Impact of Drug Adherence on Oppositional Defiant Disorder and Conduct Disorder Among Patients With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: Attention-deficit/hyperactivity disorder (ADHD) may be a predecessor of oppositional defiant disorder (ODD) and conduct disorder (CD), and medication is an effective treatment option for ADHD. This study aims to examine whether adherence to medication treatment is associated with developing ODD and CD among youths with ADHD.

Methods: A total of 33,835 youths (4 years ≤ age of diagnosis ≤ 18 years) with ADHD (*ICD-9-CM* code 314.X) undergoing medication treatment for at least 90 days were selected from Taiwan's National Health Insurance Research Database during the period of January 2000 through December 2009. Patients' medical records were monitored through December 31, 2011, or until they had a diagnosis of ODD or CD. We categorized participants as compliant or noncompliant on the basis of a medication possession ratio (MPR) of 50%.

Results: The patients with better drug adherence (MPR ≥ 50%) exhibited a significantly decreased probability of developing ODD (53% reduction, $P < .001$) or CD (58% reduction, $P < .001$) when compared to the patients with poor drug adherence (MPR < 50%). The results in our sensitivity analyses showed that good drug adherence consistently exerted protective effects on ODD or CD, irrespective of patients' characteristics. Moreover, the patients with the best drug adherence (MPR ≥ 75%) had the lowest risks of developing ODD or CD.

Conclusion: Among patients with ADHD undergoing drug therapy, a better drug adherence is associated with a lower likelihood of their developing ODD or CD in later life.

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Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder that affects about 5%–10% of all children and adolescents.[1] Patients with ADHD commonly develop comorbid disruptive behavior disorders such as oppositional defiant disorder (ODD) and conduct disorder (CD).[2,3] ODD is characterized by a frequent and persistent pattern of disobedient, negativistic, and defiant behavior toward authority figures and is commonly accompanied by irritable mood.[4,5] CD is characterized by an enduring pattern of aggression, bullying, stealing, and violations of social rules and the rights of others.[6–8] The symptoms of ADHD typically occur in early childhood and, in some cases, are regarded as a predecessor of ODD or CD.[9–14] These comorbidities aggravate severe functional impairment and psychosocial problems and increase the difficulty of treatment.[15,16] Therefore, adequate intervention strategies for preventing individuals with ADHD from developing a comorbidity of ODD or CD are important.[17]

Medication is an effective treatment option for ADHD, with stimulants and nonstimulants being the 2 main approved categories for the disorder.[18,19] In addition to its effect on ADHD core symptoms, medication treatment is beneficial for improving emotional dysregulation, which is a collective feature of ODD and CD.[20] However, medication adherence is approximately 50% in the general pediatric population,[21] which implies that achieving compliance with pediatric medication therapy is challenging.[22] Poor drug adherence is also a common problem among pharmacologically treated children with ADHD in the clinical setting.[23] One review article[24] showed that the rates of medication nonadherence range between 15% and 87% in patients with ADHD during a follow-up period of up to 9 years. More recent studies have demonstrated similar findings. A study conducted in Korea[25] indicated that 20%–57% of the patients showed adherence to stimulant treatment after 36 months. In a Turkish ADHD cohort, the persistence rate of drug therapy over a 12-month period was only 30.2%.[26] Moreover, a study in the United Kingdom[27] demonstrated that only 57% of children with ADHD received medication treatment longer than 6 months after initial prescription.

Clinical Points

- Medication is an effective treatment option for ADHD; however, whether drug compliance impacts the risk of developing oppositional defiant disorder and conduct disorder has yet to be definitively determined.
- This nationwide, population-based study found that ADHD patients with better drug adherence exhibited a decreased probability of developing oppositional defiant disorder or conduct disorder when compared with those with poor drug adherence.

Relative to the discontinuation rate, the medication possession ratio (MPR) is a generally acknowledged index for measuring drug adherence and is less likely influenced by the variety of treatment discontinuation definitions.[28,29] A systematic review indicates that the MPR is less than 0.7 among children with ADHD who are prescribed medications, for all age groups and medication classes, during a 12-month period.[30] Evidence has demonstrated that patients with ADHD undergoing drug therapy have persistently favorable clinical outcomes,[31] including a higher probability of achieving symptom remission,[32] and reduced risks of developing substance use disorders[33] or depressive disorders.[34] However, whether drug compliance influences the risk of developing ODD or CD among individuals with ADHD has yet to be definitively determined. To fill this research gap, this study aimed to analyze the probability of diagnoses with ODD or CD after medications prescribed for treating ADHD by comparing the patients with better drug adherence to those with poor drug adherence.

