The Effect of Personality Disorder Symptoms on Response to Treatment With Methylphenidate Transdermal System in Adults With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: This trial was designed to prospectively explore the relationship among personality disorder (PD) symptoms, attention-deficit/hyperactivity disorder (ADHD), and treatment response in a randomized, double-blind, crossover clinical trial of methylphenidate transdermal system (MTS) and to confirm results of a prior exploratory study.

Method: 67 adults who met the Utah and/or *DSM-IV-TR* criteria for ADHD were recruited with no attempt to include or exclude patients with PD. Responders were defined by a 50% improvement on the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), the primary outcome measure. Personality disorder was diagnosed by the clinicians using the Structured Clinical Interview for *DSM-IV-TR* Axis II Personality Disorders Questionnaire, several self-report scales, and clinical observations. Subjects were categorized as: no PD (PD-negative), 1 PD (PD-positive), and 2 or more PDs (PD-plus). The study was conducted from February 2007 to December 2009 at the Mood Disorders Clinic at the University of Utah School of Medicine, Salt Lake City.

Results: 37% (n = 25) were PD-positive, and another 27% (n = 18) were PD-plus. In those with a PD, 65% (n = 28) had a cluster C diagnosis, 44% (n = 19) cluster B, and 5% (n = 12) cluster A. PD-plus subjects had significantly higher levels of oppositional defiant disorder (ODD) symptoms ($P = .007$) and emotional dysregulation ($P = .004$). 71% (15/21) of the PD-positive and PD-negative subjects were responders in the MTS arm ($P < .001$) as opposed to 38% (6/16) of the PD-plus subjects ($P = .24$). Conversely, the interaction between treatment (placebo versus MTS) and the 3 PD groups was not statistically significant ($P = .46$) when the total WRAADDS was used as the outcome measure.

Conclusions: Personality disorder status was associated with more complex ADHD, especially high levels of emotional dysregulation and ODD symptoms. There was a significant treatment effect for PD-positive and PD-negative, but not PD-plus subjects.

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Childhood attention-deficit/hyperactivity disorder (ADHD) frequently occurs with an array of related disorders, particularly oppositional defiant disorder (ODD), conduct disorder (CD), learning disabilities, and anxiety disorders.[1] In adulthood, ADHD has been associated with substance abuse,[2] generalized anxiety disorder, obsessive-compulsive disorder, major depression, dysthymia, and bipolar disorder.[3,4] Historically, 2 of the disorders most commonly associated with ADHD have been CD in childhood and antisocial personality disorder (PD) in adults.[5–10] There is now an expanding literature connecting ADHD with a wide range of personality traits,[11–13] cluster B PDs,[14–17] and other PDs.[6,18–23]

Two complications undermine understanding the relationship between PD and ADHD. First, the symptoms of ADHD overlap with the symptoms of several PDs.[24] Second, there is limited agreement between physician assessment, self-report scales, and interview approaches[25–30] in diagnosing PD.

In a previous clinical trial using osmotic-release oral system (OROS) methylphenidate to treat adult ADHD, we carefully assessed the relationship between PD and ADHD[31] and found that 45% of the patient sample had at least 1 PD. Among patients with a PD, 62% had a cluster C diagnosis and 38% a cluster B diagnosis. The association between ADHD and PD was mediated primarily via the ADHD dimensions of emotional dysregulation and ODD, rather than attention + disorganization and hyperactivity + impulsivity.[32] Finally, PD subjects with 2 or more PDs exhibited a poor response to treatment with OROS methylphenidate, whereas patients with 1 or no PD responded positively to treatment.[33]

Since the publication of our 2007 study,[40] there have been several studies that have confirmed that PD can be diagnosed in many adult patients with ADHD.[22,23,34,35] Also, in findings similar to those in our study, Jacob et al[34] confirmed that many ADHD patients meet the criteria for more than 1 PD. Conversely, Jacob et al did not explore the consequences of an ADHD patient meeting criteria for multiple PDs.

We designed this second trial of a methylphenidate-based product (methylphenidate transdermal system [MTS]) to prospectively confirm the results from our prior trial using OROS methylphenidate. Subjects were carefully assessed for PD during a baseline screening phase and throughout their study participation. However, admission into the trial was not influenced by the presence or absence of PD.

