70938_Auto_Edited-check.docx

Retrospective Study

Generalized structural equation modeling: Symptom heterogeneity in attention-deficit/hyperactivity disorder leading to poor treatment efficacy

Tzang RF *et al*. ODD mediating ADHD remission by GSEM

Abstract

BACKGROUND

Treatment efficacy for attention-deficit/hyperactivity disorder (ADHD) is reported to be poor, possibly due to heterogeneity of ADHD symptoms. Little is known about poor treatment efficacy owing to ADHD heterogeneity.

AIM

To use generalized structural equation modeling (GSEM) to show how the heterogeneous nature of hyperactivity/impulsivity (H/I) symptoms in ADHD, irritable oppositional defiant disorder (ODD), and the presentation of aggression in children interferes with treatment responses in ADHD.

METHODS

A total of 231 children and adolescents completed ADHD inattention and H/I tests. ODD scores from the Swanson, Nolan, and Pelham, version IV scale were obtained. The child behavior checklist (CBCL) and parent's satisfaction questionnaire were completed. The relationships were analyzed by GSEM.

RESULTS

GSEM revealed that the chance of ADHD remission was lower in children with a combination of H/I symptoms of ADHD, ODD symptoms, and childhood aggressive behavior. ODD directly mediated ADHD symptom severity. The chance of reaching remission based on H/I symptoms of ADHD was reduced by 13.494% [= exp (2.602)] in children with comorbid ADHD and ODD [odds ratio (OR) = 2.602, 95% confidence interval (CI): 1.832-3.373, P = 0.000] after adjusting for the effects of other factors. Childhood aggression mediated ODD symptom severity. The chance of reaching remission based on ODD symptoms was lowered by 11.000% [= 1 - exp (-0.117)] in children with more severe baseline symptoms of aggression based on the CBCL score at study entry [OR = -0.117, 95%CI: (-0.190)-(-0.044), P = 0.002].

CONCLUSION

Mediation through ODD symptoms and aggression may influence treatment effects in ADHD after adjusting for the effects of baseline ADHD symptom severity. More attention could be directed to the early recognition of risks leading to ineffective ADHD treatment, *e.g.*, symptoms of ODD and the presentation of aggressive or delinquent behaviors and thought problems in children with ADHD.

Key Words: Attention-deficit/hyperactivity disorder; Oppositional defiant disorder; Aggression; Remission; Generalized structural equation modeling

Tzang RF, Chang YC. Generalized structural equation modeling: Symptom heterogeneity in attention-deficit/hyperactivity disorder leading to poor treatment efficacy. *World J Psychiatr* 2022; In press

Core Tip: It is important to understand the factors that influence treatment outcomes for those with attention-deficit/hyperactivity disorder (ADHD). This generalized structural equation modeling pathway analysis studied heterogeneity in ADHD. We found that higher irritable oppositional defiant disorder (ODD) symptom levels mediated the treatment outcomes in children with ADHD. Treating children with ADHD is not only a matter of treating inattentive symptoms alone. Earlier recognition of risky hyperactivity/impulsivity ADHD symptoms + irritable ODD + childhood aggression as a particular subgroup and earlier provision of a more intensive combination of pharmacotherapy and cognitive behavior therapy modalities are essential.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder among children and adolescents, with a high prevalence ranging from 5.00% to 12.76%[1], and definitely needs early treatment. Although we know

quite well the importance of early treatment of ADHD, approximately 25% to 30% of treated ADHD patients remain nonresponsive to treatment[2]. ADHD is a heterogeneous disorder in clinical presentation. The heterogeneity of ADHD in terms of clinical symptom profiles in children with co-occurring ADHD and oppositional defiant disorder (ODD) involves differentially higher levels of behavioral and emotional difficulties. ADHD comorbid with ODD is common and presents clinically in more than half of children with ADHD[3].

