How appropriate is the increased use of methylphenidate?

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CHAPTER 5

Effects of Discontinuing Methylphenidate on Strengths and Difficulties, Quality of Life and Parenting Stress

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Abstract

Objectives

To study the effects of discontinuation of long-term methylphenidate use on secondary outcome measures of strengths and difficulties, quality of life (QoL), and parenting stress.

Methods

Ninety-four children and adolescents aged 8 to 18 years who had used methylphenidate for over 2 years were randomly assigned to double-blind continuation of treatment for 7 weeks (36 or 54 mg extended release methylphenidate) or to gradual withdrawal over 3 to 4 weeks placebo. We used mixed models for repeated measures to investigate effects on parent, teacher, and child ratings of hyperactivity/inattention and comorbid symptoms with the Strengths and Difficulties Questionnaire (SDQ), investigator- and teacher-rated oppositional symptoms (Conners Teacher Rating Scale-Revised: short form [CTRS-R:S]), and parent-rated aggression with the Retrospective Modified Overt Aggression Scale. QoL was assessed with the Revised Questionnaire for Children and Adolescents to record health-related quality of life and parenting stress with the Nijmegen Parental Stress Index.

Results

Hyperactivity/inattention scores from the parent- and teacher-rated SDQ (difference in mean change over time of respectively: -1.1 [95% confidence interval, CI, -2.0 to -0.3]; $p = 0.01$; -2.9 [95% CI -2.9 to -0.7; $p = 0.01$]) and oppositional scores of the teacher-rated CTRS-R:S (difference in mean change -1.9 95% CI [-3.1 to -0.6; $p < 0.01$]) deteriorated to a significantly larger extent in the discontinuation group than in the continuation group. We did not find effects on other symptom domains, aggression, QoL, and parenting stress after discontinuation of methylphenidate.

Conclusion

Our study suggests beneficial effects of long-term methylphenidate use beyond 2 years for oppositional behaviors in the school environment. Similarly, beneficial effects were found on hyperactivity-inattention symptoms as rated by parent and teacher scales, confirming our primary study on investigator ratings of attention-deficit/hyperactivity disorder. However, discontinuation of methylphenidate did not appear to have impact on other comorbid problems or aspects of the child's or parental functioning

Introduction

Methylphenidate is the first-line pharmacological treatment for children with attention-deficit/hyperactivity disorder (ADHD) (NICE guideline, 2018) and its short-term efficacy for reducing ADHD symptoms is well established (Cortese et al., 2018). ADHD symptoms are often accompanied by comorbid symptoms such as oppositional behaviors, aggression, mood problems, anxiety, and by impaired social functioning (Biederman, 2005; Ros and Graziano, 2018). Besides, patients with ADHD often experience a lower quality of life (QoL) (Lee et al., 2016; Mulraney et al., 2017). ADHD treatment should therefore not only result in symptomatic improvement, but also increase the child's QoL, as acknowledged in the European Medicines Agency guidance on outcomes in clinical studies (European Medicines Agency, 2010).

There is evidence that psychostimulants including methylphenidate have a moderate-to-large short-term (i.e., up to 16 weeks) effect on the management of oppositional behavior, conduct problems, and aggression in children and adolescents with ADHD with or without comorbid oppositional-deviant disorder (ODD) or conduct disorder (Pringsheim et al., 2015). Furthermore, systematic reviews concluded that there may be a short-term positive effect of ADHD medication on QoL in children and adolescents (Coghill, 2010; Coghill et al., 2017). However, the effect sizes are smaller than seen for ADHD symptoms and almost exclusively based on studies examining atomoxetine.

