Review

Treatment-resistant Attention-deficit Hyperactivity Disorder: Clinical Significance, Concept, and Management

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Abstract

Background: Attention-deficit hyperactivity disorder (ADHD) is the most commonly diagnosed neurodevelopmental disorder known to cause impairment across the lifespan. ADHD was ranked as approximately the 50th leading cause of global years lived with disability for children, coming in ahead of diabetes, meningitis, and intellectual disability. About 20%–40% of patients with ADHD would not achieve the treatment response and symptomatic remission, increasing future risks of substance abuse, suicidal behavior, and premature mortality. However, there is no standard consensus for defining treatment resistance in ADHD. **Method:** In this systematic review, we intend to focus on treatment-resistant ADHD in the aspects of disease definition, psychopathology, pathophysiology, and treatment. **Results:** We suggest that the more ideal strategy of defining treatment resistance should consider the improvement of ADHD symptoms and the global functioning simultaneously. Psychiatric comorbidities (i.e. destructive behavior disorders and mood disorders), physical comorbidities (i.e. epilepsy), and psychosocial adversities (i.e. parental psychopathology and poor family functioning) should be the first to be assessed in the evaluation of treatment response or resistance. The optimal medication adjustment or the combination of medications and psychotherapy may be the potential therapeutic strategy for treatment-resistant ADHD. **Conclusion:** Further studies would be necessary to elucidate the underlying mechanisms of treatment-resistant ADHD and to research the novel treatment strategies for ADHD.

Key words: physical comorbidities, psychiatric comorbidities, psychosocial adversities, remission
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Introduction

Attention-deficit hyperactivity disorder (ADHD) is the most commonly diagnosed neurodevelopmental disorder known to cause impairment across the lifespan. It begins in childhood and manifests as an inability to marshal and sustain attention and modulate activity level and impulsive actions, and the disease course persists up to adulthood [1, 2]. ADHD is highly prevalent in children, adolescents, and young adults worldwide, affecting about 5%–7% of children and adolescents and 2% of young adults, with a male-to-female ratio in the range of 3: 1 - 4: 1 [3-5]. In Taiwan, the prevalence of ADHD is 7.5% in grade 7 students, 6.1% in grade 8 students, and 3.3% in grade 9 students [6]. However, the specific pathophysiology of ADHD remains unclear, and its etiology is complex. Multiple genetic and environmental factors induce a spectrum of neurobiological vulnerabilities.

Longitudinal studies of ADHD showed increased risk of multiple mental and physical effects, such as substance use disorders, depression, bipolar disorder, traumatic brain injury, social difficulties, and criminality, as well as premature mortality [1, 2]. Compared to individuals without ADHD, the mortality rate ratios for individuals with ADHD at age below 6 years have been reported to be 1.86 (95% confidence interval [CI] = 0.93 – 3.27), 1.58 (95% CI = 1.21 – 2.03) for those aged 6–17 years, and 4.25 (95% CI = 3.05 – 5.78) for those aged 18 years or older [7]. The increased mortality for ADHD is mainly because of deaths from unnatural causes, most (about 80%) of which being attributed to accidents, such

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as serious traffic accidents [7, 8]. The beneficial importance of medication treatment in ADHD-related health risk reduction has been stressed in the clinical practice in these decades.

The trends in ADHD medication prescriptions have been increasing from 2001 to 2015 worldwide, and the absolute increase per year has been ranged from 0.02% to 0.26% [9]. The overall prevalence of ADHD medication use in children and adolescents aged 3–18 years is 1.95% worldwide, with a prominent national variation ranging from 0.27% in France to 6.69% in the US [9]. However, the prevalence of ADHD medication use in adults is only 0.39% [9]. The national prevalence of any ADHD medication use for adults ranged from as low as 0.003% in Japan to as high as 1.48% in the US [9]. In Taiwan, the prevalence rates of a diagnosis of ADHD in children and adolescents are ranged from 0.11% in 2000 to 1.24% in 2011; among them, only 50% received medications in 2000 compared to 61% in 2011 [10, 11].

A significant gap between the prevalence of ADHD and that of ADHD medication treatment is an important clinical and public health issue both worldwide and in Taiwan, as untreated ADHD would increase the risks of mental and physical health, personal functional impairment, and familial and societal financial burdens. The Global Burden of Disease Study reported that ADHD and conduct disorder are accounted for 0.80% of total global years lived with disability (YLDs) and 0.25% of total global disability-adjusted life years [12, 13]. Specifically, ADHD is ranked as the 52nd, 44th, and 61st leading cause of global YLDs for three childhood age groups (5–9, 10–14, and 15–19 years, respectively), coming in ahead of diabetes, meningitis, and intellectual disability [12, 13].

