Original Investigation

Effects of Group Psychotherapy, Individual Counseling, Methylphenidate, and Placebo in the Treatment of Adult Attention-Deficit/Hyperactivity Disorder
A Randomized Clinical Trial

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IMPORTANCE Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with high prevalence in adulthood. There is a recognized need to assess the efficacy of psychotherapy in adult ADHD.

OBJECTIVE To evaluate the efficacy of cognitive behavioral group psychotherapy (GPT) compared with individual clinical management (CM) and that of methylphenidate hydrochloride compared with placebo.

DESIGN, SETTING, AND PARTICIPANTS Prospective, multicenter, randomized clinical trial of 18- to 58-year-old outpatients with ADHD from 7 German study centers. Patients were recruited between January 2007 and August 2010, treatment was finalized in August 2011, and final follow-up assessments occurred in March 2013.

INTERVENTIONS Sessions of GPT and CM were held weekly for the first 12 weeks and monthly thereafter (9 months). Patients received either methylphenidate or placebo for 1 year.

MAIN OUTCOMES AND MEASURES The primary outcome was the change in the ADHD Index of the Conners Adult ADHD Rating Scale from baseline to the end of the 3-month intensive treatment (blinded observer ratings). Secondary outcomes included ADHD ratings after 1 year, blinded observer ratings using the Clinical Global Impression Scale, and self-ratings of depression.

RESULTS Among 1480 prescreened patients, 518 were assessed for eligibility, 433 were centrally randomized, and 419 were analyzed as randomized. After 3 months, the ADHD Index all-group baseline mean of 20.6 improved to adjusted means of 17.6 for GPT and 16.5 for CM, with no significant difference between groups. Methylphenidate (adjusted mean, 16.2) was superior to placebo (adjusted mean, 17.9) (difference, −1.7; 97.5% CI, −3.0 to −0.4; $P = .003$). After 1 year, treatment effects remained essentially stable. Descriptive analyses showed that methylphenidate was superior to placebo in patients assigned to GPT (difference, −1.7; 95% CI, −3.2 to −0.1; $P = .04$) or CM (difference, −1.7; 95% CI, −3.3 to −0.2; $P = .03$). Regarding depression, no significant differences were found. In contrast, GPT was superior to CM for all visits in the Clinical Global Impression global assessment of effectiveness.

CONCLUSION AND RELEVANCE Highly structured group intervention did not outperform individual CM with regard to the primary outcome. Psychological interventions resulted in better outcomes during a 1-year period when combined with methylphenidate as compared with placebo.

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Adult attention-deficit/hyperactivity disorder (ADHD) is a mental disorder affecting an estimated 2.5% of the adult population.[1-3] It is associated with numerous comorbid disorders and negative psychosocial consequences.[4-7] Most guidelines recommend a multimodal treatment approach.[8-10]

The National Institute for Health and Care Excellence proposes methylphenidate hydrochloride as the first-line treatment for adult ADHD. Meta-analyses have shown robust moderate effect sizes for methylphenidate vs placebo in reducing ADHD symptoms.[11-14] However, up to 50% of individuals show less than a 30% decrease in symptoms.[12,15]

Combined treatment with medication and individual or group cognitive behavioral therapy has demonstrated significant benefits over medication alone.[16-20] Previous pilot clinical trials have evaluated a specific cognitive group psychotherapy (GPT) program for adult ADHD.[21-24] Moderate effect sizes[23,24] of these and other psychotherapy concepts have been demonstrated.[23,25,26] However, these studies have not systematically controlled for medication and include either medicated or mixed (ie, with and without medication) patient samples. To our knowledge, the only available data come from a pilot trial that revealed a nonsignificant benefit for patients treated with stimulants vs placebo.[27] Thus, the effect of medication on the outcomes of psychological therapy is still largely unknown.

Specific cognitive behavioral programs have been proven more effective than unspecific control conditions (eg, relaxation, supportive therapy, and discussion groups) for adult ADHD.[23,25,26] However, the effectiveness of a highly structured group program vs a less specific treatment, eg, clinical management (CM), which simulates practice care in an optimal way, is unknown.

Given the recognized need for research,[28] the primary aim of our study was to demonstrate the efficacy of highly structured behavioral GPT compared with less specific treatment (eg, CM) as well as that of methylphenidate compared with placebo after 3 months. Secondary analyses included a comparison of the same effects after 1 year of treatment, the 4 treatment conditions (GPT with methylphenidate; GPT with placebo; CM with methylphenidate; and CM with placebo), measures of depression, and Clinical Global Impression Scale (CGI) score.[29]

Methods

Study Design and Participants

All methodological issues have been described in detail.[21,30] The Comparison of Methylphenidate and Psychotherapy in Adult ADHD Study (COMPAS) was a factorial, multicenter, randomized clinical trial comparing GPT with CM and methylphenidate with placebo. The full trial protocol appears in Supplement 1. Inclusion and exclusion criteria are listed in eAppendix 1 in Supplement 2. The diagnosis of ADHD, according to *DSM-IV* and other psychiatric symptoms, was established by psychiatric expert assessment and validated using observer rating scales and self-rating scales, including the Wender Utah Rating Scale (WURS-k; in German),[31,32] the ADHD diagnostic checklist (ADHD-DC; in German),[33] and the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I) and Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders (SCID-II) (in German).[34,35] Concurrent use of psychopharmacologic or psychotherapeutic treatments was not allowed outside the trial. The study received ethics committee approval from University of Freiburg. Written informed consent was obtained from all participants.

Randomization and Masking

Eligible patients were randomized in batches of 14 or 15 at a time (1 × 12, 1 × 16). The randomization allowed for GPT in groups of 6 to 9 patients. Either GPT or CM plus a medication number (used to allocate either methylphenidate or placebo) was centrally assigned.[21,30] Treatments were allocated in a 1:1:1:1 ratio, stratified in blocks of 4 within the center (block size was kept confidential to help ensure concealment; the protocol stated that it was variable). Blocks were sequentially combined for application to patient batches. For patients and therapists, the study was blinded for medication and open for assignment to GPT or CM. Observers rating ADHD symptoms (ADHD-DC, Conners Adult ADHD Rating Scale [CAARS] long German version,[36-39] and CGI) were blinded to treatment allocation.

