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Comparison of the real-world safety of two different long-acting methylphenidate formulations (Medikinet® MR and Concerta®) – a Danish nationwide register-based cohort study

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Abstract

Background: Medikinet® MR and Concerta® are long-acting methylphenidate formulations used for the treatment of pediatric and adult attention-deficit/hyperactivity disorder (ADHD). The two formulations have shown comparable safety profiles in two head-to-head randomized controlled trials. However, real-world studies comparing the safety profiles of these products are not available.
Objective: This study aimed to compare the real-world safety of Medikinet® MR and Concerta® using register data.
Method: This population-based cohort study was conducted based on data from Danish registries. The study included patients with continuous long-term (i.e., ≥12 months) exposure to either Medikinet® MR or Concerta® between 1995 and 2018. Outcomes included several selected adverse events of interest. A sensitivity analysis was performed, excluding patients exposed to Concerta® generics. For each outcome, Fisher's exact test was performed to compare the number of cases between the two groups. Odds ratios (ORs) and 95% confidence intervals were estimated using logistic regression models with patients exposed to Concerta® as the reference group.
Results: The study population included 1249 patients exposed to Medikinet® MR and 2455 patients exposed to Concerta®. No cases of cerebral arteritis or priapism were identified in either cohort. ORs for sudden death and anorexia could not be calculated due to the absence of cases in the Medikinet® MR cohort. For the remaining outcomes, no statistically significant difference in risk was found between Medikinet® MR-exposed and Concerta®-exposed patients. The sensitivity analysis produced results consistent with those obtained in the main analysis.
Conclusions: The results of this population-based cohort study indicate that Medikinet® MR and Concerta® have comparable real-world safety profiles.

Keywords: Methylphenidate; real-world safety; adverse events; attention-deficit hyperactivity disorder; register study

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental disorder, affecting 8% of children and adolescents and 3.1% of adults (1, 2). The disorder is characterized by symptoms of inattention, hyperactivity, and impulsivity that cause significant impairment in academic, social, and occupational functioning (3).
Stimulant medications, including methylphenidate (MPH) and amphetamines, are first-line pharmacotherapies for the treatment of ADHD in children, adolescents and adults (4-6). MPH is the most commonly prescribed ADHD medication in most countries, and its use has considerably increased in recent years (7-9).
The short-term safety profile of MPH is well established. Adverse events (AEs) commonly associated with MPH use include insomnia, anorexia, decreased weight, headache, and abdominal pain. MPH use is also associated with increases in blood pressure and pulse (10-12). AEs are usually mild and transient or can be managed by dose adjustments (5, 10). As ADHD is a chronic condition, patients require long-term treatment. However, the long-term safety of MPH is less well documented. Additionally, few head-to-head studies have directly compared the safety profiles of two or more MPH formulations

(13). Furthermore, population-based register studies are needed to compare the real-world safety of different MPH formulations.

Several long-acting MPH formulations are available that provide efficacy throughout the day with once-daily dosing. These formulations use different drug delivery technologies, incorporating varying proportions of immediate-release (IR) and extended-release (ER) MPH, resulting in different pharmacokinetic and pharmacodynamic profiles (13). One long-acting MPH formulation is currently marketed in several countries, most commonly under the brand names Medikinet® MR or Medikinet® XL, for the treatment of ADHD in children aged 6 years and over and adults (14). The formulation consists of hard gelatin capsules containing 50% of the total MPH dose as IR pellets and the other 50% as enteric-coated ER pellets (15). The duration of action is 8 hours. Another long-acting MPH formulation (Concerta®) is available in several countries for the treatment of pediatric and adult ADHD. Concerta® uses the 'Osmotic-Release Oral System' (OROS) technology to provide an immediate release of 22% of the total MPH dose followed by a gradual release of the remaining 78% of the MPH dose throughout the day, resulting in a duration of action of 12 hours (16).

Two head-to-head randomized controlled trials (RCTs) compared the short-term efficacy and safety of Medikinet® MR and Concerta® in children and adolescents with ADHD. The two formulations showed generally comparable AE profiles (17, 18). Real-world evidence on the comparative safety profiles of the two formulations is not available.

The objective of this study was to compare the real-world safety profiles of Medikinet® MR and Concerta® using Danish register data. We conducted a comparative population-based cohort study to assess the risk of selected adverse outcomes in individuals with long-term exposure (i.e., ≥12 months) to either Medikinet® MR or Concerta®. These outcomes included, among others, AEs commonly associated with MPH use, such as insomnia, anorexia, and hypertension, as well as rare but significant AEs, such as sudden death and cerebral arteritis.

