SYSTEMATIC REVIEW

Efficacy and tolerability of Methylphenidate in children and adolescents with ADHD: A Systematic Review

Efficacité et tolérabilité du méthylphénidate chez les enfants et adolescents présentant un TDAH: Revue systématique

Nour El Houda Ayadi, Randaline Ayoub, Hela Ben Abid, Maha Ajmi, Asma Guedria

University of Monastir, Faculty of Medicine of Monastir, Fattouma Bourguiba University Hospital, Department of Child and Adolescent Psychiatry, 5000, Monastir, Tunisia

Abstract

Introduction : Methylphenidate is the most commonly prescribed first-line stimulant for managing Attention-Deficit/Hyperactivity Disorder (ADHD, yet concerns remain regarding its safety and potential impact on neurodevelopment during critical growth periods.
Aim : To systematically review the literature in order to evaluate the efficacy and tolerability of methylphenidate in the treatment of children and adolescents with Attention-Deficit/Hyperactivity Disorder, and to assess the applicability of international guidelines in Tunisia.
Methodology : A systematic literature review was conducted following the PRISMA methodology. The search was conducted in PubMed, google scholar and science direct using the following terms: « methylphenidate », « children and adolescents », « efficacy », « tolerability » and « ADHD ». The search covered the period from 2015 to 2025.
Results : Our review included 28 articles, comprising clinical trials, randomized controlled trials, and case reports. Findings consistently demonstrate that methylphenidate improves core ADHD symptoms, including attention, hyperactivity, and impulsivity, while also enhancing executive functions, social cognition, and emotional regulation. This treatment is generally well-tolerated, with commonly reported adverse events including decreased appetite, insomnia, irritability, and mild cardiovascular changes. Growth effects are typically modest and reversible, and serious adverse events are rare.
Conclusion : Our findings support the short-term efficacy and acceptable safety of methylphenidate in children and adolescents with ADHD, while highlighting uncertainties regarding long-term outcomes.

Keywords: methylphenidate, children and adolescents, efficacy, tolerability, ADHD .

Résumé

Introduction : Le méthylphénidate demeure le psychostimulant de première intention le plus prescrit pour la prise en charge du trouble déficit de l'attention avec ou sans hyperactivité (TDAH). Cependant, des préoccupations persistent quant à sa sécurité d'emploi et à son impact potentiel sur le développement neurologique au cours des périodes critiques de croissance.
Objectifs : L'objectif de cette étude était de réaliser une revue systématique de la littérature afin d'évaluer l'efficacité et la tolérance du méthylphénidate dans le traitement du TDAH chez les enfants et les adolescents, et d'examiner l'applicabilité des recommandations internationales en Tunisie.
Méthodologie : Une revue systématique a été conduite selon la méthodologie PRISMA. La recherche bibliographique a été effectuée sur PubMed, google scholar et science direct en utilisant les mots-clés : « methylphenidate », « children and adolescents », « efficacy », « tolerability » et « ADHD », pour la période allant de 2015 à 2025.
Résultats : Notre étude a inclus 28 articles, comprenant des essais cliniques, des essais contrôlés randomisés et des études de cas. Les résultats montrent de manière cohérente que le méthylphénidate améliore les symptômes centraux du TDAH ; attention, hyperactivité et impulsivité, tout en favorisant le fonctionnement exécutif, la cognition sociale et la régulation émotionnelle. Globalement, le méthylphénidate est bien toléré, les effets indésirables les plus fréquents étant la diminution de l'appétit, l'insomnie, l'irritabilité et de légères modifications cardiovasculaires. Les effets sur la croissance sont généralement modérés et réversibles, et les événements indésirables graves demeurent rares.
Conclusion : Nos résultats soutiennent l'efficacité à court terme et la tolérance satisfaisante du méthylphénidate chez les enfants et les adolescents atteints de TDAH, tout en mettant en évidence des incertitudes concernant les effets à long terme.

Mots clés : Methylphenidate, enfants et adolescents, tolérance, efficacité, trouble déficit de l'attention avec hyperactivité

Correspondance
Nour El Houda Ayadi
University of Monastir, Faculty of Medicine of Monastir, Fattouma Bourguiba University Hospital, Department of Child and Adolescent Psychiatry, 5000, Monastir, Tunisia
Email: ayadi.nourelhoudaa@gmail.com

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What is known ?

- Clinical guidelines recommend stimulants as the first-line pharmacological treatment for ADHD

- Methylphenidate, remains the most widely prescribed psychostimulant for the management of ADHD in children and adolescents.

- Methylphenidate is effective in reducing core ADHD symptoms

- Evidence regarding the balance between the benefits and risks of long-term methylphenidate use remains inconsistent.

What this article adds ?

- This review provides a comprehensive and integrative synthesis of 28 studies with heterogeneous designs, offering a global and nuanced overview of methylphenidate use in children and adolescents with ADHD.

- By examining efficacy alongside tolerability and safety, this article provides a more clinically meaningful perspective than reviews focusing on treatment effectiveness alone.

- It includes a practical discussion of the applicability of international treatment guidelines in the Tunisian clinical context.

- The findings suggest that long-term data are still limited and sometimes inconsistent, pointing to the need for better-designed longitudinal studies.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is among the most prevalent neurodevelopmental disorders of childhood and adolescence. It is characterized by persistent symptoms of inattention, hyperactivity, and impulsivity that interfere with daily functioning and developmental trajectories. According to the DSM-5 (APA, 2013) (1) and the ICD-10 (WHO, 1992) (2), symptoms must emerge in childhood, persist across multiple contexts, and cause clinically significant impairment in academic, social, or occupational domains.

Epidemiological studies estimate the global prevalence of ADHD in children and adolescents at approximately 5–7.6%, and a male-to-female ratio of roughly 2–4:1(3). In clinical populations, the prevalence is notably higher, reflecting the significant burden of the disorder on health systems and families.

This neurodevelopmental disorder, is increasingly understood as a disorder of fronto-striatal circuits, with dysregulation of dopaminergic and noradrenergic neurotransmission contributing to core attentional and behavioral deficits(4).

ADHD is associated with substantial functional impairments, including reduced academic achievement, strained peer and family relationships, and emotional dysregulation, with symptoms frequently persisting into adulthood. High rates of psychiatric comorbidity are also reported, encompassing oppositional defiant disorder, conduct disorder, anxiety, depression, and learning disabilities, further complicating clinical outcomes(5). Given its chronic course and its significant burden on individuals, families, and healthcare systems, ADHD represents a major public health challenge(6).

Clinical guidelines emphasize multimodal management strategies. Psychosocial interventions, such as parent training and behavioral therapies, are recommended for younger children and those with mild to moderate presentations(7). However, for severe and persistent forms, pharmacological treatment is indicated, with stimulants as first-line therapy(1,8).

Among available pharmacotherapies, methylphenidate (MPH; $C_{14}H_{19}NO_2$) remains the most widely prescribed psychostimulant worldwide. Its therapeutic action is primarily mediated by inhibition of dopamine and norepinephrine reuptake, resulting in enhanced catecholaminergic transmission in neural circuits underlying attention, executive control, and behavioral regulation(9). Methylphenidate is available in immediate-release, sustained-release, and extended-release formulations, allowing individualized dosing strategies.

