Methylphenidate Treatment for Attention-Deficit/Hyperactivity Disorder in Children and Adolescents With Velocardiofacial Syndrome: An Open-Label Study

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Background: Velocardiofacial syndrome (VCFS) is a common microdeletion syndrome associated with psychiatric morbidity and developmental disabilities. Although attention-deficit/hyperactivity disorder (ADHD) is the most common psychiatric problem associated with VCFS, there are no reports on methylphenidate treatment in this patient population. Indeed, clinicians have commonly avoided the use of methylphenidate in children with VCFS because of concerns about ineffectiveness or psychotic exacerbation.

Method: Forty subjects of mean ± SD age 11.0 ± 5.0 years with VCFS were assessed for DSM-IV diagnoses using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version, and its extended ADHD module (K-SADS-P-ADHD). Those found to have comorbid ADHD were treated with methylphenidate, 0.3 mg/kg once daily. Treatment efficacy was evaluated after 4 weeks with the K-SADS-P-ADHD, the Conners' Abbreviated Teacher Questionnaire, and the Conners' Continuous Performance Test. Side effects were evaluated with a modified version of the Barkley Side Effects Rating Scale.

Results: Of the 18 subjects (45%) diagnosed with ADHD, 12 agreed to participate in the study. Their ADHD symptoms, both behavioral and cognitive, improved significantly with treatment. None of the patients showed clinical worsening or psychotic symptoms. Side effects were usually mild and did not warrant discontinuation of methylphenidate. The most common side effects were anorexia and depressive-like symptoms.

Conclusion: This open-label study indicates that methylphenidate is effective and safe in patients with VCFS. Therefore, its current limited use in this population seems to be unjustified. Larger, controlled clinical and pharmacogenetic studies are needed to confirm these findings.

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Velocardiofacial syndrome (VCFS) is the most common microdeletion syndrome with a frequency of 1 in 4000 live births.[1] It is caused by a microdeletion in the long arm of chromosome 22; most cases are de novo mutations and only 10% to 28% are familial.[2] VCFS is characterized by a typical facies (hypoplastic alae nasae leading to a bulbous nasal tip, prominent nasal root, long narrow face with flat cheeks, narrow palpebral fissures, small mouth, retruded chin, and small, cupped ears), congenital anomalies of the heart and great vessels in about 75% of patients (most common are tetralogy of Fallot, interrupted aortic arch, and ventricular septal defect), and cleft palate or velopharyngeal incompetence in about 80% of patients.[2,3] Intelligence varies from normal to moderate mental retardation; on average, IQ is in the borderline range.[4]

Patients with VCFS also have a high rate of psychiatric disorders. About 25% develop schizophrenia by early adulthood.[5,6] Indeed, studies of patients with schizophrenia have shown a higher frequency of the 22q11 deletion relative to the general population.[7] Affective disorders, anxiety disorders, and pervasive developmental disorders have also been reported in patients with VCFS.[8–11] Some

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patients with VCFS tend to be impulsive, disinhibited, and prone to temper tantrums.[12,13] The most common psychiatric morbidity for children, adolescents, and young adults with VCFS is attention-deficit/hyperactivity disorder (ADHD) in 35% to 46% (inattentive and combined type and no cases of hyperactive type) and oppositional defiant disorder in 8% to 43%.[8–11,14] None of the patients with VCFS in any of these studies[8–11,14] were diagnosed with conduct disorder.

Despite the high prevalence of ADHD in VCFS patients, there are no studies on the efficacy and safety of stimulant drugs such as methylphenidate in this population. However, the issue is widely discussed among clinicians and parents in chat forums on the Internet. Many clinicians do not recommend prescribing stimulants to children with VCFS for several reasons. First, these patients are at increased risk of developing psychotic and affective symptoms, which are also possible side effects of stimulants.[15,16] Second, some authors have suggested that stimulant medications are generally ineffective in VCFS patients and have a high rate of side effects.[8,12] Third, 70% of patients with VCFS present with congenital mechanical cardiac anomalies, and stimulants can induce hypertension and tachycardia.[17] These apprehensions were also based on the finding that in all patients with VCFS, one allele of the gene encoding for catechol-*o*-methyltransferase (COMT) is deleted. The COMT enzyme degrades the catecholamines dopamine, norepinephrine, and epinephrine. Stimulants increase levels of synaptic catecholamines (especially dopamine) by increasing their release from the presynaptic terminals and by blocking their reuptake. It is thus possible that reduced levels of the gene coding for the COMT enzyme in VCFS may cause a more robust and sustained increase in synaptic catecholamine levels, which might lead to more side effects. At the same time, this factor might contribute to an increased efficacy of the drug in this patient population.