Another commonly seen clinical phenomenon is childhood aggression, which plays an essential role in the heterogeneity of ADHD. Clinically, childhood aggression commonly co-occurs in children with ADHD and ODD. As a result, these combinations of ADHD and other symptom comorbidities might further increase the highest levels of behavioral and emotional difficulties in children[4,5]. Furthermore, the treatment efficacy for ADHD in children with the commonly seen irritable subtype of ADHD presenting with childhood aggression remains ineffective. Indeed, many parents seek help from mental health experts due to irritability in children with ADHD, but they do not obtain proper treatment efficacy owing to undertreated emotional dysregulation problems associated with ADHD[6].

Prior studies

In the real world, up to 80% of children with ADHD report an irritable subtype of ADHD[7]; here, we examined the heterogeneity of ADHD comorbid with ODD and aggression. As we reviewed studies on ODD, comorbidities between ADHD and ODD in children ranged from at least 40.6% to 60.0%[8,9]. Children with ADHD comorbid with ODD may have inattentive or hyperactivity/impulsivity (H/I) symptoms of ADHD and frequently have temper tantrums, excessive arguments with family, and uncooperative, deliberately annoying, or mean and spiteful behavior when younger[10], but the ODD comorbidity problems in children with ADHD remain underdiagnosed[11]. The more irritable ODD symptoms noticed in children with ADHD, the more increased the risk of behavioral and emotional difficulties in these children with ADHD[12,13]. Clinically, there

is more parental concern about this irritable mood associated with ADHD than inattentive symptoms of ADHD. Thus, ODD symptoms in ADHD may play mediating roles that impede treatment effects for ADHD, but little is known about these associations.

Additionally, when seeing the heterogeneity of ADHD from a childhood aggression perspective, child aggression is commonly seen in children with ADHD comorbid with ODD who have increased symptoms of irritable emotional difficulties associated with ODD[14-16]. Recently, childhood aggressive behavior was found to be closely associated with symptoms of ODD[17]. However, there is a gap in the study of childhood aggression in children with irritable ADHD because ODD commonly coexists with conduct disorder (CD)[18]. An earlier study focused more on childhood CD comorbid with ADHD. We know that any kind of childhood aggression may be a small part of the symptomatology of CD. However, in the real world, children with CD are not generally noticed in the clinic as more likely to have any kind of aggressive behavior. For example, the presentation of any kind of aggressive behavior was noticed to be as high as in 58% of preschool children[19]. A higher proportion of children with ADHD will present aggressiveness without meeting the full diagnostic criteria for CD[3]. Therefore, ODD plus aggression in children can be a bad predictor for children's future criminal behavior, social problems, and internalizing problems[20]. There is a lack of studies examining heterogeneity across symptom dimensions of ADHD + ODD + aggression. Here, we suggest that current child ADHD expertise should use updated latent class and factor analysis to account for all related levels of heterogeneity in ADHD.

Goal of this study

To provide an evidence-based understanding of the heterogeneity of ADHD to optimally reflect real-world variation among children with ADHD, multiple symptoms should be simultaneously evaluated. Structural equation modeling (SEM) is necessary to show the theoretical relationships among symptom heterogeneity in ADHD and poor treatment outcomes with quite different implications. Because treatment responses are usually

expressed as binary data (yes/no), the traditional SEM method is not appropriate to explore the pathway of how ODD and aggression interfere with treatment efficacy for ADHD. A new pathway analysis, called generalized SEM (GSEM), can use more normally distributed observed variables by adding the logistic regression model into the SEM (StataCorp., 2013). By using GSEM pathway analysis, we can fit logistic, probit, poisson, multinomial logistic, ordered logit, ordered probit, and other models. In other words, the observed variables used in GSEM can be continuous, binary, countable, categorical, and ordered variables. GSEM can detail the pathways by which ODD mutually increases the symptom severity of ADHD (expressed by inattentive and H/I symptoms) and problematic aggressiveness. Furthermore, using GSEM pathway analysis can be a good way to detail how ODD and aggressive behavior possibly interfere with the treatment efficacy for ADHD due to their interacting joint influence on ADHD symptom severity[21].