Robust evidence supports the efficacy of MPH in reducing core ADHD symptoms and improving functional outcomes in academic and social domains(9). However, tolerability remains a central consideration, as adverse effects such as appetite suppression, insomnia, weight loss, and potential cardiovascular changes may limit adherence and long-term benefit (10). Treatment response may also vary according to age, sex, and ADHD subtype, with less favorable outcomes reported in inattentive presentations and in preschool children.

Therefore, the objective of this study was to systematically review the literature to evaluate the efficacy and tolerability of methylphenidate for children and adolescents with ADHD and to assess the applicability of international guidelines in the Tunisian clinical context.

Methodology

Type of the study

We conducted a literature review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

The management of sources and bibliographic references was carried out using Zotero software.

Search Strategy

Identification

Relevant articles were identified through systematic searches of electronic databases : PubMed, Google Scholar, and Science Direct, using combinations of keywords and MeSH terms related to our topic : « Methylphenidate », « Child and adolescents », « ADHD », « Efficacity », « Tolerability »

The search was initially limited to titles and abstracts, and restricted to studies published in English or French between January 2015 and June 2025.

Additional records were retrieved through manual

searches of reference lists.

Screening (Selection)
After removing duplicates, titles and abstracts of all retrieved studies were screened to exclude irrelevant records: 299 records were retained for screening.
At this stage, articles were selected based on predefined inclusion and exclusion criteria

Inclusion Criteria

- Clinical trials, randomized controlled trials and case reports published since 2015
- Articles whose objectives were to investigate the efficacy and/or tolerability of Methylphenidate in ADHD
- Studies conducted in children and/or adolescents with ADHD
- Articles published between January 2015 and June 2025
- Written in English or French.

Exclusion Criteria
We excluded :

- Reviews and meta-analyses.
- Conference abstracts or proceedings.
- Articles not available in English or French.
- Studies conducted in adult populations.
- Studies focusing on interventions or medications other than methylphenidate.
- Research carried out on animals.

Eligibility
Full-text articles were then assessed for eligibility based on predefined inclusion and exclusion criteria. Based on this assessment, 28 articles met our criteria and were included in the review.

The PRISMA flow diagram
The final selection of studies included in the review was documented and presented in this PRISMA flow diagram:

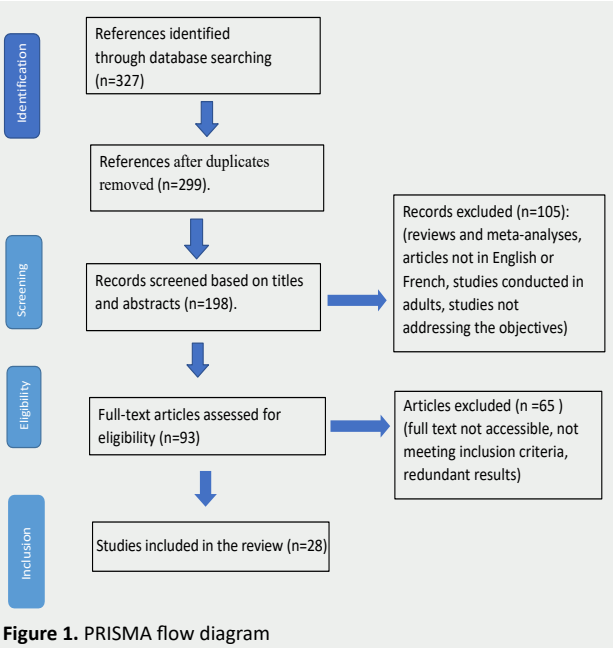


Figure 1. PRISMA flow diagram

Assessment of applicability in Tunisia

In addition to the systematic literature review, a narrative review of Tunisian clinical practices was conducted to assess the applicability of international ADHD guidelines in the Tunisian context. This assessment was based on locally available academic theses and official national regulatory documents regarding methylphenidate prescription and ADHD management in Tunisia.

Results

Our study included 28 articles focusing on the effect of Methylphenidate in children and adolescents with ADHD. These articles were categorized as follows:

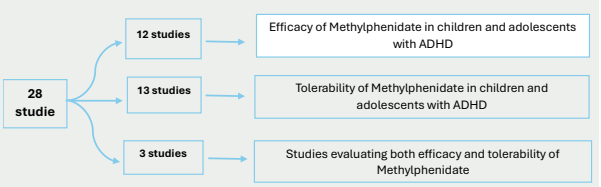


Figure 2. Distribution of studies by topic

Efficacy

This section reviews the efficacy of methylphenidate in children and adolescents with ADHD (Table 1).

Tolerability

Beyond efficacy, it is equally important to examine the tolerability and safety of methylphenidate, as treatment adherence and long-term outcomes largely depend on its side effect profile.
Several studies have specifically investigated these aspects, highlighting reported adverse events (Table 2).

Discussion

This review included 28 studies and provides updated evidence on the efficacy and tolerability of methylphenidate in children and adolescents with ADHD. Across trials, methylphenidate consistently improved core ADHD symptoms, executive functioning, academic-related outcomes, and social functioning. Overall tolerability was favorable, with mainly mild to moderate adverse events, most commonly decreased appetite, insomnia, and irritability. Long-term data suggested preserved linear growth despite early BMI reduction. Cardiovascular effects were generally modest, with a low absolute risk of serious events. No increased risk of psychosis or depression was observed.
These results are consistent with international guidelines, highlighting that methylphenidate remains an effective first-line treatment(8). Multiple meta-analyses consistently show moderate-to-large effect sizes in reducing the core symptoms of ADHD, including inattention, hyperactivity, and impulsivity(39).

Table 1. Summary of studies on the efficacy of methylphenidate in children and adolescents with ADHD

