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ARTIKEL LAPORAN KASUS

LONG-TERM SIDE EFFECTS OF METHYLPHENIDATE HYDROCHLORIDE IN CHILDHOOD ADHD IN PRIMARY CARE: AN EVIDENCE-BASED CASE REPORT

EFEK SAMPING JANGKA PANJANG PENGGUNAAN METILFENIDAT HIDROKLORIDA PADA ANAK DENGAN ADHD DI LAYANAN PRIMER: SEBUAH LAPORAN KASUS BERBASIS BUKTI

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ABSTRAK
Latar Belakang: *Gangguan Pemusatan Perhatian dan Hiperaktifitas (Attention Deficit Hyperactivity Disorder/ADHD) sering kali muncul pada masa kanak-kanak dan dapat menetap hingga masa remaja dan dewasa. Methylphenidate adalah obat utama untuk menangani ADHD di masa muda, namun efek jangka panjangnya masih belum diketahui dengan pasti. Mengevaluasi bukti mengenai efek jangka panjang methylphenidate pada anak-anak dengan ADHD sangatlah penting.*
Kasus: *Seorang anak berusia 7 tahun dengan kesulitan mengikuti pelajaran sekolah, hiperaktif, dan mudah teralihkan (skor Conner 22) didiagnosis ADHD dan diobati dengan metilfenidat. Terlihat adanya perbaikan perilaku yang signifikan (skor Conner 8), tetapi orang tua pasien merasa khawatir mengenai penggunaan obat jangka panjang.*
Metode: *Kami melakukan pencarian terstruktur di database PubMed, EBSCOhost, Cochrane, dan SAGE, dengan fokus pada penelitian terhadap manusia, berbahasa Inggris, selama 5 tahun terakhir dengan ketersediaan teks lengkap. Kami memilih uji coba kontrol acak (RCT), meta-analisis, dan tinjauan sistematis dan menyaringnya berdasarkan relevansi dengan pertanyaan klinis kami. Pencarian menghasilkan hasil dari PubMed (43 artikel), EBSCOhost (46 artikel), Cochrane (41 artikel), dan SAGE (125 artikel). Setelah penyaringan yang ketat, beberapa artikel diidentifikasi relevan.*
Simpulan: *Analisis kasus berbasis bukti yang kami lakukan mengungkapkan bahwa pengobatan methylphenidate dikaitkan dengan efek samping yang serius dan tidak serius, terlepas dari durasi pengobatan. Dokter di layanan primer perlu berhati-hati ketika meresepkan methylphenidate untuk manajemen ADHD di masa kanak.*
Kata Kunci: *masa kanak, gangguan pemusatan perhatian dan hiperaktivitas, efek samping, metilfenidat.*

ABSTRACT
Background: Attention Deficit Hyperactivity Disorder (ADHD) often emerges in childhood and can persist into adolescence and adulthood. Methylphenidate is the primary medication for managing ADHD in youth, but its long-term effects remain uncertain. Evaluating the evidence on the long-term effects of methylphenidate in children with ADHD is crucial.
Case: A 7-year-old with school difficulties, hyperactivity, and distractibility (Conner's score 22) was diagnosed with ADHD and treated with methylphenidate. Significant behavioral improvement was observed (Conner's score 8), but parental concerns regarding long-term medication use persisted.
Metode: We conducted a structured search in PubMed, EBSCOhost, Cochrane, and SAGE databases, focusing on the past 5 years of English-language human studies with full-text availability. We selected randomized control trials (RCTs), meta-analyses, and systematic reviews and screened them based on relevance to our clinical question. The search yielded results from PubMed (43 articles), EBSCOhost (46 articles), Cochrane (41 articles), and SAGE (125 articles). After rigorous screening, some articles were identified as relevant.

Conclusion: Our case analysis based on evidence revealed that methylphenidate treatment is associated with serious and non-serious side effects, irrespective of treatment duration. Primary care clinicians should exercise caution when prescribing methylphenidate for ADHD management in childhood.
Key Words: childhood, attention deficit hyperactivity disorder, side effects, methylphenidate.