The questions addressed by this confirmatory study were

(1) Could we confirm the pattern of PD reported in our previous publication, particularly the high level of cluster C diagnoses and incidence of patients with more than 1 PD?
(2) Were there clinically significant differences in adults with ADHD based on the presence of PD?
(3) Would there be a significant relationship between PD subgroup and response to treatment with methylphenidate?

Clinical Points

- Many adults with attention-deficit/hyperactivity disorder (ADHD) exhibit evidence of a personality disorder (PD).
- In this study, cluster C PDs were most common.
- This study of methylphenidate transdermal system in adults showed that subjects having 2 or more PDs were less likely to respond to ADHD treatment than those with no or 1 PD.

(4) Would either of 2 self-report personality measures (Wisconsin Personality Inventory-IV [WISPI-IV] and the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders Questionnaire [SCID-II]) successfully identify patients unlikely to show a treatment effect?

METHOD

The University of Utah Institutional Review Board approved the study, and it was conducted in accordance with the Declaration of Helsinki 1975. The trial was registered at ClinicalTrials.gov (identifier: NCT00506285). Subjects were recruited from the community, our outpatient clinic, referrals, press releases, and a limited amount of paid advertising. This was a placebo-controlled, flexible-dose trial of MTS consisting of a screening phase and a double-blind crossover phase with two 4-week arms.

Subjects were seen for an initial screening visit and 1 or 2 interim visits prior to a baseline visit at the start of the double-blind crossover phase. During the double-blind phase, subjects were seen weekly. If there were problems such as scheduling or assessment uncertainties, an additional week of treatment was allowed. Treatment response was assessed weekly. Although dosing levels were flexible, a stable dose was generally obtained within 2 weeks and held constant during the last 2 weeks of each double-blind arm. The study was conducted from February 2007 to December 2009 at the Mood Disorders Clinic at the University of Utah School of Medicine, Salt Lake City.

Subjects

Subjects were required to meet *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) criteria for current ADHD and/or the Utah Criteria[37] for ADHD. Subjects were between 18 and 65 years of age. Subjects with major depressive disorder, bipolar disorder, and schizophrenia were excluded, as were those with seizure disorders, hyperthyroidism, or hypothyroidism. A more complete description of the subjects has been previously published.[36]

Measures

Four clinical measures were used to assess the efficacy of MTS. All scales were administered by one of the study psychiatrists. Scale administration was discussed in weekly staff meetings. The ratings were reviewed, and periodically patients were interviewed by the senior author (F.W.R.).

- The Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS),[37] the primary outcome measure, is a clinician-rated scale assessing the 7 symptom areas of the Utah Criteria: attentional difficulties, hyperactivity/restlessness, temper, affective lability, emotional overreactivity, disorganization, and impulsivity. This scale was administered at each study visit. It was modified to assess the presence of ODD symptoms by attaching 9 investigator-rated items (Inv-ODD) at the end of the primary scale. These 9 items closely follow the childhood ODD items as defined by the *DSM-IV-TR* and were scored 0 (none, not present) to 2 (clearly present or often true).
- Conners Adult ADHD Rating Scales (CAARS)[38] is an investigator-rated scale consisting primarily of the *DSM-IV* ADHD symptoms. It was administered at baseline and the end of each treatment phase.
- The Clinical Global Impressions-Improvement scale (CGI-I)[39] is an investigator-rated scale assessing the overall improvement of the ADHD symptoms.
- The Self-Report Wender-Reimherr Adult Attention Deficit Disorder Scale (SR-WRAADDS)[40] is a self-report scale designed to address the 7 items of the Utah Criteria as well as ODD, social adjustment, and academic problems. (We are preparing a publication on the psychometric data on this scale.) Adult ODD was defined using previously developed criteria of at least moderate impairment in 4 of the items on the ODD section of the scale.[36]

Evaluation of PDs was conducted in a manner similar to our prior study using the following scales[31]:

- The SCID-II[41] is an interview-based assessment system for PD based on *DSM-IV* criteria using a 2-step system. The patient completes a screening questionnaire, and then a follow-up interview is conducted checking on areas that the patient has rated above a threshold level.
- The WISPI-IV is a self-administered scale consisting of 214 items. It attempts to present the *DSM-IV* PD criteria from an interpersonal perspective.[42,43]
- The Iowa Personality Disorder Screen[44] is an 11-item clinician-administered scale.