The main purpose of the present open-label study was to evaluate the efficacy and safety of methylphenidate in the treatment of children and adolescents with VCFS and ADHD.

METHOD

Subjects

The sample consisted of 40 consecutive patients with VCFS (28 boys, 12 girls) aged 5 to 20 years (mean ± SD 11.0 ± 5.0 years) who were referred to the Neurobehavioral Genetics Clinic of the Feinberg Child Study Center, Schneider Children's Medical Center of Israel, from January 2001 to September 2002. This is the only such clinic in Israel, and it receives referrals from all over the country. The study was restricted to patients in whom VCFS was confirmed with fluorescent in situ hybridization using a commercial probe (VYSIS, Downers Grove, Ill) for VCFS region. Two patients with VCFS and schizophrenia were excluded. The study protocol was approved by the Institutional Review Board of the Schneider Children's Medical Center, and written informed consent was obtained from the study participants and their parents after the procedures and possible side effects of the medication were fully explained to them.

Diagnostic Procedure

All subjects and their parents were interviewed by a senior child and adolescent psychiatrist (D.G.). A detailed developmental, medical, educational, occupational, and psychiatric history was taken, and the patient's available records were reviewed. All children and their parents were interviewed by master's level clinical psychologists (G.P., M.B.) using the Hebrew version of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime (K-SADS-PL).[18] The interrater reliability was excellent (mean kappa levels above 0.80 for all diagnoses). Best estimate diagnoses were made using a modification of the method described by Leckman et al.[19] Four diagnosticians, including 2 senior child and adolescent psychiatrists and 2 master's level clinical psychologists, participated in the procedure.

In addition to the screening K-SADS-PL, we used the module section of the K-SADS-Present on ADHD (K-SADS-P-ADHD), in which emphasis was placed on interviews with the children's primary teachers and parents. The module is composed of the 18 items from the DSM-IV (9 for attention, 6 for hyperactivity, and 3 for impulsivity) each ranked 0—not at all, 1—sometimes, or 2—often. A diagnosis of ADHD is based on a score of 2 in at least 6 symptoms of inattention and/or at least 6 symptoms of hyperactivity/impulsivity. Children were considered to have ADHD only when all 4 raters made an independent diagnosis of ADHD.

Intelligence was assessed with the age-appropriate Hebrew version of the Wechsler Intelligence Scale for Children-III.[20] Most (68%) of the children in our sample were in special education classes because of low IQ. Specific learning disabilities were not assessed because standardized achievement tests are not available for Israeli children.

Medical Evaluation

All patients underwent a comprehensive medical evaluation by a multidisciplinary team of physicians. They also underwent a physical and clinical examination by a pediatric cardiologist who approved the cardiac safety of methylphenidate in each case. Pulse, blood pressure, weight, and height were measured. In addition, the following laboratory assessments were conducted: liver and kidney function tests, calcium levels, complete blood counts, electrocardiograms (ECGs), and cardiac

echocardiograms. These evaluations were conducted for all patients at baseline and after 4 weeks of treatment.

Treatment Procedure

Patients diagnosed with ADHD entered the treatment protocol. They were prescribed methylphenidate at a relatively low weight-adjusted dose of 0.3 mg/kg once daily, in the morning after breakfast and before school. The low dose was chosen to minimize possible side effects and was held constant throughout the 4-week study.

To rate treatment response, we used only the teacher informant interview based on the suggestion of Barkley et al.[15,21] that improvement in the classroom was an accurate measure of response. To evaluate methylphenidate efficacy and side effects, several measures were used, rated at baseline and after 4 weeks of treatment. The teachers completed the scales by telephone interviews at the same time points.

Assessment

K-SADS-P-ADHD using teacher as informant. The 18-item scale is divided into 3 clusters: attention, hyperactivity, and impulsivity. The cluster scores are summed to generate an internally consistent severity scale.[22] The score for each cluster was calculated by summing the scores of each item in the cluster and dividing by the number of items. Thus, the score for each cluster was between 0 and 2.