Given that the medication intervention of ADHD may achieve optimal coverage among individuals with ADHD in the coming years, another important clinical issue regarding ADHD intervention is that not every individual with ADHD would respond well to medications, and not everyone could achieve the optimal symptom control even with optimal duration and dosage of medications approved for ADHD by the US Food and Drug Administration. In 1977, Barkley reported that an average of 75% of the children treated with stimulants is improved while 25% remain unchanged or get worse by them [14]. Unfortunately, after 40 years, treatment resistance of ADHD has rarely been discussed and investigated [15]. The treatment resistance may indicate the persistent prominence of ADHD symptoms even with medications, which may sequentially increase the mental and physical health risks and familial and societal financial burdens mentioned above. In this systematic review, we focus on treatment-resistant ADHD in the aspects of disease definition, psychopathology, pathophysiology, and treatment.

Response to attention-deficit hyperactivity disorder medication treatment, remission of attention-deficit hyperactivity disorder, and the definition of treatment resistance

Actually, ADHD medications (including stimulants and nonstimulants) are quite effective; numbers needed to treat are ranged from 2 to 3 for long-acting stimulants, from 2 to 4 for short-acting stimulants, and from 2 to 5 for nonstimulants [16]. However, a small portion of patients with ADHD may not respond well to standard ADHD medications. Until now, no standard consensus exists to define the treatment response of ADHD medications (stimulants and nonstimulants) and remission of ADHD [15]. Before we discuss the treatment resistance of ADHD, we should first understand the definition of response and remission in ADHD, as treatment resistance is reversely associated with the treatment response and remission.

Assessing the efficacy of treatments for attention-deficit hyperactivity disorder

To assess the efficacy of ADHD medications, the change in severity of ADHD core symptoms based on clinician-rated scales, such as ADHD Rating Scale (ADHD-RS), and clinical global functioning measured by the Clinical Global Impression-Severity (CGI-S) or Improvement scale (CGI-I) are commonly used in previous clinical trials. Teachers' and parents' ratings, such as Swanson, Nolan, and Pelham, Version IV (SNAP-IV), for children and adolescents and self-reported ADHD symptom scales, such as adult ADHD Self-Report Scale Symptom Checklist and Barkley Adult ADHD Rating Scale IV, for adults are also considered as an alternative efficacy outcome because they provide a complementary view to clinicians' ratings (Table 1).

How long the optimal treatment duration is for defining the efficacy of ADHD medications is another important clinical issue. It may differ between stimulants and nonstimulants because nonstimulants, such as atomoxetine, may take at least 2–3 months to achieve the optimal therapeutic efficacy, but stimulants, such as methylphenidate, can produce a therapeutic effect within days or weeks. For example, in a 12-week study, the effect size of atomoxetine at 6 weeks (0.55) increases in a linear direction to 0.82 at 12 weeks [17]. Svanborg et al. reported that the effect size is 1.3 at the end of 10-week treatment of atomoxetine, with 63% of patients having a response of > 40% of ADHD-RS scores [18], but Dittmann et al. reported that about 60% of patients who took stimulants, such as lisdexamfetamine, would meet the response criteria of ≧ 50% reduction in ADHD-RS total score in the 4th week [19]. Hence, defining treatment duration is one of the prerequisites for defining treatment efficacy of ADHD medications. A recent meta-analysis of 133 randomized controlled trials defined about 12-week treatment duration as the primary outcome of therapeutic efficacy [20].

Response to attention-deficit hyperactivity disorder medications and remission of attention-deficit hyperactivity disorder

ADHD-RS and SNAP-IV are the most commonly used rating scales to define the treatment efficacy of ADHD medications based on the changes of ADHD symptomology; CGI-S and CGI-I are the most commonly used rating scales for defining the treatment efficacy of ADHD medications

Table 1. Attention-deficit hyperactivity disorder symptom rating and screening scales and the definition of response and remission

