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# Clinical and neurobiological factors in the management of treatment refractory attention-deficit hyperactivity disorder

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent mental disorder of childhood, which often continues into adolescence and adulthood. Stimulants such as methylphenidate (MPH) and non-stimulants such as atomoxetine are effective medications for the treatment of ADHD. However, about 30% of patients do not respond to these medications. Pharmacological treatment for ADHD, although highly effective, is associated with marked variabilities in clinical response, optimal dosage needed and tolerability. This article provides an overview of up-to-date knowledge regarding the clinical and neurobiological factors which contribute to and help predict treatment-refractory ADHD. Pharmacogenetic, pharmacogenomics and neuroimaging studies are still controversial with respect to determining the associations between response to medication and genetic factors, thereby resulting in hypotheses that differences in the genetic factors and neuroimaging findings contribute to treatment outcome. Much research on the potential role of genotype in pharmacological effects has focused on the catecholaminergic gene related to executive functions. Many neuroimaging studies have also reported a relationship between treatment response and common patterns of brain structure or activity according to various genetic polymorphisms. When children, adolescents and adults with ADHD do not respond to MPH, we should consider additional pharmacological options, including other classes of psychostimulants, the nonstimulant atomoxetine, bupropion, tricyclic antidepressant, clonidine, guanfacine and lisdexamphetamine. Prudent choice of an appropriate medication and active engagement of children, parents, and teachers in daily management may help to ensure long-term adherence. Therefore, additional research might help to optimize the treatment of children, adolescents and adults with ADHD and to find new options for the treatment of patients who do not respond to stimulants and the other medications. Because these findings should be interpreted cautiously, further studies are needed to elucidate these issues more clearly.



## 1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a clinical disorder characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity. ADHD is one of the most prevalent mental disorders of childhood, with a prevalence ranging from 5 to 10% (Faraone et al., 2003). ADHD symptoms generally present early in life and ADHD can continue into adolescence and adulthood (Bush et al., 2005). Although the cause is unknown, a number of etiologic factor studies of ADHD have reported an association with neurotrophic factors (Shim et al., 2008, 2015) or specific genes.

Previous studies have reported that the etiology of ADHD includes various interactions between environmental, genetic, and neurobiological factors (Kent, 2004). In addition to dopaminergic and noradrenergic neurotransmission dysregulation (Biederman, 2005), neuropsychological and neuroimaging studies have implicated the fronto-subcortical networks of the brain as the primary candidates for the underlying dysfunction in ADHD (Bush et al., 2005; Curatolo et al., 2009). Stimulant medications for ADHD treatment, including amphetamines and methylphenidate (MPH), were introduced in 1937 (Barkley et al., 2006). MPH blocks the dopamine transporter and the norepinephrine transporter. Since 1960, it has been used to treat children with ADHD. Until the 2000s, stimulants

*Abbreviations:* ADHD, Attention deficit hyperactivity disorder; MPH, methylphenidate; PFC, prefrontal cortex; DAT, dopamine transporter; DA, dopamine; ATX, atomoxetine; VNTR, variable number tandem repeat; DRD1, dopamine D1 receptor; DRD2, dopamine D2 receptor; DRD3, dopamine D3 receptor; DRD4, dopamine D4 receptor; NET, norepinephrine transporter; ADRA2A, α-2 adrenergic receptor gene; SNP, single nucleotide polymorphism; COMT, catechol-O-methyl-transferase; SPECT, single-photon emission-computed tomography; PET, positron emission tomography; rCBF, regional cerebral blood flow; HMPAO, 99mhexamethylporphylenamineoxime.

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**Table 1**
Pharmacogenetic and pharmacogenomic studies of the clinical response of individuals with attention deficit hyperactivity disorder.

| Study | Study size (n) | Age (yrs) | Site | Gene | Improvement definition | Main findings |
|---|---|---|---|---|---|---|
| Winsberg and Comings, (1999) | 30 | 6–11 | USA | DAT1 | ABRS scores ≤1 in two consecutive assessments | Less improvement for the 10/10 genotype |
| Roman et al. (2002) | 50 | 6–17 | Brazil | DAT1 | Reduction of 50% in ABRS, continuous scores for CGAS | Less improvement for the 10/10 genotype |
| Yang et al. (2004) | 45 | 6–14 | China | NET | Significant reduction in ADHD-RS scores | Less improvement for the A/A genotype |
| Cheon et al. (2005) | 11 | 7–12 | Korea | DAT1 | Reduction of 50% in ADHD-RS | Less improvement for the 10/10 genotype |
| Mick et al. (2006) | 106 | 19–60 | USA | DAT1 | Significant reduction in AISRS scores | No association with SLC6A3 genotype |
| Cheon et al. (2007) | 83 | 7–12 | Korea | DRD4 | Reduction of 50% in ADHD-RS | Less improvement without 4/4 genotype at DRD4 |
| Polanczyk et al. (2007) | 106 | 4–17 | Brazil | ADRA2A | Significant reduction in SNAP-IV scores | Less improvement for without G allele genotype |
| Cheon et al. (2008) | 124 | 6–12 | Korea | COMT | Reduction of 50% in mean basal scores of the ADHD-RS | Less improvement for Val/Met, Met/Met genotype |
| Kereszturi et al. (2008) | 122 | 9.6 (mean) | Hungary | DAT1 | Reduction of 25% in ADHD-RS score, and ≥2 point improvement in CGI-S | Less improvement for Val/Met, Met/Met genotype |
| Purper-Ouakil et al. (2008) | 141 | 6–18 | France | DAT1 | Primary: ≥2 point improvement in CGI-S; secondary: minimum 40% improvement in ADHD-RS | Less improvement for the 10/10 genotype |
| Kooij et al. (2008) | 42 | 20–56 | The Netherlands | DAT1 | Two-point reduction in CGI-ADHD and 30% reduction in ADHD-RS scores | Less improvement for the 10/10 genotype |
| da Silva et al. (2008) | 59 | 6–18 | Brazil | ADRA2A | Significant reduction in SNAP-IV scores | Less improvement for without G allele genotype |
| Cheon et al. (2009) | 114 | 6–15 | Korea | ADRA2A | Reduction of 50% in ADHD-RS score, and CGI-I score after treatment of 1 or 2 points | Less improvement for the C/G, C/C genotype |
| McGough et al. (2009) | 82 | 6–17 | USA | COMT, DRD4, SLC6A2, SLC6A3, SLC6A4, 5HTTLPR, SNAP25 | Two-factor PCA: ADHD symptoms and correct mathematics in PERMP; four-factor PCA of SERS | Two-factor PCA: ADHD symptoms and correct mathematics in PERMP; four-factor PCA of SERS |

