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Risk of parental psychiatric disorders among adolescents with major depressive disorder according to response to antidepressant treatment: does the type of antidepressant matter?

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Abstract

Background. The genetic load for major depressive disorder (MDD) may be higher in people who develop MDD earlier in life. This study aimed to investigate whether the parents of adolescents with MDD were more likely to have MDD, bipolar disorder (BD), schizophrenic disorder (SZ), alcohol use disorder, or substance use disorder than the parents of adolescents without MDD. We also examined whether the response to antidepressant treatment predicted the likelihood of parental psychiatric disorders.

Methods. In all, 1,758 adolescents aged 12–19 years with antidepressant-resistant depression, 7,032 (1:4) age-/sex-matched adolescents with antidepressant-responsive depression and 7,032 (1:4) age-/sex-matched controls were included. Parental psychiatric disorders of individuals enrolled were assessed.

Results. The parents of the adolescents with MDD were more likely to be diagnosed with MDD, BD, SZ, alcohol use disorder, or substance use disorder than the parents of the control group. The parents of adolescents who were antidepressant resistant and the mothers of adolescents who were either treatment resistant or treatment responsive were more likely to be diagnosed with a psychiatric disorder.

Discussion. Our study demonstrated that parents of adolescents with MDD may be more likely to be diagnosed with MDD, BD, SZ, alcohol use disorder, or substance use disorder than parents of adolescents without MDD, suggesting the within-disorder transmission and cross-disorder transmission of these psychiatric disorders. Furthermore, the parent's sex and the response to antidepressant treatment may affect the within-disorder transmission of MDD.

Introduction

Major depressive disorder (MDD) is a common mental disorder in adolescents with an estimated 1-year prevalence higher than 4% in mid to late adolescence.[1,2] MDD in adolescents is a major risk factor for suicide and may lead to serious social and educational impairments and an increased rate of substance misuse and psychiatric comorbidities in adulthood.[3] Therefore, MDD in adolescents must be identified early for timely intervention. Several indicators can be used to identify adolescents who are at risk of developing MDD; these indicators include being female, having a family history of depression (FHD), having a history of family conflict, having experienced childhood abuse or neglect, having low socioeconomic status, and having poor academic performance.[4]

Despite being a risk factor for suicide, antidepressants remain a key component of the treatment of moderate-to-severe MDD in adolescents.[5] In a recent meta-analysis of 17 randomized control trials including 2537 children and adolescents with MDD, antidepressants were shown to have significantly positive effects on functioning.[6] A further subgroup analysis demonstrated that second-generation antidepressants (such as selective serotonin reuptake inhibitors [SSRIs]), but not traditional tricyclic antidepressants, led to significant improvements in functioning.[6] Similarly, another meta-analysis demonstrated that fluoxetine (an SSRI, alone or in combination with cognitive behavioral therapy) had beneficial effects on the management of MDD in children and adolescents.[7] However, the therapeutic effects of antidepressants might vary between individuals; initial treatment with an SSRI failed to produce a satisfactory clinical

outcome in approximately one-third of adolescents with MDD.[8] Some of the indicators that have been associated with favorable antidepressant treatment include having less chronic depression, higher functioning, lower suicide intent, and fewer signs of melancholic feature.[9] Brent et al. showed that for those with a poor response to initial antidepressant treatment, a switch to another SSRI was as effective as a switch to venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI).[8]

MDD is a complex psychiatric disorder involving both environmental and genetic indicators. Studies have demonstrated that an individual with FHD is more likely to develop depression due to innate vulnerabilities related to the genetic structure and function of the brain.[10] For instance, studies have shown that the first-degree offspring of patients with depression have a 2 to 3 times greater risk of developing depression.[11] In addition, an individual with FHD was more likely to have an earlier onset of MDD,[12] more likely to have chronic or recurrent depression,[13,14] and more likely to have psychiatric comorbidities.[12]

MDD has a high tendency toward coaggregation within a family and may also be an independent predictor of other mental disorders within a given family. For example, parental psychiatric disorders were associated with increased risks of within-disorder transmission for attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), MDD, and bipolar disorder (BD).[15] In addition, parental psychiatric disorders were associated with increased risks of cross-disorder transmission to offspring.[15] Despite the high comorbidity between MDD and other major psychiatric disorders, few population-based studies have examined the likelihoods of the mental disorders in parents of probands with MDD.

