National Survey of Adherence, Efficacy, and Side Effects of Methylphenidate in Children With Attention-Deficit/Hyperactivity Disorder in Taiwan

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Objectives: To identify the determinants of adherence to immediate-release (IR) methylphenidate in children and adolescents with attention-deficit/hyperactivity disorder (ADHD); to examine the impact of adherence on ADHD-related symptoms; and to compare the efficacy, adherence, and side effects of IR methylphenidate and osmotic release oral system (OROS) methylphenidate.

Method: This national survey, involving 12 hospitals, consisted of 2 phases of assessment. Treatment adherence in 240 (39.5%) of the 607 children aged 5 to 16 years with a clinical diagnosis of DSM-IV ADHD enrolled in the study was poor (defined as missing ≥ 1 dose of ADHD medication a day and on 2 days or more during school days). Children with poor adherence at phase 1 were able to switch to OROS methylphenidate, while adherents remained on the IR variant. We reassessed 124 poor adherents who switched to OROS methylphenidate. The global ADHD severity, parent-child interaction, classroom behavior, academic performance, and side effects of the child subjects were evaluated by investigators. Parents completed the rating scales about the ADHD-related symptoms. The study began in April 2005 and was completed in February 2006.

Results: Determinants for poor adherence included older age, later onset of ADHD, family history of ADHD, higher paternal education level, and multi-dose administration. Mental retardation and treatment at medical centers were inversely related to poor adherence. Overall, poor adherence was associated with more severe ADHD-related symptoms by comparison to good adherence. Similar side effect profile, superior adherence, and improved efficacy were demonstrated in intra-individual comparison of the OROS and IR methylphenidate forms.

Conclusion: Given that poor adherence to medication may be an important reason for suboptimal outcome in ADHD treatment, physicians should ensure adherence with therapy before adjusting dosage or switching medication.

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Attention-deficit/hyperactivity disorder (ADHD), a common yet most treatable neuropsychiatric disorder in children, affects approximately 5% to 10% of school-aged individuals in Western countries[1] and 7.5% in Taiwan.[2] Characterized developmentally by inattention, hyperactivity, and impulsivity, ADHD has been shown to not only result in impairment of academic and social functioning[3] but also to have an impact on family and society.[4] Patients with ADHD usually need to be treated with medication, mainly stimulants, for months to years.[5,6] Stimulants are the most widely used agents and are traditionally considered as the first-line treatment for ADHD.[4,5]

Despite the benefits of stimulant therapy for ADHD, poor adherence may lead to suboptimal symptom management and less-than-favorable outcomes in terms of psychosocial and academic functioning.[7] For example,

Charach et al.[8] have found that adherent patients showed greater improvement than nonadherent analogs, as reflected in teacher-reported symptoms after 5-year treatment with stimulants for ADHD.

Methylphenidate is the most commonly used and extensively studied stimulant.[4,5] For decades, the immediate-release (IR) formulation had been the only stimulant medication used for ADHD in Taiwan and China when osmotic release oral system (OROS) methylphenidate launched in October 2003 and 2005, respectively.[9,10] Given its relatively short half-life (3–4 hours), IR methylphenidate is usually administered 2 or 3 times a day to maintain therapeutic efficacy,[11] causing poor adherence because of forgetfulness, inconvenience, social stigmatization, privacy, and diversion.[4,6,11,12] More than half of parents interviewed suggested that taking medication at school embarrassed their child and reduced self-esteem.[6] Moreover, as forgetfulness is one of the core symptoms of ADHD, it is likely that, without adult supervision, the child may not reliably remember to take medication.

In some randomized clinical trials, OROS methylphenidate (once-daily extended release)[13] has been found to have an efficacy and safety profile comparable to[11,14] or better than IR methylphenidate (3 times daily),[15,16] particularly in terms of social functioning.[16] In addition, the efficacy and safety of OROS methylphenidate has been established in both adolescent[17] and adult populations,[18] as well as in longitudinal studies.[19]

Literature review reveals a stimulant-adherence range of 35% to 100%.[10] This substantial variability in adherence rate may have negative implications for management of the ADHD symptoms, as well as for the eventual psychosocial and academic outcomes.[20] The predictors of poor adherence to ADHD medication may include multiple daily dosing,[6,10,11] older age,[10,21] male gender,[22] lower IQ in children[22–24] and mothers,[25] more[24] or fewer[8,21] ADHD symptoms, oppositional defiance,[21] attention difficulties,[26] and lower socioeconomic status.[27] In addition, parental knowledge with respect to ADHD may also play a role in adherence to medication.[28,29] Tolerance to the stimulants also impacts patient compliance.[10,11] Hence, investigation is required to determine the potential predictors for, and impact of, poor adherence in ADHD treatment to maximize compliance and, thereby, obtain optimal treatment outcome.