METHODS

Data Source

The protocol for this study conformed to the Helsinki Declaration and was approved by the Institutional Review Board (IRB) of Chang Gung Memorial Hospital. Patient records and information were anonymized and deidentified prior to analysis, and the need for written informed consent was waived by the IRB.

The database used in this study was that of ambulatory claims from the National Health Insurance Research Database of Taiwan (NHIRD-TW). Implemented in 1995, Taiwan's National Health Insurance (NHI) program is a compulsory universal health insurance program, and the NHI Bureau is the sole payer of health care services. The electronic claim forms include such information as the patient's sex, the medical institution visited, diagnostic codes, the date of any prescriptions given, the drugs prescribed, and any claimed medical expenses. The reliability of diagnostic codes in the NHIRD has been proved by a previous study.[35]

Study Population

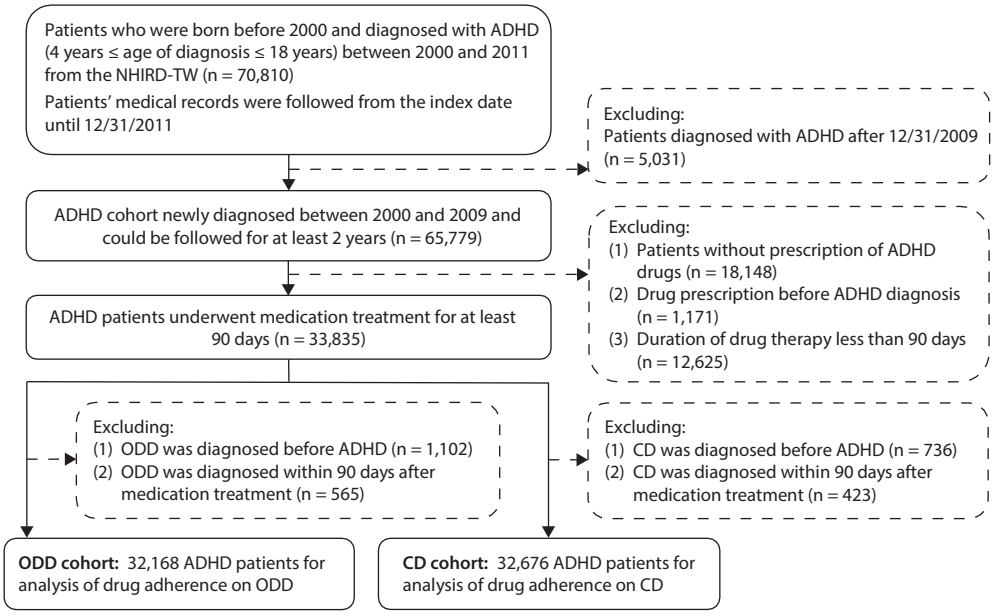
Figure 1 depicts the procedure employed to choose this study's population. The target population in this study includes patients with ADHD who received medication treatment for at least 90 days. An ADHD diagnosis was defined as at least 2 NHI claim records with any diagnosis codes per visit and the presence of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code of 314.X. ADHD subtypes included the inattentive type (314.00) and the predominantly hyperactive/impulsive or combined type (314.01, ADHD H/C type). This study considered all patients who were born before January 1, 2000, and were newly diagnosed with ADHD (4 years ≤ age of diagnosis ≤ 18 years) during the period of January 1, 2000, through December 31, 2011, in the entire NHIRD-TW (N = 70,810) database. To ensure the subjects had a follow-up time of 2 years or longer, we excluded patients who were diagnosed with ADHD after December 31, 2009 (n = 5,031). Patients' NHIRD-TW medical records were monitored through December 31, 2011. Subsequently, we excluded patients with no prescription of ADHD drugs (n = 18,148), those who had drug prescriptions prior to their ADHD diagnosis (n = 1,171), and those whose drug therapy lasted fewer than 90 days (n = 12,625).