In this study, we used data from the Taiwan National Health Insurance Research Database (NHIRD), which contains detailed registry and claims data for all residents of Taiwan. We examined the association between adolescents with MDD and the likelihood of parental psychiatric disorders. First, we investigated the likelihood that the parents of adolescents with MDD had psychiatric disorders (MDD, BD, schizophrenic disorder [SZ], alcohol use disorder, and substance use disorder). Then, we further hypothesized that the parent's sex and the response to antidepressant treatment predicted the likelihood of parental psychiatric disorders.

Methods

Data source

The Taiwan NHIRD is audited and released by the National Health Research Institute (NHRI) for scientific and study purposes upon the formal application. Claims data of individuals included in the NHIRD are anonymous to maintain the privacy. Comprehensive medical information about the insured patients, such as demographics (birthdate, sex, and residence) and clinical visits (dates and diagnoses), is available in the database. Following Chen et al.'s and Cheng et al.'s methods,[16,17] the recorded family kinships in the NHIRD were used for genealogy reconstruction, and the family triads (father, mother, and child) were identified. The diagnostic codes used were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in many epidemiologic studies in Taiwan.[16–18] This study was approved by the Institutional Review Board of Taipei Veterans General Hospital.

Study and control groups

Adolescents aged 12–19 years who were diagnosed with MDD (ICD-9-CM codes: 296.2 and 296.3) by board-certified psychiatrists between 2001 and 2011 were included, and were classified as antidepressant responsive or antidepressant resistant according to their response to antidepressant treatment during the 1-year follow-up period after depression diagnosis.[19,20] An adequate trial of antidepressant treatment was defined as use of an antidepressant within its therapeutic dosage range (exp., fluoxetine ≥ 20 mg/day) for ≥60 consecutive days.[19,20] Patients who remained on a single antidepressant were defined as the antidepressant-responsive depression group; those who changed the antidepressant treatment regimen 2 or more times were defined as the antidepressant-resistant depression group. In addition, adolescents with antidepressant-resistant depression were further divided to 2 subgroups: only resistant to SSRIs and additionally resistant to non-SSRIs groups. SSRIs include fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram. Non-SSRIs include SNRIs (venlafaxine, duloxetine, and milnacipran), norepinephrine–dopamine reuptake inhibitor (bupropion), and mirtazapine. Antidepressant-responsive and antidepressant-resistant groups were further matched (4:1) based on age, age of depression diagnosis, sex, residence, and family income. The age-, sex-, family income-, and residence-matched (1:4) control cohort was randomly identified as the control group after eliminating the study cases and those who had any diagnostic code of severe mental disorders (ICD-9-CM codes: 295 and 296) in the database.

Outcome and confounder assessment

Diagnoses of parental mental disorders, including SZ, BD, MDD, alcohol use disorder, and substance use disorder, were assessed between groups. In addition, to ensure the diagnostic validity, the diagnoses of above mental disorders were given by board-certified psychiatrists at least twice. Income level (levels 1–3 per month: ≤19 000 New Taiwanese Dollars [NTD], 19 001–42 000 NTD, and ≥42 001 NTD) and urbanization level of residence (levels 1–5, most to least urbanized) were regarded as the proxies for healthcare availability in Taiwan.[21]

Statistical analysis

Regarding between-group comparisons, the *F*-test was used for continuous variables and Pearson's X^2-test for nominal variables, where appropriate. Logistic regression analyses with adjustment of demographic characteristics (age, sex, income, and residence) were performed to investigate the likelihoods of paternal and maternal mental disorders between adolescents with antidepressant-resistant and antidepressant-responsive depression and the control group. Furthermore, we assessed the association between treatment resistance to SSRIs only or additionally to non-SSRIs (SNRIs, bupropion, or mirtazapine) and the risks of parental mental disorders. A 2-tailed *P*-value of less than .05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc.) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC).

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Results

We included 1758 adolescents with antidepressant-resistant depression, 7032 adolescents with antidepressant-responsive depression, and 7032 matched controls (Table 1). Three groups had similar age at enrollment, sex distribution, level of urbanization, and income-related insured amount (all $P > .05$). Among 1758 adolescents with antidepressant-resistant depression, 887 subjects were only resistant to SSRIs and 871 were additionally resistant to non-SSRIs (Table 1).