Symptom scales	Description	Definition of response	Definition of remission
ADHD-RS	An 18 items checklist derived from the 18 diagnostic symptoms for ADHD based on a semistructured interview with the patient's parents performed by a clinician. Each item is scored on a 0-3-point scale (0 = never or rarely, 1 = sometimes, 2 = often and 3 = very often)	A decrease from baseline of 25%, 30%, 40%, or 50% based on different clinical trials	Score of ≤ 18, never, rarely or sometimes ill (symptomatic remission)
SNAP-IV-18	A parent-/teacher-rated 18 items assessing inattention and hyperactivity. Each item is scored on a 0-3 scale similar to the ADHD-IV (0 not at all, 1 = just a little, 2 = quite a bit and 3 = very much)	A decrease from baseline of 25%, 30%, 40%, or 50% based on different clinical trials	Mean score of ≤ 1, not at all or just a little ill or ≤ 1 on each item (symptomatic remission)
Conners' ADHD Rating Scale (CRS)	Children and adolescents: Full-length (parent, 80 items; teacher, 59 items) and abbreviated (27 items; 28 items) formats Adults: Full-length (66 items) and abbreviated (18 items) formats. A 4-point scale ranging from 0 (not at all/never) to 3 (very much/very frequently)	≥ 30% decrease in physician-rated version of Conners' Adult ADHD Rating Scale-short version	
IOWA CRS-I/O	Five-item scale including five I/O items. Items are rated from 0 = not at all true/never to 3 = very much true/very often	≥ 30% reduction in total scores	Mean score of ≤ 5, not true at all/never or just a little true/occasionally
WRAADDS	A 28 items/7 -domains scale in adults: Inattention, impulsivity, hyperactivity, hot temper, affective lability, emotional overreactivity and disorganization. Each item can be rated on a 0-2 Likert scale	≥ 30% reduction in total scores	
AISRS	Each of the 18 individual criteria symptoms of ADHD in DSM-IV on a severity grid (0 = not present; 3 = severe; overall minimum score = 0; maximum score = 54)	≥ 30% reduction in total scores	
CGI-S	A 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients)	≤ 3	≤ 2 (functional remission)
CGI-I	A 7-point scale from 1 (very much improved) through to 7 (very much worse)	≤ 2	

To assess the efficacy of ADHD medications, the change in severity of ADHD core symptoms based on clinician-rated scales (i.e., ADHD-RS) and clinical global functioning measured by the CGI-S and CGI-I are commonly used. SNAP-IV for children and adolescents and self-reported ADHD symptom scales (i.e., ASRS, BAARS-IV) for adults are also considered as an alternative efficacy outcome. ADHD, attention-deficit hyperactivity disorder; ADHD-RS, ADHD Rating Scale; SNAP-IV-18, Swanson, Nolan and Pelham-IV-18; CRS, Conners' Rating Scale; IOWA, inattention/overactivity with aggression; I/O, inattentive/overactive; WRAADDS, Wender–Reimherr Adult Attention Deficit Disorder Scale; AISRS, Adult ADHD Investigator Symptom Rating Scale; CGI-S, Clinical Global Impression-severity; CGI-I, Clinical Global Impression-improvement; ASRS, ADHD Self-Report Scale; BAARS-IV, Barkley Adult ADHD Rating Scale IV; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*

based on the current severity of illness and the improvement of ADHD symptoms (Table 1). Regarding the changes of ADHD symptoms, 25%–50% reductions in total scores of ADHD-RS and SNAP-IV are defined as the treatment response of ADHD medications in different clinical trials [20-22]. Regarding the general disease condition and improvement, ≤ 3 (normal, not at all ill, borderline mentally ill, and mildly ill) of CGI-S and ≦ 2 (very much improved and much improved) of CGI-I are regarded as the response of ADHD medications [20-22].

Arnold determined that 57% of patients with ADHD responded to methylphenidate, 69% to amphetamine, 41% to both medications, and 13% do not respond to either medication. Efron et al. found that only 10% of children with ADHD responded neither methylphenidate nor dextroamphetamine based on parents' ratings, but up to 25% based on teachers' ratings; Newcorn et al. revealed that based on clinician's ratings, 60% responded to methylphenidate, 61% to atomoxetine, 44% to both medications, and 22% to neither medication [23-25]. The aforementioned examples indicated the clinical issue of who is the most suitable person to define the response and efficacy of ADHD medications: clinicians, parents, teachers, or patients. The most ideal way may be that clinicians evaluate the therapeutic effect of ADHD medications and define whether patients are responded to medications or not based on the objective rating scales mentioned above; their clinical judgment; and the comprehensive information from patients, parents, and teachers.