In this study, we hypothesized that when children and adolescents with ADHD and ODD also present with any kind of aggression, treatment efficacy is poor. Regarding inattention, H/I, and ODD symptom severity and any kind of aggression at study entry, it is expected that all these risks may affect the pathways influencing treatment efficacy for ADHD. Indirectly, we hypothesized that ODD with various aggressive symptoms in children might play a mediating role in treatment efficacy for ADHD.

We used GSEM to test the hypothesis that ODD is essentially an intermediate mediator of treatment effectiveness for ADHD (in terms of odds of reaching remission or the chance of remission) by direct and indirect pathway analysis. We hope that mental health professionals can regard the combination of ODD and aggression in children with ADHD as a warning risk for difficulty achieving remission in treating the ADHD and taking earlier steps to properly manage the symptoms of ODD and the presentation of any kind of aggressive behavior.

MATERIALS AND METHODS
Participants and data collection

Patients for this study were children recruited from the outpatient unit of Mackay Memorial Hospital, a major medical center in Taipei, Taiwan. The hospital's institutional review board approved the design of the study (Institutional Review Board No: MMH-I-S-489; name of project: Exploring the symptomatology on children with internet addiction and attention deficit hyperactivity disorder and their parent). After receiving a complete description of the study, potential participants (children and their parents) provided written informed consent in line with the institutional review board's guidelines. A total of 231 children (mean age ± standard deviation = 10.17 ± 2.59) with a clinical diagnosis of ADHD based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) were enrolled in this study. An experienced child and adolescent psychiatrist confirmed the clinical diagnosis of ADHD based on the DSM-IV criteria.

Measurements

ADHD and ODD symptoms: The primary measures in this study reflected the core symptoms of ADHD (18 items) and ODD (8 items) as defined in the DSM-IV and included the inattention subscale, H/I subscale, and the ODD subscale of the Swanson, Nolan, and Pelham, version IV scale (SNAP-IV)[22]. Each item was scored by severity based on a 4-point scale (0-3 points, where 0: Not at all, 1: Just a little, 2: Quite a bit, and 3: Very much). The intraclass correlation coefficients for the three subscales of the Chinese-language SNAP-IV (SNAP-IV-C) ranged from 0.59 to 0.72 for the parent form and from 0.60 to 0.84 for the teacher form. All subscales of both the parent and teacher forms showed excellent internal consistency with Cronbach's α greater than 0.88[23].

Remission rate measurements: The remission criteria on the SNAP were defined as 0 (no) or equal to 1 (yes) for each of the symptoms or a total score that was < 9 (not at all-0 or just a little-1 for the ADHD symptoms) on the SNAP after treatment. More specifically, a patient was in remission with regard to inattention, hyperactivity, and ODD if after 6 wk of treatment, the three subscales of the SNAP-IV were ≤ 9, ≤ 9, and ≤ 8, respectively.

Parents and investigators rated ADHD symptoms using the SNAP-IV-C at every follow-up session to measure remission after treatment.

Aggressive behavior: The child behavior checklist (CBCL) was designed to determine competencies and behavioral problems of children aged 4-18 years. The questionnaires, completed by the parents, contain 118 items to assess specific behavioral and emotional problems. The CBCL was translated into Chinese *via* a two-stage translation process[24]. The internal consistency and 1-mo test-retest reliability (all α values and reliabilities > 0.6, except for thought problems) of the Chinese version were satisfactory for Taiwanese patients[25]. The present study analyzed the following 6 scales: Aggressive behaviors (tpagbeh), attention problems (tpattpr), anxiety/depression (tpandep), social problems (tpsocpr), delinquent behaviors (tpdebeh), and somatic complaints (tpsoma).