Although previous studies of white subjects[8,21–26,29] and clinical trials[8,21–23,25,26,29] have shed some light on adherence to the stimulants, they are generally limited by small sample size and because the controlled environment characterizing the latter does not accurately model the diversity of the real world. Our previous investigation was the first to examine adherence to IR methylphenidate in ADHD patients using a large, non-Western sample of patients who were not the subjects of clinical trials but individuals recruited consecutively from psychiatric clinics.[10] However, there are other possible predictive factors of adherence that were not explored in our prior study or examined in existing research, with the former limited by sample composition, which consisted mostly of subjects at a medical center in Taipei who had not been assessed for ADHD symptoms.[10] Although the efficacy and safety of OROS methylphenidate has been established relative to IR methylphenidate in a randomized clinical trial using an ethnic Chinese population,[16] there has been no observational study comparing the 2 profiles between the OROS and IR formulations of methylphenidate within the same patients with ADHD in such an ethnically distinct population.

In view of this, a large clinical sample was employed in this multisite observation study, which employed more comprehensive measures of demographics, side effects, adherence, efficacy, ADHD, and oppositional symptoms compared to our prior investigation.[10] The aims of this study were (1) to obtain the current status of adherence to IR methylphenidate in a sample of Taiwanese patients with ADHD; (2) to identify the determinants of adherence to IR methylphenidate; (3) to examine the association between adherence to IR methylphenidate and behavioral symptoms; and (4) to compare adherence, efficacy, and side effect profile between the 2 methylphenidate variants intra-individually.

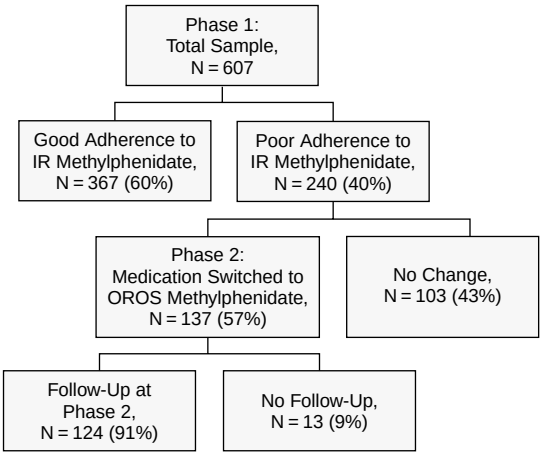
METHOD

Subjects and Procedures

This study consisted of 2 study phases involving 12 hospitals and 20 board-certificated child psychiatrists. It was designed to identify patients with ADHD who were currently being treated with IR methylphenidate but whose adherence was poor, and to compare the adherence, side effects, and efficacy after switching to other ADHD medications for 3 weeks more. This investigation was approved by the Joint Institute Review Board, Taiwan (JIRB: 06–056-P) and the institutional review boards of each study site (e.g., the unique protocol identification was 9461700338 for National Taiwan University Hospital). The ClinicalTrials.gov identifier of the Protocol Registration System was NCT00460720. Written informed consents were also obtained from participants and their parents prior to enrollment. The study began in April 2005 and was completed in February 2006.

Inclusion criteria were the following: age 5 to 16 years; clinical diagnosis of ADHD based on the relevant *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) diagnostic criteria, as determined by board-certificated child psychiatrists; treatment with IR methylphenidate for at least 3 of the preceding 6 months; IR methylphenidate treatment during the preceding month without severe adverse events or possible contraindications; and patient and parental consent.

Figure 1. Sample Distribution of Children With Attention-Deficit/Hyperactivity Disorder Meeting Inclusion Criteria



Abbreviations: IR = immediate-release, OROS = osmotic release oral system.

Exclusion criteria were any systematic disease or clinically significant gastrointestinal problem and comorbid psychiatric disorders, except for conduct disorder and oppositional defiant disorder.

In the first phase, patients with a clinical diagnosis of DSM-IV ADHD and their parents were interviewed by the investigators (board-certificated child psychiatrists) to obtain information with respect to demographics, family history of ADHD, and adherence, or reasons for nonadherence, to IR methylphenidate medication. The investigators completed the Clinical Global Impressions-ADHD-Symptom Severity (CGI-ADHD-S) scale[30] and determined if there had been any side effects during treatment. Meanwhile, parents/caregivers completed the Chinese version of the Swanson, Nolan, and Pelham, version IV (SNAP-IV) scale[31] at the clinic. Drug adherence was assessed by investigators based on the reports of patients and their parents. Patients who met the definition of poor adherence were either changed to other medication for ADHD or to psychosocial therapy only, or maintained on IR methylphenidate. Other medications included OROS methylphenidate, tricyclic antidepressants, bupropion, and clonidine. Patients whose medication was switched from IR methylphenidate to other drugs were enrolled into the second phase.

In the second phase, patients and their parents were interviewed to obtain information with respect to drug adherence, global ADHD severity, parent-child interaction, general classroom behaviors, overall academic performance, and medication side effects. Parents also completed the Chinese SNAP-IV at the clinic.