Similar to the response of ADHD medications, the definition of ADHD remission differs in the previous clinical trial (Table 1). The symptom severity defined by the symptomatic scales (i.e., ADHD-RS and SNAP-IV) and the disease conditions based on CGI-S or improvement based on CGI-I are remarkably interrelated, indicating that less symptom severity is correlated with less severe disease condition and more disease improvement (Table 2) [26, 27]. For example, 0–18 of total score and ≤ 1 of mean item score in ADHD-RS and SNAP-IV may correspond to 1–2 of CGI-S, indicating the not at all or borderline mentally ill and the remission of ADHD [26, 27]. The more ideal strategy of defining treatment resistance of ADHD may consider the changes of ADHD symptoms based on symptomatic scales (i. e., ADHD-RS and SNAP-IV) and the improvement of disease condition based

Table 2. Clinical interpretation of scores from the attention-deficit hyperactivity disorder Rating Scale-IV or the Swanson, Nolan and Pelham-IV and Clinical Global Impression-severity

Total score (range 0-54)	Mean item total score	Subscale score (range 0-27)	Mean item subscale score	CGI-S	Posttreatment monitoring (clinical interpretation)
0-18	≤ 1	0-9	≤ 1	1, 2	Symptomatic remission
19-26	< 1.5	10-13	< 1.5	3	Good response
27-36	1.5-2	14-18	1.5-2	4	Probable response, but still significantly clinical
37-54	> 2	19-27	> 2	5-7	No change or worse

The more ideal strategy of defining treatment resistance of ADHD may consider the changes of ADHD symptoms based on symptomatic scales (i.e., ADHD-RS and SNAP-IV) and the improvement of diseases condition based on CGI-S simultaneously. ADHD, attention-deficit hyperactivity disorder; ADHD-RS, ADHD Rating Scale; SNAP-IV-18, Swanson, Nolan and Pelham-IV-18; CGI-S, Clinical Global Impression-Severity

on CGI-S simultaneously [28, 29]. For example, both ≤18 of total score in ADHD-RS and ≤ 2 of CGI-S are met; they are defined as remission of ADHD [20, 21, 26].

Furthermore, if we follow the concept of treatment-resistant depression, which is defined as the failure to achieve remission with at least two different antidepressants with the optimal dosage and treatment duration [28, 29], treatment-resistant ADHD may be defined as the failure to achieve remission with at least two different ADHD medications (two stimulants or one stimulant and one nonstimulants) with the optimal dosage and treatment duration (12 weeks) [14, 21]. However, based on Biederman et al.'s study that defined the three levels of ADHD remission: syndromatic (failing to meet the full diagnostic criteria for ADHD), symptomatic (fewer than 36% of ADHD symptoms), and functional (fewer than 36% of the symptoms of ADHD and score on the Global Assessment of Functioning Scale higher than 60) remission, reporting only 10% of patients with ADHD may meet the criteria of functional remission. About 60% would achieve syndromatic remission. If we use functional remission as the remission criterion of treatment-resistant ADHD, the prevalence of treatment-resistant ADHD must be illogically high [30, 31]. Hence, the achievement of syndromatic or symptomatic remission may be a more appropriate criterion of treatment-resistant ADHD in clinical practice [32].

Factors Related to Treatment Resistance

Factors related to treatment resistance of ADHD can also be defined as factors related to the failure to achieve the optimal response and remission of ADHD, indicating the persistence of clinically significant ADHD symptoms. We delineate five major risk domains, including characteristics of ADHD, personal demographic characteristics, medical comorbidities, psychiatric comorbidities, and psychosocial factors, with the treatment resistance of ADHD in the following text (Figure 1).

Characteristics of attention-deficit hyperactivity disorder

Severe ADHD symptoms may be related to the higher rate of response to ADHD medications, but are negatively associated with remission of ADHD [33-39]. However, the Multimodal Treatment Study of Children with ADHD (MTA) study suggested that the more severe the initial ADHD symptoms, the worse the response to medications [39].

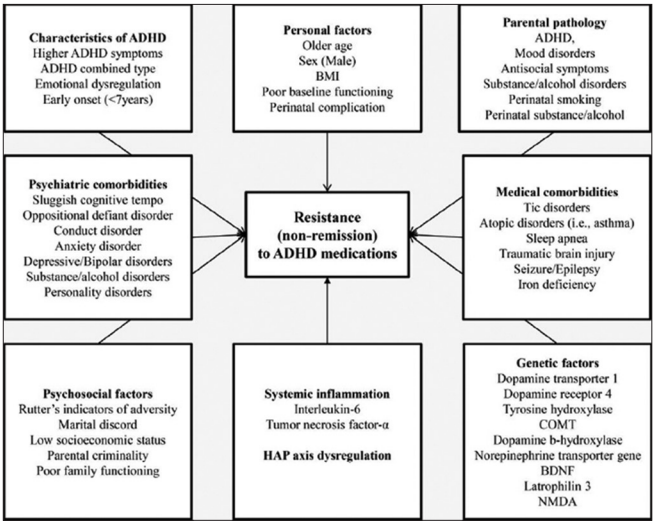

Figure 1. Factors related to the treatment resistance. Five major risk domains, including characteristics of attention-deficit hyperactivity disorder, personal demographic characteristics, medical comorbidities, psychiatric comorbidities, and psychosocial factors, with the treatment resistance of attention-deficit hyperactivity disorder, are shown.