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most diagnosed psychiatric disorders with childhood onset. A meta-analysis conducted by Thomas in 2015 stated that the worldwide prevalence of ADHD in children is 7.2%.[1] ADHD is characterized by a pattern of inattentive and/or hyperactive-impulsive behavior that is inappropriate for the developmental level and results in impairment in social, educational, or occupational functioning.[2] Impairments in children and adolescents with ADHD encompass educational and social problems, while adults with ADHD experience impairments related to employment, accidents, and substance abuse. Children with ADHD also have a greater risk of adverse outcomes in adolescence and adulthood, including poor education, antisocial behavior, and substance abuse.[3] Research by Owens, *et al*. in 2015 showed that ADHD in children persists into adolescence in 50-80% of cases and persists into adulthood in 35-65% of cases.[4]

Clinical practice guidelines issued by the American Academy of Pediatrics in 2019 recommend Evidence-Based Parent Training and Behavior Management (PTBM) as the first-line therapy for preschool-age children (4-6 years) with ADHD. Methylphenidate may be considered if behavioral interventions do not show significant improvement and moderate to severe functional impairment persists. Methylphenidate is the first-line pharmacological therapy recommended for preschool-age children with ADHD. For school-age children (6-12 years) and adolescents (12-18 years), primary care clinicians are recommended to prescribe FDA-approved medications for ADHD.[5] One of the FDA-approved medications for ADHD is psychostimulants, with methylphenidate being the most commonly prescribed and the first-line therapy for managing ADHD in children and adolescents.[6] Methylphenidate can improve attention and reduce hyperactivity-impulsivity, thus enhancing patient functioning.

A study conducted by Storebo *et al*. in 2015 concluded that short-term use of methylphenidate can lead to a reduction in clinical symptoms of ADHD, behavioral problems, and improvements in quality of life. Short-term use of methylphenidate was defined as use for less than 6 months.[7] ADHD management often requires long-term treatment. To date, there are no guidelines regarding the duration of methylphenidate use. The new law regarding the prescription for chronic patients using the National Health Insurance in Indonesia mandates all patients to be prescribed at the primary care level, including mental health conditions such as ADHD. As primary care clinicians, it is important to be aware of the long-term side effects of methylphenidate use. However, to date, the long-term side effects of methylphenidate use remain a question. Therefore, evidence-based evaluation of the

long-term side effects of methylphenidate use in children with ADHD is needed.

CASE ILLUSTRATION

A 7-year-old boy presented at a primary care clinic for medical evaluation and routine referral to a child and adolescent psychiatrist. The patient was experiencing difficulties in school, including an inability to read, write, or perform basic arithmetic. During class, the patient could not sit still, constantly wandered around the classroom, engaged in mischievous behavior with classmates, failed to complete assigned tasks, and preferred playing over studying. At home, the patient frequently ran, climbed, and exhibited mischievous behavior, such as suddenly pushing, hitting, or teasing others.

During the initial examination, the patient appeared highly active, unable to sit still, and had difficulty focusing on tasks due to easy distractibility. The Conner's score was 22. The patient was diagnosed with attention deficit hyperactivity disorder (ADHD) and prescribed 7.5 mg of methylphenidate in the morning and 5 mg in the afternoon. Following the initiation of methylphenidate treatment, the patient's behavior notably improved. The patient began sitting in their chair during class, stopped roaming around the classroom, and started completing tasks assigned by the teacher. The final Conner's score assessed by the psychiatrist (after four months of methylphenidate treatment) was 8. The patient's mother expressed satisfaction with the positive changes in her child's behavior. Still, she had questions about the necessity of continuous medication and the long-term safety of the medication.

