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The Journal of Child Psychology and Psychiatry, 2012 July 13; Epub ahead of print

Reduced GABA concentration in attention-deficit/hyperactivity disorder
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Advancing maternal age is associated with increasing risk for autism: a review and meta-analysis

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Framingham on child psychiatry / ADHD
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ATOMOXETINE IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER. SYSTEMATIC REVIEW OF REVIEW PAPERS 2009–2011. AN UPDATE FOR CLINICIANS


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BACKGROUND & AIM: The abundance of published data means that clinicians often depend on review articles to provide them with updated information on clinical issues. In the 2 years from 2009 to 2011, more than 750 articles on atomoxetine, a non-stimulant medication used in the treatment of attention-deficit/hyperactivity disorder (ADHD), were published. The aim of this study was to evaluate review articles on atomoxetine published during this period in order to determine whether they covered all available data and addressed pragmatic clinical questions.

STUDY DESIGN: Systematic review.

FINDINGS: The extent to which review articles addressed available data was assessed on the basis of five clinical questions: what is the comparative efficacy of atomoxetine and methylphenidate; are data available on the use of atomoxetine in patients with ADHD and comorbidities; what are relevant clinical endpoints; how long before a clinical response can be expected and how long should medication be continued; and are data on suicidality included.

Thirteen systematic reviews or reviews that synthesized data on the use of atomoxetine in children or adolescents with ADHD were reviewed. Most (10 of 11 relevant studies) compared the efficacy of atomoxetine and methylphenidate, but few addressed the important issue of confounding bias. Data on the use of atomoxetine in patients with comorbidities was discussed in all but one of the reviews, with broadly similar conclusions being drawn.

Six reviews considered the clinical response trajectory of atomoxetine (including when an initial and a maximal response may be seen) and for how long treatment should be continued. However, the articles drew different conclusions, with time to peak efficacy of atomoxetine varying from 2–6 weeks up to 12 weeks. There were minimal recommendations on how long atomoxetine should be used.

Only two reviews included all data on suicidality that was available at the time. In particular, reviews did not include comparative suicidality data from head-to-head comparisons of atomoxetine and methylphenidate, which had been published as a meta-analysis in 2008 (i.e., prior to the publication of the reviews included in the current evaluation). Lastly, only two review articles considered what clinically relevant efficacy or safety endpoints, other than clinical rating scales, could be used in future clinical trials.

CONCLUSIONS: Although most of the published reviews on atomoxetine were of high quality, no single review provided a comprehensive update on all available clinical data for atomoxetine. Systematic reviews will need to be updated regularly to cover the volume of new data on ADHD that is emerging.

A NEUROPHYSIOLOGICAL MARKER OF IMPAIRED PREPARATION IN AN 11-YEAR FOLLOW-UP STUDY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

The Journal of Child Psychology and Psychiatry, 2012 July 13; Epub ahead of print

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BACKGROUND & AIM: Some of the symptoms of attention-deficit/hyperactivity disorder (ADHD) can persist from childhood into adulthood, even if individuals no longer qualify for a symptomatic diagnosis. Neurophysiological studies have shown that some aspects of brain function remain abnormal throughout development, including deficits in attentional orienting, resource allocation, preparation, and time processing, deficits which can be present in children and adults with ADHD. The aim of this study was to investigate, by assessing event-related potentials (ERPs), the developmental trajectories of specific measures of brain function as individuals with ADHD progress from childhood to adulthood.

STUDY DESIGN: Prospective cohort study.

ENDPOINTS: Continuous performance test (CPT) results; attentional, preparatory and inhibitory ERP components.

METHOD: The study included 11 children with ADHD diagnosed at a mean age of 10.9±1.72 years, and 12 normal children with a mean age of 10.0±1.03 years. The participants were followed up after 1.1 and 2.4 years, and then again as young adults at a mean age of 21.9±1.46 and 21.1±1.29 years for patients and controls, respectively. At all four visits, ERP maps were recorded during a cued CPT, in which participants were presented with a sequence of letters and had to respond or withhold a response depending on specific combinations (cued Go and NoGo conditions). The developmental trajectories of attentional (Cue P300), preparatory (contingent negative variation, CNV), and inhibitory (NoGo P300) ERP components from childhood to adulthood were assessed.