Table 2 shows the risks (shown as odds ratio with 95% confidence interval) of 5 psychiatric disorders in parents of probands in the antidepressant-responsive depression and antidepressant-resistant depression groups compared with the parents of the control group, with adjustment for demographic characteristics. The parents of adolescents with MDD who were antidepressant resistant had the highest likelihood to be diagnosed with BD (3.82, 2.54–5.77) and MDD (3.53, 3.01–4.15) compared with the parents of adolescents who were antidepressant responsive (BD: 2.67, 1.91–3.73; MDD: 2.81, 2.48–3.17) and the parents of the control group. The parents of the adolescents with MDD who were antidepressant responsive or antidepressant resistant had the higher likelihood to be diagnosed with SZ (2.38, 1.71–3.31; 2.14, 1.34–3.43), alcohol use disorder (2.10, 1.66–2.67; 1.93, 1.37–2.73), and substance use disorder (2.72, 2.08–3.56; 2.42, 1.66–3.52) compared with the parents of the control group (Table 2).

Furthermore, the parents of the adolescents who were additionally resistant to non-SSRIs had a slightly trend of increased likelihood to be diagnosed with BD (3.97, 2.40–6 vs. 3.69, 2.22–6.14) and MDD (3.80, 3.11–4.65 vs. 3.28, 2.67–4.03) compared with the parents of those who were only resistant to SSRIs (Table 2). Finally, both fathers and mothers of the antidepressant-responsive and the antidepressant-resistant depression group had a higher likelihood to be diagnosed with these 5 psychiatric disorders than the parents of the control group (Table 3).

Discussion

To the best of our knowledge, the present nationwide study is the largest one to have assessed the likelihood of parental psychiatric disorders in probands with MDD. We found that the parents of the adolescents with MDD were more likely to be diagnosed with not only MDD but also BD, SZ, alcohol use disorder, and substance use disorder than the parents of the control group. In a recent Danish registry study, Thorup et al. demonstrated that the offspring of parents with a severe mental illness were more likely to be diagnosed with any child and adolescent mental disorder than the offspring of parents without a severe mental illness.[22] Findings from Thorup et al. and the current study support the notion that FHD can be used as an indicator to predict both within-disorder and cross-disorder transmission in families.[23]

Various psychiatric disorders have been shown to have a common pathogenesis in molecular studies. A genome-wide meta-analysis of 232 964 cases (ADHD, ASD, BD, MDD, and SZ) and 494 162 controls revealed 109 loci associated with at least 2 psychiatric disorders, including 23 loci with pleiotropic effects on 4 or more disorders and 11 loci with antagonistic effects on multiple disorders.[24] The study also identified at least 2 groups of disorders based on shared genomics: one comprising mood and psychotic disorders (MDD, BD, and SZ), and the second comprising 2 neurodevelopmental disorders (ADHD and ASD).[24] We found that the parents of adolescents with MDD were not only more likely to be diagnosed with MDD, BD, and SZ, but were also more likely to be diagnosed with alcohol use disorder and substance use disorder than the parents of the control group. This is consistent with a report from Lieb et al. that found that the offspring of parents with MDD were more likely to use substances than the offspring of parents without MDD.[25] Furthermore, a genetic segregation analysis found that a major locus that contributes to the expression of alcohol and other substance use

Table 1. Demographic Characteristics between Adolescents with Treatment-Responsive vs. Treatment-Resistant Depression

	Adolescents with treatment-resistant depression (n = 1758)	Adolescents with treatment-responsive depression (n = 7032)	Control group (n = 7032)	*P* value
Age at enrollment (years, SD)	17.37 (1.93)	17.32 (1.90)	17.36 (1.96)	.288
Female (n, %)	913 (51.9)	3652 (51.9)	3652 (51.9)	>.999
Treatment-resistant condition (n, %)				
Only resistant to SSRIs	887 (50.5)			
Additionally resistant to non-SSRIs[a]	871 (49.5)			
Level of urbanization (n, %)				>.999
1 (most urbanized)	411 (23.4)	1644 (23.4)	1644 (23.4)	
2	574 (32.7)	2296 (32.7)	2296 (32.7)	
3	165 (9.4)	660 (9.4)	660 (9.4)	
4	147 (8.4)	588 (8.4)	588 (8.4)	
5 (most rural)	461 (26.2)	1844 (26.2)	1844 (26.2)	
Income-related insured amount (n, %)				>.999
≤19 100 NTD/month	319 (18.1)	1276 (18.1)	1276 (18.1)	
19 001 ~ 42 000 NTD/month	622 (35.4)	2488 (35.4)	2488 (35.4)	
>42 000 NTD/month	817 (46.5)	3268 (46.5)	3268 (46.5)	