Conners' Abbreviated Teacher Questionnaire (Hebrew version). The Conners' Abbreviated Teacher Questionnaire (CATQ)[23] items tap observable behaviors relating to inattention, overactivity, and impulsivity. Each item is rated from 0-not at all to 3-very much.

Conners' Continuous Performance Test (version 3.0). The Conners' Continuous Performance Test (CCPT)[24] is a visual vigilance task that requires the child to respond to the computer screen by pressing the spacebar for every letter presented except X. The test takes 14 minutes to complete, during which time the number of omission and commission errors, reaction time, and variability of reaction times are calculated. The CCPT also provides an overall index of attention problems derived from the weighted regression equation of variables relevant to the reaction time, omission errors, and variability of responses. An overall index greater than 11 is considered the conservative cutoff.[25] The CCPT was conducted twice, once before methylphenidate ingestion and 1 hour after, on the same day.

Barkley Side Effects Rating Scale (modified Hebrew version). This scale[21] assesses the frequency and severity of 17 common side effects of methylphenidate, each rated 0-absent, 1-mild, 2-significant, or 3-discontinued medication because of the side effect. The scale was completed on the basis of reports from the teachers and parents. Teachers were also asked to report on the duration (in hours) of the clinical effect of methylphenidate based on their global estimate over the month of treatment.

Statistics

Statistical analysis was performed with SPSS for Windows (release 11.0.1, SPSS, Chicago, Ill). Paired t tests for comparing scores of the K-SADS-P-ADHD and the CCPT measures at baseline and after 4 weeks of methylphenidate treatment were conducted. Two-sided tests of significance were used, and the level of significance was set at $\alpha = .05$.

RESULTS

Of the 40 children with VCFS, 18 (45.0%) met the DSM-IV criteria for ADHD (11 [27.5%] combined type and 7 [17.5%] inattentive type). The psychiatric comorbidities of the children with ADHD were as follows: oppositional-defiant disorder (7, 41%); obsessive-compulsive disorder (without tics) (6, 35%); specific phobia (6, 35%); dysthymic disorder, generalized anxiety disorder, and social phobia (2 each, 12%); adjustment disorder, eating disorder, primary encopresis, and chronic tic disorder (1 each, 6%).

IQ (mean ± SD) of the total sample was 77.8 ± 15.2. There was no difference in IQ between the VCFS patients with and without ADHD (77.0 ± 15.0 vs. 79.8 ± 16.1, $t = 0.47$, $p = .61$), and there was no correlation between the IQ scores and the total scores on the K-SADS-P-ADHD module ($r = 0.08$, $p = .67$). The rate of ADHD was similar in the patients with high and low IQ (9/20 patients each) using the median value (79) as the cutoff point.

Psychiatric disorders in 170 total-sample first-degree relatives above age 6 years were documented. Findings included ADHD in 13 subjects (8%), anxiety disorders in 15 (9%), depression in 4 (2%), and learning disabilities in 13 (8%).

The treatment protocol was offered to all patients with a diagnosis of ADHD. In 5 cases, the parents were apprehensive about the side effects of the drug and refused participation, and in 1 case, the parents refused us permission to contact the teacher for follow-up. The remaining 12 patients entered the study.

The common medical comorbidities of the 12 treated patients were congenital cardiac anomaly (8 subjects, 67% [ventricular septal defect in 4, tetralogy of Fallot in 2, interruption of aortic arch type B in 2]), and cleft palate/velopharyngeal insufficiency (10 subjects, 83%). Nine patients had no prior psychopharmacologic treatment (drug-naive). Two patients were being treated with fluoxetine for symptoms of obsessive-compulsive disorder, and they continued with the same dose (30 and 40 mg/day) throughout the study period. One patient had been previously treated with clonidine, 0.15 mg/day, for his ADHD, but it was not effective and caused marked sedation.