Furthermore, the combined subtype of ADHD was a predictor of a worse clinical response [40]. Higher ADHD-related emotional dysregulation, which may indicate the severe ADHD symptoms and higher number of symptoms of oppositional behaviors and personality disorders, is associated with the poor response to stimulant [41]. However, evidence suggested that nonstimulants (i.e., atomoxetine) may be more effective for emotional dysregulation symptoms of ADHD [42, 43]. Later onset (> 7 years) of ADHD is related to a better response to medications compared to early onset of ADHD [33]. Low severity of disorder based on clinical judgment and improvement after a single dose of methylphenidate is found to be important contributors to response prediction [44]. Other potential factors related to remission include lack of hyperactive–impulsive ADHD and previous ADHD treatment [45].

Personal demographic characteristics

Younger age males are associated with response to medications; older age females are related to remission of ADHD [45, 46]. Better baseline functioning, such as cognitive

function, executive function, working memory and academic/work performance, and higher intelligence, is associated with higher response to medications [44, 47, 48]. In addition, greater baseline weight can positively predict the remission of ADHD [45].

Psychiatric comorbidities

Psychiatric comorbidities, including oppositional defiant disorder (ODD), conduct disorder (CD), callous/unemotional traits, mood disorders, and anxiety disorders in children, and depressive disorders, bipolar disorder, personality disorder, and substance and alcohol use disorders in adolescents and adults are associated with the poor response of ADHD medications (Figure 1). Ghuman et al. documented that the presence of no or one comorbid disorder (primarily ODD) predicted a significant treatment response, two comorbid disorders predicted moderate treatment response, and three or more comorbid disorders predicted no treatment response to ADHD medications [49].

Sluggish cognitive tempo or concentration deficit disorder, which manifests dreaminess, mental fogginess, hypoactivity, sluggishness, frequent staring behavior, inconsistent alertness, and a slow working speed, indicates a distinct disorder of attention from ADHD, yet one which may overlap with it in about half of all cases [50-53]. Conflicting evidence suggests the rôle of sluggish cognitive tempo in the treatment response to ADHD medications [54, 55]. Froehlich et al. demonstrated that sluggish/sleepy symptoms of sluggish cognitive tempo, but not the symptoms of daydreaming, predict methylphenidate nonresponse [54].

Medical comorbidities

Some studies suggested that sleep apnea, restless legs syndrome, tic disorder, seizure/epilepsy, iron deficiency, traumatic brain injury, atopic diseases, and systemic inflammatory diseases are related to the poor clinical outcome of ADHD and treatment resistance [56]. Medical comorbidities may mimic various symptoms of ADHD, especially inattention, exacerbate symptoms of ADHD, and interference with clinical course of ADHD, and are related to poor functioning among patients with ADHD. The comprehensive scrutiny for physical condition is warranted.

Psychosocial and parental psychopathological factors

Parental ADHD, depression, and antisocial symptoms are associated with worse prognosis [39, 40, 57]. However, Grizenko et al. interestingly reported that first-degree relatives of ADHD patients who responded to medications are at remarkably higher risk of ADHD than the relatives of those who did not [58]. The differential pattern of familial aggregation of ADHD-related disorders in responders and nonresponders may suggest that these two groups of patients may suffer from two types of disorders which are at least partially different with regard to pathogenesis [58].

Parental psychopathology is associated with worse family functioning, further affecting medication adherence and thus leading to a worse outcome. The higher scores on the organization and cohesion dimensions of family environment scale were associated with better response to treatment; on the other hand, more conflicted families have a worse response [40]. On the other hand, the presence of parental psychopathology may also be related to specific biologic characteristics that result in the limited response, or lead to environmental factors which limit the improvement of symptoms, independently of adherence [40].

A compelling study by Biederman et al. revealed that it is the aggregate of several psychosocial adversity factors (severe marital discord, low socioeconomic status, large family size, paternal criminality, maternal mental disorder, and foster care placement), rather than the presence of any single factor that leads to impaired development [59]. When clinicians assess the impact of psychosocial adversity in treatment response to ADHD medications, Rutter's indicators of adversity may be an appropriate evaluating tool and a reliable predictor [40].