[a]SNRIs, bupropion, and mirtazapine.
Abbreviation: NTD, New Taiwan dollar; SD, standard deviation; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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Table 2. Risk of Parental Mental Disorder between Adolescents with Treatment-Responsive vs. Treatment-Resistant Depression

	Parental mental disorder[a]									
	Schizophrenia		Bipolar disorder		Major depressive disorder		Alcohol use disorder		Substance use disorder	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Control group	51 (0.7)	1 (ref.)	48 (0.7)	1 (ref.)	389 (5.5)	1 (ref.)	103 (1.5)	1 (ref.)	74 (1.1)	1 (ref.)
Treatment-responsive depression group	120 (1.7)	**2.38 (1.71–3.31)**	127 (1.8)	**2.67 (1.91–3.73)**	993 (14.1)	**2.81 (2.48–3.17)**	213 (3.0)	**2.10 (1.66–2.67)**	198 (2.8)	**2.72 (2.08–3.56)**
Treatment-resistant depression group	27 (1.5)	**2.14 (1.34–3.43)**	45 (2.6)	**3.82 (2.54–5.77)**	301 (17.1)	**3.53 (3.01–4.15)**	49 (2.8)	**1.93 (1.37–2.73)**	44 (2.5)	**2.42 (1.66–3.52)**
Only resistant to SSRIs	16 (1.8)	**2.46 (1.40–4.35)**	22 (2.5)	**3.69 (2.22–6.14)**	143 (16.1)	**3.28 (2.67–4.03)**	26 (2.9)	**2.01 (1.30–3.11)**	20 (2.3)	**2.13 (1.29–3.51)**
Additionally resistant to non-SSRIs	11 (1.3)	1.80 (0.93–3.47)	23 (2.6)	**3.97 (2.40–6.56)**	158 (18.1)	**3.80 (3.11–4.65)**	23 (2.6)	**1.85 (1.17–2.93)**	24 (2.8)	**2.72 (1.71–4.34)**

Note. Bold type indicates statistical significance.
Abbreviation: CI, confidence interval; OR, odds ratio; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]Adjusting for demographic characteristics.

Table 3. Risk of Paternal and Maternal Mental Disorders between Adolescents with Treatment-Responsive vs. Treatment-Resistant Depression

	Schizophrenia		Bipolar disorder		Major depressive disorder		Alcohol use disorder		Substance use disorder	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Paternal mental disorder										
Control group	20 (0.3)	1 (ref.)	24 (0.3)	1 (ref.)	139 (2.0)	1 (ref.)	67 (1.0)	1 (ref.)	50 (0.7)	1 (ref.)
Treatment-responsive depression group	55 (0.8)	**2.76 (1.65–4.62)**	45 (0.6)	**1.88 (1.14–3.08)**	339 (4.8)	**2.51 (2.06–3.07)**	140 (2.0)	**2.11 (1.58–2.83)**	112 (1.6)	**2.26 (1.61–3.15)**
Treatment-resistant depression group	17 (1.0)	**3.44 (1.80–6.58)**	17 (1.0)	**2.85 (1.53–5.32)**	102 (5.8)	**3.06 (2.35–3.97)**	36 (2.0)	**2.18 (1.45–3.27)**	25 (1.4)	**2.02 (1.24–3.27)**
Maternal mental disorder										
Control group	31 (0.4)	1 (ref.)	26 (0.4)	1 (ref.)	267 (3.8)	1 (ref.)	36 (0.5)	1 (ref.)	24 (0.3)	1 (ref.)
Treatment-responsive depression group	66 (0.9)	**2.14 (1.40–3.29)**	86 (1.2)	**3.34 (2.15–5.18)**	717 (10.2)	**2.88 (2.49–3.32)**	75 (1.1)	**2.10 (1.41–3.12)**	89 (1.3)	**3.74 (2.38–5.89)**
Treatment-resistant depression group	12 (0.7)	1.55 (0.80–3.03)	30 (1.7)	**4.68 (2.76–7.94)**	218 (12.4)	**3.59 (2.98–4.33)**	15 (0.9)	1.68 (0.92–3.07)	20 (1.1)	**3.37 (1.86–6.11)**

Note. Bold type indicates statistical significance.
Abbreviation: CI, confidence interval; OR, odds ratio.
[a]Adjusting for demographic characteristics.