A total of 607 children (mean ± SD age = 9.5 ± 2.4 years) met the inclusion criteria and were recruited in the first phase (Figure 1). Of these, 240 patients (39.5%) were assigned to the poor adherence group based on the study definition, with 137 patients further switched to OROS methylphenidate based mainly on the decision of the investigators after mutual discussion with patients and their parents. The patients who took IR methylphenidate 5 mg once, twice, or thrice daily and IR methylphenidate 10 mg once, twice, or thrice daily were switched to OROS methylphenidate (18 mg) and OROS methylphenidate (36 mg) per day, respectively. After treatment for more than 3 weeks, 124 children (mean ± SD age = 10.9 ± 2.8 years) completed the second phase assessment, while 13 were lost to follow-up (9.5%).

Measures

Adherence. Subjective and objective assessment were used to determine whether the child was adherent to IR methylphenidate treatment. The subjective assessment was based on retrospective feedback in the form of yes/no responses from the patients themselves and their parents. The objective assessment of the daily occurrence and frequency of missed doses was based on a standard interview conducted by the investigators. A pilot validity study of self-reported missed doses was conducted using a sample of 26 patients observed over a 4-week treatment period. The Pearson correlation coefficients (γ) for the relationships between pill count and patient ($\gamma = 0.96$, $p < .0001$) and parent ($\gamma = 0.88$, $p < .0001$) reports were high. Poor adherence was defined as missing 1 or more doses on a school day on 2 or more days per week for 4 weeks.

Efficacy measures. The efficacy measures included the CGI-ADHD-S, which was evaluated by the investigators, and the Chinese SNAP-IV, as reported by the parents in the first and second study phases. The patients were also assessed by an investigator in the second phase for changes in parent-child interaction, general classroom behavior, and overall academic performance after switching medication.

Clinical Global Impressions-ADHD-Symptom Severity. The CGI-ADHD-S is a single item assessment of the global severity of ADHD symptoms in relation to the clinician's total experience with other ADHD patients.[30] Severity was rated on a 7-point scale with the extremes of 1 and 7 representing the ratings "normal, not at all ill" and "most extremely ill" respectively. The CGI-ADHD-S was evaluated in both study phases.

Chinese version of the Swanson, Nolan, and Pelham, version IV scale–parent form. The Chinese SNAP-IV is a 26-item instrument rating, which has frequently been used in studies related to ADHD, on a 4-point Likert scale where 0–3 represent the qualitative judgments "not at all," "just a little," "quite a bit," and "very much."[15,31] The SNAP-IV consists of inattention, hyperactivity-impulsivity, and oppositional subscales (items 1–9, 10–18, and 19–26, respectively). The normal and psychomet-

ric properties of the Chinese SNAP-IV have been established in Taiwanese child and adolescent populations.[32]

Definition of remission of ADHD symptoms. Three approaches were employed in this study to estimate the remission rate (not reaching the level of potential cases of ADHD) based on the Chinese SNAP-IV score.[33,34] In the first 2, the upper 5% of scores[33] and t score > 70 (2 standard deviations above the mean)[34] were used as the thresholds to define the presence of extreme inattention or hyperactivity-impulsivity. The t score was derived by multiplying the z score by 10 and adding 50, with a mean of 50 and a SD of 10 (t score = z score × 10 + 50). The third approach was based on the symptom-count criterion with respect to the full diagnostic DSM-IV criteria. Scores of 2 (quite a bit) or 3 (very much) on the SNAP-IV were coded as symptomatic of the presence of this behavior, with all others deemed to indicate its absence.[15,31] The inattention and hyperactivity-impulsivity syndromes were defined when at least 6 of the 9 DSM-IV items applicable to each were present. The 3 ADHD symptom subtypes were assigned based on the relevant DSM-IV diagnostic criteria for those diagnostic subtypes, with remission of symptoms defined where an individual no longer met any of the type-specific diagnostic criteria.

Safety measures. Safety measures assessed (yes/no response) by the investigators were decreased appetite, dizziness/headache, gastrointestinal (GI) disturbance, poor sleep quality, and other side effects.

Data Analysis

SAS 9.1 (SAS Institute Inc., Cary, N.C.) was used for the data analysis. In the first phase, mean (SD) score and frequency/percentages were used to describe continuous and categorical variables, respectively, with the logistic regression model and analysis of variance (ANOVA) applied for further respective comparisons. A multivariate logistical regression model was applied to identify the most predicted variables for poor drug adherence using backward model selection. The ANOVA was performed for comparison of the symptom severity as measured by the Chinese SNAP-IV and CGI-ADHD-S, with logistic regression performed for between-group (good and poor adherence) comparison of the rates of symptom remission.