RESULTS: CPT performance improved with age in both ADHD patients and normal control subjects, and developmental trajectories tended to converge so that group differences in childhood were no longer present in adulthood. All three ERP components decreased over time in ADHD patients and normal control subjects, and the shape of the developmental trajectories of these measures did not differ between the subject groups. By early adulthood, group differences in the Cue P300 or NoGo P300 measures were no longer significant, although CNV remained reduced in the ADHD patients (even though eight of them no longer qualified for a diagnosis). The CNV parameters correlated with reaction time and with the standard deviation of the reaction time, which remained high in adult ADHD subjects.

CONCLUSION: Attentional and preparatory deficits in children with ADHD persisted into adulthood.

BACKGROUND & AIM: Concomitant attention-deficit/hyperactivity disorder (ADHD) in children with autism spectrum disorder (ASD) can adversely affect clinical management. Treating the symptoms of ADHD in children with ASD may help to improve their ability to benefit from educational and behavioural interventions, but relatively little is known about the efficacy of ADHD medications in this patient group. Studies have suggested that stimulant ADHD medications are less effective and have more side effects in children with ASD and concomitant ADHD. As atomoxetine is superior to placebo in treating ADHD symptoms, the aim of this study was to investigate its efficacy and safety in treating symptoms of ADHD in children with ASD.

STUDY DESIGN: Randomized, double-blind, placebo-controlled study.

ENDPOINT: Change in ADHD Rating Scale (ADHD-RS) score from baseline.

METHOD: Children aged 6–17 years with clinically diagnosed ASD and symptoms of ADHD were randomized 1:1 to receive either placebo or atomoxetine (titrated up to a dose of 1.2 mg/kg a day) for 8 weeks. Efficacy outcomes were measured using the ADHD Rating Scale (ADHD-RS), Clinical Global Impressions of ADHD improvement (CGI-ADHD-I), and Conners’ Teacher Rating Scale-Revised: Short Form (CTRS-R:S); adverse events were also assessed.

RESULTS: Ninety-seven patients were randomized, 48 to atomoxetine and 49 to placebo. At baseline, the mean ADHD-RS total score was 40.7 in the atomoxetine group and 38.6 in the placebo group. At 8 weeks, the mixed-effect model repeated-measures mean ADHD-RS score had improved to 31.6 in the atomoxetine group versus 38.3 in the placebo group, a total change of –8.2 and –1.2 in the atomoxetine and placebo groups, respectively. The difference in the least-squares mean was –6.7 (\(p<0.001\)). The change in CTRS-R:S hyperactivity domain score was significantly greater in the atomoxetine group than in the placebo group (\(p=0.024\)). The CGI-ADHD-I indicated improvement in 20.9% of children treated with atomoxetine and in 8.7% of children treated with placebo, but the difference was not statistically significant. Adverse events, in particular fatigue, nausea, decreased appetite, and early morning awakening, were more common in the atomoxetine group than in the placebo group (81.3% versus 65.3%, respectively) and occurred more frequently than in previous studies; however, no serious adverse events were reported.

CONCLUSION: Atomoxetine for 8 weeks was effective in controlling symptoms of ADHD in children with ASD and was well tolerated in this patient group.
A RANDOMIZED CONTROLLED TRIAL OF RISPERIDONE, LITHIUM, OR DIVALPROEX SODIUM FOR INITIAL TREATMENT OF BIPOLAR I DISORDER, MANIC OR MIXED PHASE, IN CHILDREN AND ADOLESCENTS

BACKGROUND & AIM: Childhood mania, often with psychotic features, may have serious consequences that persist into adulthood, including an increased likelihood of substance abuse and suicidal behaviours. Despite the seriousness of this illness and the need for urgent and effective treatment, there are few data to guide the optimal therapy of childhood mania. The aim of this trial, the Treatment of Early Age Mania (TEAM) study, was to compare the efficacy of the three antimanic drugs, risperidone, lithium, and divalproex sodium, as first-line therapy for childhood mania.

STUDY DESIGN: Randomized, controlled trial.

ENDPOINTS: Clinical Global Impression for Bipolar Illness Improvement-Mania (CGI-BP-IM) score (primary); Kiddie Schedule for Affective Disorders and Schizophrenia Mania Rating Scale (KMRS) score (secondary).