Article	Study type	Population	Type of the treatment	Duration of the treatment	Main Findings
Acute effects of methylphenidate on impulsivity and attentional behavior among adolescents comorbid for ADHD and conduct disorder(11)	Prospective experimental study: Randomized double blinded	31 adolescents with ADHD	40 mg of a long-acting dose of methylphenidate.	5 weeks study	Methylphenidate had more pronounced effects on attentional performance than on impulsivity, with improvements in response initiation and reward choice impulsivity observed in a smaller proportion of participants
Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose Titration Study of Methylphenidate Hydrochloride Extended-Release Capsules (Aptensio XR) in Preschool Children with Attention-Deficit/ Hyperactivity Disorder(12)	Randomized, double-blind, flexible-dose, placebo-controlled, parallel-group design study, conducted in six sequential phases	119 Child aged 4 to just under 6	Methylphenidate Hydrochloride Extended-Release Capsules (Aptensio XR)		Notable improvements in ADHD symptoms and a safety profile with an extended-release version of methylphenidate.
The interactive effects of test-retest and methylphenidate administration on cognitive performance in youth with ADHD: A double-blind placebo controlled crossover study(13)	Experimental study A randomized double-blind, placebo-controlled, within-subject crossover with a same-day test–retest; matched healthy control group included	20 child and adolescents (9-17 YO)	Methylphenidate immediate release	7 days	-Methylphenidate improved response consistency and reduced mistakes in the ADHD group: It decreased reaction time variability and errors in ADHD participants. -Placebo led to worse performance and led to increased variability and errors in the ADHD group. -Control participants showed fatigue and practice effects but had better test-retest reliability than those with ADHD.
Comparative Efficacy of Methylphenidate and Atomoxetine on Social Adjustment in Youths with Attention-Deficit/Hyperactivity Disorder (14)	A randomized, open-label, crossover clinical trial comparing OROS-methylphenidate and atomoxetine in drug-naïve youths with ADHD	-Parent and self-reports used for evaluation -168 participants	OROS methylphenidate and Atomoxetine	Treatment lasted 24 weeks	-Both methylphenidate and atomoxetine significantly improved ADHD symptoms compared to baseline. -Both medicaments helped with school functions and peer relationships -Methylphenidate showed superior efficacy to atomoxetine in reducing core ADHD symptoms (inattention, hyperactivity, impulsivity).
Continued Benefits of Methylphenidate in ADHD After 2 Years in Clinical Practice: A Randomized Placebo-Controlled Discontinuation Study(15)	A Randomized placebo-Controlled Study	94 child and adolescents (8-18 YO)	Extended release methylphenidate VS placebo	More than 2 years Continuation and discontinuation groups	-The continuation group showed significantly greater improvement in ADHD symptoms compared with the discontinuation group. -Clinical deterioration was observed in 40.4% of participants in the discontinuation group versus 15.9% in the continuation group. -Subscales of inattention and hyperactivity also showed greater deterioration in the discontinuation group.
The effect of methylphenidate on social cognition and oxytocin in children with attention deficit hyperactivity disorder(16)	A randomized, double-blind, placebo-controlled, experimental study	50 children diagnosed with ADHD	Methylphenidate versus placebo	Single dose administration	-The findings indicate that methylphenidate exerts pro-social effects in children with ADHD, improving social cognitive performance and augmenting oxytocinergic responses: Methylphenidate administration resulted in improved theory of mind performance, normalizing ADHD children's performance to levels comparable with their peers. -Methylphenidate treatment enhanced Oxytocin release in ADHD children during social interaction, suggesting a neuroendocrine mechanism underlying improved social cognition.
Effects of methylphenidate and physiotherapeutic treatment on graphomotor movements in children with ADHD(17)	A prospective, interventional, controlled trial with multiple parallel groups : Methylphenidate treatment, physiotherapeutic treatment, and a control group receiving parental psychoeducation.	58 child	Methylphenidate	8 weeks	-All groups showed improvements in graphomotor fluency and velocity over time, particularly in tasks performed with eyes closed. -No significant differences were observed between the treatment groups and the control group regarding overall graphomotor performance.
Attention-deficit/hyperactivity disorder: the impact of methylphenidate on working memory, inhibition capacity and mental flexibility (18)	A prospective, interventional, controlled, longitudinal study	53 boys aged 9–12 years ADHD children were assessed on executive function tests before and after	Methylphenidate immediate release	3 months	-Methylphenidate led to significant enhancements in executive functions : ADHD children showed significant improvements in working memory, inhibitory control, and mental flexibility, with fewer test errors ($p \leq 0.001$).

Table 1. Summary of studies on the efficacy of methylphenidate in children and adolescents with ADHD

Article	Study type	Population	Type of the treatment	Duration of the treatment	Main Findings
Effects of Methylphenidate on Sleep Functioning in Children with Attention-Deficit/ Hyperactivity Disorder (19)	A prospective, randomized, controlled, open-label, double-blind trial of once-daily long-acting methylphenidate.	163 children aged 7–11 years diagnosed with ADHD	OROS methylphenidate	4 weeks	-It found that higher doses of methylphenidate were associated with increased sleep problems, particularly in children with lower weight or BMI. -However, a significant proportion of children with preexisting sleep issues experienced improvement in sleep functioning at higher doses, suggesting that dose titration could be beneficial even for those with prior sleep difficulties
Executive functions, attention and verbal fluency of children with attention deficit/ hyperactivity disorder using methylphenidate(20)	A comparative study: ADHD group with methylphenidate treatment, ADHD group without treatment, Control group	71 child aged 7-11 years	Methylphenidate	Prescribed in clinical practice	-Methylphenidate exerts beneficial effects on executive functions, attention, and verbal fluency in children with ADHD -Children treated with methylphenidate (ADHD treatment group) showed significant improvements compared to untreated ADHD children, across : Working memory, inhibitory control, cognitive flexibility and sustained, selective attention and verbal fluency.
Methylphenidate-Related Improvements in Math Performance Cannot Be Explained by Better Cognitive Functioning or Higher Academic Motivation: Evidence From a Randomized Controlled Trial(21)	A double-blind, placebo-controlled, crossover randomized controlled Trial.	Children aged 8–13 with ADHD (n=63) and typically developing controls (n=67).	Extended release methylphenidate or Placebo	7-day treatment with methylphenidate or placebo	-The results indicated that methylphenidate did not significantly affect measures of cognitive functioning (such as working memory, reaction time, lapses of attention, and interference control) or academic motivation. -However, it did improve parent-rated self-perceived competence, confidence and self-belief, which mediated the medication's effect on math productivity.
Improvements in emotional lability with delayed-release and extended-release methylphenidate treatment in children with ADHD(22)	A post-hoc analysis of two randomized, double-blind, placebo-controlled phase 3 clinical trials.	Children aged 6–12 years diagnosed with ADHD n=278 children	Extended-release methylphenidate	6 weeks	-The results demonstrated that methylphenidate treatment led to significant improvements in Emotional Lability scores compared to placebo, with improvements observed at weeks 1, 2, 3, 4, 5, and 6, potentially leading to better overall functioning and reduced caregiver burden. -These improvements were statistically significant and clinically meaningful.
A comparative study on the neurophysiological mechanisms underlying effects of methylphenidate and neurofeedback on inhibitory control in attention deficit hyperactivity disorder(23)	An experimental research study	EEG (Electroencephalography) recordings and source localization analyses	Methylphenidate		-Findings suggest that Both Methylphenidate and Neurofeedback were effective in improving inhibitory control in ADHD, and enhanced behavioral performance in tasks requiring suppression of pre-potent responses -Methylphenidate acts through catecholamine-mediated modulation in medial frontal circuits, enhancing top-down inhibition.
Effects of methylphenidate on body index and physical fitness in Korean children with attention deficit hyperactivity disorder (24)	A cross-sectional comparative study with multiple groups.	119 male children with ADHD and 60 age-matched healthy male control children	Oral Methylphenidate	12 weeks	-Methylphenidate seemed to help improve IQ and attention. -It was also associated with enhanced skill-related physical fitness, particularly in balance and agility.
A six-month open-label multicenter study of the safety and efficacy of prc-063 in adolescents with attention-deficit/ hyperactivity disorder(25)	An experimental, open label, multicenter, phase 3 study.	176 participants aged 12-17 years old	PRC063, a multilayer extended-release formulation of Methylphenidate	6 Months	-The results demonstrated significant improvement in ADHD symptoms. -Participants showed improvements in executive functioning, daily functional outcomes, and overall quality of life; all these domains exhibited statistically significant enhancements

Improvements extend beyond symptom control to executive functioning, memory, response inhibition, reaction time and reaction time variability, as confirmed by neurocognitive studies(40). MPH has also shown benefits in social adjustment and overall classroom behavior, with higher response rates and lower dropout compared to non-stimulant alternatives such as atomoxetine (41).

Evidence also suggests that methylphenidate improves certain aspects of academic performance, including mathematics productivity and accuracy as well as reading speed, though effects on reading accuracy remain limited. Importantly, these academic gains are generally smaller than the improvements observed in core ADHD symptoms(42).