During the screening phase, subjects completed the SCID-II screening questionnaire, and the SCID-II interview was administered by an experienced psychiatrist. Subjects also completed the WISPI-IV. The treating psychiatrists recorded their Axis II diagnostic impressions using the Iowa Personality Disorder Screen at baseline and at the end of each double-blind arm. The intent behind the use of the Iowa Screen was to maintain awareness of the patient's personality characteristics throughout the course of the study. At the

Table 1. Baseline Measures as a Function of Personality Disorder Categories[a]

Variable	PD-negative	PD-positive	PD-plus	*P* Value
N	24	25	18	
Age, y	32.0 ± 11.0	37.2 ± 11.6	37.9 ± 13.0	NS
Male (n = 48), n (%)	17 (35)	19 (40)	12 (25)	NS
Female (n = 19), n (%)	7 (37)	6 (32)	6 (32)	NS
Adult ODD, n (%)	10 (42)	9 (36)	9 (50)	NS
Childhood ODD, either test, n (%)	15 (63)	13 (51)	10 (56)	NS
Childhood CD, either test, n (%)	12 (50)	10 (42)	11 (61)	NS
Emotional dysregulation, n (%)	10 (42)	18 (72)	17 (94)	.001
WRAADDS	19.4 ± 4.2	21.7 ± 4.2	22.9 ± 3.5	.02
Attention + disorganization	7.0 ± 0.9	7.1 ± 1.3	7.1 ± 1.5	NS
Hyperactivity + impulsivity	5.6 ± 1.6	6.0 ± 1.7	6.2 ± 1.0	NS
Emotional dysregulation	6.9 ± 2.7	8.6 ± 2.7	9.6 ± 2.5	.004
Inv-ODD	7.2 ± 4.4	8.5 ± 3.9	11.5 ± 4.5	.007
CAARS	51.7 ± 17.7	55.3 ± 14.7	56.5 ± 13.0	NS
WISPI-IV *z* scores	−0.7 ± 0.5	−0.1 ± 0.7	0.9 ± 1.0	.001
SCID-II items endorsed, no.	28.2 ± 15.0	37.9 ± 11.9	54.8 ± 14.6	.001
Substance abuse measures				
Past alcohol abuse, %[b]	54	48	71	NS
Drug abuse history, %[b]	25	13	29	NS
Self-Report WRAADDS total ADHD	2.3 ± 0.7	2.7 ± 0.8	2.7 ± 0.7	.12
Attention + disorganization	2.8 ± 0.8	3.0 ± 0.7	3.0 ± 1.0	NS
Hyperactivity + impulsivity	2.4 ± 1.0	2.5 ± 0.9	2.4 ± 0.8	NS
Emotional dysregulation	2.0 ± 0.9	2.6 ± 1.0	2.7 ± 0.9	.02
ODD	1.5 ± 0.8	1.7 ± 0.6	2.1 ± 0.8	.04
Academic	2.0 ± 1.3	2.3 ± 1.2	2.0 ± 1.2	NS
Social	1.5 ± 0.8	2.0 ± 0.6	1.8 ± 1.1	.14
Disruptive Behavior Disorders Rating Scale (parent-rated)				
ADHD total	35.0 ± 11.3	30.7 ± 12.4	28.0 ± 14.3	NS
ODD items endorsed, no.	4.5 ± 3.0	3.0 ± 2.8	3.6 ± 3.1	NS
CD items endorsed, no.	2.1 ± 2.3	1.5 ± 2.3	2.8 ± 2.4	NS
Childhood Symptoms Scale (patient-rated)				
ADHD total	32.2 ± 10.3	33.9 ± 8.6	35.1 ± 12.7	NS
ODD items endorsed, no.	3.4 ± 2.6	3.1 ± 2.6	4.2 ± 2.7	NS
CD items endorsed, no.	2.4 ± 2.4	2.3 ± 2.0	3.4 ± 2.8	NS

[a]Unless otherwise stated, data are presented as mean ± SD.
[b]Numbers of subjects are not reported because several subjects gave inadequate information.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CAARS = Conners Adult ADHD Rating Scale, CD = conduct disorder, Inv-ODD = investigator-rated ODD items attached to the WRAADDS, NS = not significant, ODD = oppositional defiant disorder, SCID-II = Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders, PD-negative = no personality disorder, PD-plus = 2 or more personality disorders, PD-positive = 1 personality disorder, WISPI-IV = Wisconsin Personality Inventory-IV, WRAADDS = Wender-Reimherr Adult Attention Deficit Disorder Scale.

conclusion of the subject's participation in the study, all available information was reviewed, and a consensus decision regarding the subject's PD was made. In this manner, patients were divided into 3 groups: those with no PD, those with 1 PD, and those with 2 or more PDs.