A linear mixed model with both fixed and random effects was employed to test differences in the repeated measures of the Chinese SNAP-IV and CGI-ADHD-S in the first (treatment with IR methylphenidate) and second (treatment with OROS methylphenidate) phases, within the same subjects controlling for sex and age. The effect sizes (standardized difference between 2 means) were further computed using Cohen's d.[35]

Percentages of change status of parent-child interaction, general classroom behavior, and overall academic performance, together with the side effects of poor sleep quality, decreased appetite, dizziness/headache, and GI disturbance were presented to address the differences between the 2 methylphenidate treatments. The preselected α level was set at $p < .05$.

RESULTS

Sample Description

Of the 607 children recruited into the first phase, 504 (83.0%) were males, 543 (89.5%) had normal intelligence, and 149 (24.5%) had positive family history of ADHD, mostly among their siblings. The sample population was further categorized according to the combined, hyperactivity-impulsivity, or inattention ADHD subtype in 362 children (59.6%), 177 children (29.2%), and 68 children (11.2%), respectively. The mean age at onset was 6.6 years; 240 subjects (39.5%) and 367 subjects (60.5%) were assigned to the poor and good adherence groups, respectively (Table 1). The mean (SD) daily IR methylphenidate dosage was 18.0 (9.4) mg, with a mean medication duration of 16 weeks for the 607 subjects. More than half of the subjects (55.7%) were dosed twice daily. The most frequently reported side effect related to IR methylphenidate treatment was decreased appetite (21.1%, Table 1). The mean (SD) doses of IR methylphenidate and OROS methylphenidate were 20.2 (9.2) mg and 24.9 (8.8) mg, respectively, for the 124 subjects who had medication switched to OROS methylphenidate.

Reasons for Poor Adherence

The explanations for missing IR methylphenidate doses provided by the 240 patients and their parents can be categorized as follows: forgetting to take IR methylphenidate at school (67.5%), side effects (18.8%), refusal without any reason (17.5%), forgetting to bring medication to school (12.5%), safety concerns (12.5%), privacy issues (9.2%), lack of perceived effect (7.1%), bitter taste (4.2%), and teacher objection (2.9%).

Determinants for Adherence to IR Methylphenidate

Univariate analysis (Table 1) revealed that the correlates for poor adherence to IR methylphenidate were older age, later age at ADHD diagnosis, positive family history of ADHD (especially father), paternal education of college or higher, administration of methylphenidate twice or thrice daily, and higher mean dose. Correlates for good adherence were mental retardation and treatment at medical centers. The correlates for switching to OROS methylphenidate (N = 137) among poor adherents to IR methylphenidate (N = 240) were (1) treatment at national medical centers (odds ratio = 2.97, 95% confidence limits = 1.05, 8.44), (2) higher dose of methylphenidate ($F = 5.86$, df = 1,237; $p = .016$), (3) multi-dose IR methylphenidate administration (odds ratio = 3.05, 95% confidence limits = 1.34, 6.94), and (4) more severe inattention symptoms ($F = 4.89$, df = 1,238; $p = .028$).

Table 1. Sample Description and Determinants for Adherence to Immediate-Release Methylphenidate in Children with ADHD in Taiwan

Variable	Total Sample (N = 607)	Poor Adherence (N = 240)	Good Adherence (N = 367)	OR	F Value	df	95% CI	p Value
Male, N (%)	504 (83.0)	198 (82.5)	306 (83.4)	0.93			0.61 to 1.44	.747
Age, mean (SD), y	9.5 (2.4)	10.4 (2.6)	9.0 (2.2)		49.75	1,605		< .0001
Body mass index, mean (SD)	21.3 (62.8)	20.2 (26.6)	21.9 (76.9)		0.09	1,527		.760
ADHD history, N (%)				1.60			1.08 to 2.36	.018
Father	37 (6.1)	21 (8.8)	16 (4.4)	2.10			1.07 to 4.12	.030
Mother	17 (2.8)	5 (2.1)	12 (3.3)	0.63			0.22 to 1.81	.390
Siblings	69 (11.4)	33 (13.8)	36 (9.8)	1.47			0.89 to 2.43	.136
Other	26 (4.3)	11 (4.6)	15 (4.1)	1.13			0.51 to 2.50	.768
Parents' education level, college or higher, N (%)								
Father	255 (42.0)	120 (50.0)	135 (36.8)	1.72			1.24 to 2.39	.001
Mother	222 (36.6)	96 (40.0)	126 (34.3)	1.28			0.91 to 1.79	.157
DSM-IV ADHD subtype, N (%)								
Inattentive	177 (29.2)	74 (30.8)	103 (28.1)	1.72			0.95 to 3.15	.077
Combined	362 (59.6)	146 (60.8)	216 (58.8)	1.62			0.92 to 2.85	.085
Hyperactive	68 (11.2)	20 (8.3)	48 (13.1)	1.00			…	…
Methylphenidate dose, mean (SD), mg	18.0 (9.4)	20.2 (9.2)	16.6 (9.2)		22.85	1,595		< .0001
Treatment duration, mean (SD), wk	16.0 (17.9)	15.6 (18.5)	16.2 (17.5)		0.15	1,571		.697
Frequency of administration, N (%)								
Twice daily	308 (55.7)	110 (52.4)	198 (57.7)	1.49			0.98 to 2.26	.015
Thrice daily	83 (15.0)	56 (26.7)	27 (7.9)	5.56			3.13 to 9.89	< .0001
Only morning dose	162 (29.3)	44 (21.0)	118 (34.4)	1.00			…	…
Age at onset, mean (SD), y	6.6 (2.3)	7.4 (2.7)	6.0 (1.8)		48.08	1,565		< .0001
Site, N (%)								
Medical centers	477 (78.6)	147 (61.3)	330 (89.9)	0.18			0.12 to 0.27	< .0001
Other	130 (21.4)	93 (38.8)	37 (10.1)	1.00			…	…
Mental retardation (IQ < 70), N (%)	64 (10.5)	12 (5.0)	52 (14.2)	0.32			0.16 to 0.60	.0005
Side effects, N (%)	180 (29.7)	65 (27.1)	115 (31.3)	0.81			0.57 to 1.17	.263
Decreased appetite	128 (21.1)	47 (19.6)	81 (22.1)	0.86			0.57 to 1.28	.453
Dizziness/headache	21 (3.5)	7 (2.9)	14 (3.8)	0.76			0.30 to 1.91	.555
Gastrointestinal upset	36 (5.9)	12 (5.0)	24 (6.5)	0.75			0.37 to 1.53	.434
Poor sleep quality	37 (6.1)	13 (5.4)	24 (6.5)	0.82			0.41 to 1.64	.572
Other side effect	10 (1.7)	4 (1.7)	6 (1.6)	1.02			0.29 to 3.67	.971