Hence, there were 33,835 patients treated with medication for at least 90 days. We also excluded patients who had an ODD diagnosis prior to their ADHD diagnosis (n = 1,102) and whose ODD diagnosis was made within 90 days after medication treatment (n = 565). Finally, our ODD cohort for examining the impact of drug adherence on subsequent diagnosis of ODD consisted of 32,168 patients. We also excluded patients who had a CD diagnosis prior to their ADHD diagnosis (n = 736) and those whose CD diagnosis was made within 90 days after medication treatment (n = 423). Eventually, the CD cohort consisted of 32,676 patients for further analyses.

Definition of Drug Therapy and Adherence

ADHD medications were identified by using the Anatomic Therapeutic Chemical classification system.[36] Methylphenidate and atomoxetine are 2 medications approved by the NHI Bureau for the treatment of ADHD in Taiwan. Because atomoxetine is generally considered as a second-line pharmacotherapy for ADHD, duration and doses of methylphenidate and atomoxetine in use were composited as a whole. Drug adherence was defined using the MPR, which represents the ratio of total number of defined daily doses (DDD) the patients received to the total number of days of follow-up.[28,29] For example, if the amount of ADHD medication a patient received was for 6 months (183 DDD) during a 1-year period, the patient would be considered 50% compliant. If the calculated MPR for a patient was > 100%, the MPR was considered 100%. The total days of follow-up were defined as the time interval between the index date and the end point (ie, discontinuation of the patient's treatment with medication or December 31, 2011). Discontinuation of drug therapy was defined as when patients stop taking their medication for 180 days or longer.[30] We categorized participants into compliant patients and noncompliant patients based on an MPR of 50%. We further examined the results by adjusting

Figure 1. Flowchart of the Selection of Study Subjects



Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CD = conduct disorder, NHIRD-TW = National Health Insurance Research Database of Taiwan, ODD = oppositional defiant disorder.

the cutoff point upward (75%) and downward (25%) for the sensitivity analyses.

Definition of Outcome and Covariates

The study's outcome was defined as diagnosis of ODD (*ICD-9-CM* code 313.81) or CD (*ICD-9-CM* code 312.X) that followed an ADHD diagnosis and a medication prescription of at least 90 days. For the purposes of this study, the index date occurred when the ADHD medication was prescribed for the first time. Patients' NHIRD-TW medical records were monitored through December 31, 2011, or until they had a diagnosis of ODD or CD.

Other variables that were considered as covariates of developing ODD or CD were age at ADHD diagnosis, age when first medication was prescribed, sex, ADHD subtypes, and the time interval between ADHD diagnosis and the first medication prescription. We categorized patients' ages into the following 3 groups: (1) subjects younger than 6 years (preschoolers), (2) subjects between the ages of 6 and 12 years (school-age), and (3) subjects older than 12 years (adolescents). Time intervals between ADHD diagnosis and the first medication prescription were categorized into the following 3 groups: (1) < 90 days, (2) 90–365 days, and (3) > 365 days.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) Version 16.0 (SPSS Inc, Chicago, Illinois) was used to carry out all statistical analyses in this study. A 2-tailed value of $P < .05$ indicated statistical significance. A χ^2 test or t test was used to compare the characteristics between noncompliant patients (MPR < 50%) and compliant patients (MPR ≥ 50%).

Univariate logistic regression was used to examine the potential effect of each independent variable on the risk of developing ODD or CD among patients with ADHD. Moreover, multiple logistic regression models were applied to determine the impact of drug adherence on the diagnosis of ODD or CD, controlling for the effects of patients' demographic characteristics. In the logistic regression models, diagnosis of ODD or CD was set as a dependent variable (outcome), and drug adherence (MPR ≥ 50% vs MPR< 50%) was treated as an independent variable. The adjusted odds ratio (aOR) and 95% confidence interval (95% CI) were calculated.

Furthermore, we conducted a series of sensitivity analyses across various subgroups to test the robustness of our findings. First, we examined the effects of different thresholds of drug compliance (MPR at 25%, 50%, and 75%) on the risks of ODD and CD. Second, we stratified patients by their age, sex, ADHD subtype and the interval between ADHD diagnosis and first medication prescription. Third, we used the multiple logistic regression models to identify the effects of drug adherence (MPR ≥ 50% vs MPR < 50%) on the risk of developing ODD or CD in each stratification.