Adult ODD status was assessed using the investigator-rated WRAADDS and the patient-rated SR-WRAADDS. Childhood ODD symptoms were assessed retrospectively by the patient using the Childhood Symptom Scale and the parent-rated Disruptive Behavior Rating Scale.[45] These scales were used to divide the subjects into 3 groups:

(1) Subjects meeting criteria for adult ODD on the SR-WRAADDS (were at least moderately impaired on 4 or more ODD items),
(2) Subjects who did not meet criteria for adult ODD but did meet criteria for childhood ODD (were at least moderately impaired on 4 or more items in either retrospective parent- or patient-rated scale), and
(3) Subjects who did not have ODD either as an adult or child.

The childhood measures were also used to assess CD, requiring 3 or more symptoms in either the parent- or patient-rated scales to meet criteria for CD.

Statistical Analysis

Baseline clinical differences between the 3 PD groups were assessed using a 1-way analysis of variance with group category as the primary variable for continuous measures and Pearson χ^2 for categorical measures.

The efficacy of MTS versus placebo for the 3 PD groups was assessed using a mixed models design, with change from baseline in WRAADDS scores as the outcome variable, treatment and personality status as fixed variables,

Table 2. Subjects With at Least 1 Personality Disorder Within Each *DSM-IV* Cluster[a]

	All (n = 43)	PD-positive (n = 25)	PD-plus (n = 18)
Cluster A	5 (12)	1 (4)	4 (22)
Cluster B	19 (44)	6 (24)	13 (72)
Cluster C	28 (65)	12 (48)	16 (89)
Other[b]	7 (16)	6 (24)	1 (6)

[a]All values are n (%).
[b]Other personality disorders were passive-aggressive personality disorder, depressive personality disorder, and personality disorder not otherwise specified.
Abbreviations: *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; PD-plus = 2 or more personality disorders; PD-positive = 1 personality disorder.

and subject as a random variable. Chi-square was used to assess categorical outcome, with improvement defined by a rating of 1 or 2 on the CGI-I. Statistics were 2-tailed with $P < .05$ and uncorrected for multiple comparisons.

Analyses were done using the SPSS 14.0 statistical package (IBM, Armonk, New York).

RESULTS

Ninety-two subjects signed consent agreements and entered the screening phase. Sixty-seven entered the double-blind crossover phase. The 25 subjects who withdrew or were excluded during the screening/baseline phase are not included in Table 1. Patients were diagnosed as having ADHD by both the Utah and the *DSM-IV-TR* criteria. Most patients met the diagnosis of ADHD by both criteria. Several patients met the diagnosis by only 1 criterion. There was no difference in outcome when either group of patients that met the diagnosis by only 1 criterion was excluded.

Thirty-six percent of randomized subjects (n = 24) did not have a PD diagnosis (PD-negative), 37% of them (n = 25) had 1 PD (PD-positive), and 27% of them (n = 18) had 2 or more PD diagnoses (PD-plus). On both the CAARS and the *DSM-IV* measures of the WRAADDS (attention + disorganization and hyperactivity + impulsivity), there were no differences between the 3 groups at baseline. Conversely, PD status was associated with baseline differences on the total WRAADDS ($F_{2,66} = 4.1$, $P = .02$). This difference was due to higher scores on emotional dysregulation ($F_{2,66} = 5.9$, $P = .004$) in patients with a PD. There was a similar difference on the Inv-ODD scale scores ($F_{2,66} = 5.3$, $P = .007$). The same pattern of differences was found within the SR-WRAADDS. Personality disorder status was associated with higher scores on emotional dysregulation ($P = .02$) and ODD symptoms ($P = .04$) at baseline but not attention + disorganization and hyperactivity + impulsivity.