ADHD in children may also affect the well-being of their parents. Several studies have shown that parents of children with ADHD experience more parenting stress than parents of typically developing children (Herrerias et al., 2001; Brandt-Dominicus, 2005; Poulton et al., 2013; Dey et al., 2018) perhaps resulting from the increased demands of caretaking, economical costs of medical care, role dissatisfaction, increased levels of parental frustration, marital discord, or divorce (Laugesen et al., 2016). The parenting stress level that parents experience is directly related to the number of ADHD symptoms in their children, according to a range of studies (Deault, 2010; Graziano et al., 2011; Haack et al., 2016). Moreover, an open label study suggested that methylphenidate use may decrease parenting stress and depression, with Improvements in parenting mood and stress being associated with the decrease in ADHD symptom severity (Hwang et al., 2013).

Benefits of methylphenidate have been based on short-term studies; its long-term benefits remain unclear (Coghill, 2019; Cortese, 2019; Swanson, 2019). Nevertheless, 60% of the children who started stimulants continue to use these beyond 2 years (Zetterqvist et al., 2013; Beau-Lejdstrom et al., 2016). In our recently published placebo-controlled double-blind discontinuation trial, we saw that methylphenidate remains effective after 2 years of use, with regard to the investigator-rated ADHD rating scale (ADHD- RS) as our primary outcome measure (Matthijssen et al., 2019). In this study, we included children and adolescents who had been using methylphenidate for over 2 years. Here, we aimed to study the effects of discontinuing methylphenidate on secondary outcome measures based on parent, teacher, and/or child reports of hyperactivity/inattention and

comorbid symptoms such as oppositional-deviant behavior, the child's QoL, and parenting stress. Given the short-term benefits of methylphenidate on oppositional behavior, conducts problems, aggression, QoL, and parenting stress, we hypothesized that discontinuation of methylphenidate after long-term use would result in deterioration in these areas.

Methods

Participants

Participants were children between 8 and 18 years of age who had been using methylphenidate for more than 2 years, in the form of extended release 36 or 54 mg/day during at least the last 4 weeks. To allow children who were originally not using 36 or 54 mg/day of extended-release methylphenidate to participate they could switch to one of these dosages, whichever was the closest to the dosage they were already using. We included children with an IQ over 70. Both parents and children who were 12 years and older provided written informed consent. For children under 12 years, the parents provided written informed consent, and the children oral assent, in accordance with Dutch medical ethical laws. On the consent forms parents could separately give permission to obtain teacher-ratings, which was optional. The study was approved by national and local institutional review board committees. More detailed information about inclusion criteria can be found in Matthijssen et al. (2019).

Design and interventions

Participants were randomly assigned in a 1:1 ratio to either continue active medication at the same maintenance dose for 7 weeks or to gradual withdrawal to placebo over a 3-week period followed by 4 weeks of complete placebo. We obtained ratings at baseline and after 7 weeks, or earlier in case of study drop out (i.e., at time of study drop out).

Outcomes

Strengths and difficulties.

To investigate the effects of methylphenidate discontinuation on symptom domains, we used the parent-, teacher-, and child-reports (ages 11–16) of the Strengths and Difficulties Questionnaire (SDQ, Dutch version) (Van Widenfelt et al., 2003). The SDQ is a widely used, brief screening questionnaire, aimed at identifying behavioral and emotional problems in children, containing 25 items rated on a three-point scale ranging from "0 = not true" to "2 = very true." It contains five subscales with each five items (range 0–10); (1) Emotional symptoms, (2) Conduct problems, (3) Hyperactivity/inattention, (4) Peer relationship problems, and (5) Prosocial behavior; and a Total score (sum score of the first four subscales, range 0–40).

To assess oppositional behavior in the school environment, we used the teacher-rated Oppositional subscale (range 0–15) of the Conners Teacher Rating Scale-Revised: short form (CTRS-R:S) (Conners et al., 1998). The CTRS-R:S is a 28-item, four-point Likert rating scale, ranging from "0 = not at all" to "3 = very often"', that contains items on ADHD and comorbid conditions.