Table 1. Response of 12 Subjects With Velocardiofacial Syndrome and Attention-Deficit/Hyperactivity Disorder (ADHD) to Methylphenidate Treatment

	Baseline Score		Score After Methylphenidate Treatment		Statistics		
Measure	Mean	SD	Mean	SD	t	df	p
Clinical (N = 12)							
CATQ	15.5	4.2	7.6	3.0	6.7	11	< .0001
K-SADS-P-ADHD							
Attention	1.26	0.37	0.65	0.38	4.4	11	< .001
Hyperactivity	1.19	0.49	0.28	0.34	5.8	11	< .0001
Impulsivity	1.31	0.52	0.42	0.46	5.2	11	< .0001
Total	1.25	0.35	0.48	0.33	6.7	11	< .0001
Neuropsychological							
CCPT (N = 6)							
Omission errors	45.5	27.3	16.0	12.8	2.7	5	< .05
Commission errors	21.7	5.8	21.5	6.3	0.08	5	NS
Reaction time (msec)	514.1	111.6	401.4	52.8	3.1	5	NS
Variability of reaction time (msec)	58.9	27.6	36.0	23.7	2.1	5	< .05
Hits	278.5	27.3	308.0	12.8	2.7	5	< .05
Overall index	16.8	4.8	5.8	7.4	5.5	5	< .001

Abbreviations: CATQ = Conners' Abbreviated Teacher Questionnaire; CCPT = Conners' Continuous Performance Test; K-SADS-P-ADHD = Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present, ADHD module; NS = not significant.

The mean ± SD daily dose of methylphenidate, prescribed according to 0.3 mg/kg, 9.4 ± 5.2 mg, and the mean duration of clinical effect according to the teachers' reports was 3.2 ± 1.4 hours. Overall, the medication induced a significant improvement in ADHD symptoms, as reflected by the CATQ and the K-SADS-P-ADHD attention, hyperactivity, impulsivity, and total scores (Table 1). The response by individual subject is given in Table 2. Significant clinical improvement occurred in 9 patients (75%) (Table 2) and was defined according to the magnitude suggested by Spencer et al.[26] criteria as a reduction of 30% or more in total score on both the CATQ and the K-SADS-P-ADHD.

Only 6 of the 12 treated patients completed the CCPT. Five patients did not comprehend the Hebrew instructions properly (4 Arabs, 1 moderate mental retardation), and 1 patient was below age 6 years (the minimal age for CCPT norms). All patients who completed the scale showed a significant decline after treatment in omission errors, reaction time, hits, and overall index, but not in the commission errors (Table 1). There was a strong negative correlation between the methylphenidate-related improvement in the CCPT overall index and IQ score ($r = –0.68$, $p = .01$), meaning that patients with high IQ improved more than patients with low IQ.

The prevalence of side effects of methylphenidate is shown in Table 3. In none of the subjects were the adverse effects severe enough to warrant discontinuation of the medication. The most common reported side effects were poor appetite (92%), irritability (50%), sadness (42%), stomachaches (42%), talking little with others (42%), and proneness to crying (33%). None of the patients exhibited psychotic symptoms or manic or hypomanic status.

None of the patients exhibited hypertension, tachycardia, or a change in ECG recordings after 4 weeks of methylphenidate treatment. The respective baseline and 4-week values were as follows: diastolic blood pressure (63.3 ± 9.1 and 64.1 ± 7.9 mm Hg), systolic blood pressure (103.7 ± 16.2 and 104.9 ± 16.9 mm Hg), and pulse (76.1 ± 10.2 and 78.3 ± 10.1 bpm).

DISCUSSION

Patients with VCFS have a high rate of psychiatric disorders. Although the characteristics of these psychiatric morbidities have been relatively well defined, there are limited data on the psychopharmacologic treatment in this patient population. In agreement with previous studies,[8–11] we found that almost half of our patients with VCFS had ADHD, making ADHD the most common psychiatric comorbidity of VCFS.

ADHD is more common in children with low intelligence.[27] However, the high rate of ADHD in subjects with VCFS is apparently not merely an epiphenomenon of developmental disability since the mean IQ in the VCFS subjects with ADHD as in those without ADHD was almost the same. Rather, it is probably related to one of the genes in the region of the 22q11 deletion, such as the COMT gene.