Procedures

Following randomization and baseline assessment, participants received methylphenidate hydrochloride (sustained release; initial dosage of 10 mg/d; titration with 10 mg/wk over 6 weeks up to 60 mg/d; individual dosage to a maximum daily dosage of 1.3 mg/kg of body weight) or placebo. Medication adherence was assessed by pill count.

The GPT sessions followed a validated manual (eAppendix 2 in Supplement 2).[40,41] Individual CM was the active, nonpharmacological control condition chosen to simulate general practice. The CM participants received nonspecific counseling in individual sessions (15-20 minutes) (eAppendix 2 in Supplement 2).[21,30] Twelve weekly sessions of GPT and CM were followed by 10 monthly sessions over 52 weeks.[21,30] The CM sessions were audio recorded and the GPT sessions were video recorded to assess treatment fidelity by 3 blinded, independent, expert raters.[21,30]

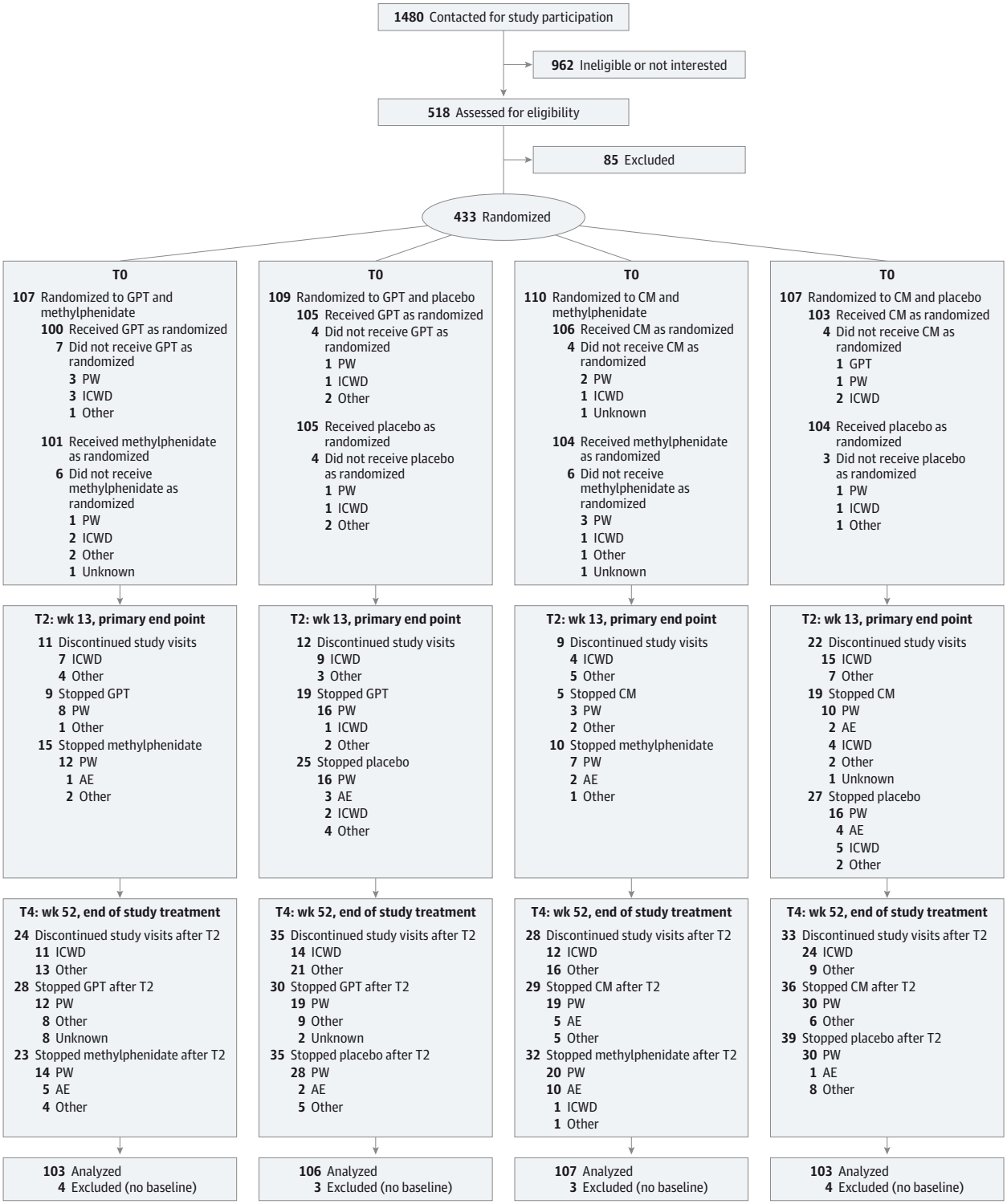
Outcome Measures

Visits for assessing primary and secondary end points took place after randomization (baseline, or time 1 [T1]), after 12 weeks of intensive treatment (T2), during maintenance after 24 weeks (T3), at the end of treatment (week 52; T4), and at 2.5 years after T1 (follow-up; T5). The primary outcome was the change in the observer-rated CAARS ADHD Index from T1 to T2. Secondary outcome measures included other CAARS subscales, the ADHD-DC, the Beck Depression Inventory,[42,43] and CGI subscales; we report results for these end points at T2 and T4.

Sample Size Estimation

The sample size was derived assuming an effect size (ES) of 0.33 for the 2 primary 2 × 2 comparisons (GPT or methylphenidate vs control conditions[21,30]). To achieve a power of 80% for a *t* test at a 2-sided α of 2.5% to adjust for multiplicity, 350 patients were needed. A target of 448 randomizations was

Figure 1. Trial Design and Flow of Patients



AE indicates adverse event; CM, clinical management; GPT, group psychotherapy; ICWD, informed consent withdrawn; PW, patient wish; T2, time 2 (week 13); and T4, time 4 (week 52). Details on enrollment are described by Philipsen et al.[30]

Table 1. Demographic and Screening Characteristics of the 419 Participants in the Full Analysis Set by Randomized Intervention