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.
Symbol: … = not applicable.

Table 2. Final Model for Determinants of Poor Adherence to Immediate-Release Methylphenidate

Determinant	OR	95% CI	Wald χ^2	p Value
Older age	1.19	1.07 to 1.32	9.84	.002
Frequency of administration				
Twice daily vs once daily	1.73	1.00 to 2.98	3.88	.049
Thrice daily vs once daily	3.71	1.69 to 8.14	10.71	.001
Mental retardation (IQ < 70)	0.41	0.17 to 0.99	3.98	.046
Later age at onset	1.21	1.06 to 1.38	7.74	.005
Family history of ADHD	2.01	1.18 to 3.41	6.62	.010
Medical centers vs others	0.23	0.12 to 0.43	20.39	< .0001

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Table 2 summarizes the odds ratios and 95% confidence intervals for the first-phase variables that were significantly related to poor adherence to IR methylphenidate in the final model using backward elimination in model selection. The most predictive variables to poor adherence to IR methylphenidate were older age, increased frequency of drug administration, older age at ADHD diagnosis, and positive family history of ADHD. Mental retardation and treatment at medical centers were associated with lower risk of poor adherence.

Influence of Adherence to IR Methylphenidate on ADHD Symptom Severity

Our findings reveal that, compared to the good adherence group, the poor adherence group had significantly higher scores for inattention and oppositional symptoms, as measured by the SNAP-IV, and greater global severity of ADHD symptoms, as assessed by the investigator (Table 3).

Regarding symptom remission, we found that patients in the good adherence group were less likely than the poor adherents to meet the SNAP-IV symptom criteria (above the 95th percentile and t score > 70) and the DSM-IV criteria for ADHD (see Table 3). In addition, 45.8% of the poor adherents were rated by investigators as higher than 4 on the CGI-ADHD-S (i.e., moderately ill or worse) as compared to 31.9% of the good adherents.

Changes in Adherence, Efficacy, and Side Effects After Switching Medication

Of the 240 patients who had poor adherence to IR methylphenidate, 137 (57.1%) had their IR methylphenidate medication switched to OROS methylphenidate and

Table 3. Influence of Adherence to Immediate-Release Methylphenidate on Symptom Severity

Variable	Poor Adherence (N = 240), Mean ± SD	Good Adherence (N = 367), Mean ± SD	F (df = 1,605)	p Value
SNAP-IV dimensions t score				
Inattention	66.1 ± 12.1	63.4 ± 11.6	7.62	.006
Hyperactivity	65.5 ± 15.5	64.9 ± 13.2	0.22	.638
Oppositional symptoms	62.0 ± 13.3	59.4 ± 12.1	6.22	.013
CGI-ADHD-S score	3.3 ± 1.1	3.0 ± 1.1	10.66	.001
	N (%)	N (%)	OR (95% CI)	
Remission rate based on the SNAP-IV				
95% cutoff (N = 337)	117 (34.7)	220 (65.3)	1.57 (1.13 to 2.18)	.007
DSM-IV criteria (N = 334)	116 (34.7)	218 (65.3)	1.56 (1.13 to 2.17)	.008
t Score < 70 (N = 322)	116 (36.0)	206 (64.0)	1.37 (0.99 to 1.90)	.060
CGI-ADHD-S score < 4	130 (54.2)	250 (68.1)	1.81 (1.29 to 2.53)	.001

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CGI-ADHD-S = Clinical Global Impressions-ADHD-Symptom Severity; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; SNAP-IV = Swanson, Nolan, and Pelham, version IV scale.