METHOD: Outpatients aged 6–15 years with a DSM-IV diagnosis of bipolar I disorder, manic or mixed phase were randomized in a 1:1:1 ratio to receive lithium, risperidone, or divalproex sodium. Treatment dose could be increased weekly if there was an inadequate therapeutic response, to maximum doses of 1.1–1.3 mEq/L, 4–6 mg, and 111–125 µg/mL, respectively. Laboratory values were measured at baseline and at week 8.

RESULTS: Results were available for 279 subjects: 89 treated with risperidone, 90 treated with lithium, and 100 treated with divalproex. Response rates on the CGI-BP-IM were significantly higher in risperidone-treated subjects (68.5%) than in lithium-treated subjects (35.6%; p < 0.001) or divalproex-treated subjects (24.0%; p < 0.001). There was no significant difference between lithium and divalproex on pairwise comparison. Mean KMRS scores were significantly lower in risperidone-treated subjects than in lithium- or divalproex-treated subjects (16.4 versus 26.2 and 27.6, respectively; p < 0.001 for both). Discontinuation rates were significantly higher in lithium-treated subjects than in risperidone subjects (32.2% versus 15.7%; p = 0.011) but did not differ significantly between either group and the divalproex group (26.0%). Mean weight gain and increase in body mass index were greater in risperidone-treated subjects, and significantly more of these subjects developed hyperprolactinaemia. Thyrotropin levels increased significantly in lithium-treated subjects and electrocardiographic changes were observed in the lithium- or divalproex-treated subjects. Lipid levels were decreased in divalproex-treated subjects.

CONCLUSION: Risperidone was significantly more effective than lithium or divalproex for the first-line treatment of mania in children and adolescents, but it gave rise to serious adverse metabolic effects.
BACKGROUND & AIM: A recent study reported that short intercortical inhibition (SICI) was reduced in school-age children with attention-deficit/hyperactivity disorder (ADHD), and that the reduced SICI correlated with ADHD symptom severity and with motor skills. SICI is modulated by gamma-aminobutyric acid (GABA) agonists and is thought to be mediated by GABA-A cortical interneurons. These findings suggest that there is a deficit in cortical inhibition via the GABAergic system in ADHD. The aim of this study was to investigate the GABAergic component of ADHD, using magnetic resonance spectroscopy.

STUDY DESIGN: Cross-sectional study.

ENDPOINT: GABA concentrations.

METHOD: The study included 13 children (11 boys and 2 girls) with ADHD (median age 10.4 years, range 8.2–12.5 years) and 19 age-matched typically developing control subjects (12 boys and 7 girls; median age 10.7 years, range 8.4–12.8 years). GABA concentration in a volume that included primary somatosensory and motor cortices was measured with J-difference–edited magnetic resonance spectroscopy with a 3-T imaging system. Stimulant medication taken by 7 children with ADHD was withheld the day before and on the day of testing. Participants were recruited through local schools, local paediatric and other community clinics, and through advertisement in regional publications. Magnetic resonance spectroscopy was performed in the research institute.

RESULTS: Mean GABA concentrations were lower in children with ADHD than in typically developing control subjects (p=0.01 by t test) (see Table). On linear regression analysis, there was a significant effect of diagnosis (β=−0.34, p=0.03) but not sex (β=−0.16, p=0.33) on GABA concentrations. No significant effect of age on GABA concentrations was observed in univariate or regression analysis (p>0.36 for both). In the ADHD group, no significant difference in GABA concentration was observed between participants who were taken off stimulant medication for the study and participants who were not receiving medication (p=0.67 by t test).

CONCLUSION: Children with ADHD had significantly lower GABA concentrations in a measurement volume that included primary somatosensory and motor cortices, which suggests that there is a GABAergic deficit in ADHD.
BACKGROUND & AIM: Stimulants are commonly used to treat children with attention-deficit/hyperactivity disorder (ADHD) and have been shown to improve the core symptoms of inattention, hyperactivity, and impulsivity. However, it is less clear whether they have a beneficial effect on academic performance – long-term improvements in mathematics performance have been reported but inconsistent results for reading. The aim of this study was to investigate the effects of stimulant treatment of ADHD on academic progress, and specifically to compare children whose treatment was started at different times (to limit bias due to treatment indication).