Characteristic	No. (%)			
	GPT + Methylphenidate (n = 103)	GPT + Placebo (n = 106)	CM + Methylphenidate (n = 107)	CM + Placebo (n = 103)
Age, y				
Mean (SD)	35 (10)	35 (11)	35 (10)	35 (10)
Range	18-57	18-58	18-54	19-56
Male	53 (51.5)	58 (54.7)	54 (50.5)	45 (43.7)
Verbal IQ				
Mean (SD)	112 (15)	111 (14)	113 (14)	110 (17)
Range	88-145	89-143	92-143	23-145[a]
White	100 (97.1)	104 (98.1)	107 (100.0)	101 (98.1)
University entrance diploma, from year 5 to 12/13	44 (42.7)	42 (39.6)	58 (54.2)	45 (43.7)
Employment				
Full- or part-time	75 (72.8)	70 (66.0)	81 (75.7)	77 (74.8)
Unemployed[b]	16 (15.5)	21 (19.8)	13 (12.1)	16 (15.5)
Family life				
≥2 Children	35 (34.0)	39 (36.8)	37 (34.6)	36 (35.0)
Single according to marital status	64 (62.1)	54 (50.9)	59 (55.1)	55 (53.4)
Living with a partner	41 (39.8)	53 (50.0)	46 (43.0)	55 (53.9)[c]
Previous psychopharmacological treatments				
≥1 Previous psychopharmacological medication	44 (42.7)	53 (50.0)	50 (46.7)	53 (51.5)
Antidepressants	25 (24.3)	33 (31.1)	36 (33.6)	31 (30.1)
Methylphenidate, amphetamine, other psychostimulants	23 (22.3)	26 (24.5)	17 (15.9)	24 (23.3)
Sedatives, neuroleptics, atomoxetine hydrochloride, mood stabilizers, others	10 (9.7)	17 (16.0)	16 (15.0)	17 (16.5)
Previous psychiatric or psychotherapeutic treatments				
Outpatient				
Psychiatric	30 (29.1)	38 (35.8)	36 (33.6)	44 (42.7)
Psychotherapeutic	61 (59.2)	57 (53.8)	55 (51.4)	50 (48.5)
Psychiatric or psychotherapeutic	72 (69.9)	72 (67.9)	69 (64.5)	68 (66.0)
Inpatient	23 (22.3)	18 (17.0)	22 (20.6)	20 (19.4)
WURS-k score, mean (SD)	40.6 (9.1)	41.4 (10.7)	42.1 (10.4)	42.2 (10.3)
ADHD subtype				
Combined	65 (63.1)	54 (50.9)	58 (54.2)	63 (61.2)
Predominantly inattentive	36 (35.0)	44 (41.5)	43 (40.2)	34 (33.0)
Predominantly hyperactive-impulsive	2 (1.9)	8 (7.5)	6 (5.6)	6 (5.8)
Current comorbid Axis I disorders[d]				
≥1 Current clinical disorder	35 (34.0)	38 (35.8)	38 (35.5)	48 (46.6)
Affective disorders	24 (23.3)	23 (21.7)	23 (21.5)	36 (35.0)
Anxiety disorders	17 (16.5)	19 (17.9)	20 (18.7)	21 (20.4)
Other disorders	3 (2.9)	5 (4.7)	2 (1.9)	6 (5.8)
Current comorbid Axis II disorders[d]				
≥1 Current personality disorder	22 (21.4)	17 (16.0)	16 (15.0)	20 (19.4)
Cluster A, schizoid, paranoid	1 (1.0)	0	0	4 (3.9)
Cluster B, borderline, narcissistic, histrionic	4 (3.9)	4 (3.8)	7 (6.5)	4 (3.9)
Cluster C, avoidant, obsessive-compulsive, dependent	18 (17.5)	11 (10.4)	10 (9.3)	13 (12.6)
Other, depressive, negativistic, NOS	3 (2.9)	4 (3.8)	4 (3.7)	4 (3.9)
Comorbid Axis I disorders in remission[d]				
≥1 Clinical disorder in remission	44 (42.7)	60 (56.6)	52 (48.6)	39 (37.9)
Affective disorders	28 (27.2)	31 (29.2)	32 (29.9)	22 (21.4)
Anxiety disorders	6 (5.8)	8 (7.5)	10 (9.3)	8 (7.8)
Substance abuse or dependence	14 (13.6)	30 (28.3)	22 (20.6)	11 (10.7)
Other disorders	11 (10.7)	9 (8.5)	6 (5.6)	11 (10.7)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CM, clinical management; GPT, group psychotherapy; NOS, not otherwise specified; WURS-k, Wender Utah Rating Scale (in German).

[a] Verbal IQ was estimated as 23 in 1 patient for whom German was not the native language.

[b] Including patients also engaged in training, retraining, university studies, and professional education (GPT with methylphenidate, n = 3; GPT with placebo, n = 6; CM with methylphenidate, n = 2; and CM with placebo, n = 1).

[c] Sample size was 102.

[d] In some patients, more than 1 disorder was diagnosed.

planned to compensate for dropouts. After a recruitment delay, a power of 78% (430 patients) was deemed acceptable to the study team, and no more patients were enrolled.

Statistical Analysis

Primary End Point

Changes in the CAARS ADHD Index from T1 to T2 were analyzed by randomized treatment in the full analysis set. To model a stable postdropout response, missing postbaseline data were replaced using multiple imputation through last mean carried forward (LMCF)[44] in an analysis of covariance linear model, using time, treatments, center, and baseline measurements as fixed covariates (eAppendix 3 in Supplement 2). Adjusted means per treatment were calculated from this. For the primary treatment comparisons at T2, an additional interaction term (GPT × MPH; kept if significant at 10%) was pretested.

The 2 primary comparisons were reported with confirmatory 97.5% confidence intervals (corrected for multiple testing of GPT vs CM and methylphenidate vs placebo) and descriptive 95% confidence intervals. These were statistically significant if $P < .025$ ($P < .05$ for other comparisons). If a primary treatment comparison was statistically significant, a confirmatory closed-test procedure sequentially compared GPT with methylphenidate vs CM with methylphenidate; GPT with methylphenidate vs GPT with placebo; CM with methylphenidate vs CM with placebo; and GPT with methylphenidate vs CM with placebo (descriptive reporting with nominal *P* values after the first nonsignificant result[21,30]).

Secondary End Points

Responses were defined as decreases in the observer rating variant of the CAARS ADHD Index of 30% or more. To calculate response rates, we analyzed only complete cases and used logistic regression. Other rating scales (other CAARS subscales, ADHD-DC, and Beck Depression Inventory) were evaluated using LMCF. Complete cases of CGI subscales (ordinal data) were analyzed in a proportional odds model.