Table 4. Symptom Severity Between Treatment With IR Methylphenidate and OROS Methylphenidate Within the Same Subjects

Measure	IR Methylphenidate (N = 124), Mean (SD)	OROS Methylphenidate (N = 111), Mean (SD)	F Statistics[a] F Value (df = 1,108)	p Value	Cohen's d
SNAP-IV dimensions t score					
Inattention	63.5 (11.6)	60.1 (11.1)	5.23	.024	0.28
Hyperactivity	64.6 (14.8)	60.3 (14.3)	5.81	.018	0.27
Oppositional symptoms	61.2 (13.2)	56.9 (12.9)	6.04	.016	0.36
CGI-ADHD-S score	3.6 (0.7)	2.8 (0.9)	53.60	< .0001	0.99

[a]Adjusted for sex and age.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CGI-ADHD-S = Clinical Global Impressions-ADHD-Symptom Severity; IR = immediate-release; OROS = osmotic release oral system; SNAP-IV = Swanson, Nolan, and Pelham, version IV scale.

Table 5. Descriptive Results of Adherence, Efficacy, and Side Effect After Changing From IR to OROS Methylphenidate

Variable	Presence of Side Effects, N (%) Phase 1, IR Methylphenidate (N = 607)	Phase 2, OROS Methylphenidate (N = 124)	Degree of Changes, N (%) Much Better	A Little Better	No Change	Become Worse
Side effect						
Decreased appetite	128 (21.1)	27 (21.8)	1 (2.7)	11 (29.7)	17 (46.0)	8 (21.6)
Dizziness/headache	21 (3.5)	6 (4.8)	2 (12.5)	4 (25.0)	8 (50.0)	2 (12.5)
Gastrointestinal upset	36 (5.9)	10 (8.1)	2 (11.1)	4 (22.2)	8 (44.5)	4 (22.2)
Poor sleep quality	37 (6.1)	8 (6.5)	3 (18.8)	3 (18.8)	5 (31.2)	5 (31.2)
Other	10 (1.7)	1 (0.8)	0 (0)	1 (20.0)	4 (80.0)	0 (0)
Change of adherence						
Patient	…	…	41 (34.2)	57 (47.5)	19 (15.8)	3 (2.5)
Parent/caregiver	…	…	48 (39.7)	55 (45.5)	16 (13.2)	2 (1.7)
Investigator	…	…	46 (39.0)	53 (44.9)	18 (15.3)	1 (0.9)
Changes of efficacy						
Parent-child interaction	…	…	22 (18.2)	64 (52.9)	33 (27.3)	2 (1.6)
Overall classroom behavior	…	…	25 (20.7)	66 (54.6)	26 (21.5)	4 (3.3)
Overall academic performance	…	…	19 (15.7)	56 (46.3)	46 (38.0)	0 (0)

Abbreviations: IR = immediate-release, OROS = osmotic release oral system.
Symbol: … = not applicable.

subsequently entered the second phase of the investigation. At the endpoint, 124 subjects (90.5%) had completed assessments of efficacy and safety on schedule (3–5 weeks after completion of the first phase). A linear mixed model was used for intra-individual comparison of symptom severity for the 2 studied treatments. Significant decreases were demonstrated in the 3 subscales of the Chinese SNAP-IV and in the CGI-ADHD-S after switching the medication to OROS methylphenidate (Table 4). The effect sizes for mean change on the Chinese SNAP-IV ranged from 0.27 to 0.36, and the effect size for mean change was 0.99 for the CGI-ADHD-S.

Table 5 summarizes the descriptive results of the changes in side effects, adherence, overall classroom behavior, academic performance, and parent-child interaction after treatment with OROS methylphenidate for more than 3 months as compared with IR methylphenidate. In general, side effect rates were similar for the 2 treatments, with decreased appetite the most prevalent of these for both groups (21.1% vs. 21.8% for IR vs. OROS methylphenidate, respectively). The extent of side effect change was equally distributed across the 3 response categories (no change, better, and worse).

In terms of treatment adherence, more than 80% of the children, as well as their parents and investigators, evaluated adherence to OROS methylphenidate as "a little better" or "much better" compared to previous IR methylphenidate. In addition, parent-child interaction, overall classroom behavior, and academic performance improved with OROS methylphenidate.

DISCUSSION

The current study, one of few to examine the adherence to medication for ADHD in a large clinical sample, has 3 main findings. First, increased age, multiple dose administration, later diagnosis and family history of ADHD, paternal education level of college or higher, and higher methylphenidate dose increased the likelihood of poor adherence; in contrast, mental retardation and treatment at medical centers decreased the likelihood of poor compliance. Second, poor adherence was associated with more severe ADHD-related symptoms. Third, poor adherents who were switched to OROS methylphenidate subsequently had better adherence, with efficacy improved in terms of not only the ADHD symptoms but also parent-child interaction, classroom behavior, and academic performance.