Methods

Study design

This was a Danish nationwide register-based comparative cohort study. The following Danish registries were used: the Danish Civil Registration System, the Danish National Patient Registry, and the Danish National Prescription Registry.

The Danish Civil Registration System assigns a unique personal identification number, the CPR number, to all Danish citizens at birth or upon immigration. The CPR number is used in all national health registers and allows linkage at the individual level between the registers (19). The Danish National Patient Registry was established in 1977 and contains detailed clinical and administrative data on all patients treated in Danish hospitals. Since 1994, the diagnoses are classified according to the tenth revision of the International Classification of Diseases and Related Health Problems (ICD-10) (20). The Danish National Prescription Registry contains data on all prescriptions filled at community pharmacies in Denmark since 1995. The registry records information on dispensed drugs such as the product name, dispensing date, Anatomical Therapeutic Chemical (ATC) Classification System code, number of packages dispensed, pack size, strength, and number of defined daily doses (DDD) per package (21).

Study population

The study population consisted of patients with continuous long-term exposure to either Medikinet® MR (marketed as Medikinet® CR in Denmark) or Concerta® (branded and generic) between 1 January 1995 and 31 December 2018.

Patients were included if they had been continuously exposed to Medikinet® MR or Concerta® for at least 12 months, defined as retrieval of at least two prescriptions within 12 months, and one prescription at least every 6 months. The start of the treatment period (index date) was defined as the date of first prescription retrieval. The end of the treatment period was defined as the date of the last retrieved prescription that fulfilled the criterion of at least one prescription every 6 months, plus the number of days corresponding to the amount of DDDs dispensed. Patients had to be at least 6 years old at initiation of ADHD medication. If a patient met the inclusion criteria for exposure to Medikinet® MR at some point during the study period (1995 – 2018) and the inclusion criteria for exposure to Concerta® at another point during the study period, only the period with exposure to Medikinet® MR was included in the analysis.

Individuals with previous exposure to ADHD medications were included if the exposure to the previous ADHD medication included a "wash-out" period of at least 7 days for stimulants and at least 90 days for non-stimulants. Stimulants included MPH (N06BA04, analyzed by brand), dexamfetamine (N06BA02), and lisdexamfetamine (N06BA12), and non-stimulants included atomoxetine (N06BA09) and guanfacine (C02AC02) (Supplementary Table 1). The "wash-out" period was calculated taking into account the size and number of the retrieved packages.

To minimize confounding of the results, we excluded

individuals with concomitant use of selected medications known or suspected to have potential pharmacodynamic or pharmacokinetic interactions with MPH that may alter its safety profile: antipsychotics (N05A), antiepileptics (N03), melatonin receptor agonists (N05CH), modafinil (N06BA07), escitalopram (N06AB10), citalopram (N06AB04), fluvoxamine (N06AB08), fluoxetine (N06AB03), paroxetine (N06AB05), sertraline (N06AB06), venlafaxine (N06AX16), and mirtazapine (N06AX11). Concomitant use was defined as having retrieved a prescription in the period from 6 months before the start until the end of treatment with Medikinet® MR or Concerta®.

Outcomes

The study focused on a range of preselected adverse outcomes of interest. Patients with these adverse outcomes were identified through the Danish National Patient Registry using ICD-10 codes (Table 1). We only considered outcomes that were documented during the period of exposure to Medikinet® MR or Concerta®.

Definition of cases and controls

Cases were defined as individuals with at least one AE during exposure to Medikinet® MR or Concerta®, and controls were defined as individuals without an AE during exposure to Medikinet® MR or Concerta®. Cases and controls were identified individually for each AE, meaning that a case for a specific AE can serve as control for another AE. Each case was matched with up to five randomly selected controls based on sex and age (±1 year).