RESULTS

Table 1 lists the characteristics of the ODD cohort and the CD cohort. For the ODD cohort, 4.1% of patients had an ODD diagnosis during the follow-up period. The mean MPR was 41.1% in the ODD cohort. On the basis of the MPR scores, 67.6% and 32.4% of patients were categorized into a noncompliant group (MPR < 50%) and compliant group (MPR ≥ 50%), respectively. For the CD cohort, 4.0%

Table 1. Characteristics of Patients With Poor Drug Adherence (MPR < 50%) and Better Drug Adherence (MPR ≥ 50%) in the ODD and CD Cohorts

	ODD Cohort[a]				CD Cohort[a]			
Characteristic	Total (n = 32,168)	MPR < 50% (n = 21,760)	MPR ≥ 50% (n = 10,408)	Statistic*	Total (n = 32,676)	MPR < 50% (n = 21,958)	MPR ≥ 50% (n = 10,718)	Statistic*
Age at ADHD diagnosis, y	9.13 ± 2.87	8.79 ± 2.74	9.85 ± 2.99	30.726	9.15 ± 2.86	8.79 ± 2.73	9.88 ± 2.97	31.821
< 6 y	3,653 (11.4)	2,773 (12.7)	880 (8.5)		3,637 (11.1)	2,764 (12.6)	873 (8.1)	
6–12 y	22,609 (70.3)	15,805 (72.6)	6,804 (65.4)	678.301	23,000 (70.4)	15,984 (72.8)	7,016 (65.5)	723.168
> 12 y	5,906 (18.4)	3,182 (14.6)	2,724 (26.2)		6,039 (18.5)	3,210 (14.6)	2,829 (26.4)	
Sex				31.011				33.359
Female	5,576 (17.3)	3,595 (16.5)	1,981 (19.0)		5,701 (17.4)	3,645 (16.6)	2,056 (19.2)	
Male	26,592 (82.7)	18,165 (83.5)	8,427 (81.0)		26,975 (82.6)	18,313 (83.4)	8,662 (80.8)	
ADHD subtypes				28.992				33.370
Inattentive type (314.00)	15,304 (47.6)	10,578 (48.6)	4,726 (45.4)		15,337 (46.9)	10,551 (48.1)	4,786 (44.7)	
H/C type (314.01)	16,864 (52.4)	11,182 (51.4)	5,682 (54.6)		17,339 (53.1)	11,407 (51.9)	5,932 (55.3)	
Age at first prescription, y	9.75 ± 2.75	9.36 ± 2.64	10.57 ± 2.80	36.844	9.77 ± 2.74	9.37 ± 2.63	10.59 ± 2.77	38.023
< 6 y	1,285 (4.0)	10,59 (4.9)	226 (2.2)		1,266 (3.9)	1,049 (4.8)	217 (2.0)	
6–12 y	23,651 (73.5)	16,842 (77.4)	6,809 (65.4)	936.690	24,049 (73.6)	17,025 (77.5)	7,024 (65.5)	977.593
> 12 y	7,232 (22.5)	3,859 (17.7)	3,373 (32.4)		7,361 (22.5)	3,884 (17.7)	3,477 (32.4)	
Interval between ADHD diagnosis and medication, mo	7.59 ± 17.17	7.03 ± 15.58	8.76 ± 20.02	7.733	7.50 ± 17.08	6.96 ± 15.53	8.61 ± 19.82	7.555
< 3 mo	23,622 (73.4)	15,867 (72.9)	7,755 (74.5)		24,125 (73.8)	16,099 (73.3)	8,026 (74.9)	
3–12 mo	2,969 (9.2)	2,177 (10.0)	792 (7.6)	48.807	2,966 (9.1)	2,154 (9.8)	812 (7.6)	43.856
> 12 mo	5,577 (17.3)	3,716 (17.1)	1,861 (17.9)		5,585 (17.1)	3,705 (16.9)	1,880 (17.5)	
Diagnosed with ODD	1,329 (4.1)	1,093 (5.0)	236 (2.3)	134.966	…	…	…	…
Age at diagnosis, y	12.21 ± 2.45	12.43 ± 2.40	11.21 ± 2.48	7.033	…	…	…	…
Diagnosed with CD	…	…	…	…	1,308 (4.0)	1,087 (5.0)	221 (2.1)	156.372
Age at diagnosis, y	…	…	…	…	12.78 ± 3.04	12.96 ± 3.01	11.88 ± 3.02	4.844

[a]Data are expressed by n (%) or mean ± SD; statistical values were obtained using Pearson χ^2 or *t* using an independent *t* test.
*$P < .001$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CD = conduct disorder, H/C type = hyperactive/impulsive or combined type, MPR = medication possession ratio, ODD = oppositional defiant disorder. Symbol: … = not applicable.