Possible Pathophysiology of Treatment Resistance

Genetic susceptibility

Some norepinephrine- and dopamine-related single-nucleotide polymorphisms (SNPs), such as variable number of tandem repeats (VNTR) polymorphism in the 3′-untranslated region of dopamine transporter 1, VNTR in exon 3 of dopamine receptor (DRD4), rs2070762C of tyrosine hydroxylase, Val158Met of catechol-O-methyltransferase (COMT), rs1541332T–rs2073833C of dopamine β-hydroxylase (DBH), α-2 adrenergic receptor gene (*ADRA2A*), and norepinephrine transporter gene (*SLC6A2* rs192303), would predict the response of ADHD medications [60, 61]. Several SNPs, such as *GRIN2B* rs2284411 C/C and *GRIN2A* rs2229193 G/G, of NMDA receptors are important predictors of medication response [62]. Latrophilin 3 (LPHN3) is a brain-specific member of the G-protein-coupled receptor family associated with ADHD genetic susceptibility. Homozygous individuals for the CGC haplotype derived from SNPs rs6813183, rs1355368, and rs734644 of *LPHN3* gene have shown a faster response to methylphenidate [63]. Val/Val genotype of brain-derived neurotrophic factor (BDNF) Val66Met polymorphism is associated with a better response to methylphenidate [64].

Furthermore, the gene–environment interaction is another important marker to assess the treatment response of ADHD medications [65]. Pagerols et al. documented that the offspring of mothers who reported smoking cigarettes during pregnancy have a poorer treatment response than those who were not prenatally exposed to nicotine [65]. They further found that the risk for treatment failure is higher for carriers of the risk variants in DRD3 (rs2134655G–rs1800828G haplotype), DBH (rs1541332T–rs2073833C haplotype), or TH (rs2070762C/C genotype) whose mothers smoked during pregnancy [65].

Brain dysfunction

Dysregulation of dopamine and norepinephrine system is the most important hypothesis in the pathophysiology of ADHD. Both stimulants and nonstimulants improve ADHD symptoms through the modulation of dopamine and norepinephrine system and are also related to brain regions, including prefrontal cortex, cingulate cortex, and the limbic system. Dysfunction in dopamine- and norepinephrine-rich brain regions, such as prefrontal cortex, anterior cingulate, striatum, thalamus, caudate nucleus, posterior cingulate, and cerebellum, may be responsible for the pathophysiology of ADHD as well as the treatment response to ADHD medications (Figure 2) [2, 15, 66-68].

Structural and functional neuroimaging studies found that the smaller the volumes in the caudate and anterior superior cortex, the higher the concentration of gray matter in the caudate and nucleus accumbens, and high striatal dopamine transporter availability are associated with the better treatment response [15, 69, 70]. The downward trajectory in volumes of the inferior posterior cerebellum; the thinner medial prefrontal cortex; and the higher regional cerebral blood flow in the anterior cingulate cortex, the claustrum, and the right putamen are associated with a worse clinical outcome [71, 72]. Functional dysconnectivity, such as reduced positive functional correlation between posterior cingulate and medial prefrontal cortices (two major components of the default-mode network) and reduced ventral caudate/nucleus accumbens connectivity with the inferior frontal cortices, is associated with the persistence or nonresponse/remission of ADHD [66, 73].

Pharmacologic magnetic resonance imaging study indicated that an increased cerebral blood flow response (a surrogate marker of dopamine level) to a 16-week treatment of methylphenidate within the striatum and thalamus (dopamine-rich brain regions) is only noted in children with ADHD, but not in adults, which may correspond to the above evidence that older age is a negative predictor to medication response [74, 75]. Animal studies reported that long-term methylphenidate treatment with clinically relevant doses causes long-lasting reductions in striatal dopamine transporters, expression of D_3 receptors in the prefrontal cortex, increased dopamine levels, and a reduction in prefrontal neuronal excitability and synaptic transmission in juvenile (but not adult) rats [74, 76-78]. Those evidence may imply the important rôles of prefrontal cortex, striatum and thalamus function between children and adults in the treatment efficacy of ADHD medications.