METHODS

Based on the case illustration, the examiner has a clinical question: What is the safety of long-term use compared to short-term use of methylphenidate hydrochloride in children with ADHD in the setting of primary health care? This clinical question is formulated in the PICO format: P (patient): Children and adolescents with attention deficit hyperactivity disorder (ADHD). I (intervention): Long-term use of methylphenidate hydrochloride. C (comparison/control): Short-term use of methylphenidate hydrochloride. O (outcome): The proportion of serious and non-serious side effects.

The search was conducted using key words created based on Boolean operators. Evidence search engines such as Pubmed, Cochrane, EBSCOhost, and SAGE were utilized. During this search, keyword selection was employed to obtain relevant results.

The search results were screened to avoid duplicate articles, and then limitations were applied, including articles published within the last 5 years, written in English, involving human research, and available in full text. The types of articles sought were restricted to randomized controlled trials (RCTs), meta-analyses, and systematic reviews. Subsequently, the obtained articles were further selected based on titles and abstracts that aligned with the clinical question.

After the selection process, one meta-

analysis article that aligned with the clinical question was identified: Storebø, *et al*. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of adverse events in non-randomized studies. Cochrane Database of Systematic Reviews 2019.

In the selected article, a critical appraisal process was conducted, assessing validity, importance, and applicability in the case using the assessment sheet for meta-analysis provided by the Centre for Evidence-Based Medicine (CEBM) at the University of Oxford.

Table 1. Results of journal article search

Search Engine	Key Words	Results
Pubmed	(child OR children) AND (adolescence) AND (ADHD) AND (methylphenidate) AND (long term safety OR long term adverse event OR long term effect)	43
Scopus	(child OR children) AND (adolescence) AND (ADHD) AND (methylphenidate) AND (long term safety OR long term adverse event OR long term effect)	41
EBSCOhost	(child OR children) AND (adolescence) AND (ADHD) AND (methylphenidate) AND (long term safety OR long term adverse event OR long term effect)	125
SAGE	(child OR children) AND (adolescence) AND (ADHD) AND (methylphenidate) AND (long term safety OR long term adverse event OR long term effect)	46

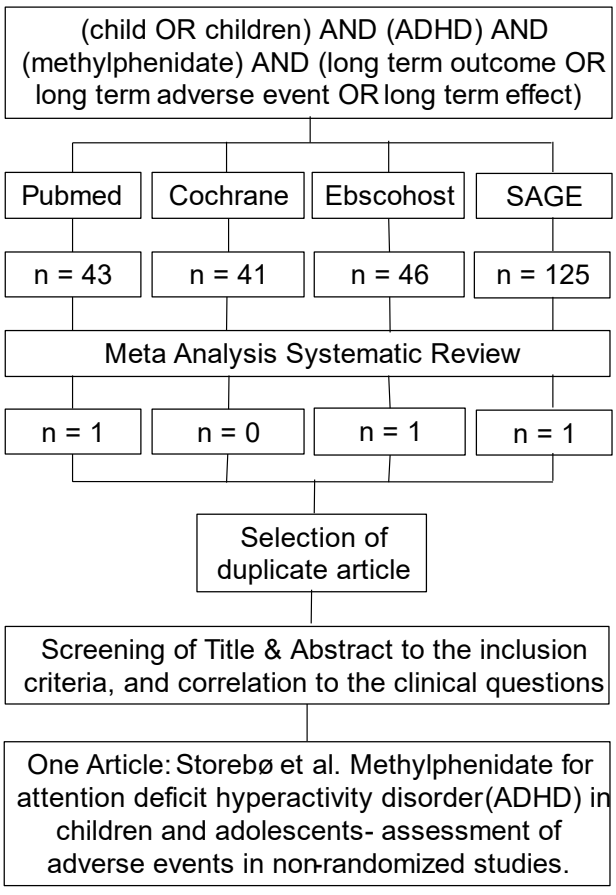

Figure 1. Results of Journal Article Search

RESULT

This meta-analysis is deemed valid for the following reasons: The article clearly outlines the objectives of the conducted meta-analysis, which aim to assess the side effects associated with administering methylphenidate in children and adolescents with ADHD in non-randomized studies. The inclusion criteria, including the study types, participants, interventions, and outcome measures, are also explicitly mentioned. The researchers searched for articles published in 17 databases, 2 trial registries, and unpublished ones; all included studies are presented in the article. Each study included in this article is assessed for its methodological quality using the GRADE approach, with the overall methodological quality of the included studies being very low based on the GRADE approach.