To assess ODD symptoms, we used the investigator administered total score on the ODD rating scale (ODD-RS) Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5) (Hommersen et al., 2006). This is the adapted version of the ODD- RS DSM-IV, in accordance with the changes of ODD criteria introduced in the DSM-5 (American Psychiatric Association, 2013). The ODD-RS contains eight items scored on a four-point Likert scale, ranging from "0 = never" to "3 = very often", and assesses ODD symptom severity (sum score range 0–24) over the past week.

Aggressive behavior was assessed by the parent-completed Retrospective Modified Overt Aggression Scale [R-MOAS, as used in Blader et al. (2009, 2010)]. Parents rated the weighted frequency of 16 aggressive behaviors across four areas over the past week: verbal aggression (range 0–20), physical aggression toward others (range 0–120), aggression toward oneself (range 0–90), and destruction or hostile misuse of property (range 0–60) on three- or four-point Likert scales ranging from "none or 0–1 times" to "5 times or more". We used the total sum score of all subscales (range 0–290).

Quality of life.

The parent- and child-rated Revised questionnaire for Children and adolescents to record health-related quality of life (KINDL-R) assesses children's QoL in six domains, namely Physical Well-Being, Emotional Well-Being, Self-Esteem, Friends, Family, and School (Ravens-Sieberer and Bullinger, 1998, 2000). It contains 30 items using a five-point Likert scale from "1 = never" to "5 = always". The subscale scores range from 4 to 20 and the total score represents the sum of the subscales scores (range 24–120).

Parenting stress

The short version of the Nijmegen Parental Stress Index (NOSI-K, the Dutch version of the Parental Stress Index) (Brock de et al., 1992; Abidin, 2012), measures the amount of stress or pressure of several aspects within the context of parenting a child. It consists of 10 subscales assessing a parent (Competence, Attachment, Depression, Health, Adjustment, and Mood) and child domain (Distractibility, Demanding, Positive Ratification, and Acceptance), and a total score. Parents score 25 items on a six-point Likert scale ranging from 1 = completely agree to 6 = completely disagree. In our study, we calculated a total score as the sum of the child domain subscales (range 14–84).

Randomization

For each dosage, the trial pharmacy made a separate computer-generated randomization list. The study medication for either continued active medication or discontinuation was dispensed in accordance with these lists. We used a block-randomization of six to establish even groups.

Statistical methods

We used the group time interaction of the mixed model for repeated measures to analyze differences in outcome measures from baseline to 7 weeks between both randomized groups, using group (continuation or discontinuation) and time point (baseline or 7 weeks) as fixed effects. An unstructured covariance matrix was used. Analyses were conducted on the full dataset, which included all participants who received at least one dose of the study drug. In those who had with-

drawn from the study we used ratings that were obtained at the time of study termination. The significance threshold for all analyses was $p < 0.05$. We first conducted analyses on the total scores of the different outcome measures and only if significant further analyzed the subscale scores, to reduce the number of tests where appropriate.

Results

Strengths and difficulties

Tables 1 and 2 indicate a significant effect of discontinuation on the parent- and teacher-rated SDQ total scores. Subsequent analyses on the SDQ subscales revealed significant differences between the discontinuation and continuation group in the level of mean change regarding the Hyperactivity/inattention subscale, both parent- and teacher-rated, but not on the other subscales. Thus, the Hyperactivity/inattention scores deteriorated to a significantly larger extent in the discontinuation group than in the continuation group.

Tables 1 and 2 also shows a significant difference regarding the teacher-rated CTRS-R:S Oppositional subscale between the discontinuation and continuation group in the level of mean change after 7 weeks from baseline, indicating that on average the teacher-rated Oppositional scores deteriorated to a significantly larger extent in the discontinuation group than in the continuation group. The result for investigator-rated oppositional symptoms by the ODD-RS reached marginal significance.

Lastly, we did not find significant differences in the level of mean change between the discontinuation and continuation groups between baseline and 7 weeks for the total score of the child-reported SDQ and parent-rated aggression by the R-MOAS (Tables 1 and 2).