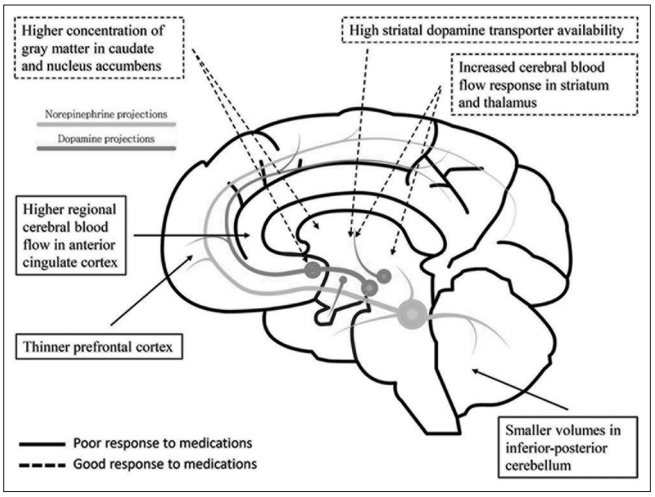

Figure 2. Brain dysfunction and response to attention-deficit hyperactivity disorder medications. Dysfunction in dopamine- and norepinephrine-rich brain regions, such as the prefrontal cortex, anterior cingulate, striatum, thalamus, caudate nucleus, posterior cingulate, and cerebellum, may be responsible for the pathophysiology of attention-deficit hyperactivity disorder as well as the treatment response to attention-deficit hyperactivity disorder medications.

Systemic inflammation

Increasing evidence suggested the crucial rôle of systemic inflammation in the pathophysiology and clinical course of ADHD. Patients with ADHD who had other systemic inflammatory diseases, such as asthma, atopic dermatitis, and psoriasis, may exhibit severe ADHD symptoms with more commonly developed affective symptoms, especially anxiety and depression later in life, which may further be associated with treatment resistance [79, 80]. Pro-inflammatory cytokines, including interleukin (IL)-2, IL-4, IL-6, interferon-γ, and tumor necrosis factor-α, may play an important rôle in the pathophysiology of ADHD [79, 81-84]. In addition, although cellular (cytokine-related) rather than antibody-mediated immune mechanisms are involved in the pathophysiology of ADHD, specific immune-inflammatory markers have not been systematically studied in ADHD [79, 82]. Therefore, if inflammatory pathways contribute to ADHD and further interfere with the clinical course and treatment outcome of ADHD, both its diagnosis and treatment should be reconsidered. Modulation of immune system activity may have potential in ADHD treatment [82].

Hypothalamic–pituitary–adrenal axis dysregulation

Chronic stress from the psychosocial adversities in Rutter's indicators of adversity is remarkably related to hypothalamic–pituitary–adrenal (HPA) axis dysregulation [59]. Patients with ADHD and comorbid disruptive behavior disorders exhibit blunted cortisol responses, whereas those with comorbid anxiety disorders show enhanced cortisol responses to stress [85, 86]. In addition, van der Meer et al. analyzed 17,374 SNPs across 29 genes previously linked to HPA axis activity with information on exposure to 24 individual long-term difficulties or stressful life events and found that the stress-related genes, including *SLC6A3*, *NPSR1*, *DRD4*, and *GABRA6*, in interaction with stress exposure are associated with ADHD severity, a factor related to treatment response [87]. Glucocorticoid receptor-encoding gene NR3C1 has an effect on ADHD comorbid with CD, which increases the risk of treatment resistance [88]. Furthermore, the vicious cycle of systemic inflammation

and HPA axis dysregulation may have an additive effect on the poor clinical outcome of ADHD and treatment resistance to medications.

Therapeutic Strategies for Treatment Resistance

Pharmacological intervention

The U.S. Food and Drug Administration approved several stimulants (i.e., methylphenidate and lisdexamfetamine) and nonstimulants (i.e., atomoxetine and α_2 agonists: clonidine and guanfacine) for ADHD treatment [89]. In Taiwan, only methylphenidate and atomoxetine are approved to treat ADHD [90, 91]. A recent meta-analysis of 133 double-blind, randomized controlled trials has also indicated the clinical efficacy of bupropion and modafinil in the treatment of ADHD [16, 92-94]. Based on the pharmacologic mechanisms of ADHD medications, drugs that can increase the levels of dopamine or norepinephrine in the synapse, including serotonin–norepinephrine reuptake inhibitor (i.e., venlafaxine, duloxetine, and reboxetine), dasotraline, and agomelatine, are potential therapeutic candidates for ADHD. The Cochrane Database of Systematic Reviews suggested that tricyclic antidepressants, especially desipramine, improve the core symptoms of ADHD, but its effects on the cardiovascular system remain an important clinical concern [89]. Other candidate medications, such as theophylline (an adenosine receptor antagonist) and pemoline (a central neural system stimulant), may alleviate ADHD symptoms [16, 95-97]. Second-generation (atypical) antipsychotics, such as risperidone and aripiprazole, may be used for the refractory or severe ADHD-related aggression and destructive behavioral and emotional dysregulation symptoms (Table 3).