The study assesses various types of heterogeneity in reporting, including clinical (variability in participants, interventions, or settings), methodological (variation in study design), and statistical heterogeneity (variation in intervention effects). The study assesses heterogeneity between studies through visual inspection of the forest plot, using the Chi2 test for homogeneity and the I2 value. The study refrains from conducting meta-analysis in cases of very high heterogeneity. When meta-analysis is not feasible, the study provides narrative descriptions to estimate the effects. The risk of bias in each included study is assessed using the ROBINS-I tool. The risk of bias in comparative studies varies from moderate to critical, with most studies showing critical bias risk. The researchers assess all non-comparative studies as having bias risk.

To assess the safety profile of short-term methylphenidate use compared to long-term use, the study conducted subgroup analyses to determine whether the duration of treatment influenced the side effects of methylphenidate. The study compared a group of children receiving methylphenidate treatment for less than six months with a group receiving methylphenidate treatment for more than six months. Subgroup analysis was conducted using Comprehensive Meta-Analysis software, although the study did not specify this in the article. From the subgroup analysis, the study found no significant difference (p=0.83) in the proportion of participants receiving methylphenidate and experiencing serious side effects in short-term use or less than six months (1.20%, 95% CI 0.7% to 2.1% involving 41 non-comparative studies with 159,407 participants) compared to long-term use or more than six months (1.1%, 95% CI 0.3% to 3.4%; involving 10 non-comparative studies with 3015 participants). This can be interpreted as 1.2 out of 100 patients receiving short-term methylphenidate treatment (less than 6 months) experiencing serious side effects, while 1.1 out of 100 patients receiving long-term methylphenidate treatment experiencing serious side effects. This difference is not statistically significant.

Additionally, there was also no significant difference (p=0.74) in the proportion of participants receiving methylphenidate and experiencing non-serious side effects in short-

term use or less than six months (52.3%, 95% CI 52.3% to 52.3%, involving 35 non-comparative studies with 11,411 participants) compared to long-term use or more than six months (48.9%, 95% CI 33.7% to 64.3%; involving 14 non-comparative studies with 2567 participants). This can be interpreted as 52.3 out of 100 patients receiving short-term methylphenidate treatment (less than 6 months) experiencing non-serious side effects, while 48.9 out of 100 patients receiving long-term methylphenidate treatment experiencing non-serious side effects. Again, this difference is not statistically significant.

The researchers described their study population, allowing conclusions to be drawn about applicability. The results of Storebo et al.'s (2019) study can be applied to outpatient patients at primary care clinics due to their homogeneity with the research. Most of these studies included participants with attention deficit hyperactivity disorder, with or without comorbidities. The majority of studies also evaluated participants in outpatient settings, which is similar to the encountered patients. Therefore, the results of this study are generalizable to everyday clinical practice. Primary care clinicians can use these findings as considerations regarding the potential side effects of long-term methyl-phenidate use in children with ADHD.

DISCUSSION

ADHD is one of the most frequently encountered neurodevelopmental disorders in childhood. Individuals with ADHD exhibit difficulties in cognitive and attention functions such as problem-solving, planning, orientation, flexibility, response inhibition, and working memory.[8] The therapy options for ADHD in children and adolescents include stimulant medications, primarily methylphenidate and dextroamphetamine, atomoxetine (a non-stimulant selective noradrenaline reuptake inhibitor), guanfacine (an alpha 2A agonist), and psychosocial therapy.[5] The choice of medication by primary care clinicians and families is based on accompanying conditions, drug-related side effects, compliance issues, and the child's and family's preferences.