Table 2. Logistic Regression Models for the Factors Associated With Diagnosis of ODD or CD Among Patients With ADHD

	ODD Cohort				CD Cohort			
Variable	OR (95% CI)	*P* Value	aOR (95% CI)	*P* Value	OR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
Age at ADHD diagnosis								
< 6 y	1		1		1		1	
6–12 y	0.78 (0.67–0.92)	.002	0.82 (0.69–0.97)	.019	0.83 (0.71–0.98)	.031	0.80 (0.67–0.96)	.018
> 12 y	0.40 (0.32–0.50)	< .001	0.49 (0.37–0.63)	< .001	0.72 (0.58–0.88)	.001	0.77 (0.61–0.96)	.023
Sex								
Female	1		1		1		1	
Male	1.75 (1.47–2.08)	< .001	1.68 (1.41–2.01)	< .001	1.38 (1.17–1.62)	< .001	1.35 (1.15–1.59)	< .001
ADHD subtypes								
Inattentive type (314.00)	1		1		1		1	
H/C type (314.01)	1.02 (0.91–1.14)	.767	1.00 (0.90–1.12)	.982	0.92 (0.83–1.03)	.156	0.92 (0.82–1.03)	.131
Interval between ADHD diagnosis and medication								
< 3 mo	1		1		1		1	
3–12 mo	1.31 (1.10–1.57)	.002	1.17 (0.98–1.40)	.092	1.05 (0.87–1.27)	.614	0.97 (0.80–1.17)	.723
> 12 mo	1.16 (1.01–1.34)	.041	0.99 (0.84–1.16)	.871	0.90 (0.77–1.05)	.167	0.81 (0.68–0.96)	.015
Drug adherence								
MPR < 50%	1		1		1		1	
MPR ≥ 50%	0.44 (0.38–0.51)	< .001	0.47 (0.41–0.55)	< .001	0.40 (0.35–0.47)	< .001	0.42 (0.36–0.48)	< .001

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, aOR = adjusted odds ratio, CD = conduct disorder, CI = confidence interval, H/C type = hyperactive/impulsive or combined type, MPR = medication possession ratio, ODD = oppositional defiant disorder, OR = odds ratio.

of patients had a CD diagnosis during the follow-up period, and the mean MPR was 41.5% (67.2% were noncompliant and 32.8% were compliant).

In comparison with the noncompliant patients in the ODD cohort (Table 1), the compliant patients were older (mean age at ADHD diagnosis: 9.85 ± 2.99 years), contained a higher proportion of female subjects (19.0%) and ADHD H/C type (54.6%), were prescribed an ADHD medication at an older age (10.57 ± 2.80 years), had a longer interval between ADHD diagnosis and first prescription (8.76 ± 20.02 months), and were less likely to have a diagnosis of ODD (2.3%). For the CD cohort, the comparisons between the noncompliant patients and the compliant patients exhibited similar trends as those in the ODD cohort.

Table 2 shows the results of the logistic regression models, which demonstrate the factors associated with risks of developing ODD or CD. We found that the risks of ODD and CD among compliant patients were 53% (aOR = 0.47; 95%

Table 3. Sensitivity Analyses of the Impact of Drug Adherence on the Diagnosis of ODD or CD Among Patients With ADHD[a]