Psychotherapy and psychoeducation

In the Multimodal Treatment Study of Children with ADHD (MTA) of 579 children with ADHD that were assigned to 14 months of medication management, intensive behavioral treatment (parent, school, and child components, with therapist involvement gradually reduced over time), the two combined, or standard community care determined that children in the combined treatment and medication management groups showed significantly greater improvement than those given intensive behavioral treatment and community care [98, 99]. Furthermore, the MTA study supported that the combined intervention of medication and intensive behavioral therapy would be more beneficial for the severe ADHD in the presence of psychiatric comorbidity (i.e., anxiety disorder and destructive behavioral disorders) and low socioeconomic status [39].

Psychotherapy and psychoeducation, such as neurofeedback, cognitive training, cognitive behavioral therapy, behavioral parental training, behavioral peer intervention, behavioral classroom management, and organization skill training, are of clinical importance in the treatment of ADHD (Table 3).

Complementary and alternative medicine interventions

Dietary interventions (i.e., restricted elimination diet), supplement with fatty acids (i.e., omega-3), vitamins, minerals, amino acids, herbal treatment (i.e., St. John's wort, gingko, and pycnogenol), homeopathy, and mind–body interventions (i.e., massage, chiropractic, acupuncture, yoga, meditation, and Tai Chi), may be helpful for ADHD treatment. In addition, optimal exercise may increase the effectiveness of methylphenidate on clinical symptoms and brain activity within the frontal and temporal cortices in response to the cognitive task (Table 3) [100-102].

Table 3. Therapeutic strategies for the treatment resistant attention-deficit hyperactivity disorder

Pharmacological treatment		Nonpharmacological treatment
DFA-approved	Non-FDA-approved	Psychotherapy and psychoeducation
Stimulants	Bupropion	Cognitive behavioral therapy
Amphetamine	Modafinil	Behavioral parental training
Dextroamphetamine	Venlafaxine	Behavioral peer intervention
Dexmethylphenidate	Duloxetine	Behavioral classroom management
Lisdexamfetamine	Agomelatine	Neurofeedback
Methylphenidate	Desipramine	Cognitive training
Nonstimulants	Vortioxetine	Organization skill training
Atomoxetine	Dasotraline	Complementary and alternative medicine interventions
Clonidine	Reboxetine	Omega-3, Vitamin B, iron, zinc
Guanfacine	Theophylline	Restricted elimination diet
	Pemoline	Herbal treatment (i.e., St. John's Wort, Gingko, Pycnogenol)
	For aggression	Exercise
	Risperidone	Neuromodulation and neurostimulation
	Aripiprazole	rTMS
		TDCS

The combined intervention of medication and nonpharmacological therapy would be more beneficial for the severe ADHD and improve the general treatment outcome of ADHD. rTMS, repetitive transcranial stimulation; TDCS, transcranial direct current stimulation; ADHD, attention-deficit hyperactivity disorder; FDA, U.S. Food and Drug Administration

Neuromodulation and neurostimulation

Repetitive transcranial stimulation (rTMS) and transcranial direct current stimulation (TDCS) affect dopaminergic secretion in the prefrontal cortex and have been considered a potential therapeutic strategy to improve ADHD symptoms, such as inattention and inhibitory control (Table 3). A pilot study of rTMS that was applied to the right prefrontal cortex at 10 Hz at 100% of the observed motor threshold for 2,000 pulses per session in a 10-session course over 2 weeks has supported the therapeutic effectiveness of rTMS in the treatment of ADHD [103]. TDCS studies of 2.0 mA anodal stimulation over the left dorsal lateral prefrontal cortex for 12 sessions have reported remarkable improvement of inattention and impulsivity symptoms in ADHD [104, 105].

Conclusion

Treatment resistance of ADHD is common in the clinical psychiatric practice; about 20%–40% of patients with ADHD cannot achieve the treatment response and symptomatic remission and meet the criteria of treatment resistance. To survey and establish the therapeutic adherence to medications should be the first step when clinicians meet patients who cannot achieve symptomatic improvement. To survey the biopsychosocial factors related to treatment resistance, including psychiatric comorbidities, medical comorbidities, parental psychopathology, and psychosocial adversities, is the next step. The optimal medication adjustment or the combination of medications and psychotherapy may be the potential therapeutic strategy for treatment-resistant ADHD. Further studies would be necessary to elucidate the underlying mechanisms of treatment-resistant ADHD and to research for novel treatment strategies for ADHD treatment.

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Conflicts of Interest

There are no conflicts of interest.

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