Safety

Adverse events (AEs) were evaluated according to received treatment in safety set 1 (patients who attended ≥1 GPT or CM session) and safety set 2 (patients who received ≥1 dose of methylphenidate or placebo).

All analyses were prespecified and performed using SAS version 9.2 statistical software (SAS Institute, Inc).

Effect Sizes

Descriptive pre-post ESs were calculated using LMCF means and square roots of the residual variance, averaged over LMCF imputations as standard deviation.

Interim Analysis

An interim report on recruitment, compliance, and safety (no efficacy data) was presented to the independent data monitoring committee in April 2010, based on data up to T3 for the 231 patients randomized as of May 2009. The independent data monitoring committee recommended continuing the trial without modifications.

Results

Sample

Figure 1 illustrates patient flow.[30] Patients were recruited between January 2007 and August 2010, with randomization between April 10, 2007, and August 18, 2010. Treatment was finalized in August 2011, and final follow-up assessments occurred in March 2013 (data not reported here). In sum, 1480 patients were contacted. In 962 prescreened patients (65.0%), no standardized assessment for eligibility was carried out owing to lack of interest or inability to meet time requirements (391 of 962 [40.6%]) or contraindications against methylphenidate (194 of 962 [20.2%]). The remaining 518 patients were assessed for eligibility; 85 were excluded, primarily for refusing further participation (47 of 85 [55.3%]).[29]

Of the 433 randomized individuals, 107 were randomized to GPT with methylphenidate, 109 to GPT with placebo, 110 to CM with methylphenidate, and 107 to CM with placebo. **Table 1** summarizes the sociodemographic and clinical characteristics at baseline.

We obtained baseline ratings in 419 of the 433 randomized participants; these constituted the full analysis set for the primary LMCF efficacy analysis. Only one-third of the patients (138 of 419 [32.9%]) had never undergone psychiatric or psychotherapeutic outpatient treatment. The majority (277 of 419 [66.1%]) fulfilled criteria for at least 1 current or remitted Axis I disorder; 75 of 419 (17.9%) fulfilled the diagnostic criteria for at least 1 Axis II disorder. Primary outcome data (ADHD Index at T2) were available before LMCF for 91 of 103 participants (88.3%) receiving GPT with methylphenidate; 86 of 106 (81.1%) receiving GPT with placebo; 95 of 107 (88.8%) receiving CM with methylphenidate; and 80 of 103 (77.7%) receiving CM with placebo.

Treatment fidelity (GPT, CM) is shown in eAppendix 4 in Supplement 2. Interrater reliability is shown in eTable 1 in Supplement 2.

The mean (SD) daily medication dosage prescribed at T2 was 53.3 (20.4) mg total and 0.71 (0.27) mg/kg of body weight. The mean (SD) daily medication dosage was 48.8 (20.2) mg in 179 patients receiving methylphenidate and 58.5 (19.3) mg among 158 receiving placebo. The mean (SD) daily medication dosage was 53.6 (20.4) mg for 166 patients assigned to GPT and 53.1 (20.3) mg for 171 assigned to CM.

Primary End Point at T2

The test for GPT × methylphenidate interaction was nonsignificant ($P = .95$). Therefore, a 2 × 2 approach (vs a 4-arm approach) was applied evaluating GPT vs CM and methylphenidate vs placebo.

Confirmatory 2-Arm Comparisons

The study detected no advantage for the decline in ADHD symptoms for GPT vs CM (**Table 2**, **Table 3**, and **Figure 2**). The ADHD Index scores improved from the all-group baseline mean of 20.6 to an adjusted mean of 17.6 at T2 for GPT (n = 209; ES = −0.55) and 16.5 for CM (n = 210; ES = −0.75) (Table 2 and

Table 2. Observer-Rated CAARS ADHD Index at Baseline (T1), 13 Weeks (T2), 26 Weeks (T3), and 52 Weeks (T4) Based on Last Mean Carried Forward Analysis for the 419 Participants in the Full Analysis Set by Randomized Intervention, Adjusted for Baseline Measurement and Center