QoL and parenting stress

There were no significant differences in QoL between the discontinuation and continuation groups in the level of mean change between baseline and 7 weeks for the parent- and child-rated KINDL-R total score, nor for the parenting stress total score (child domain) measured with the NOSI-K (Table 3).

Table 1a. Baseline scores of parent-, teacher-, child- and investigator- rated symptom domains

Measure	Discontinuation			Continuation		
Baseline	**Mean**	**SE**	**95% CI**	**Mean**	**SE**	**95% CI**
Parent-rated						
	n=45			n=46		
SDQ-Parent						
Total score	13.8	.84	12.2-15.5	15.7	.82	14.1-17.4
Emotional symptoms	2.4	.31	1.8-3.1	3.1	.32	2.4-3.7
Conduct problems	2.7	.26	1.6-2.7	2.6	.28	2.0-3.1
Hyperactivity/inattention	6.4	.35	5.7-7.0	7.0	.34	6.3-7.7
Peer relations	2.3	.32	1.7-3.0	3.1	.32	2.5-3.8
Prosocial behavior	7.6	.33	6.9-8.2	6.8	.32	6.2-7.4
R-MOAS aggression	109.3	2.3	104.8-113.9	108.1	2.3	103.6-112.6
Teacher-rated						
	n=38			n=40		
SDQ-Teacher						
Total score	10.0	.96	8.0-11.9	13.4	.94	11.5-15.2
Emotional symptoms	2.2	.35	1.5-2.9	2.4	.34	1.7-3.1
Conduct problems	1.0	.28	.4-1.5	1.8	.38	1.2-2.3
Hyperactivity/inattention	4.6	.46	3.7-5.5	5.8	.45	4.9-6.7
Peer relations	2.2	.39	1.4-3.0	3.4	.38	2.7-4.2
Prosocial behavior	7.0	.36	6.3-7.7	5.7	.35	5.0-6.4
CTRS-Oppositional	7.2	.52	6.1-8.2	8.1	.51	7.1-9.1
Child-rated						
	n=38			n=41		
SDQ-Child						
Total score	13.0	.78	11.5-14.6	14.5	.75	13.0-16.0
Investigator-rated						
	n=47			n=47		
ODD-RS	4.8	.71	3.4-6.2	5.6	.71	4.2-7.0

Note: CI = confidence interval. SE = standard error. SDQ = Strength and Difficulties Questionnaire. R-MOAS = Retrospective Modified Overt Aggression Scale. CTRS-R:S = Conners Teacher Rating Scale-Revised: short form. ODD-RS= Oppositional-Deviant Disorder Rating Scale.

Table 1b. Change scores from baseline to seven weeks of parent-, teacher-, child- and investigator-rated symptom domains