Statistical analysis

AE data for Medikinet® MR and Concerta® users were analyzed descriptively (frequencies and percentages). For each AE, Fisher's exact test was performed to compare the number of cases between the two groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression models with patients exposed to Concerta® as the reference group. This model was applied to have a relative measure of the magnitude of difference in the incidence of the AE between the two exposure groups. For both Fisher's exact test and the logistic regression model, only the AE cases and their (up to five) matched controls were included in the analyses. This meant that the samples on which the analyses were conducted were lower in number than the total population of patients exposed to Medikinet® MR and Concerta®, respectively. However, as the age distribution in the two exposure groups largely differed, it was necessary to balance out these differences to make the groups comparable. In all statistical analyses, a p value or adjusted p value below 0.05 (2-tailed) was considered significant. The interpretation of the results was based on adjusted p values. All analyses were performed using SAS 9.4.

Sensitivity analysis

The group of patients exposed to Concerta® was based on all retrieved prescriptions of Concerta® (both branded and generic versions of the drug). Concerta® generics were included in this study because they account for a significant proportion of all Concerta® prescriptions sold in Denmark.

Although Concerta® and generic formulations are bioequivalent, there may be differences in their pharmacokinetic profiles and excipients due to different drug delivery technologies. Several studies have indicated that there are clinically significant differences between branded Concerta® and some of its generics, including differences in AE profiles (22,

TABLE 1. Outcomes with ICD-10 codes

Outcome	*ICD-10 codes*
Essential hypertension	I10
Sudden death (cause unknown), cardiac arrest	R96, R99, I46
Mental and behavioral disorders due to psychoactive substance use	F10-F19
Cerebral arteritis	I67.7
Priapism	N48.3
Psychiatric disorders	
Schizophrenia, schizotypal and delusional disorders	F20-F29
Mood (affective) disorders	F30-F39
Neurotic, stress-related and somatoform disorders	F40-F48
Behavioral syndromes associated with physiological disturbances and physical factors	F50-F59
Conduct disorder	F91
Suicidal tendency, intentional self-harm	X60-X84, EUW
Tics	F95
Episodic and seizure disorders	G40-G47
Anorexia	R63.0
Non-organic sleep disorders	F51

Notes. ICD-10, International Statistical Classification of Diseases and Related Health Problems-10

23). Therefore, we conducted a sensitivity analysis that excluded individuals who were exposed to Concerta® generics.

Ethics

The study was approved by the national Danish Health Data Authority (application number FSEID-00005700) and Statistics Denmark (application number 708333).

Results

Study population

We identified 1929 patients exposed to Medikinet® MR and 4234 patients exposed to Concerta®. Exclusion of patients with comedications resulted in a final study population of 1249 Medikinet® MR-exposed patients and 2455 Concerta®-exposed patients. Table 2 shows the demographic characteristics of the study population at index date. The two cohorts had a similar sex distribution, while the age distribution was skewed towards higher ages in the Concerta® cohort.

TABLE 2. Demographic characteristics of the study population.

	Patients exposed to Medikinet® MR (N=1249)	*Patients exposed to Concerta® (N=2455)*
Sex, n (%)		
Female	347 (27.8)	671 (27.3)
Male	902 (72.2)	1784 (72.7)
Age at index date, n (%)		
6-11 years	707 (56.6)	630 (25.7)
12-17 years	349 (27.9)	1010 (41.1)
≥18 years	193 (15.5)	815 (33.2)

Main analysis

The number of cases in each cohort and ORs are shown in Table 3. Psychiatric disorders were the most common adverse outcome in both cohorts. No cases of cerebral arteritis or priapism were found in either cohort. ORs for sudden death and anorexia could not be calculated due to the absence of cases in the Medikinet® MR cohort. For the remaining AEs, no statistically significant difference in risk was found between patients exposed to Medikinet® MR and those exposed to Concerta®.

Sensitivity analysis

A sensitivity analysis was conducted, excluding individuals exposed to Concerta® generics from the Concerta® cohort. The cohort of patients exposed to Concerta® excluding generics included 1528 patients. The sensitivity analysis produced results consistent with those obtained in the main analysis (Table 4).

Discussion

This is the first nationwide register-based cohort study that evaluated the risk of selected adverse outcomes in patients with long-term exposure to Medikinet® MR or Concerta®. The study found low and comparable numbers of adverse outcomes in both cohorts. The results were consistent in the sensitivity analysis excluding patients exposed to Concerta® generics.

This is the first study to provide real-word evidence on the comparative safety profiles of Medikinet® MR and Concerta® during long-term use. Two short-term RCTs compared the efficacy and safety of the two formulations in children and adolescents with ADHD. The formulations showed generally comparable AE profiles, although one of the studies reported an increased frequency of insomnia and euphoria with Concerta® compared to Medikinet® MR (17, 18). No head-to-head RCTs have been performed on the long-term (i.e., ≥12 months) safety of Medikinet® MR and Concerta®.