STUDY DESIGN: Population-based study.

ENDPOINT: Performance on mathematics and language arts tests.

METHOD: The study population consisted of 11,872 children born between 1994 and 1996 and registered in the Icelandic school system, and who took a standardized test in both the fourth and seventh grades (aged 9 and 12, respectively). Data on prescriptions for ADHD drugs were obtained from the Icelandic Medicines Registry. Children who started treatment between their fourth and seventh grade tests were categorized according to treatment initiation: within 12 months, 13–24 months, or 25–36 months of the fourth grade test. These data were linked to the standardized test results in mathematics and in language arts obtained from the Database of National Scholastic Examinations. A decline in academic performance was defined as a decrease of at least 5% in test score.

RESULTS: Children who started treatment with a stimulant (most commonly methylphenidate) between their fourth and seventh grade tests were more likely to have a decline in academic test performance than those who did not receive medication. In non-medicated children, mean test scores increased by 0.4% in mathematics and were unchanged for language arts. Medicated children had an increased risk of academic decline in mathematics, which was particularly high in those who started treatment 25–36 months after their fourth grade test (crude risk ratio 1.8, absolute increase in risk 32%). The risk of academic decline in language arts was less pronounced (crude RR for children who started treatment later was 1.1, with an absolute increase in risk of 4%). The absolute risk of academic decline in mathematics was greater among girls (RR 3.6) than boys (RR 1.4).

CONCLUSION: Starting simulant drug treatment for ADHD later was associated with an increased risk of academic decline in mathematics.
BACKGROUND & AIM: The inattention and hyperactivity that characterize attention-deficit-hyperactivity disorder (ADHD) typically appear in children before the age of 7 years; however, few studies have investigated the diagnosis and treatment of ADHD in preschool or early school-aged children. Magnetic resonance imaging (MRI) is widely used to identify structural and functional abnormalities in the brains of older children, adolescents, and adults with ADHD. The aim of this study was to investigate whether abnormalities in the neural circuits related to ADHD are associated with parental reports of inattention and hyperactivity/impulsivity in 6-year-old boys.

STUDY DESIGN: Imaging study.

ENDPOINTS: Cortical thickness; subcortical shapes and volumes; fractional anisotropy of deep white matter tracts.

METHOD: Chinese Singaporean boys (n = 96, mean age 78.6 months) underwent large deformation diffeomorphic metric brain mapping using MRI and diffusion tensor imaging. Associations between measures of brain structures and mothers’ ratings of their child’s inattention and hyperactivity/impulsivity, assessed using Conners’ Parent Rating Scale (CPRS), were identified using linear regression.

RESULTS: Thinner thickness of the temporal and parietal cortices was significantly associated with higher CPRS scores for inattention and hyperactivity/impulsivity, even after correction for IQ. There was no such association with CPRS scores for oppositional behaviour. Subcortical shapes and volumes were not significantly associated with CPRS scores for inattention, hyperactivity/impulsivity, or oppositional behaviour. A reduced fractional anisotropy in posterior white matter and callosal tracts was significantly associated with CPRS scores for inattention and hyperactivity/impulsivity, but not with scores for oppositional behaviour. Although inattention and hyperactivity/impulsivity symptoms appeared to share common neural circuits, hyperactivity/impulsivity ratings were associated with more extensive cortical areas, such as frontal regions and white matter tracts (see Table).

CONCLUSION: Specific brain regions were found to be associated with inattention and hyperactivity/impulsivity, but not with oppositional behaviour in young boys.

<table>
<thead>
<tr>
<th>Cortical regions significantly associated with symptoms of inattention and hyperactivity/impulsivity</th>
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</thead>
<tbody>
<tr>
<td>Inattention</td>
</tr>
<tr>
<td>Left fusiform, parahippocampus</td>
</tr>
<tr>
<td>Left supramarginal gyrus</td>
</tr>
<tr>
<td>Right fusiform, parahippocampus</td>
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http://www.jaacap.com
BACKGROUND & AIMS: The prevalence of attention-deficit/hyperactivity disorder (ADHD), and the more severe hyperkinetic disorder (HD), is increased in children with intellectual disability. Although current treatment guidelines typically recommend first-line therapy with methylphenidate, most intervention trials for ADHD have excluded children with sub-average intelligence. Available data suggest that CNS stimulants are less effective in these children than in typically developing children, but no studies have used individually optimized dosing or tested the effects of such medication for longer than 4 weeks in this patient group. The aims of this study were to investigate the efficacy and safety of optimally titrated methylphenidate used for 16 weeks and to determine whether efficacy is moderated by the level of intellectual disability, the presence of autistic symptoms, or the severity of ADHD symptoms.