Observer-Rated CAARS Score[a]	T1, Mean	T2, Mean (95% CI)	T2 − T1, Mean	T3, Mean (95% CI)	T3 − T1, Mean	T4, Mean (95% CI)	T4 − T1, Mean
ADHD Index[b]	20.6						
GPT with methylphenidate		16.7 (15.6 to 17.8)	−3.8	15.4 (14.3 to 16.5)	−5.1	14.9 (13.6 to 16.1)	−5.7
GPT with placebo		18.4 (17.2 to 19.5)	−2.2	17.6 (16.4 to 18.8)	−3.0	16.4 (15.2 to 17.6)	−4.2
CM with methylphenidate		15.6 (14.5 to 16.7)	−5.0	14.6 (13.4 to 15.7)	−6.0	14.6 (13.4 to 15.8)	−6.0
CM with placebo		17.3 (16.2 to 18.5)	−3.2	17.4 (16.2 to 18.6)	−3.2	17.5 (16.1 to 18.8)	−3.1
Difference, GPT − CM		1.1 (0.0 to 2.2)		0.5 (0.6 to 1.7)		−0.4 (−1.6 to 0.8)	
P value		.06		.36		.53	
Difference, methylphenidate − placebo		−1.7 (−2.8 to −0.6)		−2.5 (−3.7 to −1.3)		−2.2 (−3.5 to −1.0)	
P value		.003		<.001		<.001	
Inattention/memory problems[c]	20.8						
GTP with methylphenidate		17.1 (15.9 to 18.3)	−3.7	16.1 (14.9 to 17.4)	−4.7	15.0 (13.8 to 16.3)	−5.8
GPT with placebo		18.0 (16.8 to 19.2)	−2.8	17.4 (16.1 to 18.7)	−3.5	16.0 (14.7 to 17.4)	−4.8
CM with methylphenidate		15.7 (14.5 to 16.8)	−5.2	14.9 (13.6 to 16.2)	−5.9	15.2 (14.0 to 16.5)	−5.6
CM with placebo		17.8 (16.5 to 19.0)	−3.1	17.8 (16.4 to 19.2)	−3.0	17.5 (16.1 to 19.0)	−3.3
Difference, GPT − CM		0.8 (−0.4 to 2.0)		0.4 (−0.9 to 1.7)		−0.8 (−2.1 to 0.5)	
P value		.18		.56		.21	
Difference, methylphenidate − placebo		−1.5 (−2.7 to −0.3)		−2.1 (−3.4 to −0.8)		−1.7 (−3.0 to −0.3)	
P value		.01		.001		.02	
Hyperactivity/restlessness[c]	18.3						
GPT with methylphenidate		14.8 (13.6 to 15.9)	−3.5	13.6 (12.4 to 14.8)	−4.7	13.0 (11.8 to 14.3)	−5.2
GPT with placebo		15.8 (14.5 to 17.0)	−2.5	15.0 (13.7 to 16.2)	−3.3	14.9 (13.5 to 16.3)	−3.4
CM with methylphenidate		14.5 (13.4 to 15.6)	−3.8	13.4 (12.2 to 14.7)	−4.8	13.3 (12.1 to 14.5)	−5.0
CM with placebo		15.2 (13.9 to 16.4)	−3.1	15.2 (13.9 to 16.5)	−3.1	15.2 (13.8 to 16.5)	−3.1
Difference, GPT − CM		0.4 (0.7 to 1.6)		−0.1 (−1.3 to 1.2)		−0.3 (−1.6 to 1.0)	
P value		.47		.92		.68	
Difference, methylphenidate − placebo		−0.9 (−2.0 to 0.3)		−1.6 (−2.8 to −0.4)		−1.9 (−3.2 to −0.6)	
P value		.15		.01		.005	
Impulsivity and emotional lability[c]	18.6						
GPT with methylphenidate		15.7 (14.6 to 16.9)	−2.8	14.0 (12.7 to 15.3)	−4.6	13.6 (12.4 to 14.9)	−4.9
GPT with placebo		16.0 (14.8 to 17.2)	−2.6	15.9 (14.5 to 17.2)	−2.7	14.3 (13.0 to 15.6)	−4.3
CM with methylphenidate		13.7 (12.5 to 14.8)	−4.9	13.5 (12.2 to 14.8)	−5.1	13.7 (12.5 to 14.9)	−4.9
CM with placebo		15.3 (14.1 to 16.4)	−3.3	15.5 (14.0 to 16.9)	−3.1	15.7 (14.4 to 17.0)	−2.8
Difference, GPT − CM		1.4 (0.2 to 2.6)		0.5 (−0.9 to 1.8)		−0.8 (−2.0 to 0.5)	
P value		.02		.50		.23	
Difference, methylphenidate − placebo		−0.9 (−2.1 to 0.2)		−2.0 (−3.3 to −0.6)		−1.3 (−2.6 to −0.1)	
P value		.12		.004		.04	
Problems with self-concept[d]	9.9						
GPT with methylphenidate		8.7 (8.0 to 9.4)	−1.2	8.2 (7.4 to 8.9)	−1.7	7.7 (6.9 to 8.5)	−2.2
GPT with placebo		9.2 (8.5 to 9.9)	−0.7	9.0 (8.3 to 9.8)	−0.8	8.4 (7.5 to 9.2)	−1.5
CM with methylphenidate		8.3 (7.6 to 8.9)	−1.6	7.9 (7.1 to 8.7)	−2.0	7.9 (7.1 to 8.7)	−1.9
CM with placebo		9.0 (8.3 to 9.7)	−0.9	8.8 (8.0 to 9.5)	−1.1	8.7 (7.8 to 9.6)	−1.2
Difference, GPT − CM		0.3 (−0.4 to 1.0)		0.3 (−0.5 to 1.1)		−0.3 (−1.1 to 0.5)	
P value		.41		.49		.49	
Difference, methylphenidate − placebo		−0.6 (−1.3 to 0.1)		−0.9 (−1.6 to −0.1)		−0.7 (−1.5 to 0.1)	
P value		.08		.03		.09	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CAARS, Conners Adult ADHD Rating Scale, long version; CM, clinical management; GPT, group psychotherapy.

[a] Lower score values represent better outcomes.

[b] Possible range is 0 to 36. Primary outcome was at T2.

[c] Possible range is 0 to 36.

[d] Possible range is 0 to 18.

Table 3. Observer-Rated CAARS ADHD Index at Baseline (T1), 13 Weeks (T2), 26 Weeks (T3), and 52 Weeks (T4) With Logistic Regression of Complete Cases by Randomized Intervention, Adjusted for Baseline Measurement and Center

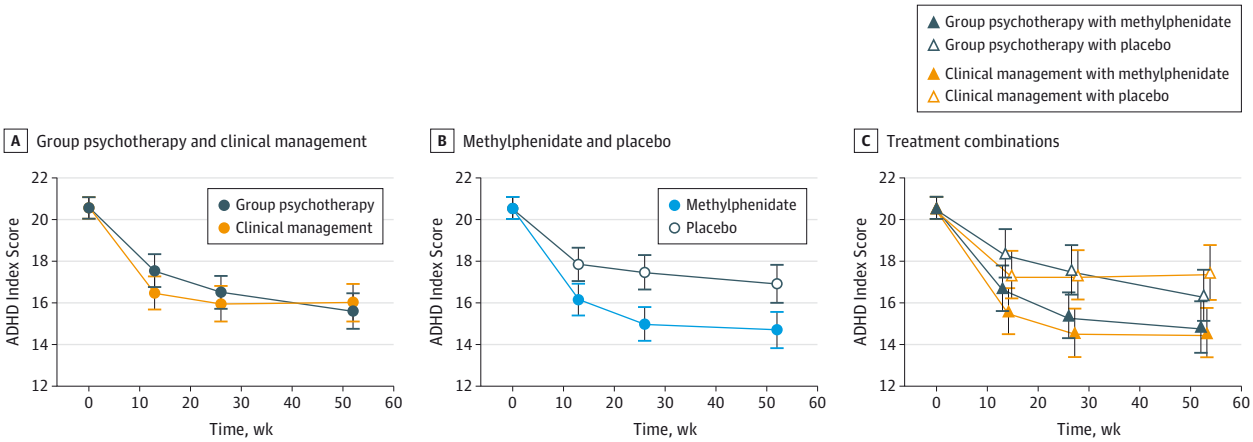
Observer-Rated CAARS Score Response[a]	T2	T3	T4
Patients with response, No./total patients, No. (%)			
GPT with methylphenidate	27/91 (29.7)	38/82 (46.3)	35/69 (50.7)
GPT with placebo	21/86 (24.4)	25/75 (33.3)	26/59 (44.1)
CM with methylphenidate	45/95 (47.4)	50/85 (58.8)	37/70 (52.9)
CM with placebo	26/80 (32.5)	21/62 (33.9)	21/45 (46.7)
GPT vs CM, OR (95% CI)[b]	0.55 (0.35 to 0.86)	0.71 (0.44 to 1.12)	0.91 (0.54 to 1.53)
P value	.009	.14	.72
Methylphenidate vs placebo, OR (95% CI)[b]	1.57 (1.00 to 2.47)	2.17 (1.35 to 3.50)	1.19 (0.70 to 2.01)
P value	.05	.001	.52