Methylphenidate is the most frequently prescribed medication for children and adolescents with ADHD and has been in practice for over 50 years.[6] It is used because it is effective in reducing symptoms of hyperactivity, impulsivity, and inattention in children and adolescents with ADHD, both in the short term and long term.[9,10] The most commonly reported side effects associated with methylphenidate are headaches, sleep problems, fatigue, and reduced appetite. Methylphenidate also interferes with children's height growth and leads to weight loss.[11] It has been reported to cause serious side effects such as psychosis and mood disorders.[12]

Methylphenidate is a dopamine-norepinephrine reuptake inhibitor. It binds to dopamine transporters on the presynaptic cell membrane, inhibiting dopamine reuptake and causing an increase in dopamine levels in the synaptic cleft. Elevated dopamine levels in the prefrontal cortex are believed to trigger psychotic symptoms.[13] The increased levels of dopamine and norepinephrine lead to

enhanced neurotransmission in specific brain circuits, particularly those involved in attention, impulse control, and executive function. This helps improve focus, attention span, and behavioral control in individuals with ADHD. Increased plasma dopamine and adrenaline may also mediate the sympathetic, central, and peripheral catecholaminergic systems. This mechanism is believed to be related to cardiovascular side effects and sleep disturbances associated with methylphenidate use.[14] Growth disturbances in children are thought to be related to the effects of dopamine, which is believed to suppress growth hormone secretion.[15]

Data obtained from non-randomized studies can be used to understand better the profile of side effects of a drug, especially those that are rare and take a long time to occur. Non-randomized studies have several advantages, including a larger sample size (which allows for the detection of rare side effects), a wider range of samples, more extended follow-up periods, and lower costs. Non-randomized studies can detect drug-related side effects associated with long-term drug exposure.[16] This data can help children, adolescents, families, and primary care clinicians understand the risks and benefits of choosing methylphenidate as a treatment.

Methylphenidate, a commonly prescribed medication for ADHD in children and adolescents, offers various formulations to cater to individualized treatment needs. These formulations include the immediate-release (IR) form of methylphenidate, which typically lasts for about 3 to 4 hours, is usually taken multiple times a day, and is indicated for short-term symptom control during the school day. Extended-release (ER) methylphenidate is designed to provide longer-lasting effects compared to immediate-release versions. Depending on the specific ER formulation, the duration of action can range from 6 to 12 hours, is taken once daily in the morning, and is indicated for comprehensive symptom management. The advanced Osmotic Release Oral System (OROS) ensures consistent blood concentration and even a transdermal patch option for those who prefer non-oral administration. The choice of formulation and dosage hinges on factors such as the patient's age and lifestyle, and it is essential to stick with one type of formulation. Another important note is that the exact way methylphenidate affects neurotransmitter levels and brain function may vary among individuals, and research into its mechanism of action is ongoing. Additionally, methylphenidate is not a cure for ADHD. Instead, it helps manage its symptoms when used as part of a comprehensive treatment plan that may include behavioral therapy and other interventions. Primary care physicians should collaborate with psychiatrists to determine the most appropriate treatment approach.[17]

In primary care settings, effective use of methylphenidate involves comprehensive patient evaluation, including medical history and physical examination, wherein primary care physicians (PCPs) play a pivotal role. PCPs are often the first point of contact for patients with ADHD symptoms and are responsible for diagnosing and initiating treatment in many

cases. They educate patients and their families on medication benefits, potential side effects, and the importance of adherence to the prescribed regimen. Furthermore, treatment plans are individualized by PCPs, considering factors such as the patient's age, daily routines, and response to medication. PCPs also provide regular monitoring of patients receiving methylphenidate, collaborating with mental health specialists for complex cases when necessary, remaining vigilant for the emergence of side effects, and integrating psychosocial interventions as part of a comprehensive care approach. Through these measures, PCPs play a crucial role in ensuring safe and effective management of ADHD in children and adolescents, thereby fostering better outcomes and improving the quality of life for patients and their families.[15,17]