STUDY DESIGN: Randomized, controlled trial.

ENDPOINT: Parent and teacher Conners’ ADHD index score at 16 weeks.

METHOD: Children (n=122) aged 7–15 years with HD and an intelligence quotient (IQ) of 30–69 were randomized (1:1), stratified by referral source and IQ level, to receive either immediate-release methylphenidate or placebo. Methylphenidate was titrated over 3 or more weeks, followed by optimal dosing until week 16. Efficacy was assessed using the Parent and Teacher ADHD index of the Conners’ Rating Scale-Short Version and the Clinical Global Impressions-Improvement rating (CGI-I) scale. Body weight, pulse, and blood pressure were monitored and adverse events were recorded.

RESULTS: Compared with children on placebo, children on methylphenidate had a significantly greater reduction in parent- and teacher-rated symptoms on the Conners’ ADHD index, with effect sizes of 0.39 (95% confidence interval 0.09–0.70) and 0.52 (95% CI 0.23–0.82), respectively. On the CGI-I scale, 40% of children on methylphenidate showed improvement, compared to 7.1% of children on placebo. None of the potential moderators (IQ, autistic symptoms, parent- and teacher-rated ADHD severity) affected treatment efficacy. Children on methylphenidate reported difficulty sleeping, loss of appetite, and weight loss. There were no differences in mean change in pulse or blood pressure between the two treatment groups.

CONCLUSIONS: An optimal dose of methylphenidate was effective in reducing symptoms in about 40% of children with HD and intellectual disability. Moreover, efficacy was not moderated by IQ, autistic symptoms, or severity of ADHD. Adverse events were typical of those found in children of normal intellectual ability.


CENTRE FOR CORRESPONDENCE: Department of Child and Adolescent Psychiatry, King’s College London, Institute of Psychiatry, London, UK

The Journal of Child Psychology and Psychiatry, 2012 June 7; Epub ahead of print
CHILDHOOD TRAJECTORIES OF INATTENTION, HYPERACTIVITY AND OPPOSITIONAL BEHAVIORS AND PREDICTION OF SUBSTANCE ABUSE/DEPENDENCE: A 15-YEAR LONGITUDINAL POPULATION-BASED STUDY

Molecular Psychiatry, 2012 June 26; Epub ahead of print

CENTRES FOR CORRESPONDENCE: International Laboratory for Child and Adolescent Mental Health Development, University of Montreal, Montreal, Canada; and Woodview House, School of Public Health, Physiotherapy and Population Sciences, University College Dublin, UK

BACKGROUND & AIM: Studies have shown that children with attention-deficit/hyperactivity disorder (ADHD) are at higher risk of long-term substance abuse/dependence. However, the unique role of inattention and hyperactivity symptoms in predicting substance abuse/dependence is unclear. It is also unknown whether this association remains significant after controlling for the co-occurrence of other externalizing problems, such as oppositional behaviours, anxiety, and adversity. The aim of this study was to analyse the contributions of childhood inattention and hyperactivity symptoms and possible confounders to substance abuse/dependence in early adulthood.

STUDY DESIGN: Longitudinal study.

ENDPOINT: Behavioural problems assessed with the Social Behavior Questionnaire (SBQ).

METHOD: The analysis included a large population-based sample of kindergarten boys and girls in Quebec’s French-speaking public schools who were followed up between the ages of 6 and 21 years. Teachers and mothers rated the behavioural problems of children annually between the ages 6 and 12 years, using the SBQ. Behavioural trajectories of 1803 individuals diagnosed with substance abuse/dependence at 21 years of age were compared with those of 2000 controls.