DAT1: Dopamine transporter; NET: norepinephrine transporter; DRD4: dopamine receptor D4; ADRA2A: adrenergic a2A receptor; COMT: catechol-O-methyltransferase; SLC6A2: norepinephrine transporter; SLC6A3: dopamine transporter; SCL6A4: serotonin transporter; SNAP25: synaptosomal-associated protein 25.

options were limited to immediate release (IR) and first-generation extended release (ER) formulations (Stein, 2004). However, the exact modes of action of MPH have not been fully identified. MPH can improve prefrontal cortex (PFC) function in the dopaminergic and noradrenergic pathways. Most MPH studies have focused on its activity to block the dopamine transporter (DAT), thus increasing the synaptic and extracellular concentrations of dopamine (DA). Methylphenidate can increase the levels of DA in the PFC, thus improving executive functions such as working memory (Solanto, 1998; Volkow et al., 2005). However, not all patients experience an adequate reduction in ADHD symptoms at well tolerated doses of MPH. MPH is effective in eliminating symptoms only in 45–50% of patients with ADHD (Biederman et al., 2006; Jensen et al., 2001; Blader et al., 2010). Approximately 70% of patients with ADHD respond to stimulant medications over short periods and for periods up to 18 months (Olfson, 2004). The high rates of multi-agent treatment in ADHD also suggest that suboptimal stimulant response is common (Connor et al., 1997; Safer, 1997; Blader, 2006). Additional agents such as antipsychotics and mood stabilizers are often used as adjuncts to stimulant medications (Blader et al., 2009; Patel et al., 2005; Safer, 1997; Blader, 2006). Atomoxetine (ATX) is a norepinephrine reuptake inhibitor with demonstrated efficacy for the treatment of ADHD. The clinical data on ATX are more recent than for MPH, as ATX has only been available since 2002. The effect sizes for ATX, particularly in longer studies and in treatment-naïve populations, are greater than previously reported and may be similar to those for MPH (Bushe and Savill, 2014). If a child's ADHD symptoms do not improve after a minimum of two appropriate psychostimulant or non-psychostimulant trials, we should consider this to be treatment-refractory ADHD. Due to the limitations of MPH for ADHD treatment, other classes of psychostimulant and non-stimulant medications are needed. It is the aim of this article to provide an overview of up-to-date knowledge regarding the clinical and neurobiological factors which contribute to and help to predict treatment-refractory ADHD.

## 2. Clinical aspects related to treatment refractory ADHD

The Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (Owens et al., 2003) examined variables associated with treatment outcomes and found that parental depressive symptoms, severity of childhood ADHD, and below-average child IQ were associated with the outcomes of medication management and combined treatments. Before children and adolescents with ADHD are considered to be treatment refractory, a variety of clinical issues should be addressed (Wagner, 2002). First, we should consider the diagnostic accuracy. Symptoms of excessive energy and distractibility may be a feature of bipolar disorder. ADHD and bipolar disorder are both neurodevelopmental disorders with onsets in childhood and early adolescence, and commonly persist into adulthood. Both disorders are often underdiagnosed, misdiagnosed, and sometimes overdiagnosed, leading to high rates of morbidity and disability. The characterization of these conditions is based on their clinical features, comorbidity, psychiatric family history, course of illness, and response to treatment (Marangoni et al., 2015). Additionally, inattention may be similar to preoccupation with intrusive thoughts in children with obsessive–compulsive disorder. Second, overlooked comorbid disorders may adversely affect treatment outcome. Third, psychosocial factors, including family problems, worsen ADHD treatment response. The fourth variable is treatment dose and adherence. This issue is especially relevant in adolescents and adults. Non-adherence is related to worse ADHD treatment outcomes in adults. Factors that can contribute to non-adherence in adults with ADHD include: young age, low education, little family history of ADHD, low ADHD baseline severity, and low medication efficacy (Sobanski et al., 2014). However, further prospective studies measuring adherence to treatment are needed to clarify which factors contribute to non-adherence. Usually, using controlled treatment trials, we can identify the impact of specific variables on treatment outcome, as well as the efficacy and tolerability of a drug. Gender, age, and cigarette smoking are not associated with response rates in adults with ADHD, whereas a higher dose of