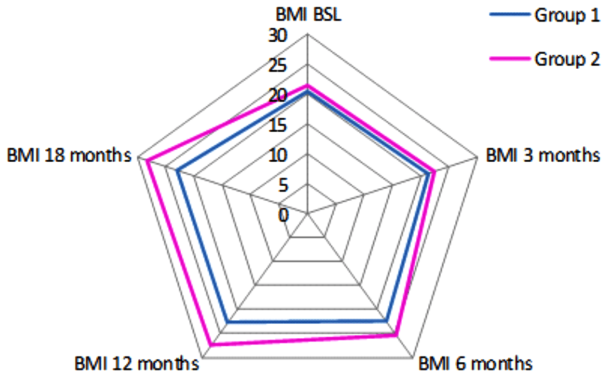

Figure 1 – ***Comparisons of BMI between group G1 and group G2 in the different timepoints. BMI: Body mass index; BSL: Baseline.***

So that, we observe that BMI and also insulinemia have statistically significant higher values for the group G2, without pharmacogenetic testing, in different timepoints, especially after six months, one year and 18 months.

These results prove us, that if the antidepressant treatment is indicated without pharmacogenetic testing before, not taking the genotype and the polymorphisms of the patient into account, severe adverse events are encountered, with BMI, weight increase and high insulin blood levels.

These results bring another proof of the clinical utility of the pharmacogenetic testing and of the personalized treatment, also for the administration of antidepressant medication.

Table 5 highlighted the Spearman's rank correlation coefficient (r) and transformed z, between the BMI and insulin values increase and the presence of CYP polymorphisms for the studied groups of depressive patients – G1 (with pharmacogenetic testing) and G2 (without pharmacogenetic testing) –, with the highest correlations of BMI and insulin increase for group G2.

Table 5 – ***Spearman's rank correlation coefficient (r) and transformed z between the BMI and insulin values increase and presence of CYP polymorphisms for the studied groups***

Correlations	Patients with depressive disorders					
	Group G1, with pharmacogenetic testing			*Group G2, without pharmacogenetic testing*		
	*r**	*z***	*z-STD***	*r**	*z***	*z-STD***
Highest BMI values increase – present CYP polymorphisms	.335	.362	.362	.996	.525	.362
Highest insulin values increase – present CYP polymorphisms	.226	.31	.252	.987	.784	.675

r: Spearman's rank correlation coefficient; *z*: Transformed values; STD: Standard deviation; *: Coefficient of determination; **: Coefficient of non-determination; BMI: Body mass index.

Comparisons of insulin blood levels between group G1 and group G2 in the different timepoints – BMI BSL (baseline), after three months, six months, one year (12 months), and 18 months, are presented in Figure 2.

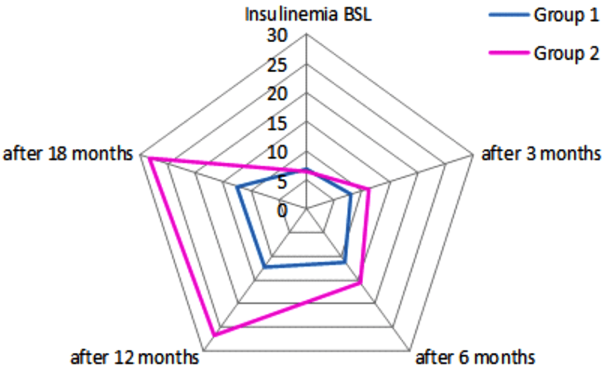

Figure 2 – ***Comparisons of insulinemia between group G1 and group G2 in the different timepoints. BMI: Body mass index; BSL: Baseline.***

So that, through applying the Pearson's χ^2 (chi-square) test, we obtained as correlations' results, in the group G2 (without pharmacogenetic testing), the following statistical significant positive correlations between: the BMI and insulin increase and the presence of identified CYP polymorphisms.

Discussions

To our knowledge, there is a lack of studies assessing whether the pharmacogenetic-guided selection of treatment is more effective than unguided treatment in improving patients' with depressive disorders response and tolerability and also the specific adverse event, especially weight gain in the pediatric population.

In the actual general context, our present research offers new perspectives, especially because of the lack of consistent studies for children and adolescents with depressive disorders, concerning the modern molecular, pharmacogenetic testing correlated with weight gain and insulin blood levels.

Some of the pharmacogenetic aspects, concerning weight gain after antidepressant treatment, have been approached in some studies in adults and also the effects of combinatorial pharmacogenomics testing but there is a lack of research concerning the pediatric population [8–10]. So that, Winner *et al.* found a statistical trend for better outcomes, no relevant adverse events in a trial conducted in 51 study subjects – 26 pharmacogenetic-guided *versus* 25 unguided. The pharmacogenetic studies in general in Romanian population are rare [14].

So that, the approach of pharmacogenomic variability in pertinent drug targets-children and adolescents exposed to antidepressants, proved to be a fruitful pathway especially because of the lack of consistent research for these age groups [20, 23, 29, 32]. The pharmacokinetic of antidepressants and their impact on the adverse effects, weight gain in correlation with the genotype, have been approached in some studies in adults, but there is a lack of research involving children and adolescents, although this medication is extensively used in this population [8–10].