Despite these findings, the long-term efficacy of methylphenidate remains controversial. The Multimodal Treatment Study of ADHD and subsequent follow-ups revealed that while initial improvements were significant, treatment effects decreased over time, particularly with regard to academic outcomes(42). Several reviews have also reported mixed results for long-term school performance, with some trials finding transient benefits and others showing no meaningful differences compared to placebo or non-stimulant comparators(43).

However, the ethical dimension of research on methylphenidate has also been highlighted. Some authors, such as Hoekstra and colleagues, have criticized the use of nocebo (Defined as an inert treatment designed to produce adverse effects through negative expectations) and placebo tablets as comparators to assess bias, arguing that such designs raise important methodological and ethical concerns, particularly in pediatric populations. They emphasize that the current body of evidence remains of very low quality, and call for more independent, rigorously conducted trials, a deeper understanding of prescription practices, and greater integration of non-pharmacological interventions within clinical guidelines(44).

In terms of tolerability, methylphenidate is generally considered safe in the short term, with adverse events usually described as mild to moderate.

The most frequently observed side effect is loss of appetite, often leading to weight loss and, in prolonged use, raising concerns about growth suppression; this effect is dose-dependent, particularly pronounced with immediate-release formulations, and clinically significant reductions in weight have been documented in patients receiving higher doses or intensive treatment(45,46). This appetite-suppressing effect is believed to result from methylphenidate's action in the brain, increasing dopamine and norepinephrine in the prefrontal and insular cortices, which likely influences appetite through insular cortex-mediated signals of aversion; importantly, this effect is usually temporary, with children's weight typically normalizing over the course of long-term treatment(47).

Insomnia is another commonly reported adverse event, often linked to late-day dosing, and while generally reversible, it may significantly affect daily functioning and adherence to treatment(48,49).

Headaches and gastrointestinal symptoms, including nausea, abdominal pain, and irritability, are frequent but generally mild and transient, although their subjective severity may still lead patients to discontinue treatment(50).

Dermatological reactions have also been reported as adverse events associated with methylphenidate use. These include skin irritation, rash, or other mild to moderate cutaneous effects, which may occur with oral or transdermal formulations and should be monitored during treatment(51).

Less common but clinically significant events include cardiovascular effects such as tachycardia, elevated heart rate, and increases in blood pressure, that have been documented, sometimes emerging within the first week of treatment; these effects appear to correlate with dose and are usually mild, but warrant monitoring, particularly in individuals with pre-existing vulnerabilities(29,46).

In addition, psychotic symptoms, including hallucinations and mood disturbances, have been observed in a small proportion of users, and long-term treatment has also been associated with emotional and behavioral changes such as low mood, anxiety, irritability, and heightened emotional reactivity. Although these events are relatively rare, their potential severity underscores the importance of careful monitoring during long-term therapy and highlights the need to individualize treatment based on patient vulnerability and history(52,53).

Overall, long-term data from large cohort studies suggest that cardiovascular and psychiatric safety of methylphenidate is generally reassuring, yet rare but clinically significant risks cannot be entirely excluded. Careful specialist follow-up and monitoring are therefore recommended, particularly in high-risk populations, including preschool children, adolescents with comorbidities such as tics, or those with a family or personal history of psychiatric disorders or substance abuse(46,52).

However, it is important to consider that these adverse reactions can differ substantially between patients, influenced by factors such as dosage, formulation, timing of administration and duration of treatment(54).

Furthermore, genetic variability plays a significant role in individual susceptibility to adverse effects. Variants in dopaminergic genes (e.g., DBH, DRD2) have been linked to increased risk of side effects, while polymorphisms in metabolic enzymes—such as CES1 and CYP2D6 can affect methylphenidate pharmacokinetics and tolerability, with some individuals experiencing adverse events even at low doses(55,56).

Despite being well characterized, these adverse reactions are likely underreported, as most trials are short-term and industry-funded, potentially leading to selective reporting of safety outcomes. That's why the paucity of independent, long-term investigations remains a significant limitation, leaving considerable uncertainty about the true risk–benefit balance of methylphenidate in routine clinical practice.

Clinical implications and applicability of international guidelines in the Tunisian context :

International guidelines acknowledge both the strengths and limitations of the current evidence base. The European ADHD Guidelines Group and the National Institute for Health and Care Excellence (NICE, 2018) recommend methylphenidate as a first-line pharmacological treatment only for children and adolescents with severe ADHD and significant functional impairment, while prioritizing behavioral interventions in milder cases. These recommendations emphasize the need for careful benefit–risk assessment prior to treatment initiation, particularly in long-term treatment scenarios.

Table 2. Summary of studies on the tolerability of methylphenidate

Article	Authors and year	Methodology	Main findings
Chemical Leukoderma Associated with Methylphenidate Transdermal System: Data From the US Food and Drug Administration Adverse Event Reporting System	Carmen Cheng, et al, 2017 (26)	-A retrospective observational study based on pharmacovigilance data.	-51 cases of chemical leukoderma associated with the methylphenidate transdermal system (MTS). -Depigmentation generally persisted after discontinuation of MTS, with some cases showing continued extension
Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose Titration Study of Methylphenidate Hydrochloride Extended-Release Capsules (Aptensio XR) in Preschool Children with Attention-Deficit/ Hyperactivity Disorder	Ann C. Childress, et al, 2020 (12)	-A randomized, double-blind (DB), flexible-dose, placebo-controlled, parallel-group design conducted in six sequential phases -119 children, aged 4 to just under 6 -6-weeks treatment	-In Phase 4, 79.8% of children experienced at least one treatment-emergent adverse event, mostly mild or moderate. The most common were decreased appetite, insomnia, decreased weight, and irritability, with only one severe case of insomnia. -In Phase 5, the most frequent adverse event included hypertension and emotional changes, negativism, pollakiuria, onychophagia, decreased appetite, and tachycardia, all mild or moderate except for one severe case of negativism.
Effects of methylphenidate on body index and physical fitness in Korean children with attention deficit hyperactivity disorder	Kyoung Doo Kang, et al, 2017 (24)	-A cross-sectional observational study	-Methylphenidate didn't cause growth delays in height, weight, or BMI.
Methylphenidate effects on height and bone age in ADHD children. 24 month follow up within the prospective ADDUCE project	S. Carucci, et al,2016 (27)	-A prospective longitudinal cohort study. -44 children, aged 6-12 years old -24 months	-ADHD children had normal baseline growth, which was largely maintained after 24 months of MPH treatment. -BMI reduction may occur during early treatment, but height is preserved. -Bone age monitoring indicated a potential normalization or slight acceleration in bone maturation. -Predicted adult height remained stable, suggesting no clinically significant impact on final height within the 2-year follow-up.
Effects of Methylphenidate on Sleep Functioning in Children with Attention-Deficit/ Hyperactivity Disorder	Stephen P. Becker, et al, 2016 (19)	-A 4-week, randomized, double-blind, placebo-controlled trial. -163 children aged 7–11 years diagnosed with ADHD	-Methylphenidate affects sleep in children, with higher doses generally worsening sleep, particularly in those with lower weight or BMI, although some children with preexisting sleep issues experienced improvements, suggesting careful dose titration may be beneficial.
Efficacy, Safety, and Tolerability of an Extended-Release Orally Disintegrating Methylphenidate Tablet in Children 6–12 Years of Age with Attention-Deficit/ Hyperactivity Disorder in the Laboratory Classroom Setting	Ann C. Childress, et al, 2017 (28)	-A randomized, multicenter, double-blind, placebo-controlled, parallel-group laboratory classroom study. -87 children aged 6–12 years diagnosed with ADHD	-The results indicated that the extended-release orally disintegrating methylphenidate tablet was effective and well-tolerated, demonstrating significant improvements in ADHD symptoms compared to placebo. -Common adverse events included decreased appetite, upper abdominal pain, headache, insomnia, upper respiratory tract infection, affective lability, irritability, cough, and vomiting were considered mild.
Evaluation of acute cardiovascular effects of immediate-release methylphenidate in children and adolescents with attention-deficit hyperactivity disorder	Marco Lamberti, et al, 2015 (29)	-A prospective, interventional, within-subject study -54 children and adolescents, aged 6-19 years old	-No major changes were seen in key ECG measures like QTc and QT dispersion. -Blood pressure and heart rate showed slight increases but stayed in a normal range. -A small, significant rise in the TpTe/QTc ratio suggests it might help spot borderline heart effects. ⇨ no clinically significant ECG abnormalities were detected after methylphenidate administration.
Methylphenidate has mild hyperglycemic and hypokalemia effects and increases leukocyte and neutrophil counts	Gideon Charach, et al, 2020 (30)	-A prospective observational study 64 young patients -3 months	-Methylphenidate may induce mild hyperglycemia, hypokalemia, and leukocytosis in patients with ADHD. -These effects are generally mild, reversible, and clinically manageable.
A case of delayed hypersensitivity reaction to methylphenidate	K. Weinmeister, et al,2023 (31)	-A case report -5 year-old child	-Five days after initiating treatment with short-acting methylphenidate (5 mg twice daily), the patient developed a diffuse, fixed, pruritic, maculopapular rash. ⇨ This case highlights the potential for delayed hypersensitivity reactions to methylphenidate.
Long-Term Treatment With Extended-Release Methylphenidate Treatment in Children Aged 4 to <6 Years	Ann C. Childress, et al, 2022 (32)	-A prospective, open-label, 12-month longitudinal clinical trial.	-Extended-release methylphenidate was generally well-tolerated in preschool-aged children with ADHD, with most adverse events being mild to moderate. -ADHD symptoms remained controlled over 12 months, though some children experienced decreases in weight and height, as well as increases in diastolic blood pressure
Oros methylphenidate induced diffuse maculopapular skin in an adolescent with attention deficit hyperactivity disorder: a case report	I. Suzer Gamli, et al, 2024 (33)	-A case report An adolescent diagnosed with ADHD.	-This case highlights the potential for skin reactions : Development of a diffuse maculopapular skin rash, as an adverse effect of OROS methylphenidate in adolescents with ADHD.