PD-plus subjects had significantly higher levels of ODD symptoms ($P = .007$) and emotional dysregulation ($P = .004$). Not only did PD-plus subjects have more symptoms of emotional dysregulation (analyzed as a continuous variable), but they were also more likely to be categorized with emotional dysregulation than PD-positive or PD-negative subjects ($\chi^2_2 = 13.4$, $P = .001$).

There were no significant differences in childhood ODD or conduct disorder status. The 3 groups did not differ in substance abuse measures. Mean *z* scores on the WISPI-IV ($F_{2,61} = 20.8$, $P = .001$) and the number of endorsed items on the SCID-II ($F_{2,66} = 19.4$, $P = .001$), which are both quantitative measures of severity of PD, indicated more impairment for PD-plus subjects.

Types of Personality Disorders Displayed

Table 2 shows the number of subjects with any PD in the 3 *DSM-IV* clusters as well as passive-aggressive, depressive, and NOS (not otherwise specified). This table understates the total number of PDs experienced by these subjects, since, if a subject had 2 or more PDs within a cluster, they were only counted once. Cluster C disorders were most common in both PD groups, with cluster B disorders second most frequent.

Treatment Response

Treatment with MTS produced a significant treatment effect on every outcome measure, including emotional dysregulation and Inv-ODD ($P = .001$) (Table 3). There were no significant interactions between treatment (MTS versus placebo) and PD group (PD-negative, PD-positive, and PD-plus). Use of the total WRAADDS as the outcome measure resulted in a nonsignificant value of $P = .46$. However, when the impact of treatment was assessed for each group individually, the PD-negative and PD-positive groups had consistently significant differences in improvement on medication compared to placebo. In contrast, the PD-plus group had significant improvement only on the Inv-ODD ($P = .03$). In general, the PD-negative and PD-positive groups displayed large treatment effects, while the PD-plus group displayed equivocal treatment effects. On the CGI-I, 71% of both the PD-positive and PD-negative patients were considered responders versus only 38% of the PD-plus patients. On this measure, PD-negative and PD-positive subjects had significant treatment effects ($P < .001$), while PD-plus subjects did not ($P = .24$).

In the current trial, 54 subjects were below the cutoff point on the WISPI-IV, and 8 subjects had mean *z* scores of 0.9 or higher. As seen in Table 4, only those below the cutoff point had a significant treatment response. Similarly, subjects in the prior trial who endorsed 60 or more items on the SCID-II were unlikely to respond to treatment. In the current trial, 85 subjects were assessed with the SCID-II, and 67 were randomized. Of these, 60 endorsed fewer than 60 items, and 6 endorsed 60 or more items. Again, there was a significant treatment response only for those below the cutoff score. Given the limited number of subjects above the cutoff scores, it is unclear if the scales successfully selected nonresponders.

DISCUSSION

Similar to the findings in our OROS methylphenidate trial,[31] 37% of adults with ADHD had 1 PD, and 27% had

Table 3. Mean WRAADDS Scores After Treatment (MTS versus placebo) Subdivided by Personality Disorder Status (PD-negative, PD-positive, and PD-plus)[a]