Psychiatric disorders were the most common AEs in both cohorts. Psychiatric AEs commonly associated with MPH use include depression, anxiety, irritability, and aggression (14). The 2-year naturalistic, prospective ADDUCE study found that long-term use of MPH was not associated with a significantly increased risk of psychiatric symptoms in children and adolescents with ADHD (24). Overall, the available evidence suggests that long-term MPH use is associated with favorable outcomes regarding depression (25-27). Findings from a population-based cohort study from South Korea suggest that long-term MPH use may be associated with a decreased risk of depression, conduct disorders and oppositional defiant disorder (28). The existing evidence is not sufficient to conclude whether or not MPH increases the risk of psychotic symptoms. However, the available data indicate that psychotic symptoms may occur in 1.1% to 2.5% of children and adolescents with ADHD (25, 29). Two population-based cohort studies found that long-term treatment with MPH was associated with a significantly decreased risk of suicide attempt in pediatric and adult ADHD patients (30, 31). Fewer than five cases of essential hypertension were identified in each cohort. MPH treatment is associated with small increases in blood pressure and heart rate, although some patients may experience higher increases (24, 32, 33). Therefore, blood pressure and heart rate should be regularly monitored during MPH treatment (5).

No cases of sudden death were identified in the Medikinet® MR cohort and fewer than five cases were identified in the Concerta® cohort. Sudden cardiac death is rare in children and young adults without structural heart disease.

TABLE 3. Number of cases and odds ratios with 95% confidence intervals for all outcomes (main analysis – statistical testing conducted on cases and matched controls).

Outcome	*Patients exposed to Medikinet® MR (N=1249), n (%)*	*Patients exposed to Concerta® (N=2455), n (%)*	*p value**	*Adjusted p value**	*OR (95% CI)*
Essential hypertension	<5	<5	0.68	1	1.5 (0.28-8.036)
Sudden death (cause unknown), cardiac arrest	0	<5	-	-	-
Mental and behavioral disorders due to psychoactive substance use	11 (0.88)	53 (2.16)	0.33	1	0.69 (0.343-1.389)
Cerebral arteritis	0	0	-	-	-
Priapism	0	0	-	-	-
Psychiatric disorders					
All patients	41 (3.28)	77 (3.14)	0.59	1	1.134 (0.747-1.72)
6-11 years	14 (1.98)	12 (1.91)	-	-	-
12-17 years	17 (4.87)	33 (3.27)	-	-	-
≥18 years	10 (5.18)	32 (3.93)	-	-	-
Conduct disorder	5 (0.40)	14 (0.57)	0.30	1	0.491 (0.164-1.474)
Suicidal tendency, intentional self-harm	<5	11 (0.45)	0.16	1	0.196 (0.024-1.631)
Tics	23 (1.84)	24 (0.98)	0.87	1	1.071 (0.572-2.003)
Episodic and seizure disorders	13 (1.04)	15 (0.61)	0.29	1	1.61 (0.709-3.654)
Anorexia	0	<5	-	-	-
Non-organic sleep disorders	0	0	-	-	-

*Note. Numbers between 1 and 4 are reported as <5 to ensure anonymity according to Danish legislation. * Fisher's exact t-test. CI, confidence interval; OR, odds ratio*

Studies investigating the association between MPH use and sudden death have provided mixed findings. Schellemann et al. found an increased risk of sudden death or ventricular arrhythmia (adjusted hazard ratio 1.84; 95% CI 1.33-2.55) in adult MPH users compared to non-users, while several cohort studies found no evidence of an increased risk of sudden cardiac death associated with the use of ADHD medications in children and adults (34, 35). A recent meta-analysis of 10 cohort studies found no association between ADHD medications and sudden death/arrhythmia, stroke, myocardial infarction and all-cause death, although some of these outcomes are associated with uncertainty due to wide confidence intervals (36).

Few cases of tics were identified in either cohort. Some studies have suggested an increased risk of tics with long-term MPH use (25). MPH should be used with caution in patients with tics or tic disorders (5, 14).

The number of mental and behavioral disorders due to psychoactive substance use was comparable between the cohorts. Substance use disorder (SUD) is a common comorbidity of ADHD (37). According to a recent meta-analysis, treatment with stimulant medication for ADHD neither increases nor decreases the risk of developing SUD (38). The presence of risk factors and a history of SUD should be considered before initiation of MPH treatment.