Table 2. Summary of studies on the tolerability of methylphenidate

Article	Authors and year	Methodology	Main findings
Medication for attention deficit/hyperactivity disorder and risk for depression: A nationwide longitudinal cohort study	Zheng Chang, et al,2016 (34)	-Nationwide longitudinal cohort study	-It suggested a potential protective effect, indicating that ADHD medication may reduce the risk of subsequent depression.
Use of methylphenidate and risk for valvular heart disease: A case-control study nested in the BIFAP cohort	Luis Carlos Saiz, et al, 2020 (35)	-Nested case-control study within a large primary care cohort (BIFAP database, Spain). -Patients 5–25 years old between 2002 and 2014.	-No significant association was found between methylphenidate exposure and increased risk of VHD. -Methylphenidate use was not associated with an increased risk of valvular heart disease in young people. The adjusted odds ratio for current use did not show an elevated risk compared to non-users.
Methylphenidate and atomoxetine treatment negatively affect physical growth indexes of school-age children and adolescents with attention-deficit/hyperactivity disorder	Lanliu Deng et al,2021 (36)	-A prospective cohort study	-Methylphenidate treatment is associated with early reductions in weight and BMI, primarily linked to appetite suppression, but these effects tend to attenuate with prolonged use; long-term height growth appears largely unaffected.
Methylphenidate and the risk of psychosis in adolescents and young adults: a population-based cohort study	Chris Hollis, et al, 2019 (37)	-A population-based cohort study. -Over 23,000 young people getting methylphenidate across Sweden.	-No significant rise in psychotic events was found right after starting treatment, even in those with prior psychosis.
Methylphenidate and Short-Term Cardiovascular Risk	Miguel Garcia-Argibay, et al,2024 (38)	-A retrospective, population-based cohort study based on national Swedish registry data. -Over 26,000 people with ADHD	-Short-term methylphenidate use was linked to a modestly increased risk of cardiovascular events, though the absolute risk remained low and did not differ between patients with or without preexisting cardiovascular disease.

Table 3. International ADHD Recommendations and Their Applicability in Tunisia

	Recommandations	Applicability in Tunisia
Baseline Assessment	Document psychiatric/medical history, family cardiac history, heart rate/Blood pressure, height/weight; no routine ECG unless risk factors (NICE)(8).	Baseline assessments (Heart rate/Blood pressure, growth tracking) are feasible in routine practice; ECG only when clinically indicated(57).
Initiation and Age	• ≥5 years: Methylphenidate as first-line (after psychosocial). • <5 years: behavioral parent-training first, specialist 2nd opinion before meds (NICE, AAP) (8,28,58).	In Tunisia, behavioral therapies are prioritized before starting medication, which is generally initiated only after age 6, with individualized assessment and shared decision-making with families(57).
Prescription and Access	Prescribe methylphenidate only after ADHD diagnosis by a trained psychiatrist; psychostimulants are under strict regulation and require a Tableau B prescription, filled within 48 hours in hospital or authorized pharmacies(8).	In Tunisia, methylphenidate may only be prescribed following an ADHD diagnosis by a trained child and adolescent psychiatrist. Psychostimulants are strictly regulated and require a Tableau B prescription, to be dispensed within 48 hours at hospitals or authorized pharmacies(59).
Dosing and Titration	"Start low, go slow" : start with the lowest effective dose(8).	In Tunisia, treatment initiation begins with low doses, typically 5 mg twice daily, with gradual titration based on clinical response and tolerability(57).
Availability and Formulations	Use extended-release formulations (eg Concerta) when possible to improve adherence and reduce insomnia and misuse risks(8,60).	In Tunisia, Concerta was available for approximately one year, while Ritalin has also experienced periods of unavailability, reflecting intermittent access to these formulations.
Multimodal Approach	Combine medication with non-pharmacological interventions such as behavioral therapy or school-based programs(8).	Local studies encourage such complementary strategies, with Tunisian programs showing cognitive and behavioral benefits(61–63).
Monitoring and Follow-Up	Perform baseline assessments for growth (height, weight), heart rate, blood pressure; monitor these regularly (every 3–6 months). Watch for adverse effects; involve a specialist if tachycardia, Blood pressure elevation, growth delays, or neuropsychiatric symptoms emerge(8,60). Follow up every 3–6 months once stable. Review benefit–risk regularly(58).	While not formalized in Tunisian guidelines, these measures align with international standards and are feasible in clinical practice. Follow up frequency adapted to family availability and resource constraints; ideally aligns with guideline recommendations(57).
Adverse effects management	Monitor and manage common adverse effects (appetite loss, insomnia, headache..) with dose/formulation adjustments, timing strategies, nutritional support; monitor cardiovascular parameters (HR/BP) and neuropsychiatric status (mood, irritability, psychotic symptoms); increase surveillance in high-risk groups (preschool children, comorbidities, family psychiatric history)(8).	In accordance with current recommendations : Appetite/weight loss: dose with/after food; reinforce nutrition plan; monitor growth; consider dose/formulation changes if trajectory falters. Insomnia: morning dosing preferred; adapt formulation to profile; avoid afternoon boosters; consider shorter-acting formulation if needed. Headache/GI symptoms : often transient; give with food; consider slower titration or formulation switch if persistent(57).
Family Education	Educate on goals, AEs, adherence, drug holidays, red flags (NICE) (8).	In Tunisia, limited time, resources, and specialized personnel constrain the implementation of structured patient and family education programs. Nevertheless, efforts are made to provide education during therapeutic consultation sessions, including psychoeducational guidance at treatment initiation, as well as through small groups or locally adapted interventions, such as Barkley-style behavioral therapy sessions(61,64).