Rating Scale	MTS	Placebo	Treatment *P* Value	Effect Size[b]	Treatment-by-PD Group *P* Value
WRAADDS total	11.0 ± 7.5	18.0 ± 6.9	.001	1.0	.46
PD-negative	8.7 ± 6.8	15.7 ± 5.9	.008	1.1	
PD-positive	10.4 ± 8.0	19.5 ± 6.5	.006	1.3	
PD-plus	14.4 ± 7.0	18.7 ± 7.8	.22	0.6	
WRAADDS attention + disorganization	3.6 ± 2.4	6.1 ± 2.3	.001	1.1	.45
PD-negative	3.0 ± 2.3	5.9 ± 2.5	.006	1.2	
PD-positive	3.4 ± 2.6	6.5 ± 2.0	.005	1.3	
PD-plus	4.6 ± 2.4	6.1 ± 2.5	.18	0.6	
WRAADDS hyperactivity + impulsivity	3.3 ± 2.1	5.0 ± 2.1	.001	0.8	.45
PD-negative	2.7 ± 1.7	4.3 ± 2.0	.007	0.9	
PD-positive	3.2 ± 2.3	5.4 ± 2.0	.013	1.0	
PD-plus	4.2 ± 2.0	5.1 ± 2.3	.26	0.4	
WRAADDS emotional dysregulation	4.0 ± 3.4	6.8 ± 3.4	.001	0.8	.51
PD-negative	3.0 ± 3.3	5.5 ± 2.9	.044	0.8	
PD-positive	3.8 ± 3.4	7.6 ± 3.3	.007	1.1	
PD-plus	5.5 ± 3.3	7.2 ± 3.9	.26	0.5	
WRAADDS Inv-ODD	4.8 ± 3.7	7.6 ± 4.9	.001	0.7	.49
PD-negative	3.8 ± 3.4	5.5 ± 3.7	.07	0.5	
PD-positive	4.2 ± 3.2	7.2 ± 4.8	.01	0.8	
PD-plus	6.9 ± 4.2	10.6 ± 5.2	.03	0.8	
CAARS	30.7 ± 20.0	48.4 ± 18.8	.001	0.9	.49
PD-negative	23.1 ± 15.5	42.6 ± 20.5	.001	1.1	
PD-positive	30.7 ± 21.3	52.1 ± 15.5	.007	1.2	
PD-plus	40.1 ± 20.2	50.3 ± 20.5	.25	0.5	
CGI-I improved, % (n/n)[c]					
PD-negative	71 (15/21)	18 (3/17)	<.001	NA	NA
PD-positive	71 (15/21)	14 (3/21)	<.001	NA	
PD-plus	38 (6/16)	20 (3/15)	.24	NA	

[a]Data are presented as mean ± SD unless otherwise indicated.
[b]Effect size: Cohen *d* was not calculated for categorical variables.
[c]Number of improved subjects/total number of subjects.
Abbreviations: CAARS = Conners Adult ADHD Rating Scales, CGI-I = Clinical Global Impressions-Improvement scale, Inv-ODD = investigator-rated oppositional defiant disorder items attached to the WRAADDS, MTS = methylphenidate transdermal system, NA = not applicable, NS = not significant, PD-negative = no personality disorder, PD-plus = 2 or more personality disorders, PD-positive = 1 personality disorder, WRAADDS = Wender-Reimherr Adult Attention Deficit Disorder Scale.

2 or more PDs. We found that high PD symptom loads were associated with a more complex ADHD. PD-plus subjects had higher levels of emotional dysregulation and adult oppositional symptoms than the other 2 groups. Conversely, there were no differences in the symptoms of inattention and hyperactivity/impulsivity among the 3 groups. The relationship between PD category and emotional dysregulation was significant whether it was treated as a continuous or a categorical variable. The relationship with ODD was significant only when we looked at current ODD symptoms, but not by retrospective measures of childhood ODD.

In general, ADHD research has concentrated on cluster B PDs. In contrast, studies by Miller et al[22] and Matthies et al,[23] as well as our OROS methylphenidate trial,[31] found that cluster B diagnoses were less frequent than cluster C diagnoses. The data from the current trial replicated that finding. Forty-four percent of subjects had a PD in cluster B compared to 65% in cluster C and 12% in cluster A, and another 16% of subjects were experiencing passive-aggressive, depressive, and/or NOS PDs. This high prevalence of other PDs suggests that ADHD, combined with ODD and emotional dysregulation, leads to a more complex pattern of PD. Avoidant, dependent, and obsessive-compulsive PDs in adult ADHD deserve increased attention.

In our OROS methylphenidate trial,[33] there was a significant interaction between PD group and treatment outcome. In the current trial, none of the treatment-by-PD group interactions achieved statistical significance ($P = .46$). However, the PD-negative and PD-positive subjects had significant treatment effects across all outcome measures. In contrast, the PD-plus subjects had a positive treatment effect only for oppositional symptoms (an outcome not seen in the prior study), while *P* values for the other outcome measures varied from $P = .18$ to $P = .26$.