Caregiver satisfaction: To assess the medication adherence of children with ADHD, parents/caregivers completed the caregiver's satisfaction form, which included the frequency of adverse events and the mean dose of methylphenidate (MPH), to understand the noncompliance risk. Parent/caregiver satisfaction with the current ADHD treatment was measured on a 5-point Likert scale as follows: (1) Completely dissatisfied; (2) Somewhat dissatisfied; (3) Neutral; (4) Somewhat satisfied; and (5) Completely satisfied. The only treatment was MPH (long- or short-acting formulations).

Statistical analyses
In this study, we wanted to simultaneously explore the potential relationships among the remission odds (based on inattention, H/I, and ODD symptoms) and the aforementioned measurements. We used a typical multiple-indicators and multiple-causes model. The GSEM method was used to include the logistic regression model in the SEM first with Stata 13 for Windows to test the mediation model that specified the relationships between inattention, H/I, and ODD symptom severity, any kind of aggression, and remission (StataCorp., 2013). First, we used multiple logistic regression models using GSEM

notations to understand the odds of remission based on each measure. The goodness-of-fit indices in this part were P values of the fitted coefficients, deviance, and McFadden's pseudo R^2. The second part was the (combined) mediation model, which combined those three multiple logistic regression models in the first part presented by GSEM notations. All statistical analyses were performed using STATA v.13.0 (StataCorp., 2013). Statistical significance was defined as a $P < 0.05$.

RESULTS

Overall, 231 eligible patients with ADHD were enrolled. In terms of patient characteristics, 158 ADHD patients had a combined subtype (68.7%). The comorbidity rate was 73.0%. The remission rates with regard to inattention, H/I, and ODD symptoms were 30.7%, 53.7%, and 49.4%, respectively (Table 1).

As shown in Table 2, the results of the logistic regression showed that the chance of reaching remission based on inattentive symptoms of ADHD was significantly reduced by 22.7% [= 1 - exp (-0.258)] in those with more severe inattentive symptoms [odds ratio (OR) = -0.258, 95% confidence interval (CI): (-0.350)-(-0.167), $P < 0.001$] after adjusting for the effects of other factors. This means that the more severe the inattention problem at study entry, the poorer the ADHD treatment response. The chance of reaching remission was significantly reduced by 10.6% [= 1 - exp (-0.112)] in those with higher baseline CBCL aggression scores [OR = -0.112, 95%CI: (-0.186)-(-0.038), $P = 0.003$] after adjusting for the effects of other factors. The results of deviance, D (226) = 214.144 ($P = 0.704$), and McFadden's pseudo R^2 = 0.2485 indicated a very good model fit (Table 2, Figure 1).

Similarly, as shown in Table 3, the chance of reaching remission based on H/I symptoms of ADHD was significantly reduced by 9.7% [= 1 - exp (-0.102)] for each increase in the baseline CBCL aggression score [OR = -0.102, 95%CI: (-0.170)-(-0.073), $P = 0.004$) after adjusting for the effects of other factors. Moreover, for each increase in the parental satisfaction level, the chance of reaching remission based on H/I symptoms was significantly increased by 57.4% [= exp (0.579) – 1]. The results of goodness-of-fit indices, namely, deviance and McFadden's pseudo R^2, were D (224) = 242.862 ($P = 0.184$) and

pseudo R^2 = 0.2386, respectively, which indicated a very good model fit. The corresponding multiple logistic regression model presented by GSEM is shown in Figure 2.

The chance of reaching remission based on ODD symptoms decreased by 11.0% [= 1 - exp (-0.117)] with each increase in the baseline CBCL aggression score [OR = -0.117, 95%CI: (-0.190)-(-0.044), P = 0.002] (Table 4). Again, the deviance and McFadden's pseudo R^2, D (226) = 255.740 (P = 0.085) and pseudo R^2 = 0.2013, indicated that the model fit was good. The corresponding multiple logistic regression model of remission based on ODD symptoms presented by GSEM is shown in Figure 3.