RESULTS: The prevalence of substance abuse/dependence at age 21 years was 30.7% for nicotine, 13.4% for alcohol, 9.1% for cannabis, and 2.0% for cocaine. Inattention and oppositional behaviour were significant predictors of nicotine dependence (odds ratio 2.25, 95% confidence interval 1.63–3.11 and OR 1.65, 95% CI 1.20–2.28, respectively). Conversely, only oppositional behaviour was a predictor of cannabis dependence (OR 2.33, 95% CI 1.40–3.87) and cocaine dependence (OR 2.97, 95% CI 1.06–8.57). The best behavioural predictor of alcohol abuse/dependence was oppositional behaviour rated by mothers but not by teachers, but it was only marginally significant (OR 1.38, 95% CI 0.98–1.95). Inattention was an important predictor of nicotine abuse/dependence and its severity (measured as number of lifetime symptoms). Hyperactivity did not predict any outcome nor did it predict age of onset of first symptoms.

CONCLUSIONS: Childhood oppositional behaviours were the most pervasive predictors of nicotine, cannabis, cocaine, and alcohol abuse/dependence at 21 years of age. Inattention made a unique contribution to nicotine dependence in early adulthood, whereas hyperactivity was not associated with any outcome.
ADVANCING MATERNAL AGE IS ASSOCIATED WITH INCREASING RISK FOR AUTISM: A REVIEW AND META-ANALYSIS

BACKGROUND & AIM: Although genetic factors are thought to have a key role in the aetiology of autism, there is evidence that non-heritable, prenatal or perinatal events and/or exposure to environmental agents may also be risk factors for autism. A link between advanced maternal age and autism has long been proposed, but the results of individual studies have been contradictory. The aim of this study was to elucidate the association between advanced maternal age and autism.

STUDY DESIGN: Systematic review and meta-analysis.

ENDPOINT: Association between maternal age and autism spectrum disorder (ASD).

METHOD: A search of PubMed for all population-based epidemiological studies published between January 1990 and December 2011 that investigated the association between advancing maternal age and ASD identified 11 studies (including 25,687 patients with ASD and 8,655,576 controls) that were included in the meta-analysis, conducted using random effect models. Pooled risk estimates comparing categories of advancing maternal age adjusted for possible confounding factors were calculated. Meta-regression was used to assess whether the effect of maternal age on the risk of autism was modified by other study-specific covariates.

RESULTS: Meta-analysis revealed that the risk of autism was higher in the children of mothers aged 35 years and older than in the children of mothers aged 25–29 years (adjusted relative risk of autism 1.31, 95% confidence interval 1.19–1.45, \( p < 0.001 \)); it was also higher in the children of mothers aged 40 years and older than in the children of mothers aged 25–29 years (adjusted RR 1.37, 95% CI 1.19–1.58). The risk of autism in children was significantly lower in mothers younger than 20 years than in mothers aged 25–29 years (RR 0.76, 95% CI 0.60–0.97, \( p = 0.028 \)). There was no evidence of publication bias or significant heterogeneity between studies. Meta-regression suggested a stronger effect of maternal age in studies with more male offspring and when children were diagnosed in later years (Figure).

CONCLUSION: The risk of autism in offspring was found to increase with increasing maternal age.
WHY DO CHILDREN WITH ADHD DISCONTINUE THEIR MEDICATION?

Clinical Pediatrics, 2012 August; 51(8):763–9

AUTHORS: Toomey SL, Sox CM, Rusnak D, Finkelstein JA
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BACKGROUND & AIM: Treatment with stimulants has been shown to improve the symptoms of attention-deficit/hyperactivity disorder (ADHD), but many parents are reluctant to give these medications to their children, and early discontinuation is common. ADHD medication adherence rates of 36–84.8% have been reported. A number of factors might influence adherence, including adverse effects and concerns about stigmatization, and a better understanding of these factors may help improve ADHD care. The aim of this study was to investigate the factors associated with parent-reported discontinuation of ADHD medication.

STUDY DESIGN: Telephone survey.

ENDPOINT: Reasons for ADHD medication discontinuation.