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CAARS, Conners Adult ADHD Rating Scale, long version; CM, clinical management; GPT, group psychotherapy; OR, odds ratio.

[a] Decrease in ADHD Index score by 30% or more compared with T1.

[b] The ORs are from the logistic regression of complete cases without missing data, adjusted for the baseline ADHD Index and center. An OR > 1.00 indicates higher odds for a better outcome for the first vs second intervention.

Figure 2. Mean Attention-Deficit/Hyperactivity Disorder (ADHD) Index Scores by Randomized Intervention for the 419 Participants in the Full Analysis Set



Means (last mean carried forward) for the primary outcome measure, observer-rated Conners Adult ADHD Rating Scale ADHD Index, for group psychotherapy and clinical management (A), methylphenidate and placebo (B), and group psychotherapy with methylphenidate, group psychotherapy with placebo, clinical management with methylphenidate, and clinical management with placebo. Error bars indicate 95% CIs.

Figure 2). The difference between GPT and CM was nonsignificant (ADHD Index score difference for GPT vs CM, 1.1; 97.5% CI, −0.2 to 2.4; 95% CI, 0.0 to 2.2; *P* = .06).

Symptoms decreased considerably more in patients assigned to methylphenidate (n = 210; adjusted mean ADHD Index score, 16.2; ES = −0.81) vs placebo (n = 209; adjusted mean ADHD Index score, 17.9; ES = −0.50) (Table 2 and Figure 2). This difference proved significant (ADHD Index score difference for methylphenidate vs placebo, -1.7; 97.5% CI, −3.0 to −0.4; 95% CI, −2.8 to −0.6; *P* = .003).

Confirmatory 4-Arm Comparisons

Because the difference between methylphenidate and placebo proved significant, we applied sequential 4-arm analyses. In patients randomized to methylphenidate, GPT vs CM produced nonsignificant findings (ADHD Index score difference, 1.1; 95% CI, −0.4 to 2.7; *P* = .16). Thus, confirmatory statistical testing was terminated.

Further Descriptive Analyses

The following preplanned exploratory comparisons were conducted. Comparing methylphenidate with placebo in patients assigned to GPT showed that methylphenidate was superior to placebo (ADHD Index score difference, −1.7; 95% CI, −3.2 to −0.1; *P* = .04). This superiority was also evident in patients randomized to CM (ADHD Index score difference for methylphenidate vs placebo, −1.7; 95% CI, −3.3 to −0.2; *P* = .03). In contrast, comparing both interventions (GPT and methylphenidate) with the control treatments produced a nonsignificant benefit (ADHD Index score difference for GTP with methylphenidate vs CM with placebo,−0.6; 95% CI, −2.2 to 0.9; *P* = .43).

Secondary Outcomes

Long-term ADHD Index

At T3 and T4, the treatment effects of GPT vs CM and methylphenidate vs placebo remained stable (Table 2 and Figure 2). The slight disadvantage of GPT vs CM at T2 and T3 became a

Table 4. Self-rated CAARS ADHD Index and Self-rated BDI at Baseline (T1), 13 Weeks (T2), 26 Weeks (T3), and 52 Weeks (T4) Based on Last Mean Carried Forward Analysis for the 419 Participants in the Full Analysis Set by Randomized Intervention, Adjusted for Baseline Measurement and Center

Self-rated Scale Score[a]	T1, Mean	T2, Mean (95% CI)	T2 − T1, Mean	T3, Mean (95% CI)	T3 − T1, Mean	T4, Mean (95% CI)	T4 − T1, Mean
CAARS ADHD Index[b]	20.8						
GPT with methylphenidate		16.6 (15.4 to 17.8)	−4.2	16.4 (15.3 to 17.6)	−4.4	15.3 (14.1 to 16.6)	−5.5
GPT with placebo		18.5 (17.4 to 19.7)	−2.3	17.7 (16.6 to 18.9)	−3.1	16.9 (15.6 to 18.2)	−3.9
CM with methylphenidate		15.8 (14.7 to 17.0)	−5.0	15.3 (14.2 to 16.4)	−5.5	15.1 (13.8 to 16.4)	−5.8
CM with placebo		17.3 (16.1 to 18.5)	−3.5	17.4 (16.2 to 18.7)	−3.4	18.0 (16.7 to 19.3)	−2.8
Difference, GPT − CM		1.0 (−0.2 to 2.2)		0.7 (−0.5 to 1.9)		−0.4 (−1.7 to 0.9)	
P value		.09		.23		.56	
Difference, methylphenidate − placebo		−1.7 (−2.8 to −0.5)		−1.7 (−2.9 to −0.6)		−2.3 (−3.5 to −1.0)	
P value		.004		.003		<.001	
BDI total score[c]	12.5						
GPT with methylphenidate		11.1 (9.9 to 12.3)	−1.4	9.5 (8.2 to 10.9)	−3.0	8.9 (7.5 to 10.3)	−3.6
GPT with placebo		10.7 (9.4 to 12.0)	−1.8	10.7 (9.3 to 12.1)	−1.8	9.4 (8.0 to 10.8)	−3.1
CM with methylphenidate		10.2 (9.0 to 11.4)	−2.3	9.7 (8.4 to 11.0)	−2.8	9.6 (8.2 to 11.1)	−2.8
CM with placebo		10.8 (9.5 to 12.1)	−1.7	10.6 (9.2 to 12.0)	−1.9	10.1 (8.5 to 11.7)	−2.4
Difference, GPT − CM		0.4 (−0.8 to 1.6)		0.0 (−1.4 to 1.4)		−0.7 (−2.2 to 0.7)	
P value		.54		>.99		.31	
Difference, methylphenidate − placebo		−0.1 (−1.4 to 1.2)		−1.0 (−2.4 to 0.3)		−0.5 (−2.0 to 1.1)	
P value		.89		.14		.54	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BDI, Beck Depression Inventory; CAARS, Conners Adult ADHD Rating Scale, long version; CM, clinical management; GPT, group psychotherapy.