	ODD Cohort		CD Cohort	
Variable	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
Drug adherence threshold				
MPR < 25%	1		1	
MPR 25%–49%	0.36 (0.31–0.41)	<.001	0.38 (0.33–0.43)	<.001
MPR 50%–74%	0.37 (0.32–0.44)	<.001	0.32 (0.27–0.38)	<.001
MPR ≥ 75%	0.19 (0.14–0.25)	<.001	0.20 (0.15–0.26)	<.001
Age at ADHD diagnosis[b]				
< 6 y	0.48 (0.32–0.72)	<.001	0.50 (0.32–0.79)	.003
6–12 y	0.49 (0.41–0.58)	<.001	0.47 (0.40–0.56)	<.001
> 12 y	0.40 (0.27–0.58)	<.001	0.25 (0.17–0.35)	<.001
Sex[b]				
Female	0.41 (0.26–0.62)	<.001	0.29 (0.19–0.44)	<.001
Male	0.48 (0.42–0.56)	<.001	0.44 (0.38–0.51)	<.001
ADHD subtypes[b]				
Inattentive type (314.00)	0.44 (0.35–0.55)	<.001	0.42 (0.34–0.53)	<.001
H/C type (314.01)	0.50 (0.42–0.61)	<.001	0.41 (0.34–0.50)	<.001
Interval between ADHD diagnosis and medication[b]				
< 3 mo	0.48 (0.41–0.57)	<.001	0.39 (0.33–0.46)	<.001
3–12 mo	0.43 (0.27–0.69)	.001	0.52 (0.32–0.84)	.008
> 12 mo	0.46 (0.33–0.63)	<.001	0.51 (0.36–0.71)	<.001

[a]Adjusted for all variables in Table 2.
[b]The effect of better drug adherence (MPR ≥ 50%) vs poor adherence (MPR < 50%) in each stratification.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, aOR = adjusted odds ratio, CD = conduct disorder, CI = confidence interval, H/C type = hyperactive/impulsive or combined type, MPR = medication possession ratio, ODD = oppositional defiant disorder.

CI, 0.41–0.55) and 58% (aOR = 0.42; 95% CI, 0.36–0.48) lower, respectively, than those of their noncompliant counterparts. In addition, female sex and ADHD diagnosis at an older age were associated with a lower risk of developing ODD. Furthermore, the following subjects had a lower risk of developing CD: female subjects, those with ADHD diagnosed at an older age, and those with an interval between ADHD diagnosis and first prescription of > 365 days.

Table 3 shows the sensitivity analyses for drug adherence on the risk of developing ODD or CD. We found that drug compliance exhibited dose-response effects of developing ODD or CD. The risks of ODD and CD among patients who had the best drug compliance (MPR ≥ 75%) were 81% (aOR = 0.19; 95% CI, 0.14–0.25) and 80% (aOR = 0.20; 95% CI, 0.15–0.26) lower than those among patients who had the worst drug compliance (MPR < 25%), respectively. Moreover, drug adherence (MPR ≥ 50% vs MPR < 50%) consistently exerted protective effects on ODD or CD in each stratification.

DISCUSSION

The main finding in this study is that, among patients with ADHD undergoing drug therapy, better drug adherence is associated with a lower likelihood of later developing ODD or CD. Some possible explanations may be related to this phenomenon. First, improving drug adherence may be beneficial for preventing the occurrence of ODD or CD in patients with ADHD. The pathophysiology of ODD or CD has been associated with neurobiological factors and negative environmental events.[13,14] Medication is an effective treatment option for ADHD,[18,19] and persistence of drug therapy for ADHD is linked to better outcomes.[31] Regular medication treatment for ADHD may improve patients' academic performance, family function, and peer relationships and reduce the likelihood of difficult life events.[37] Therefore, patients with better drug compliance may benefit more from medication treatment and have reduced risks of ODD or CD. Second, many factors potentially contribute to both drug compliance and diagnosis of ODD or CD, including treatment responses, adverse effects to treatment, patients' temperaments or personality traits, family function, parenting skills, and socioeconomic status.[38] Therefore, the correlation of good drug compliance and reduced rates of ODD or CD should be controlled for the above factors. Nonetheless, such factors have not been identified in the claims data.

We found the mean MPR was approximately 40% in our study population, which is generally compatible with previous international studies.[23,24,30] This finding implies that medication nonadherence (eg, drug holiday or temporary discontinuation and irregular use of medication) is common in realistic settings for treating ADHD. However, the current study recruited only patients with ADHD undergoing drug therapy for longer than 90 days. In addition, individuals in our cohort were observed within a wide age range of 4 to 18 years, but not within a fixed time period. Moreover, we found that patients' characteristics were significantly associated with MPR (Table 1). Previous studies[23,24] have also suggested that various factors potentially influence drug compliance in patients with ADHD, including patients' age, ethnicity, family structure, and neuropsychiatric comorbidities and drug formulations in use. It is noteworthy that most of the previous studies used premature discontinuation, not MPR, as an indicator of nonadherence to medication. Therefore, we should be cautious of comparing the drug adherence and its associated factors in the current study with those reported in previous investigations.