In line with these recommendations, methylphenidate was generally well tolerated in the present review, supporting guideline-based monitoring of growth parameters, sleep, appetite, cardiovascular measures, and neuropsychiatric status. As summarized in Table 3, most core components of guideline-based care, including standardized diagnostic assessment, cautious initiation with low-dose titration, and structured follow-up, are feasible within routine clinical practice in Tunisia. However, access to extended-release formulations and structured psychosocial interventions remains variable, underscoring the need for locally adapted care pathways.

Strengths and limitations of the literature review:

This literature review is strengthened by the inclusion of recent, high-quality studies, predominantly randomized double-blind controlled trials, which provide convergent evidence supporting the efficacy of methylphenidate across multiple outcome domains. The consistency of findings observed across randomized controlled trials, longitudinal cohort studies, and comparative designs reinforces the internal validity and overall reliability of the conclusions. Nevertheless, several limitations should be acknowledged. A number of the reviewed trials involved relatively small sample sizes and short follow-up periods, which may restrict the generalizability of the results and limit conclusions regarding long-term outcomes. In addition, substantial methodological heterogeneity was noted across studies, particularly with respect to study design, outcome measures, and dosing regimens, complicating direct comparisons and synthesis of results. Finally, the absence of direct head-to-head comparisons between different methylphenidate formulations or dosing strategies limits the ability to draw firm conclusions regarding their relative effectiveness and tolerability.

In conclusion, the present findings support the short-term efficacy and overall safety of methylphenidate in children and adolescents with ADHD, while underscoring persistent uncertainties regarding long-term outcomes. Sustained treatment, therefore, requires careful monitoring of growth, sleep, appetite, and cardiovascular parameters to ensure safety and adherence. In Tunisia, where access to methylphenidate and standardized treatment protocols remains limited, these results provide a valuable evidence base to inform clinical practice. Future implementation of national protocols, clinician training, and context-specific research on combined pharmacological and behavioral approaches could further strengthen ADHD care pathways, improve equity of access, and support better long-term outcomes for affected children and adolescents.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders [Internet]. Fifth Edition. American Psychiatric Association; 2013 [cited 2025 Sep 4]. Available from: https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596 doi:10.1176/appi.books.9780890425596
2. World Health Organization, editor. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992. 362 p.
3. Salari N, Ghasemi H, Abdoli N, Rahmani A, Shiri MH, Hashemian AH, et al. The global prevalence of ADHD in children and adolescents: a systematic review and meta-analysis. Ital J Pediatr. 2023 Apr 20;49(1):48. doi:10.1186/s13052-023-01456-1
4. Arnsten AFT. ADHD and the Prefrontal Cortex. J Pediatr. 2009 May;154(5):I-S43. doi:10.1016/j.jpeds.2009.01.018
5. Njardvik U, Wergeland GJ, Riise EN, Hannesdottir DKr, Öst LG. Psychiatric comorbidity in children and adolescents with ADHD: A systematic review and meta-analysis. Clin Psychol Rev. 2025 Jun;118:102571. doi:10.1016/j.cpr.2025.102571
6. Wu X, Ohinmaa A, Veugelers P. The Influence of Health Behaviours in Childhood on Attention Deficit and Hyperactivity Disorder in Adolescence. Nutrients. 2016 Dec 2;8(12):788. doi:10.3390/nu8120788
7. Palakodeti SS, Sarangi A, Mehta TR. The ADHD Conundrum- A Review of Non-pharmacological Approach to Management. Curr Dev Disord Rep. 2025 Feb 8;12(1):6. doi:10.1007/s40474-025-00317-2
8. National Institute for Health and Care Excellence (NICE). Attention deficit hyperactivity disorder: diagnosis and management (NG87). National Institute for Health and Care Excellence [Internet]. 2018. Available from: https://www.nice.org.uk/guidance/ng5
9. Storebø OJ, Krogh HB, Ramstad E, Moreira-Maia CR, Holmskov M, Skoog M, et al. Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials. BMJ. 2015 Nov 25;h5203. doi:10.1136/bmj.h5203
10. Silczuk A, Lewandowska A, Filip M, Atroszko PA, Podolec J, Gałecka M, et al. Current insights into the safety and adverse effects of methylphenidate in children, adolescents, and adults - narrative review. Pharmacol Rep. 2025 Jul 22. doi:10.1007/s43440-025-00763-0
11. Dougherty DM, Olvera RL, Acheson A, Hill-Kapturczak N, Ryan SR, Mathias CW. Acute effects of methylphenidate on impulsivity and attentional behavior among adolescents comorbid for ADHD and conduct disorder. J Adolesc. 2016 Dec;53(1):222–30. doi:10.1016/j.adolescence.2016.10.013
12. Childress AC, Kollins SH, Foehl HC, Newcorn JH, Mattingly G, Kupper RJ, et al. Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose Titration Study of Methylphenidate Hydrochloride Extended-Release Capsules (Aptensio XR) in Preschool Children with Attention-Deficit/Hyperactivity Disorder. J Child Adolesc Psychopharmacol. 2020 Mar 1;30(2):58–68. doi:10.1089/cap.2019.0085
13. Horowitz I, Avirame K, Naim-Feil J, Rubinson M, Moses E, Gothelf D, et al. The interactive effects of test-retest and methylphenidate administration on cognitive performance in youth with ADHD: A double-blind placebo-controlled crossover study. Psychiatry Res. 2020 Sep;291:113056. doi:10.1016/j.psychres.2020.113056
14. Shang CY, Shih HH, Pan YL, Lin HY, Gau SSF. Comparative Efficacy of Methylphenidate and Atomoxetine on Social Adjustment in Youths with Attention-Deficit/Hyperactivity Disorder. J Child Adolesc Psychopharmacol. 2020 Apr 1;30(3):148–58. doi:10.1089/cap.2019.0139
15. Matthijssen AFM, Dietrich A, Bierens M, Kleine Deters R, Van De Loo-Neus GHH, Van Den Hoofdakker BJ, et al. Continued Benefits of Methylphenidate in ADHD After 2 Years in Clinical Practice: A Randomized Placebo-Controlled Discontinuation Study. Am J Psychiatry. 2019 Sep 1;176(9):754–62. doi:10.1176/appi.ajp.2019.18111296
16. Levi-Shachar O, Gvirts HZ, Goldwin Y, Bloch Y, Shamay-Tsoory S, Zagoory-Sharon O, et al. The effect of methylphenidate on social cognition and oxytocin in children with attention deficit hyperactivity disorder. Neuropsychopharmacology. 2020 Jan 2;45(2):367–73. doi:10.1038/s41386-019-0522-5
17. Rothe J, Kattlun FA, Kaufmann J, Uhlmann A, Wanderer S, Bluschke A, et al. Effects of methylphenidate and physiotherapeutic treatment on graphomotor movements in children with ADHD.