Despite interstudy differences with respect to the definitions and measures of adherence used and investigative duration, the adherence rate of 60.5% for our sample population is within the reported range of 35% to 100%.[8,10,21–23,25–27,29,36] Our figure may be an overestimation, however, because informed consent was only obtained from subjects who did not miss appointments. If this unreliability (around 10%–20% at child psychiatric clinics in Taiwan), which is one of the surrogates for poor adherence, is taken into consideration, the adherence rate would be under 60%.

Distribution of the reasons for missing doses is similar to that of a study conducted in 2003 in northern Taiwan.[10] The most frequent explanation for IR methylphenidate dosing failure is general forgetfulness, which includes not remembering to bring the medication to school and overlooking noon or afternoon doses. As in previous studies, this finding is understandable because forgetfulness is one of the core symptoms of ADHD,[6] and social stigmatization and lack of monitoring by school nurses or classroom teachers may exacerbate the status of poor adherence in Taiwan.[10] Our finding that the rate of teacher objection (3%) decreased as compared to that of our study (10%) in 2003 indicates increased school awareness with respect to medical treatment for ADHD in Taiwan.

The current investigation offers further evidence that increased age[10,21,37–39] and multi-dose administration[4,6,10–12] predict poor adherence. Older children, particularly adolescents, are more likely to miss medication because of concerns about social stigmatization, which may be heightened during this period of rapid development, and decreased parental involvement with drug therapy. In contrast, some researchers have found no association between age and adherence,[25] while still others suggest the inverse relationship, with younger children less likely to adhere.[22] Further, some researchers have indicated that adherence rates decrease as the dosing frequency and complexity increase.[4,6,10–12] Based on the above evidence, therefore, it appears reasonable to suggest that treatment with OROS methylphenidate or the use of a morning dose of IR methylphenidate would be superior to multi-administration of IR methylphenidate, owing to the simpler dosing schedule and parental monitoring of the morning medication.

As in some studies,[10,26,37] we did not demonstrate any sex difference in adherence status, in contrast to the poorer male adherence revealed in an earlier report.[22] Moreover, unlike others,[8,21] we were not able to show an inverse relationship between treatment duration and adherence; however, our failure to do so might be due to the relatively short term treatment period.

In contrast to some ADHD research that has shown the relationships between poor adherence and low child IQ[22–24] and low socioeconomic status,[27] or other work that has failed to reveal relationships between adherence and socioeconomic status[25,40] and parental education,[10] our findings demonstrate that, in terms of poor adherence, low IQ (< 70) and higher paternal education (college or above) decreases and increases the risks, respectively. One explanation for these findings is that more supervision is required from parents and teachers for children with mental retardation, thereby improving the adherence to medication. Although prediction of higher paternal education level from poor adherence was not included in the final multivariate logistical model, this possible relationship needs to be tested in future research.

In addition to the variables for adherence tested in previous studies, we also examined the effect of other factors such as ADHD subtypes and body mass index (BMI); however, no influence on adherence status was demonstrated. Surprisingly, our finding that family history of ADHD predicted poor adherence suggests decreased organization and monitoring of medication compliance in the context of familial ADHD traits. However, these 3

factors were largely or completely overlooked in previous studies, and further research would appear to be indicated to confirm the extent of their influence on adherence.

Our prior study has demonstrated that poor adherence is associated with maternal psychological distress, inappropriate parenting, less perceived family support, impaired parent-child interaction, and increased behavioral problems at home[10]; however, this earlier investigation did not assess the relationship between compliance and ADHD symptomatology, which was one of the goals of the present work. The effect of methylphenidate on reducing ADHD symptoms and improving school performance has been documented.[7,41] Our current findings demonstrate a relationship between poor adherence to IR methylphenidate in the preceding month and increased severity of current global ADHD symptoms and analogous signs related to inattention, hyperactivity-impulsivity, and opposition. However, we were not able to resolve the direction of adherence and severity of ADHD symptoms in this study because children with attention difficulties are more likely to miss doses,[26] while analogs with ADHD who are comorbid with oppositional symptoms are more likely to refuse medication.[21] On the other hand, the ADHD and oppositional defiance symptoms may be the result of suboptimal treatment outcome due to poor adherence.

Our finding that higher dosage and thrice daily administration of IR methylphenidate and more severe inattention symptoms predicted the switch to OROS methylphenidate among poor adherents to IR methylphenidate implies a relationship between this switch and symptom severity and/or adherence problems.[10] Furthermore, inattention, one of the core symptoms of ADHD strongly related to academic performance, is generally considered the main concern of Taiwanese parents.[42] Hence, parents of children with greater severity of inattention may be more likely to request a switch to OROS methylphenidate to improve their children's attention for better academic performance.