[a] Lower score values represent better outcomes.

[b] Possible range is 0 to 36.

[c] Possible range is 0 to 63.

slight nonsignificant benefit at T4. In contrast, methylphenidate was significantly better than placebo during the entire study period.

Response

At T2, responses were highest in the CM with methylphenidate arm at 47.4%, compared with 32.5% in CM with placebo, 29.7% in GPT with methylphenidate, and 24.4% in GPT with placebo (GPT vs CM, *P* = .009; methylphenidate vs placebo, *P* = .05). At T4, response rates were similar in all 4 treatment arms, varying between 44.1% for GPT with placebo and 52.9% for CM with methylphenidate (GPT vs CM, *P* = .72; methylphenidate vs placebo, *P* = .52) (Table 3).

Other Measures of ADHD Severity

For the self-ratings of the ADHD Index, GPT's nonsignificant disadvantage vs CM at T2 and T3 became a nonsignificant advantage at T4. Methylphenidate proved superior to placebo at all 3 measurement times (**Table 4**).

The CAARS ratings and the ADHD-DC revealed comparable results in total and subscale scores, with no difference between GPT and CM (Table 2; eTable 2 in Supplement 2).

Depression

Regarding depression, no significant differences were found between patients treated with GPT vs CM or methylphenidate vs placebo. Methylphenidate exhibited nonsignificantly better Beck Depression Inventory ratings at all 3 times. Moreover, GPT's nonsignificant disadvantage at T2 became a nonsignificant advantage at T4 (Table 4).

CGI Scores

Comparison of CGI severity score between GPT and CM revealed no major differences (**Table 5**). Concerning CGI global change, GPT performed better than CM at all times; however, it was significant only at T4 (*P* = .047). Methylphenidate always performed better than placebo, but this was significant only at T3 (*P* = .008) (Table 5). The end point CGI global assessment of effectiveness always favored GPT over CM and methylphenidate over placebo. This difference in GPT's favor was highly significant at T4 (*P* < .001) (Table 5).

Safety

Frequencies of AEs and serious AEs are shown in eTable 3 in Supplement 2. No suicides occurred. Two patients receiving methylphenidate became pregnant, despite contraception. One terminated her pregnancy for psychosocial reasons; the other experienced no AEs during delivery or early development of the child. Changes in heart rate, blood pressure, and body weight from T1 to T4 are shown in eTable 4 in Supplement 2.

Discussion

The COMPAS is the first multimodal, multicenter randomized clinical trial to examine the efficacy of nonpharmacologi-

Table 5. Observer-Rated CGI at Baseline (T1), 13 Weeks (T2), 26 Weeks (T3), and 52 Weeks (T4) Based on Cumulative Logistic Regression of Complete Cases With No Missing Values for the 419 Participants in the Full Analysis Set by Randomized Intervention, Adjusted for Baseline Severity of Illness and Center[a]

Observer-Rated CGI Score	T1	T2	T3	T4
Severity[b]				
Mean (No.)[c]				
GPT with methylphenidate	4.7 (103)	4.0 (89)	3.7 (81)	3.4 (69)
GPT with placebo	4.6 (104)	4.2 (84)	4.0 (74)	3.6 (57)
CM with methylphenidate	4.7 (106)	4.0 (93)	3.8 (84)	3.7 (67)
CM with placebo	4.7 (101)	4.2 (79)	4.0 (61)	3.7 (45)
GPT vs CM, OR (95% CI)[d]		0.94 (0.64 to 1.39)	1.03 (0.68 to 1.56)	0.75 (0.47 to 1.20)
P value		.76	.87	.23
Methylphenidate vs placebo, OR (95% CI)[d]		0.63 (0.43 to 0.94)	0.59 (0.39 to 0.90)	0.71 (0.45 to 1.14)
P value		.02	.01	.16
Global change[e]				
Mean (No.)[c]	NA			
GPT with methylphenidate		2.9 (91)	2.7 (82)	2.5 (69)
GPT with placebo		3.0 (84)	3.0 (74)	2.7 (58)
CM with methylphenidate		3.0 (94)	2.9 (84)	2.9 (67)
CM with placebo		3.2 (79)	3.2 (61)	3.0 (45)
GPT vs CM, OR (95% CI)[d]		0.71 (0.48 to 1.05)	0.74 (0.48 to 1.13)	0.62 (0.38 to 0.99)
P value		.08	.16	.047
Methylphenidate vs placebo, OR (95% CI)[d]		0.69 (0.47 to 1.02)	0.56 (0.36 to 0.86)	0.69 (0.43 to 1.12)
P value		.07	.008	.13
Global assessment of effectiveness[f]				
Mean (No.)[c]	NA			
GPT with methylphenidate		2.5 (91)	2.7 (82)	2.9 (69)
GPT with placebo		2.3 (84)	2.4 (74)	2.7 (58)
CM with methylphenidate		2.2 (94)	2.3 (83)	2.5 (67)
CM with placebo		1.8 (79)	2.0 (61)	2.0 (45)
GPT vs CM, OR (95% CI)[g]		2.22 (1.50 to 3.28)	1.99 (1.30 to 3.04)	2.72 (1.67 to 4.45)
P value		<.001	.001	<.001
Methylphenidate vs placebo, OR (95% CI)[g]		1.77 (1.20 to 2.61)	1.86 (1.22 to 2.84)	1.80 (1.11 to 2.91)
P value		.004	.004	.02

Abbreviations: CGI, Clinical Global Impression Scale; CM, clinical management; GPT, group psychotherapy; NA, not applicable; OR, odds ratio.

[a] Lower score values represent better outcomes except for the CGI global assessment of effectiveness.

[b] Possible scores range from 1 (not at all ill) to 7 (extremely ill).

