Received: 1 May 2022 | Revised: 21 September 2022 | Accepted: 17 October 2022

DOI: 10.1002/npr2.12299

NEUROPSYCHOPHARMACOLOGY REPORTS

WILEY

ORIGINAL ARTICLE

Predictors of response to pharmacotherapy in children and adolescents with psychiatric disorders: A combined post hoc analysis of four clinical trial data

Takashi Tsujii[1,2] | Hitoshi Sakurai[3] | Hiroyoshi Takeuchi[1] | Takefumi Suzuki[4] | Masaru Mimura[1] | Hiroyuki Uchida[1,5]

[1]Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

[2]Department of Psychiatry, Asaka Hospital, Fukushima, Japan

[3]Department of Neuropsychiatry, Kyorin University Faculty of Medicine, Tokyo, Japan

[4]Department of Neuropsychiatry, University of Yamanashi Faculty of Medicine, Yamanashi, Japan

[5]Geriatric Mental Health Program, Centre for Addiction and Mental Health, Toronto, Canada

Correspondence
Hiroyuki Uchida, Department of Neuropsychiatry, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160–8582, Japan.
Email: hiroyuki_uchida@keio.jp

Funding information
National Institutes of Health

Abstract

Objective: The prediction of response to pharmacotherapy has not been sufficiently explored in children and adolescents with psychiatric disorders, which was addressed in this study.

Methods: Data from four double-blind, placebo-controlled studies (sertraline and fluvoxamine for anxiety disorders, risperidone for autistic disorder, and fluoxetine for major depressive disorder) in children and adolescents funded by the National Institute of Mental Health were used. The response was defined as a score of 1 or 2 on the Clinical Global Impression-Global Improvement (CGI-I) at the endpoint. Logistic regression analysis was performed to evaluate associations between response status and the following variables: sex, diagnosis, treatment allocation, and CGI-Severity of Illness (CGI-S) score at baseline. Moreover, the presence of early improvement (a score of ≤3 in the CGI-I) at Week 1 was added to the independent variables in an additional binary logistic regression analysis, using the data from two studies.

Results: A total of 599 patients were included in the analysis. In the binary logistic regression analysis, active drug use (odds ratio [OR] = 8.64, $P<0.001$) and female sex (OR = 1.89, $P = 0.002$) were significantly associated with treatment response. In the second binary logistic regression, the presence of early improvement in the CGI-I (OR = 3.47, $P = 0.009$), as well as active drug use (OR = 15.05, $P<0.001$) and female sex (OR = 2.87, $P = 0.016$), were associated with subsequent responses.

Conclusion: Allocation to active drugs, female sex, and early improvement may predict treatment response to pharmacotherapy among children and adolescents with psychiatric disorders.

KEYWORDS
anxiety disorder, autism spectrum disorder, major depressive disorder, pediatrics, pharmacotherapy

Takashi Tsujii and Hitoshi Sakurai contributed equally to this work.

1 | INTRODUCTION

The prevalence of psychiatric disorders among children and adolescents has been increasing for decades.[1,2] Since prolonged psychiatric problems in this population are associated with serious psychosocial consequences and economic burden due to medical costs,[3,4] timely treatment intervention is critical.

Conventionally, treatment for child and adolescent psychiatric disorders has included pharmacotherapy or psychological interventions such as psychodynamic psychotherapy, cognitive–behavioral therapy (CBT), and family therapy.[5,6] For example, while caution is necessary for increased suicidality in youths, selective serotonin reuptake inhibitors (SSRIs) are recommended in youths with major depressive disorder (MDD) and anxiety disorders such as generalized anxiety disorder (GAD).[7–11] Risperidone and aripiprazole reduce repetitive behaviors associated with autism spectrum disorders (ASD).[3] However, it has been reported that approximately 30%–50% of children and adolescents with psychiatric conditions do not respond to the drug treatment,[3,12,13] which emphasizes the need for predictors of treatment response status at the earliest opportunity.

Among possible predictors, early improvement with treatment has been reported to be linked to subsequent clinical response in children and adolescents with MDD, bipolar disorder, and schizophrenia.[14–16] However, the sample sizes of these previous studies were relatively small with a range of 107–168. To examine the predictors of treatment, including early improvement, in children and adolescents with psychiatric disorders, combining the data from multiple clinical studies would be relevant in this population. We therefore conducted a combined analysis of four double-blind, placebo-controlled studies which were available in the National Institute of Mental Health (NIMH) database.