Our intra-individual findings comparing the IR and OROS methylphenidate forms in ADHD lend credibility to the notion that the side effect profiles are similar,[11,14,16] while the efficacy profiles are different.[15,16] Differences in adherence, duration of action, and methylphenidate formulation are possible explanations for the superiority of once daily OROS methylphenidate over IR methylphenidate (thrice daily) in terms of the overall reduction in ADHD symptoms and improvements in academic performance, overall classroom behavior, and the parent-child relationship. The present investigation confirms the findings of other studies,[11,13,16] which have also shown that OROS methylphenidate, developed to overcome adherence problems associated with IR methylphenidate, is associated with improved compliance relative to the latter. By contrast, however, other teams have shown that IR methylphenidate (3 times daily) has an efficacy equivalent to OROS methylphenidate where there is good compliance.[11,14] It appears reasonable to suggest, therefore, that the improved adherence to OROS methylphenidate contributes to the significant improvement seen in patients with ADHD after switching from the IR to the OROS variant. By contrast, however, other studies have found superior efficacy for OROS methylphenidate compared to IR methylphenidate (thrice daily) even with good compliance, and it has been proposed that this therapeutic benefit is derived from the difference between the relatively more constant methylphenidate levels delivered by the OROS formulation.[15,16] While, as yet, there is no definitive conclusion with respect to the efficacy between IR and OROS formulations, what is certain is that adherence plays a crucial role in the treatment of ADHD, with good compliance essential to obtain the maximum benefit from therapy, especially in a chronic condition such as ADHD.

Strengths

Relative to analogous investigations, the strengths of this study of methylphenidate adherence include: (1) the employment of the largest sample population of children and adolescents with ADHD; (2) the recruitment of subjects from a number of hospitals across Taiwan, and the study was not a relatively confined clinical trial; and (3) the comprehensiveness of the assessments for the status and determinants of adherence, as well as the side effect profiles, ADHD symptoms, and other efficacy measures. Further, the correlates for adherence were not only confined to those examined previously but also included some important variables not investigated before such as BMI, ADHD subtype, and family history of ADHD.

Limitations

Nonetheless, the results of this study must be interpreted in the context of several limitations: the lack of a baseline measure of ADHD symptoms prior to medication, reliance on child and parent reports with respect to adherence, no teacher assessment of efficacy, questionable external validity, and the lack of psychiatric interview to determine ADHD diagnosis. Without evaluation of baseline ADHD symptoms prior to treatment with medication, we were unable to determine whether more[24] or fewer[8,21] ADHD symptoms at baseline were associated with adherence to medication. Another limitation is that the investigator's judgment with respect to adherence was based on patient and parent reports of missed doses without pill count; therefore, overestimate of adherence is very likely. However, child and parental reports are considered the most feasible method of studying adherence to methylphenidate,[43] with our pilot study validating the accuracy of these reports from pill counts. Moreover, laboratory examination is more time and manpower consum-

ing and is not suitable for short half-life medication such as methylphenidate.[44] Lack of teacher reports as efficacy measures substantially reduces our ability to determine symptom severity and treatment efficacy in a school setting. Moreover, there was no structured psychiatric interview for each subject; instead, the diagnosis of ADHD and other psychiatric disorders was based on the clinical diagnosis of experienced board-certificated child psychiatrists with extensive experience conducting Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version interviews.[2] In addition, the diagnosis of ADHD was further validated by treatment with IR methylphenidate for at least 3 months. Finally, only half of the patients with poor adherence to IR methylphenidate were switched to OROS methylphenidate, restricting generalization of the results for comparative efficacy between the 2 forms of methylphenidate in ADHD patients with poor adherence. As methylphenidate is the only first-line medication in Taiwan, it is assumed that clinicians will prescribe OROS methylphenidate to patients who fail to adhere to IR methylphenidate (twice/thrice daily). However, Taiwan's National Health Insurance limits the right of clinicians to prescribe the newer variant for financial and policy reasons, meaning that some patients are kept on IR methylphenidate treatment despite compliance problems.

Clinical Implications

Using a large, nationwide sample of clinical subjects with ADHD in Taiwan, the current study provides evidence supporting several predictors for poor adherence, an association between more severe ADHD symptoms and poor adherence, and improved adherence and efficacy for OROS methylphenidate relative to IR methylphenidate. Our findings strongly emphasize the importance of adherence in pediatric populations with chronic disorders such as ADHD where long-term treatment is needed. If the desired outcome is not achieved, in addition to taking inadequate effectiveness or misdiagnosis into consideration, clinicians should assess drug adherence before altering dosage or changing medication. The potential reasons for poor adherence in ADHD should be identified to determine the optimal intervention, which may include switching to alternative medication such as OROS methylphenidate, dosage adjustment, and/or psychoeducation with respect to treatment options.

Drug names: bupropion (Wellbutrin and others), clonidine (Catapres, Duraclon, and others), methylphenidate (Ritalin, Concerta, and others).

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