CONCLUSION

Based on research findings, the treatment of methylphenidate in children and adolescents with ADHD increases the risk of serious side effects, including psychotic disorders, arrhythmias, seizures, and hypertension. Children and adolescents receiving methylphenidate may experience non-serious side effects such as sleep difficulties, stomach pain, reduced appetite, anxiety, and depressed mood. The occurrence of side effects is not dependent on the duration of methylphenidate treatment. Before initiating and during the administration of methylphenidate treatment, primary care clinicians should assess for comorbidities, cardiovascular irregularities, eating and sleep patterns, family history, and various other risk factors. Regular follow-up appointments are crucial to monitor the patient's response to treatment, assess for the emergence of any side effects, and make necessary adjustments to the treatment plan. Primary care clinicians should also discuss with the patient and their family regarding dosage, different formulations, and the potential side effects that may occur, emphasizing the importance of open communication and regular monitoring to ensure the safety and effectiveness of methylphenidate therapy.

REFERENCES

1. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention deficit/hyperactivity disorder: A systematic review and meta-analysis. Pediatrics. 2015;135(4):994-1001.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edition. Arlington. American Psychiatric Publishing; 2013.
3. Barbareai WJ, Campbell L, Diekroger EA, Froehlich TE, Liu YH, O'Malley E, et al. Society for developmental and behavioral pediatrics clinical practice guideline for the assessment and treatment of children and adolescents with complex attention-deficit/hyperactivity disorder. J Dev Behav Pediatr. 2020;41:S35–S57.
4. Owens EB, Cardoos SL, Hinshaw SP. Developmental progression and gender differences among individuals with ADHD. In: RA Barkley (Ed.), Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment. The Guilford Press. 2015.
5. Wolraich ML, Hagan JF, Allan C, Chan E, Davidson D, Earls M, et al. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2019;144(4).
6. NICE. Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults. 2008.

7. 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 Database of Systematic Reviews. 2015;11.
8. Pasini A, Paloscia C, Alessandrelli R, Porfirio MC, Curatolo P. Attention and executive functions profile in drug naive ADHD subtypes. Brain and Development 2007;29(7):400–8.
9. Faraone SV, Buitelaar J. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. Eur Child Adolesc Psychiatry. 2010;19:353–64.
10. Maia CR, Cortese S, Caye A, Deakin TK, Polanczyk GV, Polanczyk GV, et al. Long-term efficacy of methylphenidate immediate-release for the treatment of childhood ADHD. Journal of Attention Disorders. 2017;21(1):3–13.
11. Swanson J. The MTA follow-up into adolescence: implications for personalized treatment. International Society for Research in Child and Adolescent Psychopathology (ISRCAP). Seattle. 2009.
12. MTA Cooperation Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/ hyperactivity disorder. The MTA Cooperative Group. Archives of General Psychiatry. 1999; 56(12):1073–86.
13. 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;6:651–58.
14. Liang EF, Lim SZ, Tam AA, Ho CS, Zhang MW, McIntyre RS, et al. The effect of methylphenidate and atomoxetine on heart rate and systolic blood pressure in young people and adults with attention-deficit hyperactivity disorder (ADHD): Systematic review, meta-analysis, and meta-regression. Int J Environ Res Public Health. 2018;15(8):1789.
15. Goldman RD. ADHD stimulants and their effect on height in children. Can Fam Physician. 2010;56(2): 145–6.
16. Silverman SL. From randomized controlled trials to observational studies. American Journal of Medicine. 2009;122(2):114–20.
17. National Health Service: Methylphenidate for children [Internet]. London: National Health Service Online Resources, [updated 27 July 2021; cited 2023 Sept 15]. Available from https://www.nhs.uk/medicines/methylphenidate-children/