There is lack of data regarding the impact of CYP isoenzymes polymorphisms on the short and long-term adverse effects, including the weight gain in the case of the child and adolescent patients using antidepressants.

Our study is especially valuable in the light of personalized pharmacotherapy, tailored to the genetic variability, correlated with the CYP genotype of the pediatric depressive patient [45–47].

The implementation of the CYP genotype testing to this category of patients, before choosing the suitable antidepressants in the clinical practice, could avoid the severe side effects like morbid weight gain or the non-response to medication, being a valuable perspective for the future. This could be a way of improving the quality of life of children and adolescents with a diagnosis of depressive disorders [43].

There is a substantial phenotypical difference between patients with CYP polymorphisms. In our study, we have found that the patients with CYP polymorphisms have significantly higher weight gain values, especially in the group where the antidepressant medication was chosen without pharmacogenetic testing. Our study proves to be a successful pathway towards assessing the genetic liability and its plausible clinical application for children and adolescents [41].

It is obvious that the delay in finding an adequate treatment for depression, especially in the case of children, has a detrimental effect on their development, on prognosis and the chances of recovery. The genetic determination of the patient's status brings numerous benefits by helping in choosing a suitable antidepressant, in adjusting the therapeutic doses and reducing the adverse effects [23, 29–32].

We also noted in our study group, without pharmacogenetic testing, that the patients had a progressive weight gain even after 18 months. This could be because our study is on children and adolescents, who are highly metabolically and hormonally sensitive during the period of development. This proves that in the case of children with depressive disorders, even more attention and care should be paid to this category, when choosing the antidepressants [8–10].

It is important to note the fact that excessive weight gain in children and adolescents brings other undesirable effects like more stigmatization, further social withdrawal non-compliance with medication, but also the high-risk state for cardiovascular morbidity and mortality [20, 23].

In this context, the pharmacogenetics provides a valuable tool to fulfill the promise of personalized interventions by adopting the most indicated treatment based on the genetic markers of the patients. It is obvious, that it would be much easier and cost-effective to prevent the weight gain and other major side effects through choosing the suitable antidepressant treatment from the beginning, than changing and switching the antidepressants because of major adverse events or non-compliance. This also would be much more ethical [20].

However, also the translation of pharmacogenetics' findings to clinical recommendations regarding antidepressant responses is still in its early stages [41].

The genes are related to functions in drug metabolism, transport, signaling, stress response, and neuroplasticity. Clinical recommendations already exist for *CYP2D6* and *CYP2C19* cytochrome P450 drug metabolism genes. The other genes are: *ABCB1*, with SNPs rs2032583 and rs2235015; *FKBP5*, with SNPs rs1360780, rs3800373, and rs4713916; *GNB3*, with SNP rs5443; *BDNF*, with SNP rs6265; *HTR2A*, with SNPs rs7997012 and rs6313; and *SLC6A4*, with polymorphisms 5-HTTLPR and STin2 [36–40].

The US *Food and Drug Administration* (FDA) has issued instructions for labeling over 20 psychotropic drugs with recommendations and precautions on their use based on the results of some existing studies. The drugs include SSRIs and tricyclic antidepressants (TCAs) [11, 16, 44]. A major role has also the brain-derived neurotrophic factor (BDNF). BDNF is part of the nerve growth factor family, induced by cortical neurons and necessary for survival of striatal neurons. It is involved in neuroprotection and plasticity and plays a role in reversal of hippocampus atrophy during antidepressant treatment. There is a reduction of BDNF in serum and leukocytes of depressed patients that may be reversed with successful

treatment. BDNF may be involved in memory and various functions of the hippocampus. The rs6265 Val66Met polymorphism of the *BDNF* gene was shown to impact the secretion of BDNF in the hippocampus and may be involved in neuronal pathology. Several studies have demonstrated a significant association with this polymorphism and antidepressant response. People who carry the Val66Met polymorphism have a better response rate and remission to SSRI treatment [45]. Another study showed a significant association with the Val/Val genotype and response to SSRI, while carriers of the Met allele had higher six-month remission with SNRI or TCA treatment.

The efficacy of SSRI *versus* SNRI or TCA treatment may depend on the genotype of this polymorphism. Further research would be needed also in our study group concerning BDNF and its impact [45].

Guidelines for antidepressant treatment with SSRIs and TCAs already exist for two of the genes: *CYP2D6* and *CYP2C19* [5–7].

Our study is especially valuable in the light of a multidisciplinary approach, implying complex correlations between the pharmacogenetic testing and the safety, efficacy of antidepressants, concerning adverse events like the weight gain and the clinical evolution.

Our present research opens the perspective of the personalized pharmacotherapy for children and adolescents, which is tailored to the genetic variability and neurobiological particularities [18, 20, 23].