Regarding the combined (mediation) model (Table 5), we first noted that the chance of reaching remission based on H/I ADHD symptoms was reduced by 13.494% [= exp (2.602)] in the children with ODD (OR = 2.602, 95%CI: 1.832-3.373, P = 0.000) after adjusting for the effects of other factors. Moreover, the chance of reaching remission based on inattention ADHD symptoms was reduced by 29.785% [= exp (3.394)] in children with H/I ADHD symptoms (OR = 3.394, 95%CI: 1.862-4.927, P = 0.000) and reduced by 5.094% [= exp (1.628)] in children with ODD symptoms (OR = 1.628, 95%CI: 0.600-2.656, P = 0.002) after adjusting for the effects of other factors. The chance of reaching remission based on ODD symptoms was lowered by 11.000% [= 1 - exp (-0.117)] in children with more severe baseline symptoms of aggression in the CBCL scores at study entry [OR = -0.117, 95%CI: (-0.190)-(-0.044), P = 0.002]. The corresponding combined (mediation) model presented by GSEM is shown in Figure 4.

<u>DISCUSSION</u>

This study examined the structure of ADHD symptoms in child adolescent samples using GSEM. This GSEM pathway analysis first supported that poor treatment outcomes in ADHD can be predicted as irritable ODD subtype of ADHD with aggressive behavior. This pathway analysis indicated higher ODD symptom levels mediated treatment outcomes for ADHD through enhancing inattentive and H/I symptoms. Treating children with ADHD is not only a matter of treating inattentive symptoms alone, but

there is also a need to recognize and manage symptoms of ODD and the presented aggressive behavior, delinquent behavior, and thought problems in children with ADHD to improve ADHD treatment outcomes.

Comparison with prior work

Hinshaw *et al*[26] suggested that only detailed pathway analysis can further assist clinicians in understanding the internal joint relationships among aggressive behavior, symptoms of ODD, and symptom severity of ADHD. Such pathway analysis might remind clinicians to recognize earlier risky irritable symptoms of ADHD + ODD + childhood aggression as a special subgroup and provide more effective therapeutic treatment modalities earlier.

Aggression in children and adolescents with irritable ADHD is a serious clinical and public health problem. Especially in the recent internet age, many children and adolescents present inattentive symptoms, externalizing behavior, or risk-taking behavior after excessive use of the internet[27,28]. We know that this unrecognized aggression in early childhood becomes more aggressive or violent behavior later in these irritable children[5,29]. Alternatively, the results of this study indicated that children with the irritable ODD subtype of ADHD characterized by symptoms of irritable ODD and aggressive behavior is harder to treat well. However, previous studies have focused more on conduct behavior (CD)[30,31] instead of any kind of aggression in children with ODD, which warrants more attention. Therefore, the implication of this study is that we suggest using a CBCL scale to identify aggressive children and adolescents in child and adolescent clinics or internet gaming disorder clinics in the future. The presented aggressive behavior we derived from CBCL included relational aggression (argues a lot, bragging, boasting, demands much attention), disobedience at home, disobedience at school, easily jealous, screams a lot, showing off or clowning, stubborn, sullen or irritable, sudden changes in mood or feelings, talks too much, teases a lot, temper tantrums or hot temper, direct aggression (cruelty, bullying or meanness to others, destroys his or her own things, destroys things belonging to his or her family or others), and gets in many

fights (physically attacks people, threatens other people), which can all be regarded as early recognition of any kind of aggression in children with ADHD and ODD. Earlier and effective treatment inventions for children with particular heterogeneous subtypes of ADHD should be provided by ADHD experts in these days with digital technology.