Measure	Discontinuation			Continuation			Analysis				
Seven weeks	**Mean**	**SE**	**95% CI**	**Mean**	**SE**	**95% CI**	**Δ Change between groups[a]**	**95% CI**	**F**	**df**	**p-value**
Parent-rating											
	n=40			*n=45*							
SDQ-Parent											
Total score	14.0	.87	12.3-15.8	13.8	.83	12.2-15.5	-2.1	-4.0, -.2	4.92	90	.03
Emotional symptoms	2.4	.33	1.7-3.0	2.4	.32	1.8-3.0	-.62	-1.4, .1	2.79	90	.10
Conduct problems	2.2	.26	1.6-2.7	2.0	.25	1.5-2.5	.10	-.5, .6	.027	90	.87
Hyperactivity/inattention	7.1	.34	6.5-7.8	6.6	.33	6.0-7.3	-1.1	-2.0, -.3	6.54	90	.01
Peer relations	2.4	.31	1.8-3.0	2.8	.30	2.2-3.3	-.43	-1.0, .2	2.04	90	.16
Prosocial behavior	7.0	.37	6.3-7.7	6.6	.35	5.9-7.3	.38	-.4, 1.1	0.97	90	.33
R-MOAS aggression	111.4	3.0	105.3-117.4	109.7	3.0	103.7-115.6	-.52	-5.7, 4.7	.04	90	.84
Teacher-rating											
	n=38			*n=37*							
SDQ-Teacher											
Total score	12.1	.98	10.2-14.1	12.6	.95	10.8-14.5	-2.9	-5.1, -.7	6.85	76	.01
Emotional symptoms	2.4	.35	1.7-3.1	2.4	.34	1.7-3.1	.4	-.4, 1.1	.97	76	.57
Conduct problems	1.4	.27	.8-1.9	1.8	.28	1.2-2.3	-.7	-1.3, .1	3.40	76	.07
Hyperactivity/inattention	6.0	.48	5.0-7.0	5.7	.47	4.8-6.6	-1.5	-2.4, -.5	8.76	76	<.01
Peer relations	2.4	.38	1.7-3.1	3.1	.35	2.4-3.8	-.6	-1.3, .2	1.99	76	.16
Prosocial behavior	6.7	.38	5.9-7.4	5.9	.37	5.1-6.6	.5	-.3, 1.4	1.46	76	.23
CTRS-R:S-Oppositional	8.3	.53	7.2-9.3	7.3	.53	6.3-8.4	-1.9	-3.1, -.6	8.60	77	<.01

Table 1b. Change scores from baseline to seven weeks of parent-, teacher-, child- and investigator-rated symptom domains (continued)

Measure	Discontinuation			Continuation			Analysis				
Seven weeks	Mean	SE	95% CI	Mean	SE	95% CI	Δ Change between groups[a]	95% CI	F	df	p-value
Child-rating											
	n=35			*n=41*							
SDQ-Child											
Total score	11.6	.86	9.9-13.3	12.4	.81	10.8-14.0	-.65	-2.9, 1.6	.32	77	.57
Investigator-rating											
	n=47			*n=47*							
ODD-RS	6.4	.76	4.9-7.9	5.3	.76	3.8-6.8	-1.9	-4.0, .1	3.49	92	.07

Note: CI = confidence interval. df = degrees of freedom. SE = standard error. SDQ = Strength and Difficulties Questionnaire. R-MOAS = Retrospective Modified Overt Aggression Scale. CTRS-R:S = Conners Teacher Rating Scale-Revised: short form. ODD-RS= Oppositional-Deviant Disorder Rating Scale.

[a] Indicates the difference (Δ) in mean change from baseline to endpoint between the discontinued and continued treatment groups, including 95% confidence interval by mixed models for repeated measurements (MMRM) analysis.

Table 2. Baseline scores and change scores from baseline to 7 weeks in Quality of Life (KINDL-R) and parenting stress scores (NOSI-K)

	Discontinuation			Continuation							
Baseline	Mean	SE	95% CI	Mean	SE	95% CI					
		n=45			*n=46*						
Kindl-R Parent-rating Total score	71.3	.79	69.7-72.8	69.8	.78	68.3-71.4					
		n=45			*n=46*						
Kindl-R Child-rating Total score	70.6	.85	68.9-72.3	71.1	.85	70.0-73.4					
		n=42			*n=43*						
NOSI-K Parent-rating Total score (child domain)	35.4	2.2	31.1-39.6	37.5	2.1	33.3-41.8					
Seven weeks	Mean	SE	95% CI	Mean	SE	95% CI	Δ Change between groups[a]	95% CI	F	df	p-value
		n=46			*n=47*						
Kindl-R Parent-rating Total score	71.0	.73	69.5-72.4	69.5	.72	68.0-70.9	-.06	-2.1, 2.0	.003	89	.95
		n=46			*n=46*						
Kindl-R Child-rating Total score	71.1	.92	69.3-72.9	70.8	.92	69.0-72.7	-1.35	-4.1, 1.3	.99	89	.32
		n=43			*n=41*						
NOSI-K Parent-rating Total score (child domain)	37.4	2.3	32.9-41.9	35.2	2.3	30.7-39.6	-4.4	-9.1, .4	3.4	83	.07

Note: KINDL-R = quality of life rating scale. NOSI-K = Nijmegen Parental Stress Index. CI = confidence interval. df = degrees of freedom. SD = standard deviation.