2 | METHODS

We searched for double-blind, placebo-controlled studies in child and adolescent mental disorders in the NIMH database (ie https://nda.nih.gov/general-query.html) and obtained datasets of the corresponding studies from the NIMH. The data derived from the following four NIMH-funded studies were used in this report: the Child–Adolescent Anxiety Multimodal Study (CAMS; NCT0052078),[17] the Placebo-Controlled Study of Risperidone in Children and Adolescents with Autistic Disorder (Risperidone-Autistic Disorder Study; NCT00005014),[12] the Research Unit on Pediatric Psychiatric Psychopharmacology (RUPP) Anxiety Study (NCT00000389),[18] and the Treatment for Adolescents with Depression Study (TADS; NCT00006286).[19] After a complete description of the study, written informed consent was obtained from all participants and at least one of the parents or guardians in each study. Owing to the completely anonymous nature of this analysis and the absence of direct human involvement, no ethical approval was sought for the present post hoc analysis.

The CAMS enrolled 488 patients aged 7–17 years with anxiety disorders, including GAD, separation anxiety disorder, and social phobia, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) from 2002 to 2007. Participants were randomly assigned to up to 200 mg/d of sertraline, 14 sessions of CBT, their combination therapy, or placebo for 12 weeks. Assessment with the Clinical Global Impression-Severity of Illness and Global Improvement (CGI-S and CGI-I) was performed at baseline and 4, 8, and 12 weeks. The Risperidone-Autistic Disorder Study was conducted between 1999 and 2001. A total of 101 patients between the ages of 5 and 17 years with autistic disorder in the DSM-IV were randomly administered 2.5 mg/d of risperidone or placebo for 8 weeks. The efficacy measures included the CGI at baseline and 1, 2, 3, 4, 5, 6, 7, and 8 weeks. The RUPP Anxiety Study was conducted between 1997 and 1999 to compare the 8-week outcomes of fluvoxamine and placebo in 128 patients aged 6 to 17 years with anxiety disorders, including GAD, separation anxiety disorder, and social phobia, according to the DSM-IV. The CGI was evaluated at baseline and 1, 2, 3, 4, 5, 6, and 8 weeks. The TADS enrolled 439 patients between the ages of 12 and 17 years who had a DSM-IV diagnosis of MDD from 2000 to 2003. Participants were assigned to 10–40 mg/d of fluoxetine, CBT, their combination therapy, or placebo. Efficacy measures included CGI scores at baseline and 6 and 12 weeks.

Scores of CGI-S and CGI-I in participants who were allocated to the active drug or placebo were extracted. Response to active drug or placebo was defined as a score of 2 or less in the CGI-I (1 = very much improved and 2 = much improved) at the endpoint of each study. Logistic regression analysis was performed to evaluate associations between response status and the following variables: sex; diagnosis (autistic disorder, anxiety disorders, or MDD); medications (active drug or placebo); and CGI-S score at baseline. These variables were selected as they were commonly reported in all of the four studies. The response rates in each subgroup, classified by the significant variables, were calculated. Furthermore, to examine the association between early improvement and subsequent treatment outcome, the CGI-I score (a score of ≤3 in the CGI-I) at Week 1 was added to the independent variables in a binary logistic regression analysis, using the combined data from the Risperidone-Autistic Disorder Study and the RUPP Anxiety Study. The positive and negative predictive values for subsequent response from an early improvement were also calculated among those who received the active drug and placebo in each study, respectively. Statistical analysis was conducted using Statistical Package for Social Science version 23.0, for Windows (IBM Corporation), and a two-tailed $P < 0.05$, was considered statistically significant.

3 | RESULTS

3.1 | Sample characteristics

A total of 1149 patients participated in one of the four studies. Among them, 559 patients who were allocated to active drugs or placebo and had CGI-S score at baseline and CGI-I score at the endpoint

TABLE 1 Associations between clinical characteristics and subsequent response in the combined analysis of four studies

	B	Odds ratio	95% CI	*P*-value
Female	0.637	1.89	1.27–2.81	0.002
Diagnosis	−0.036	0.96	0.72–1.30	0.81
Allocation to active drug	2.156	8.64	5.84–12.78	<0.001
CGI-S at baseline	0.135	1.15	0.90–1.46	0.28

Abbreviations: CGI-S, Clinical Global Impressions-Severity; CI, confidence interval.