In our OROS methylphenidate trial,[33] 27% of subjects had elevated scores on the WISPI-IV (mean *z* scores of ≥ 0.9), while 22% of subjects had elevated SCID-II scores (at least 60 items endorsed). In the current trial, fewer subjects had elevated scores on the WISPI-IV or the SCID-II. These scores agreed with the clinical assessments such that 55% of the subjects with high WISPI-IV *z* scores were PD-plus and 75% of the subjects with elevated SCID-II scores were PD-plus. Both measures were mildly successful in identifying treatment nonresponders but not as successful as in the prior study. One possible reason is that the current trial had an extensive screening protocol. This protocol resulted in potential subjects leaving prior to randomization, and it may have selectively removed subjects with high PD loads who would have been treatment nonresponders.

Table 4. ADHD Symptoms as a Function of Treatment (MTS vs placebo) Subdivided by PD Categories for the WISPI-IV ($z < 0.9$ vs $z \geq 0.9$) and the SCID-II (< 60 items endorsed vs ≥ 60 items endorsed)[a]

Rating Scale	MTS	Placebo	Treatment *P* Value
Wisconsin Personality Inventory-IV			
WRAADDS total	11.5 ± 7.4	17.5 ± 6.6	.001
$z < 0.9$	11.2 ± 7.1	17.3 ± 6.7	.001
$z \geq 0.9$	13.6 ± 9.3	19.8 ± 6.4	.13
CGI-I improved, % (n/n)[b]			
$z < 0.9$	63 (31/49)	17 (8/48)	.001
$z \geq 0.9$	43 (3/7)	17 (1/6)	.25
SCID-II			
WRAADDS total	11.0 ± 7.5	18.0 ± 6.9	.001
< 60 items endorsed	10.7 ± 6.8	17.4 ± 6.6	.001
≥ 60 items endorsed	16.4 ± 9.9	23.2 ± 3.6	.11
CGI-I improved, % (n/n)[b]			
< 60 items endorsed	64 (35/55)	17 (9/52)	.001
≥ 60 items endorsed	60 (3/5)	0 (0/5)	.08

[a]Data are presented as mean ± SD unless otherwise indicated.
[b]Number of improved subjects/total number of subjects.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGI-I = Clinical Global Impressions-Improvement scale, MTS = methylphenidate transdermal system, PD = personality disorder, SCID-II = Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders, WRAADDS = Wender-Reimherr Adult Attention Deficit Disorder Scale.

This very extensive diagnostic assessment included parental reports, careful assessment of both Utah Criteria and *DSM-IV-TR* diagnosis of ADHD, and assessment of personality using several self-report scales and the SCID-II interview. It usually required 3 visits to complete this set of evaluations. During this extended period of evaluation, a number of patients withdrew voluntarily, and a smaller number had inconsistent ADHD symptom levels. In the analysis of the study results, we were impressed by the relatively high level of medication response and low level of placebo response. We think that this extended period of pretreatment assessment helped eliminate patients who were not ideal study candidates.

Limitations

Although larger than our first study of PD and ADHD, the size of this sample was determined by the underlying clinical trial of MTS. Consequently, there is a risk of a type II error because of our limited sample size.

Assessment of PD is difficult under the best of circumstances, but it is especially challenging with ADHD. Numerous symptoms of ADHD overlap with PDs, making it difficult to ascertain whether a symptom should be attributed to ADHD or to a comorbid PD or to both. More important is the fact that the final PD diagnosis was made at the end of the trial. Although the study was double-blind, it is possible that treatment response influenced final PD assessment.

This study had an extensive intake that may have selected a sample with a high degree of motivation and fewer characteristics of noncompliance, thus selectively removing subjects with PDs. The high attrition rate (27%) between entry and randomization is very likely due to the extensive intake and should be acknowledged.

CONCLUSION

Although PD status was neither an inclusion nor an exclusion criterion, this adult ADHD trial included numerous subjects with 1 or more PDs. The diagnosis of 2 or more PDs was associated with higher levels of emotional dysregulation and oppositional symptoms. No relationship was found between the PD categories and the ADHD symptoms of attention + disorganization and hyperactivity + impulsivity. Cluster C PDs were most common. These data replicated a previous observation[33] that subjects with no PD or 1 PD responded to ADHD therapy, while subjects with 2 or more PDs were less likely to respond to treatment. These data demonstrate that a significant portion of adults with ADHD will exhibit evidence of a PD. A comprehensive assessment of ADHD-related emotional and oppositional symptoms is an important first step in the diagnosis of PD adults with ADHD.

Drug names: methylphenidate (Focalin, Daytrana, and others).
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