In the present study, the GSEM results found that ADHD symptom severity was determined by the joint effects between ODD, aggression, and delinquent behavior symptoms. With the under recognition and undertreatment of ODD and aggression in children with ADHD, there is always a significant risk that predicts poor treatment efficacy. Here, we suggest that children and psychiatrists should record a more extensive history of oppositional symptoms because one previous study indicated that there was an underdiagnosed ODD comorbidity problem in children with ADHD[11]. The treatment effects on ODD depend on how the underlying comorbid ADHD is treated. Usually, the core symptoms of ODD are not amenable to pharmacotherapy alone[32]. For children with ADHD with ODD, treatments with only pharmacotherapy for inattention alone always remains noneffective for these ODD symptoms[33,34]. The use of nonstimulant drugs such as atomoxetine was recently noticed to be effective in treating ODD symptoms in children with ADHD[35,36]. However, for children with ADHD with severe ODD and behavioral symptoms, there is still a need to use pharmacotherapy with stimulants (MPH), mood stabilizers such as sodium valproate (Depakin), and antipsychotics such as risperidone with concurrent behavioral therapy[37].

Cognitive behavior psychotherapy in children with ADHD is also essential to regulate emotion regulation circuitry by reducing reactive aggression[38]. Essentially, clinicians should provide effective combined pharmacotherapies with additional effective behavioral modification interventions, parenting programs, and cognitive behavioral therapy to improve treatment outcomes in this particular group of children with ADHD.

Based on the pathway analysis, both ODD and aggressive symptoms interacted as joint effects to exacerbate ADHD symptom severity, as a previous study had noticed[15,16]. We revealed the insight that aggression during childhood rarely occurs alone and is closely correlated with other symptoms of childhood psychopathology. Both ODD symptoms

and aggression are important influences on the efficacy of ADHD treatment[39]. Clinicians should consider additional assessments to detect dimensional behavioral symptoms such as childhood aggressive or destructive behaviors to further provide effective treatment modalities to achieve remission of ADHD[40].

Regarding the childhood H/I symptoms of ADHD, previous findings showed that hyperactive ADHD symptoms had a role in predicting children becoming more socially immature, aggressive, and peer rejected[41]. Additionally, one recent meta-analysis indicated more severe symptoms of H/I, and children with ADHD were less likely to obtain better treatment outcomes[42]. In this GSEM, we found that childhood H/I symptoms resulted in a greater risk of increasing the inattention symptom severity, leading to subsequent poor treatment outcomes for ADHD. ODD symptoms and the presentation of aggressive behavior mediated an increase in inattentive and H/I symptom severity of ADHD. Nevertheless, children and adolescents need more attention regarding the diagnosing and managing of H/I symptoms of ADHD. ODD, aggression, and H/I symptoms of ADHD interactively increased the symptom severity of ADHD.

A previous study indicated that the coexistence of a diagnosis of ODD/CD, learning difficulties, anxiety, younger age, family dysfunction, and socioeconomic adversity were all risk factors for predicting poor treatment efficacy for ADHD[43]. This pathway analysis further focused on children with ADHD with ODD, and aggression led to poor treatment outcomes. ADHD is a heterogeneous disorder with complicated emotional and impulsivity deficits. From the Research Domain Criteria perspective, ADHD patients have deficits in the domains of cognition (specifically in working memory) and positive valence (in rewarding anticipation/delay/receipt)[44]. Emotional dysregulation defects may be highly associated with abnormal reward processing systems[45]. Therefore, for children with ADHD presenting symptoms of irritable ODD and aggression, our pathway analysis suggests that the children may have deficits in both cognition and reward domains. Thus, the children with symptoms of ADHD + ODD + aggression should be a clinically distinct emotional irritability subgroup, and clinicians should

provide more specific treatment guidelines for these children with ADHD. Future DSM systems need to regard ODD as an essential risk for poor treatment effects for ADHD.