TABLE 2 Associations between clinical characteristics and subsequent response in the risperidone-autistic disorder study and RUPP anxiety study

	B	Odds ratio	95% CI	*P*-value
Female	1.052	2.87	1.21–6.76	0.016
Diagnosis	−0.786	0.46	0.19–1.10	0.810
Allocation to active drug	2.711	15.05	6.78–33.41	<0.001
CGI-S at baseline	−0.347	0.71	0.43–1.15	0.164
A CGI-S score of ≤3 at Week 1	1.244	3.47	1.37–8.78	0.009

Abbreviations: CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; Risperidone-Autistic Disorder Study, Placebo-Controlled Study of Risperidone in Children and Adolescents with Autistic Disorder; RUPP Anxiety Study, Research Unit on Pediatric Psychiatric Psychopharmacology Anxiety Study.

were included in the analysis. During the study period, 192 patients (34.3%) withdrew from the studies due to withdrawal of consent ($n = 91$, 16.3%), deviation from the protocol ($n = 82$, 14.7%), and side effects ($n = 19$, 3.4%). The numbers of males and females in each study were 92 and 93 in the CAMS, 71 and 14 in the Risperidone-Autistic Disorder Study, 48 and 55 in the RUPP Anxiety Study, and 85 and 100 in the TADS, respectively.

3.2 | Factors associated with subsequent response

In the first binary logistic regression, the allocation to an active drug (odds ratio [OR] = 8.64, 95% confidence interval [CI] = 5.84–12.78, $P < 0.001$) and being female (OR = 1.89, 95% CI = 1.27–2.81, $P = 0.002$) were significantly associated with response at the endpoint (Table 1). A sensitivity analysis excluding the Risperidone-Autistic Disorder Study demonstrated a similar result (Table S1).

In the second binary logistic regression, using the combined data of the Risperidone-Autistic Disorder Study and the RUPP Anxiety Study, the following factors were associated with subsequent response: allocation to active drug (OR = 15.05, 95% CI = 6.78–33.41, $P < 0.001$), an early improvement in the CGI-I at Week 1 (OR = 3.47, 95% CI = 1.37–8.78, $P = 0.009$), and female sex (OR = 2.87, 95% CI = 1.21–6.76, $P = 0.016$) (Table 2). In the Risperidone-Autistic Disorder Study, the positive and negative predictive values of an early improvement for subsequent response were 91.3% and 28.6% for risperidone and 33.3% and 93.1% for placebo, respectively. Likewise, in the RUPP Anxiety Study, the positive and negative predictive values of an early improvement for subsequent response were 80.0% and 45.0% for fluvoxamine and 0.0% and 86.3% for placebo, respectively.

4 | DISCUSSION

To the best of our knowledge, this is the largest study to examine the predictors of response to pharmacotherapy in children and adolescents with a wide range of psychiatric disorders. In the binary logistic regressions, an early improvement at Week 1, female sex, and allocation to active drugs were significantly associated with subsequent responses. These factors may help identify patients who are more likely to respond to current regimen; alternatively, they may offer an opportunity to pursue other potentially effective treatment options for those who will unlikely benefit from ongoing treatment among pediatric and adolescent patients with psychiatric disorders at the earliest opportunity.

Early improvement within the first week of the treatment was associated with subsequent responses in the present analysis using the datasets of autistic and anxiety disorders. This finding is consistent with the results in pediatric and adolescent MDD, bipolar disorder, and schizophrenia.[14–16] Given the high-positive predictive values among patients taking active drugs that we found in the present study, children and adolescents with autistic and anxiety disorders who show early improvement at Week 1 are likely to achieve subsequent responses by continuing the ongoing pharmacological regimen, which represents good clinical practice. Interestingly, whereas the positive predictive values were low among those receiving placebo in both autistic and anxiety disorders, the negative predictive values were as high as 86.3%–93.1%, indicating that initial improvements with placebo treatment may not be sustainable thereafter.

This study has several limitations. First, this is a secondary, post hoc analysis of the four combined NIH-funded datasets. Study designs were heterogeneous in terms of target diagnoses, medications used, timing of assessments, and study duration. Second,

psychological interventions which play an important role in the treatment of child and adolescent psychiatric disorders were not investigated in the present analysis. Third, the CGI may be too simple to comprehensively assess psychopathology. However, CGI was the only common assessment scale among the four studies analyzed. While the early change in some individual depressive symptoms predicts subsequent treatment outcome in adult population with depression,[20,21] we could not analyze individual symptoms in the present study because of the small sample size in each study. Lastly, the selection of factors in this analysis and the choice of 1 week as the timing of early improvement may be considered arbitrary.