[a] Indicates the difference (Δ) in mean change from baseline to endpoint between the discontinued and continued treatment groups, including 95% confidence interval by mixed models for repeated measurements (MMRM) analysis.

Discussion

We investigated the effects of discontinuing methylphenidate after more than 2 years of use on a number of broad symptom domains, QoL, and parenting stress. This was based on parent-, teacher-, child-, and investigator-rated outcome measures in a 7-week double-blind placebo-controlled discontinuation trial, as a follow-up to our initial study assessing investigator-rated ADHD symptoms as the primary outcome measure using the ADHD-RS (Zhang et al., 2005). In line with our previous results, we found long-term benefits of continued treatment with methylphenidate on the hyperactivity/inattention subscale of the parent- and teacher-rated SDQ. This supports sufficient sensitivity of the brief screening questionnaire SDQ pointing to the beneficial use of methylphenidate regarding the home and school environment.

We also found significantly deteriorated oppositional problems after discontinuation of methylphenidate as indicated by teacher-ratings, while deterioration of investigator-rated oppositional symptoms was marginally significant, as was deterioration of teacher-rated conduct problems. This is consistent with a meta-analysis of short-term efficacy studies (i.e., up to 16 weeks) of methylphenidate regarding oppositional behavior and conduct problems (Pringsheim et al., 2015). Still in contrast to this study, we did not find a significant effect of continued methylphenidate treatment on parent-rated aggression. A possible explanation for less evident findings regarding parent-ratings could be that teachers report a lower placebo response than parents do, as found in a recently published placebo-controlled crossover trial with methylphenidate (Fageera et al., 2018). No effects of discontinuation were observed on child-rated symptoms, child- and parent-rated QoL, or parenting stress, suggesting that patients may be withdrawn from methylphenidate without deterioration of QoL, aggression, nor an increase in parenting stress. One should keep in mind, however, that we do not know to what extent participants in this study experienced these problems at the start of their methylphenidate treatment.

Strengths and limitations

A strength was the high ecological validity of the study, given the embedding in regular clinical care and the use of rating scales based on multiple informants. It should be noted, however, that the study had not been primarily powered to investigate changes other than ADHD symptoms. Therefore, it cannot be ruled out that a larger sample size would still indicate long-term benefits of methylphenidate use on certain comorbid symptoms, aggression, QoL, or parenting stress. Another limitation may be that the study reports on data assessed briefly after discontinuation of methylphenidate and that some measures, such as QoL, may have a longer latency to take effect. In future studies thus larger sample sizes and longer follow-up periods may be needed.

Conclusion

Our study indicates beneficial effects of long-term methylphenidate use on hyperactivity/inattention and oppositional behaviors. However, we did not find evidence for long-term benefits on other comorbid symptoms, QoL, or parenting stress. These latter results are in contrast with short-term effectiveness findings of methylphenidate.

Clinical Significance

This suggests that, in line with guidelines recommendations, there should be periodical assessments whether continued use of methylphenidate is still needed in the individual child or adolescent by considering a temporary discontinuation. This may be done without negative consequences for QoL, parenting stress, or comorbid symptoms, beyond ADHD symptoms at home and school and oppositional symptoms at school. While our study suggests beneficial effects of long-term methylphenidate use regarding oppositional symptoms, it should be noted that nonpharmacological treatment (i.e., parent training) may also lead to long-term improvement of oppositional behavior (Hautmann et al., 2009; Högström et al., 2017; Döpfner et al., 2018).

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