The diagnostic rates of ODD and CD were only 4.1% and 4.0%, respectively, in our study population. These comorbid rates were much lower than those reported in systematic review articles.[5–7] The low comorbid rates in our cohort may be partly attributed to the case-recruitment procedure. In this study, patients whose ODD or CD diagnosis was made before ADHD diagnosis or occurred within 90 days of first prescription were considered as having no relationship with medication treatment. Hence, we excluded a large number of patients who had comorbidity of ODD (n = 1,667) or CD (n = 1,159), and this led to a low comorbid rate. A 3-year panel study in Taiwan[39] revealed that the prevalence rates of ODD and CD among general adolescent population were 1.3%–2.8% and 2.5%–2.9%, respectively. By contrast, the estimated lifetime prevalence of ODD and CD in the US general population is 10.2% and 9.5%.[40,41] It is likely that disruptive behavior disorders are less prevalent

in Taiwan compared to Western countries. However, we previously found that around 11% of youths with ADHD in the same nationwide dataset had comorbid ODD or CD,[34,42] but the rate is still lower than the reports using structural interviews in Taiwan (69% of ADHD comorbid with ODD and 33% of ADHD comorbid with CD).[43,44] On the other hand, the prevalence rates of ODD and CD in youths with ADHD are around 60% and 15% in the United States, respectively.[5–7] Therefore, the findings in our study indicate that ODD and CD may be still underdiagnosed among the ADHD population in Taiwan, and we suggest that clinicians increase their awareness of ODD and CD in clinical settings.

Some methodological issues warrant concern. First, the target population in this study was patients with ADHD who received medication treatment. In real-world nonrandomized conditions, patients with ADHD who receive drug therapy may actually experience greater symptom severity and functional impairments than patients who have never been exposed to medication.[38] These manifestations were not easily identified from the claims data. Therefore, we did not recruit patients who never received drug therapy for comparison. Future longitudinal study with assessment of severity of ADHD (eg, symptom counts, severity ratings, or scores of functional impairments) would help to elucidate the role of severity of ADHD in development of ODD or CD. Second, the follow-up period was not analyzed for the purpose of examining adherence. The main reason for this is that patients who underwent longer medication treatment before ODD or CD diagnosis naturally had a lower hazard ratio of ODD or CD occurrence than those who underwent shorter treatments. Therefore, we used a logistic regression model, not a Cox regression model, to avoid the survival bias in the study analyses.[45] Third, because drug switching could be complex in real-world clinical settings, duration and doses of medications for treating ADHD were composited. We were unable to determine whether stimulants (eg, methylphenidate) or nonstimulants (eg, atomoxetine) exerted differential effects on subsequent ODD or CD.

This study has a number of limitations. First, we used reimbursement data, so the diagnoses of ADHD, ODD, and CD were not validated using structural diagnostic instruments and instead were identified solely on the basis of *ICD* codes, which could have been improperly classified. Hence, some patients may already have had a tendency toward ODD or CD at the initial visit with clinicians, but the clinicians missed the diagnosis. Second, several predictors (eg, patients' emotional regulation, family function, socioeconomic status, and frequency of outpatient visits or psychosocial intervention) have been associated with the risk of developing ODD or CD among youths with ADHD.[13,14] But the claims data retrieved for this study did not include this information or other potential mediating factors. Third, ODD and CD could be a continuity and may appear in patients with ADHD in sequence. However, the interrelationship between ODD and CD was not analyzed in this study. Finally, significant differences were found regarding various demographic characteristics within the compliant and the noncompliant groups. We did not apply a propensity score matching strategy; instead, we used stratification analyses to clarify the influence of drug adherence on patients with ADHD.

In conclusion, this study finds that among patients with ADHD receiving medication treatment, those with better drug adherence had a decreased risk of developing ODD or CD in comparison with their counterparts with worse drug adherence. This indicates that improving drug adherence may be beneficial for preventing the occurrence of ODD or CD in patients with ADHD. However, further investigation of the causal relationships between ADHD diagnoses in childhood, persistence of medication treatment, and the onset of ODD or CD would benefit from a longitudinal study containing comprehensive assessments of potential confounding factors.

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