In summary, the present study found that early improvement, female sex, and taking active drugs are associated with better treatment responses in children and adolescents with psychiatric disorders. These results will guide physicians in predicting subsequent treatment outcomes and considering the next treatment options at the earliest opportunity, although further studies are needed to replicate these preliminary findings in wider pediatric populations.

ACKNOWLEDGMENTS

Data used in the preparation of this manuscript were obtained from the National Institute of Mental Health (NIMH) Data Archive (NDA). NDA is a collaborative informatics system created by the National Institutes of Health to provide a national resource to support and accelerate research in mental health. Dataset identifier(s): [NIMH Data Archive Collection IDs: 2160, 2151, 2152, and 2145]. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or of the Submitters submitting original data to NDA.

CONFLICT OF INTEREST

Dr. Tsujii has received manuscript or speaker honoraria from Otsuka Pharmaceutical within the past 3 years. Dr. Sakurai has received grants from Takeda Science Foundation, manuscript or speaker fees from Eisai, Takeda Pharmaceutical, Otsuka Pharmaceutical, Meiji Seika Pharma, Shionogi Pharma, Yoshitomiyakuhin, Sumitomo Pharma, Kyowa Pharmaceutical, and Lundbeck Japan. Dr. Takeuchi has received speaker fees from EA Pharma, Kyowa, Janssen, Lundbeck, Meiji Seika Pharma, Mochida, Otsuka, Sumitomo Dainippon Pharma, Takeda, and Yoshitomiyakuhin. Dr. Suzuki received manuscript or speaker fees from Astellas, Dainippon Sumitomo Pharma, Eisai, Eli Lilly, Elsevier Japan, Janssen Pharmaceuticals, Kyowa Yakuhin, Lundbeck, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, MSD, Nihon Medi-Physics, Novartis, Otsuka Pharmaceutical, Shionogi, Shire, Tsumura, Wiley Japan, and Yoshitomi Yakuhin, as well as research grants from Eisai, Mochida Pharmaceutical, Meiji Seika Pharma, and Shionogi. Dr. Mimura has received speaker's honoraria from Byer Pharmaceutical, Daiichi Sankyo, Dainippon-Sumitomo Pharma, Eisai, Eli Lilly, Fuji Film RI Pharma, Hisamitsu Pharmaceutical, Janssen Pharmaceutical, Kyowa Pharmaceutical, Mochida Pharmaceutical, MSD, Mylan EPD, Nihon Medi-physics, Nippon Chemipher, Novartis Pharma, Ono Yakuhin, Otsuka Pharmaceutical, Pfizer, Santen Pharmaceutical, Shire Japan, Takeda Yakuhin, Tsumura, and Yoshitomi Yakuhin within the past 3 years. Also, he received grants from Daiichi Sankyo, Eisai, Pfizer, Shionogi, Takeda, Tanabe Mitsubishi, and Tsumura within the past 3 years outside the submitted work. Dr. Uchida has received grants from Daiichi Sankyo, Eisai, Mochida, Otsuka, and Sumitomo Dainippon Pharma; speaker's fees from Eisai, Janssen, Lundbeck, Meiji Seika Pharma, Otsuka, and Sumitomo Dainippon Pharma; and advisory board fees from Lundbeck, Sumitomo Pharma and Boehringer Ingelheim Japan.

DATA AVAILABILITY STATEMENT

Data used in the preparation of this manuscript were obtained from the National Institute of Mental Health (NIMH) Data Archive (NDA).

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

Owing to the completely anonymous nature of this analysis and the absence of direct human involvement, no ethical approval was sought for the present post hoc analysis.

INFORMED CONSENT

After a complete description of the study, written informed consent was obtained from all participants and at least one of the parents or guardians in each study.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

The data derived from the following four NIMH-funded studies were used in this report: the Child-Adolescent Anxiety Multimodal Study (CAMS; NCT0052078),[17] the Placebo-Controlled Study of Risperidone in Children and Adolescents with Autistic Disorder (Risperidone-Autistic Disorder Study; NCT00005014),[12] the Research Unit on Pediatric Psychiatric Psychopharmacology (RUPP) Anxiety Study (NCT00000389),[18] and the Treatment for Adolescents with Depression Study (TADS; NCT00006286).[19]

ORCID

Hiroyuki Uchida https://orcid.org/0000-0002-0628-7036

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Tsujii T, Sakurai H, Takeuchi H, Suzuki T, Mimura M, Uchida H. Predictors of response to pharmacotherapy in children and adolescents with psychiatric disorders: A combined post hoc analysis of four clinical trial data. Neuropsychopharmacol Rep. 2022;42:516–520. https://doi.org/10.1002/npr2.12299