Limitations

This study has the following limitations. First, the construction of the subscale of the SNAP and CBCL, without a direct interview with the parents, seems to be arbitrary. Additionally, the fact that most of the scale is provided by a main caregiver, mainly mothers and teachers, may lead to sampling bias. Another limitation is the cross-sectional design of the study, which may not necessarily represent the longitudinal relationships among ADHD, ODD, aggression, and remission rate. As the main purpose of this study was to explore the association among disruptive symptoms in children and remission rates, aggression scores from the CBCL were used to represent disruptive child behaviors instead of CD measures. This was a naturalistic observational study performed in Taiwan. Most patients from the outpatient department at that time received psychopharmacologic treatment, including short-term or long-acting MPH, or long-acting drugs such as atomoxetine rather than parenting behavior therapy. However, the thrust of this study was to predict poor treatment efficacy in the children with co-occurring ADHD, ODD, and aggressive symptoms by special GSEM statistical analysis. Therefore, we did not show the detailed treatment response after different kinds of drugs or other psychosocial interventions. Finally, the definitions of direct, indirect, and total effects in SEM have not yet been established in the GSEM. Although three out of four requirements for the mediation model were satisfied in our GSEM, it might not be appropriate to call the results in Figure 4 a mediation model. Here, we only borrowed the concept and spirit of the mediation model to emphasize the relationships among remissions based on ODD, H/I, and inattention symptoms for treating children with ADHD.

CONCLUSION

Despite these limitations, to the best of our knowledge, this is the first study to determine mediators in reaching remission of ADHD. ODD is a categorical diagnosis, and aggressive behavior is a dimensional problem. Such interactive categorical and dimensional information provides an added dimension in the understanding of the etiology of heterogenicity of ADHD. This pathway study revealed additional insights into devising more efficacious pharmacotherapies and cognitive behavior therapies. Clinicians should regard ADHD + ODD + aggression comorbidity as a distinct entity that needs an early and combined intensive biopsychosocial model approach, as recent research demonstrated[46]. Future longitudinal and systemic research is needed to validate this as a potential obstacle, with the ODD symptoms dynamically interacting with childhood aggressive behavior symptoms.

Clinical significance

GSEM pathway analysis was used to demonstrate that disruptive childhood symptoms, including categorical diagnoses such as ODD and dimensional problems such as aggressive symptoms before treatment, apparently lower the remission rate for those with ADHD. This paper suggests that clinicians should directly examine the joint effects of ADHD, ODD, and aggression to assess the risk for poor treatment outcomes. An early and more intensive combined biopsychosocial model approach for ADHD should be warranted for these children.

ARTICLE HIGHLIGHTS

Research background

Many parents seek help from mental health experts due to irritability in children with attention-deficit/hyperactivity disorder (ADHD). But treatment efficacy for irritable and aggressive ADHD in children remains ineffective. Therefore, the heterogeneity to ADHD treatment should be proposed by a specific mathematical method.

Research motivation

Treating children with ADHD is not only a matter of treating inattentive symptoms alone. It is important to understand the factors that influence treatment outcomes for those with ADHD.

Research objectives

This study used the generalized structural equation modeling (GSEM) pathway analysis to analyze heterogeneity in ADHD.

Research methods

We used the GSEM to test the hypothesis that ODD is essentially an intermediate mediator of treatment effectiveness for ADHD (in terms of odds of reaching remission or the chance of remission) by direct and indirect pathway analysis.

Research results

Higher irritable oppositional defiant disorder (ODD) symptom levels mediated the treatment outcomes in children with ADHD. Earlier recognition of risky hyperactivity/impulsivity ADHD symptoms + irritable ODD + childhood aggression as a particular subgroup and earlier provision of a more intensive combination of pharmacotherapy and cognitive behavior therapy modalities are essential.

Research conclusions

Treating children with ADHD is not only a matter of treating inattentive symptoms alone, but there is also a need to recognize and manage symptoms of ODD and the presented aggressive behavior, delinquent behavior, and thought problems in children with ADHD to improve ADHD treatment outcomes.

Research perspectives

Poor treatment outcomes in ADHD can be predicted as irritable ODD subtype of ADHD with aggressive behavior. An early and more intensive combined biopsychosocial model

approach for ADHD should be warranted for these children. This study revealed additional insights into devising more efficacious pharmacotherapies and cognitive behavior therapies.

70938_Auto_Edited-check.docx