[c] Descriptive numerical evaluation.

[d] The ORs are from cumulative logistic regression of complete cases, adjusted for baseline CGI severity of illness subscale score and center. An OR < 1.00 indicates higher odds for a better outcome for the first vs second intervention.

[e] Possible scores range from 1 (very much improved) to 7 (very much worse).

[f] Possible scores range from 1 (minimal) to 4 (very good).

[g] The ORs are from cumulative logistic regression of complete cases, adjusted for baseline CGI severity of illness subscale score and center. An OR > 1.00 indicates higher odds for a better outcome for the first vs second intervention.

cal treatments (GPT vs CM) in combination with methylphenidate or placebo. We recruited a large representative sample that compares well with other trials.[45,46] In contrast to our hypothesis, GPT could not be shown to be more effective than the CM control condition, except in CGI-related secondary outcomes. Methylphenidate was superior to placebo in nearly all outcome domains. All 4 treatment arms exhibited improvements in both symptoms and CGI ratings.

This finding contrasts with previous findings in which preliminary evidence has shown the superiority of structured disorder-oriented GPT over unspecific group control conditions.[23,25,26] However, our study used an individual CM control condition to simulate practice care in an optimal way. As a consequence, the investigated group program, although found effective in earlier preliminary studies, may not have been sufficiently effective to outperform the individual control condition. Another explanation may be that our control treatment—although performed adherent to the protocol—was not an attention placebo; instead, it included face-to-face counseling activities, which potentially responded better to the individual needs of participants than the groups. We cannot extrapolate to specific psychotherapy methods beyond the one tested.

While CM appeared superior to specific GPT after 3 months, long-term effects after 1 year favored GPT slightly. In particular, CGI global assessments of effectiveness of the interventions were significantly better for GPT at all measurement times. This is remarkable because this scale represents more general measures of well-being (eg, improved acceptance, self-esteem, coping skills), which were the focus of GPT.

Confirming preliminary evidence,[27] our trial clearly showed that combinations of GPT or CM with methylphenidate were superior to combinations with placebo.

Our study provides no evidence that methylphenidate reduces depressive symptoms. This contrasts with some preliminary evidence,[47] but it supports more recent research.[48,49]

Our results relate well to the large childhood Multimodal Treatment Study of Children With ADHD,[50] which also found

significant improvements in all treatment conditions (medication management, intensive behavioral treatment, the two combined, or standard community care). As in our trial, medication proved to be superior to intensive behavioral therapy.[50]

A nonsignificant interaction term does not exclude the possibility that the effect of GPT may depend on MPH and vice versa. However, the 2-arm and 4-arm comparisons of GPT vs CM and GPT with methylphenidate vs CM with methylphenidate, as well as methylphenidate vs placebo and GPT with methylphenidate vs GPT with placebo, gave identical results, implying that our data do not suggest such dependencies.

Blinding was restricted to medication and to observer ratings of ADHD and CGI. We did not systematically assess whether blinding was effective in patients. However, because patients who received methylphenidate and those who received placebo both reported high numbers of AEs, with minimal effects to vital signs and weight, we believe the blinding was effective. As in other studies[51] and in line with the nature of the disorder, compliance was a challenge: more than one-third of the randomized patients dropped out. These missing data can be viewed as a study result[51] rather than as a shortcoming, since most dropouts occurred in the CM with placebo condition. Because the available data (eTable 5 in Supplement 2) and the imputed LMCF analyses of the full analysis set showed similar results, we conjecture that our findings were not confounded by dropouts.

Our findings may not be generalizable to routine care settings in which comorbidities are not excluded and patients may have more psychosocial impairments or difficulties meeting the time and effort requirements for this trial.

Despite the significant superiority of methylphenidate vs placebo on most ADHD scales, the mean differences between methylphenidate vs placebo and GPT vs CM were relatively small. Our data could not show whether superior CGI ratings of GPT reflected otherwise hidden differences in patients' daily functioning.

Conclusions

The COMPAS trial sheds light on issues that, to our knowledge, have not yet been addressed. First, it almost doubles the observation period of the longest randomized study conducted globally so far.[52] Second, it systematically addresses the effect of medication on the outcome of psychotherapy. Previous studies were pilot studies,[27] not placebo controlled,[22-26] or included medication-treated patients with persistent ADHD symptoms.[16,17,25] Third, we compared a highly structured GPT with a less controlled CM condition, also an untested area.

To our knowledge, COMPAS is the first trial to demonstrate long-term maintenance effects of ADHD treatments under controlled conditions. We demonstrate that psychological interventions result in better outcomes when combined with methylphenidate as compared with placebo. Our data do not suggest that highly structured group intervention outperforms individual CM, which is much easier to implement in practical care than specifically tailored and highly structured GPT.

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Conflict of Interest Disclosures: Dr Philipsen reported serving on advisory boards, giving lectures, performing phase 3 studies, or receiving travel grants within the last 3 years from Eli Lilly and Co, Janssen-Cilag, MEDICE Arzneimittel Pütter GmbH and Co KG, Novartis, and Shire; and has authored books and articles on psychotherapy published by Elsevier, Hogrefe, Schattauer, Kohlhammer, and Karger. Dr Matthies reported receiving a speaker's fee from Janssen-Cilag; and involvement in clinical trials conducted by Janssen-Cilag and Eli Lilly and Co. Dr Colla reported serving on advisory boards, receiving speaker's honoraria, or performing phase 3 studies within the last 3 years with Shire, Eli Lilly and Co, and Novartis. Dr Jacob reported receiving speaker's honoraria from MEDICE; serving as an advisory board member of Eli Lilly and Co; performing phase 3 studies at MEDICE, Novartis, Janssen-Cilag, Eli Lilly and Co; and performing an investigator-initiated trial with Eli Lilly and Co. Dr Sobanski reported receiving speaker's honoraria from MEDICE, Eli Lilly and Co, and

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Additional Information: Other projects in our network on psychotherapy research in ADHD (speaker: Dr Philipsen; 2006-2012, Andreas Warnke, MD, University Hospital of Würzburg, Würzburg, Germany) are coordinated by Dr Jans (ADHD in mothers and children), Dr Tebartz van Elst (functional and morphometric brain mapping), and Klaus-Peter Lesch, MD, University Hospital of Würzburg (molecular genetics).

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