Eur Child Adolesc Psychiatry. 2024 Jan;33(1):127–37. doi:10.1007/s00787-023-02144-5

18. Bolfer C, Pacheco SP, Tsunemi MH, Carreira WS, Casella BB, Casella EB. Attention-deficit/hyperactivity disorder: the impact of methylphenidate on working memory, inhibition capacity and mental flexibility. Arq Neuropsiquiatr. 2017 Apr;75(4):204–8. doi:10.1590/0004-282x20170030
19. Becker SP, Froehlich TE, Epstein JN. Effects of Methylphenidate on Sleep Functioning in Children with Attention-Deficit/Hyperactivity Disorder. J Dev Behav Pediatr. 2016 Jun;37(5):395–404. doi:10.1097/DBP.0000000000000285
20. Minervino C, Cruz LFP. Executive functions, attention and verbal fluency of children with attention deficit/hyperactivity disorder using methylphenidate. Eur Neuropsychopharmacol. 2017 Oct;27:S1090–1. doi:10.1016/S0924-977X(17)31895-3
21. Kortekaas-Rijlaarsdam AF, Luman M, Sonuga-Barke E, Bet P, Oosterlaan J. Methylphenidate-Related Improvements in Math Performance Cannot Be Explained by Better Cognitive Functioning or Higher Academic Motivation: Evidence From a Randomized Controlled Trial. J Atten Disord. 2020 Nov;24(13):1824–35. doi:10.1177/1087054717713640
22. Arnold V, Lopez F, Childress A, Po M, Gregg R, Sallee F, et al. IMPROVEMENTS IN EMOTIONAL LABILITY WITH DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE TREATMENT IN CHILDREN WITH ADHD. J Am Acad Child Adolesc Psychiatry. 2021 Oct;60(10):S257. doi:10.1016/j.jaac.2021.09.412
23. Bluschke A, Friedrich J, Schreiter ML, Roessner V, Beste C. A comparative study on the neurophysiological mechanisms underlying effects of methylphenidate and neurofeedback on inhibitory control in attention deficit hyperactivity disorder. NeuroImage Clin. 2018;20:1191–203. doi:10.1016/j.nicl.2018.10.027
24. Kang KD, Yun SW, Chung U, Kim TH, Park JH, Park IH, et al. Effects of methylphenidate on body index and physical fitness in Korean children with attention deficit hyperactivity disorder. Hum Psychopharmacol Clin Exp. 2016 Mar;31(2):76–82. doi:10.1002/hup.2514
25. Kollins SH, Cutler AJ, Khattak S, Weiss MD, Donnelly G, Reiz JL. 6.41 A Six-Month Open-Label Multicenter Study Of The Safety And Efficacy Of Prc-063 In Adolescents With Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry. 2016 Oct;55(10):S217. doi:10.1016/j.jaac.2016.09.361
26. Cheng C, La Grenade L, Diak IL, Brinker A, Levin RL. Chemical Leukoderma Associated with Methylphenidate Transdermal System: Data From the US Food and Drug Administration Adverse Event Reporting System. J Pediatr. 2017 Jan;180:241–6. doi:10.1016/j.jpeds.2016.09.008
27. Carucci S, Romaniello R, Lampis A, Panei P, Coghill D, Zuddas A. Methylphenidate effects on height and bone age in ADHD children. 24 month follow up within the prospective ADDUCE project. Eur Neuropsychopharmacol. 2016 Oct;26:S731–2. doi:10.1016/S0924-977X(16)31883-1
28. Childress AC, Kollins SH, Cutler AJ, Marraffino A, Sikes CR. Efficacy, Safety, and Tolerability of an Extended-Release Orally Disintegrating Methylphenidate Tablet in Children 6–12 Years of Age with Attention-Deficit/Hyperactivity Disorder in the Laboratory Classroom Setting. J Child Adolesc Psychopharmacol. 2017 Feb;27(1):66–74. doi:10.1089/cap.2016.0002
29. Lamberti M, Italiano D, Guerriero L, D'Amico G, Siracusano R, Ingrassia M, et al. Evaluation of acute Cardiovascular effects of immediate-release Methylphenidate in children and adolescents with attention deficit Hyperactivity disorder. Clin Ther. 2015 Aug;37(8):e47. doi:10.1016/j.clinthera.2015.05.143
30. Charach G, Karniel E, Grosskopf I, Rabinovich A, Charach L. Methylphenidate has mild hyperglycemic and hypokalemia effects and increases leukocyte and neutrophil counts. Medicine (Baltimore). 2020 Jul 2;99(27):e20931. doi:10.1097/MD.0000000000020931
31. Weinmeister K, Spriet S. A CASE OF DELAYED HYPERSENSITIVITY REACTION TO METHYLPHENIDATE. Ann Allergy Asthma Immunol. 2023 Nov;131(5):S96–7. doi:10.1016/j.anai.2023.08.284
32. Childress AC, Foehl HC, Newcorn JH, Faraone SV, Levinson B, Adjei AL. Long-Term Treatment With Extended-Release Methylphenidate Treatment in Children Aged 4 to <6 Years. J Am Acad Child Adolesc Psychiatry. 2022 Jan;61(1):80–92. doi:10.1016/j.jaac.2021.03.019
33. Gamli IS. OROS Methylphenidate Induced Diffuse Maculopapular Skin in an Adolescent with Attention Deficit Hyperactivity Disorder: A Case Report. Neurosci Appl. 2024;3:105096. doi:10.1016/j.nsa.2024.105096
34. Chang Z, D'Onofrio BM, Quinn PD, Lichtenstein P, Larsson H. Medication for Attention-Deficit/Hyperactivity Disorder and Risk for Depression: A Nationwide Longitudinal Cohort Study. Biol Psychiatry. 2016 Dec;80(12):916–22. doi:10.1016/j.biopsych.2016.02.018
35. Saiz LC, Gil M, Alonso A, Erviti J, Garjón J, Martínez M. Use of methylphenidate and risk for valvular heart disease: A case-control study nested in the BIFAP cohort. Pharmacoepidemiol Drug Saf. 2020 Mar;29(3):288–95. doi:10.1002/pds.4954
36. Deng L, Zhou P, Zhu L, Zhang Y, Yang T, Zhao Q, et al. Methylphenidate and atomoxetine treatment negatively affect physical growth indexes of school-age children and adolescents with attention-deficit/hyperactivity disorder. Pharmacol Biochem Behav. 2021 Sep;208:173225. doi:10.1016/j.pbb.2021.173225
37. Hollis C, Chen Q, Chang Z, Quinn PD, Viktorin A, Lichtenstein P, et al. Methylphenidate and the risk of psychosis in adolescents and young adults: a population-based cohort study. Lancet Psychiatry. 2019 Aug;6(8):651–8. doi:10.1016/S2215-0366(19)30189-0
38. Garcia-Argibay M, Bürkner PC, Lichtenstein P, Zhang L, D'Onofrio BM, Andell P, et al. Methylphenidate and Short-Term Cardiovascular Risk. JAMA Netw Open. 2024 Mar 6;7(3):e241349. doi:10.1001/jamanetworkopen.2024.1349
39. Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2018 Sep;5(9):727–38. doi:10.1016/S2215-0366(18)30269-4
40. Faraone SV, Buitelaar J. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. Eur Child Adolesc Psychiatry. 2010 Apr;19(4):353–64. doi:10.1007/s00787-009-0054-3
41. Cunill R, Castells X, Tobias A, Capellà D. Pharmacological treatment of attention deficit hyperactivity disorder with co-morbid drug dependence. J Psychopharmacol (Oxf). 2015 Jan;29(1):15–23. doi:10.1177/0269881114544777
42. Kortekaas-Rijlaarsdam AF, Luman M, Sonuga-Barke E, Oosterlaan J. Does methylphenidate improve academic performance? A systematic review and meta-analysis. Eur Child Adolesc Psychiatry. 2019 Feb;28(2):155–64. doi:10.1007/s00787-018-1106-3
43. Storebø OJ, Ramstad E, Krogh HB, Nilausen TD, Skoog M, Holmskov M, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). Cochrane Developmental, Psychosocial and Learning Problems Group, editor. Cochrane Database Syst Rev. 2015 Nov 25;2016(11). doi:10.1002/14651858.CD009885.pub2
44. Hoekstra PJ, Buitelaar JK. Is the evidence base of methylphenidate for children and adolescents with attention-deficit/hyperactivity disorder flawed? Eur Child Adolesc Psychiatry. 2016 Apr;25(4):339–40. doi:10.1007/s00787-016-0845-2
45. Bou Khalil R, Fares N, Saliba Y, Tamraz J, Richa S. L'effet de la méthylphénidate sur l'appétit et le poids. L'Encéphale. 2017 Dec;43(6):577–81. doi:10.1016/j.encep.2017.01.007
46. Vitiello B. Understanding the Risk of Using Medications for Attention Deficit Hyperactivity Disorder with Respect to Physical Growth and Cardiovascular Function. Child Adolesc Psychiatr Clin N Am. 2008 Apr;17(2):459–74. doi:10.1016/j.chc.2007.11.010
47. Dela Peña IC, Shen G, Shi WX. Methylphenidate significantly alters the functional coupling between the prefrontal cortex and dopamine neurons in the ventral tegmental area. Neuropharmacology. 2018 Mar;131:431–9. doi:10.1016/j.neuropharm.2018.01.015
48. Leite B, Vidal J, Silva A, Brito G, Souza K, Freitas M, et al. Evidence of Efficacy and Safety of Methylphenidate in the Treatment of Children