Our study is the first to report on the efficacy, tolerability, and safety of methylphenidate treatment in VCFS patients with comorbid ADHD. We found that a low dose of methylphenidate (0.3 mg/kg) was generally effective and well tolerated. This was supported in both the clinical and neuropsychological measures. Teachers reported a very robust and significant improvement in ADHD symptoms, and the CATQ and K-SADS-P-ADHD scales showed an

Table 2. Changes in ADHD Symptom Severity by Individual Subject Following Methylphenidate Treatment

Patient	Age (y)	Methylphenidate Dosage (mg/d)	Conners' Abbreviated Teacher Questionnaire Score			K-SADS-P-ADHD Score			
			Baseline	Wk 4	D Δ %	Baseline	Wk 4	D Δ %	D Δ > 30%[a]
Male	12	20	14	7	50	20	18	10	
Male	9	10	20	6	70	28	9	68	*
Male	12	10	18	7	61	20	7	65	*
Male	7	7.5	17	11	35	21	9	57	*
Male	6	5	12	8	33	29	24	17	
Female	10	10	15	4	73	28	4	86	*
Male	6	5	9	2	78	26	2	92	*
Male	8	7.5	20	9	55	31	5	84	*
Female	5	5	20	10	50	34	9	74	*
Male	10	17.5	21	13	38	24	6	75	*
Male	9	10	14	6	57	21	5	76	*
Male	8	7.5	9	8	11	10	12	–20	

[a]Asterisks refer to patients in whom there was more than 30% improvement in both the Conners' Abbreviated Teacher Questionnaire and the K-SADS-P-ADHD module.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, K-SADS-P-ADHD = Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present, ADHD module.

Table 3. Prevalence of Side Effects in Subjects With Velocardiofacial Syndrome Treated With Methylphenidate

Side Effect	Mild N (%)	Significant N (%)	Total N (%)
Poor appetite	3 (25)	8 (67)	11 (92)
Irritability	5 (42)	1 (8)	6 (50)
Sadness/unhappiness	2 (17)	3 (25)	5 (42)
Stomachaches	3 (25)	2 (17)	5 (42)
Talking little with others	4 (33)	1 (8)	5 (42)
Proneness to crying	1 (8)	3 (25)	4 (33)
Uninterested in others	2 (17)	1 (8)	3 (25)
Drowsiness	3 (25)	0	3 (25)
Headaches	3 (25)	0	3 (25)
Daydreams	3 (25)	0	3 (25)
Biting fingernails	3 (25)	0	3 (25)
Anxiousness	1 (8)	0	1 (8)
Dizziness	1 (8)	0	1 (8)
Tics or nervous movements	1 (8)	0	1 (8)
Trouble sleeping	0	0	0
Nightmares	0	0	0
Unusually happy	0	0	0

average decrease of more than 50% in the severity of symptoms of inattention, hyperactivity, and impulsivity in 75% of the study group (Table 1). These findings are similar to the figures reported for non-VCFS children with ADHD.[28,29] In addition, the CCPT, though performed in a small number of children, indicated improvement in attention as reflected by omission errors, reaction time, and overall index. Interestingly, there was no change in the number of commission errors (Table 1). Thus, according to the CCPT, methylphenidate seems to improve the attention deficit but not the impulsivity of patients with VCFS.

The mean duration of the effect of methylphenidate, as reported by the teachers, was 3.2 hours, similar to that found in non-VCFS children.[30] However, because this was a rough global estimate over the month of treatment, we could not reach a definite conclusion regarding that aspect.

In this pilot study, we compared the prevalence of side effects in our population with rates reported in the literature. The absence of a control group of ADHD patients without VCFS limits our conclusions regarding the efficacy and tolerability of methylphenidate in the VCFS population. However, methylphenidate seemed to be relatively well tolerated, and none of the patients had to discontinue its use because of side effects. The rate of each individual side effect was similar to, or in most cases even lower than, the rates reported for non-VCFS ADHD patients.[15,25,29] For example, irritability occurred in 50% of our sample versus 65% to 80% in non-VCFS patients, sadness in 42% versus 48% to 56%, stomachaches in 42% versus 24% to 32%, talking little with others in 42% versus 20% to 28%, and proneness to crying in 33% versus 59% to 71%. The high incidence of depression-like side effects (sadness, irritability, reduced social talking, and crying) suggests that our VCFS sample might have been depression-prone or might have had undiagnosed major depression prior to stimulant treatment beyond the dysthymia (12%) that we found. The most common side effect in our sample was decreased appetite, reported in 92% of our patients compared with 45% to 69% in non-VCFS patients. In most cases, the appetite decreased during school hours, and the child "caught up" with the afternoon and evening meals. The methylphenidate-induced decreased appetite may be related to the high rate of a wide range of feeding problems, including food refusal, in VCFS patients.[31] None of our patients had insomnia, a common side effect of methylphenidate, probably because in this pilot study methylphenidate was given once daily in the morning. No significant changes in blood pressure and heart rate were found. However, our sample was too small to detect several point changes in these parameters. None of our patients experienced euphoria or manic or psychotic symptoms, and none were diagnosed with bipolar affective disorder. Other studies found the