disorders within families can be used to identify probands with recurrent, early-onset MDD.[26] Various psychiatric disorders have also been shown to have a common pathogenesis in neuroimaging studies. In a functional magnetic resonance imaging study of patients with MDD, BD, and SZ, transdiagnostic dysconnectivities were identified within somatomotor and salience networks and between subcortical-limbic and subcortical-dorsal attention networks.[27] Another systematic review of 401 neuroimaging studies found that the concentrations of glutamate-glutamine and white matter abnormalities were commonly found in patients with MDD, BD, and SZ.[28]

We performed a subgroup analysis where the sample was segmented by response to antidepressant treatment and found that parents of adolescents with a poor response to antidepressant treatment were more likely to be diagnosed with MDD and BD than parents of adolescents with a good response to antidepressant treatment. In addition, parents of the individuals who were resistant to both SSRIs and non-SSRIs were more likely to be diagnosed with MDD than parents of the individuals who were only resistant to SSRIs. Adolescents with a poor response to antidepressant treatment reported FHD more frequently[29] and were more likely to have a change in diagnosis from MDD to BD[20] than adolescents with a good response to antidepressant treatment. A study in Germany found that parental MDD was associated with an earlier onset and a worse prognosis (severity, impairment, and recurrence) of MDD in offspring.[25] Our findings imply that adolescents with MDD who have a poor response to antidepressant treatment have a higher genetic load for mood disorders than those who have a good response to antidepressant treatment; however, further research is required.

We performed a subgroup analysis where the sample was segmented by sex. The results illustrated in Table 3 show that mothers of adolescents with MDD were more likely to be diagnosed with BD or MDD than fathers. Substantial evidence supports the genetic and sex interaction effect in MDD. A Swedish national twin study of lifetime MDD tested whether genetic risk factors are the same in the 2 sexes,[30] and it found that the heritability of liability to MDD was significantly higher in women (42%) than in men (29%).[30] Reporting a similar finding, another twin study suggested that genetic factors play a greater role in the etiology of MDD in women than in men and that the genes that influence risk for MDD in the 2 sexes are correlated but are probably not completely the same.[31]

The findings from this study have important clinical implications. Parents of adolescents with MDD, especially adolescents with a poor response to antidepressant treatment, should receive a thorough assessment to rule out psychiatric disorders; this is because parents with psychiatric disorders may lack the ability to cope with the psychiatric disorders of their children. Evidence suggests that offspring with psychiatric disorders are better off once their mothers have recovered from depression.[32] Parental substance abuse has been found to be associated with suicide intent in offspring.[33] Furthermore, analysis of the association between parental psychiatric disorders and the prevalence of work disabilities in offspring suggests that parental psychiatric disorders influence an offspring's ability to work and other social factors.[34]

The strength of our study lies in our use of a nationwide dataset with data on many adolescents with MDD and the psychiatric diagnoses of their parents. Furthermore, psychiatric disorders were diagnosed by board-certified psychiatrists. However, our study has some weaknesses that limit the generalizability of our results. First, the prevalence of MDD in adolescents in the present study was significantly lower than those in Western countries.[1,2] We might have underestimated the prevalence of MDD in adolescents in Taiwan because only those who seek medical services are included in the database. Second, a growing number of studies indicate that the genetic basis for the propensity for psychiatric disorders vary depending on ethnicity.[35] Because the individuals in the study were Taiwanese, further investigation is required to determine whether the results may be generalized to other ethnic groups. Third, certain confounding factors, such as education level, lifestyles, and environmental information, were unavailable in the NHIRD. Without this information, we were unable to assess their influence.

In conclusion, parents of adolescents with MDD are more likely to have a diagnosis of MDD, BD, SZ, or alcohol use disorder and substance use disorder than parents of adolescents without MDD. The parent's sex and response to antidepressant treatment may affect the within-disorder transmission of MDD. Our findings further support the within-disorder transmission as well as the cross-disorder transmission of psychiatric disorders. Further cross-diagnostic research should be conducted to determine the common pathogenesis among these psychiatric disorders. In addition, the mental health statuses of parents and children have a multifaceted relationship. Parents who have their own mental health disorders may have more difficulty providing care for their children than parents without mental health disorders. Identifying the mental health of parents of adolescents with MDD, especially adolescents with a poor response to antidepressant treatment, and ensuring that parents get the support they need are critical for the treatment of adolescent depression.

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Data availability statement. The NHIRD was released and audited by the Department of Health and Bureau of the NHI Program for the purpose of scientific research (https://nhird.nhri.org.tw/). The NHIRD can be obtained through the formal application that is regulated by the Department of Health and Bureau of the NHI Program.

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