METHOD: The study included the parents of children aged 6–18 years who had recently started treatment for ADHD, according to insurance claims. In total, 127 out of 398 parents contacted via their primary care provider (43% response rate) agreed to participate in a telephone survey that investigated sociodemographic and ADHD characteristics, reasons for discontinuation (where applicable), ADHD care characteristics (including evaluation, mental health specialist involvement, and discussion of the risks and benefits of medication), and parental attitudes about ADHD. Information about parental report of possible side effects (including sleeping difficulties, decreased appetite, headaches, and psychological problems) and perceived medication effectiveness was also collected.

RESULTS: Twenty-one percent of parents reported that their child had discontinued ADHD medication, 42% within 1 month of initiation, 33% within 2–3 months, 21% within 4–6 months, and 4% after 6 months. The most common reasons given were side effects (62%) and minimal efficacy (34%). Discontinuation rates were higher for children with comorbid mental health conditions (34% versus 14%, p=0.01). Parents who discontinued ADHD medication were less likely to have discussed the risks and benefits of ADHD medication with primary care providers (59% versus 82%, p=0.03) and were more likely to report their child experienced psychological side effects (62% versus 22%, p<0.001). Overall, 53% of parents reported that ADHD medication worked very well, 33% somewhat well, and 14% not very well or not at all. Multivariate logistic regression analysis revealed that treatment discontinuation was associated with psychological side effects and perceived poor medication effectiveness.

CONCLUSION: Discontinuation of ADHD medication in the first year was mainly because of psychological side effects or perceived inadequate effectiveness of medication.
DEVELOPMENT OF CORTICAL SURFACE AREA AND GYRIFICATION IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Biological Psychiatry, 2012 August 1; 72(3):191–7

AUTHORS: SHAW P, MALEK M, WATSON B, SHARP W, EVANS A, GREENSTEIN D
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BACKGROUND & AIM: Recent neuroimaging research has found that attention-deficit/hyperactivity disorder (ADHD) is characterized by a delay in the age at which prefrontal cortical thickness reaches its maximum (maturation) before thinning again in adolescence. This occurs at about 7 years in normally developing children, but 10 years in children with ADHD. It is not clear whether the maturation of other components of cortical morphology is also delayed in the disorder, since there is evidence of dissociations between these properties, as well as a certain degree of dependence. The aim of this study was to investigate whether the maturation of cortical surface area and gyrification are also delayed in ADHD.

STUDY DESIGN: Cohort study.

ENDPOINT: Age at which peak cortical surface area and gyrification were attained.

METHOD: The study included 234 children with ADHD (217 with the combined type, 12 with the inattentive subtype, and 5 with the hyperactive/impulsive subtype) and 231 normally developing children. Neuroanatomical magnetic resonance images were acquired longitudinally and then processed to analyse the cortical surface. The cortical surface area was measured at the middle cortical surface; the gyrification index was calculated as the ratio between the total surface area and the exposed cortical surface or convex hull area. Mixed model regression analysis was used to determine the developmental trajectories of these parameters, and cortical maturation was determined as the age at which each reached its peak.

RESULTS: In both children with ADHD and normally developing children, maturation of the cortical surface area developed in centripetal waves both laterally and medially, but was delayed in the children with ADHD (see Table). In contrast, the maturation of cortical gyrification was similar in the children with ADHD and the normally developing children, and in both groups of children peak gyrification was reached before the children entered the study.

CONCLUSION: The maturation of cortical surface area was delayed in ADHD, suggesting that mechanisms that guide cortical maturation are disturbed in ADHD.

<table>
<thead>
<tr>
<th>Brain area</th>
<th>Control Age (years) ± SE</th>
<th>ADHD Age (years) ± SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefrontal cortex</td>
<td></td>
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</tr>
<tr>
<td>Right</td>
<td>12.7 ±0.03</td>
<td>14.6 ±0.03</td>
<td>&lt;0.00001</td>
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<tr>
<td>Left</td>
<td>13.2 ±0.03</td>
<td>13.5 ±0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td></td>
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<tr>
<td>Right</td>
<td>11.1 ±0.03</td>
<td>12.5 ±0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left</td>
<td>9.9 ±0.03</td>
<td>12.2 ±0.06</td>
<td>&lt;0.001</td>
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<tr>
<td>Temporal lobe</td>
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</tr>
<tr>
<td>Right</td>
<td>13.2 ±0.04</td>
<td>13.9 ±0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left</td>
<td>10.9 ±0.05</td>
<td>12.6 ±0.04</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>