Our obtained results of the present study are in line with some in the adult population existing researches concerning pharmacogenetic testing in depressive disorders but as far as we know, there is a lack of information concerning the pediatric population.

We obtained good clinical evolution and no relevant adverse events for the pharmacogenetic-guided treatment group, our results being in line with the results obtained through the study of Singh [15]. Our results are in agreement with previous studies reporting that pharmacogenetic tools are effective in patients with depressive disorders. Non-adherence is a global challenge for psychiatry, while improved tolerability obtained through the pharmacogenetic-guided chosen treatment facilitates long-term adherence [34].

Adverse events like weight gain can be sometimes avoided, if proper, carefully chosen pharmacotherapy, in function of the pharmacogenetic and clinical profile of the patient, is administered [8–10, 46, 47].

Further research is needed in the field of child psychiatry/psychiatry and pharmacogenetics, in order to develop a genetically informed, personalized medicine, although some promising researches concerning the genetic liability and its clinical application have already been done.

The pediatric patients with depressive disorders, being in development, their whole developmental trajectory could be compromised because of the lack of efficacy of the intervention and medication [20, 23].

For this category, particularly, issues like medication safety are crucial. So that the suitable evaluation of the pharmacogenetic, neurobiological markers can bring significant benefits, helping the clinician to choose the best adapted medication [23, 29, 32].

The clinical implications of the pharmacogenetic testing are very significant. We must keep in mind the fact that, in the case of more than 50% of the patients with depressive disorders, the treatment is a failure because of the CYP polymorphisms, especially because of relevant adverse events, weight gain being one significant parameter.

So that, for the patients with SNPs polymorphisms or WT/SNP, the clinician must avoid the antidepressant medication metabolized through that CYP [43].

We also must avoid the antidepressant medication Paroxetine, Fluvoxamine, Venlafaxine, for the patients with SNPs CYP2D6, Sertraline and Fluoxetine, in case of SNPs CYP2D6 and/or CYP2C19, and Citalopram for CYP2C19, in order to avoid relevant weight gain [23].

From the antidepressant medication classes, we avoided especially the SSRIs for the patients with SNPs CYP2D6. When the CYP polymorphisms appear, a medication not extensively metabolized through that CYP level would be indicated. The careful monitoring of the plasmatic concentrations is also needed [5].

Therefore, the decrease of medication dose or the administration of an alternative medication is of clinical utility. In other cases, it could be of clinical utility to decrease the medication dose with 50%, in order to avoid the encountered adverse events and also weight gain [8–10].

Our study suggests that the pharmacogenetic testing is a feasible, reliable prediction tool of the antidepressants'-induced weight gain. Structured procedures should be used in predicting the probability of the depressive patient to gain weight under antidepressants, in correlation with their genotype, considering the genetic polymorphisms. So that, the pharmacogenetics holds the promise of predicting treatment emergent side effects and for the future of personalized antidepressant treatment and we are one-step closer to a routine clinical utilization of pharmacogenetic testing in children and adolescents [43, 44, 46, 47].

This represents a valuable future perspective in the clinical practice, because a personalized therapy adapted in function of the genetic, pharmacogenetic, neurobiological profile, could bee chosen as first line indication. The results of our research and clinical practice plead for the utility of this modern approach in child depressive disorders.

Personalization of psychiatric treatments using pharmacogenetic information is emerging as a valuable tool to identify which medications will be more effective, which will require dose adjustments or which may cause serious adverse reactions, like the stigmatizing weight gain [8–10, 41].

Conclusions

With advanced technology and bioinformatics, our understanding of the complex genetic factors influencing treatment responses for antidepressant medications will improve, and the costs of genotyping and DNA genotyping will decrease. So that, we will be able to develop genetic biomarker panels to predict the most efficacious therapies and reduce toxicity, adverse events, including weight gain for depressive patients.

Our study contributes to demonstrate that the use of the pharmacogenetic testing precision medicine may have a significant impact on the clinical improvement of depressive patients and reduction of drug side effects compared to standard of care.

The pharmacogenetic testing represents a strongly predictive factor for the safety of treatment and the presence of adverse events, especially weight gain, also in pediatric patients with depressive disorders. The administration of pharmacotherapy after the prior pharmacogenetic testing proved higher safety, being correlated with the decrease of the incidence of adverse events, like weight gain, also in the case of patients with depressive disorders. This represents the key to a personalized, individualized, medicine, tailored to the needs of the patient.

So that, in our study, the CYP genotype proved to be also a good predictor for the metabolic ratio and the side effects, after antidepressant treatment administration.

In the case of children and adolescents, being in development and very exposed, it is ethical and cost-effective to prevent the adverse effects and weight gain, through choosing the suitable antidepressant treatment from the beginning, than permanently switching antidepressants.

As future perspective, the CYP prescreening, the emergence of pharmacogenetics, as a modern approach, announces a new stage in the clinical psychiatry, in which the genotype and the biomarkers influence the election of therapy, increasing the safety and efficacy of antidepressant medication.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Codrina Mihaela Levai has equal contribution and thus shares first authorship.

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