or Adolescents with Attention Deficit Disorder and Hyperactivity (Adhd). Value Health. 2015 Nov;18(7):A837. doi:10.1016/j.jval.2015.09.353

49. Krinzinger H, Hall CL, Groom MJ, Ansari MT, Banaschewski T, Buitelaar JK, et al. Neurological and psychiatric adverse effects of long-term methylphenidate treatment in ADHD: A map of the current evidence. Neurosci Biobehav Rev. 2019 Dec;107:945–68. doi:10.1016/j.neubiorev.2019.09.023
50. Leonard BE, McCartan D, White J, King DJ. Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. Hum Psychopharmacol Clin Exp. 2004 Apr;19(3):151–80. doi:10.1002/hup.579
51. Kaya I, Coskun M. Diffuse Maculopapular Rash With Increasing Dosage of Methylphenidate. J Clin Psychopharmacol. 2016 Feb;36(1):106–7. doi:10.1097/JCP.0000000000000438
52. Krinzinger H, Hall CL, Groom MJ, Ansari MT, Banaschewski T, Buitelaar JK, et al. Neurological and psychiatric adverse effects of long-term methylphenidate treatment in ADHD: A map of the current evidence. Neurosci Biobehav Rev. 2019 Dec;107:945–68. doi:10.1016/j.neubiorev.2019.09.023
53. Ekinci O, Gunes S, Ekinci N. Psychotic symptoms associated with switching from OROS methylphenidate to modified-release methylphenidate. Anatol J Psychiatry. 2017;1. doi:10.5455/apd.227212
54. Cortese S, D'Acunto G, Konofal E, Masi G, Vitiello B. New Formulations of Methylphenidate for the Treatment of Attention-Deficit/Hyperactivity Disorder: Pharmacokinetics, Efficacy, and Tolerability. CNS Drugs. 2017 Feb;31(2):149–60. doi:10.1007/s40263-017-0409-0
55. Patrick KS, Radke JL, Raymond JR, Koller L, Nguyen LV, Rodriguez W, et al. Drug Regimen Individualization for Attention-Deficit/Hyperactivity Disorder: Guidance for Methylphenidate and Dexmethylphenidate Formulations. Pharmacother J Hum Pharmacol Drug Ther. 2019 Jun;39(6):677–88. doi:10.1002/phar.2190
56. Nemoda Z, Angyal N, Kruk E, Bognar E, Tarnok Z. Genetic determinants of methylphenidate response in children with attention deficit hyperactivity disorder. Eur Neuropsychopharmacol. 2016 Oct;26:S737–8. doi:10.1016/S0924-977X(16)31892-2
57. Ben Aicha D. Profil socio-démographique et clinique des enfants suivis pour trouble déficit de l'attention/hyperactivité à la consultation de pédopsychiatrie de Monastir entre les années 2017 et 2018 [mémoire]. Faculté de médecine de Monastir, Monastir; 2022.
58. Wolraich ML, Hagan JF, Allan C, et al; Subcommittee on Children and Adolescents with Attention-Deficit/Hyperactive Disorder. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019;144(4):e20192528. Pediatrics. 2020 Mar 1;145(3):e20193997. doi:10.1542/peds.2019-3997
59. Ministère de la santé Tunisie. circulaire du Ministère de la Santé Publique (Tunisie) n°133/99 relative à la prescription des médicaments faisant l'objet d'abus. n°133/99 [Internet]. Available from: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.ordre-medecins.org.tn/wp-content/uploads/2024/12/bulletin23_06.pdf 18/12/1999.
60. (for the European Guidelines Group), Graham J, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, et al. European guidelines on managing adverse effects of medication for ADHD. Eur Child Adolesc Psychiatry. 2011 Jan;20(1):17–37. doi:10.1007/s00787-010-0140-6
61. Guedria Tekari Asma. Prise en charge en thérapie cognitivo-comportementale du trouble déficit de l'attention/hyperactivité de l'enfant : étude à propos d'un cas [mémoire, à propos d'un cas]. [Faculté de médecine de Sousse, Sousse]; 2016.
62. Souid Ons. Thérapies cognitives et comportementales de la gestion de colère chez les enfants avec trouble déficitaire de l'attention avec ou sans hyperactivité [mémoire]. [Faculté de médecine de Sousse, Sousse]; 2021.
63. Ayoub Randaline. La thérapie par pleine conscience chez les adolescents avec TDAH [mémoire]. [Faculté de médecine de Sousse, Sousse]; 2024.
64. Fayala Ahlem, Guedria Asma. Effectiveness Of Behavioral Parent Training For Parents Of Children With Attention Deficit/Hyperactivity Disorder In A Tunisian Context [trial]. [Child and adolescent psychiatry Department of Fattouma Bourguiba University Hospital of Monastir]: Monastir University; 2025.