prevalence of bipolar affective disorder to be between 0% and 4%.[5,6,9,10,11] Papolos et al.[8] reported a 52% rate of bipolar affective disorder in their sample of VCFS patients, with 2 of 3 VCFS patients developing manic symptoms after the initiation of methylphenidate. The reason for this discrepancy is unclear and may be related to sample selection or differences in diagnostic threshold. Furthermore, none of our patients met the DSM-IV criteria for major depressive disorder. Two of the VCFS patients in our clinic (5%) who were diagnosed as suffering from schizophrenia were excluded from the study. The relatively low rate of schizophrenia in our VCFS population might be related to their young age, which was below the common threshold of schizophrenia onset. The similar efficacy and tolerability of methylphenidate treatment in our VCFS sample and non-VCFS patients with ADHD are contrary to the assumption that the decreased dosage of the COMT gene significantly alters the pharmacodynamic properties of methylphenidate in these patients. It is, however, in line with recent findings of an absence of significant change in basal brain dopamine and norepinephrine levels in mice with a heterozygous deletion of the COMT gene.[32] Unfortunately, that study provides no data on the impact of challenge with stimulants on catecholamine brain content and behavior.

Interestingly, a functional and common biallelic polymorphism has been identified in the COMT gene which codes for COMT variants with high and low biochemical activities.[33,34] The interaction between the polymorphism of the remaining COMT allele and the response and tolerability to methylphenidate treatment in patients with VCFS merits further pharmacologic and pharmacogenetic investigations. Also interesting are the interactions of methylphenidate response with the genotype of COMT and genotypes of other relevant genes reported to be associated with ADHD or catecholamine metabolism, such as dopamine transporter (DAT1) and monoamine oxidase A and B genes. Moreover, VCFS, which is characterized by a deletion of one copy of the COMT gene, may serve as an excellent model for studying the pharmacogenetic effects of the COMT genotype.

The present study has several limitations: the open-label design, the relatively small sample size (although the only one reported to date), and the small number of patients included in the computerized neuropsychological evaluation (due to language and comprehension difficulties). In this pilot study, we prescribed methylphenidate only for the school hours. Thus, our behavioral outcome data were restricted to teachers' observations. In addition, the study examined only a fixed and relatively moderate dose of methylphenidate. We found that anorexia and depressive symptoms were quite common already at this low dose, which may imply that VCFS subjects are more sensitive to lower methylphenidate doses than the non-VCFS ADHD population. This sensitivity may stem from the COMT enzyme deficiency present in VCFS patients and should be tested in future studies with flexible and multiple dosages of methylphenidate throughout the day and not only during school hours. The outcome data should also be collected from parents' observations in the afternoon and evening hours. We used the CATQ and CCPT in our naturalistic study, as these are the standard tools applied in clinical evaluations of treatment of children with ADHD in Israel. In future studies, we recommend the use of more elaborate scales for the assessment of ADHD symptom improvement, such as the Conners' Parent and Teacher Rating Scales-Revised.[35] We also recommend a more simple continuous performance test such as that described by Snyder et al.,[36] which would possibly be more appropriate for VCFS subjects with mental retardation.

In conclusion, this pilot study shows that methylphenidate seems to be effective, safe, and well tolerated in patients with VCFS and ADHD. The use of methylphenidate in children with VCFS is currently quite limited because of concerns about severe side effects, especially manic and psychotic symptoms. No empirical evidence was found in this study to support such apprehensions, warranting further large-scale, double-blind, placebo-controlled trials. A large-scale, double-blind, head-to-head comparative study of ADHD treatment in VCFS and non-VCFS ADHD patients is warranted.

Drug names: clonidine (Catapres, Duraclon, and others), fluoxetine (Prozac and others), methylphenidate (Ritalin, Concerta, and others).

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