Overall, the study found low and comparable numbers of adverse outcomes in both cohorts, indicating a similar safety profile for the two medications. These findings may have positive implications for prescribing practices. The favorable safety profiles of the two medications may enhance physicians' confidence in prescribing the studied treatments. Physicians may be more willing to switch a patient from one formulation to another if the initial treatment proves ineffective or the drug does not align with the patient's preferences (e.g., onset of action, duration of action, sleep problems). This flexibility may lead to more individualized treatment plans.

The present study has several strengths. The main strength is the use of Danish nationwide registry data covering the entire Danish population, which reduces the risk of selection bias (20). In addition, recall bias is eliminated, since the data are collected prospectively rather than by interview or questionnaire. A limitation from this study is that we

TABLE 4. Number of cases and odds ratios with 95% confidence intervals for all outcomes (sensitivity analysis – statistical testing conducted on cases and matched controls).

Outcome	*Patients exposed to Medikinet® MR (N=1249), n (%)*	*Patients exposed to Concerta® (N=1528), n (%)*	*p value**	*Adjusted p value**	*OR (95% CI)*
Essential hypertension	<5	<5	0.66	1	1.625 (0.262-10.096)
Sudden death (cause unknown), cardiac arrest	0	<5	-	-	-
Mental and behavioral disorders due to psychoactive substance use	11 (0.88)	29 (2.16)	0.28	1	0.646 (0.305-1.369)
Cerebral arteritis	0	0	-	-	-
Priapism	0	0	-	-	-
Psychiatric disorders	41 (3.28)	33 (2.16)	0.02	0.1386	1.864 (1.125-3.087)
Conduct disorder	5 (0.40)	10 (0.65)	0.10	0.6972	0.372 (0.116-1.195)
Suicidal tendency, intentional self-harm	<5	11 (0.72)	0.44	1	0.299 (0.035-2.521)
Tics	23 (1.84)	16 (1.05)	0.73	1	1.158 (0.576-2.327)
Episodic and seizure disorders	13 (1.04)	8 (0.52)	0.15	1	2.192 (0.835-5.753)
Anorexia	0	<5	-	-	-
Non-organic sleep disorders	0	0	-	-	-

*Note. Numbers between 1 and 4 are reported as <5 to ensure anonymity according to Danish legislation. * Fisher's exact t-test. CI, confidence interval; OR, odds ratio*

used retrieved prescriptions as a proxy for drug exposure. On the one hand, this may not accurately reflect actual drug intake, as patients may be non-adherent to treatment, which is not uncommon among those on long-term medications. Studies have shown that the average rates of non-adherence to medication in pediatric and adult patients with ADHD range from 15% to 87% (39). As our approach does not account for patient adherence, it may lead to an overestimation of exposure, which in turn may result in an underestimation of AEs. On the other hand, patients experiencing AEs are likely not only to be non-adherent but also to be receiving no further prescriptions, which in turn does not lead to an underestimation. Another limitation of this study is that the Danish National Patient Registry only contains information from hospitals, meaning our analysis is restricted to AEs recorded during a hospital contact (i.e., severe/serious AEs). Thus, our analysis does not include less severe AEs recorded and managed in primary care by general practitioners and specialists in private practice. Furthermore, while register studies are highly valuable for "hard" outcomes, such as cerebral arteritis and seizures, they are less reliable for AEs that do not typically receive a diagnostic code, such as priapism or non-organic sleep disorders. This limitation may impact the validity of the analysis for these types of AEs. Additionally, children are more likely to receive diagnostic codes for such AEs since they are usually followed in a hospital setting, where these AEs are more likely to be coded diagnostically. Given that the Concerta® group includes a higher proportion of adult patients, this could lead to an underestimation of the actual risk in this group.

Clinical Significance

This is the first study to provide real-world evidence on the comparative safety profiles of Medikinet® MR and Concerta® during long-term use. The number of adverse outcomes was low and comparable in both cohorts, indicating a similar safety profile for the two formulations.

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Conflict of interests

JØ has received conference support and speakers fees from MEDICE Nordic and Takeda DK. AM and OD are employees of MEDICE Arzneimittel Pütter GmbH & Co. RA is managing owner of MEDICE Arzneimittel Pütter GmbH & Co. KG.

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