

Seasonality of Methylphenidate Administration among Children in Israel

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ABSTRACT: **Background:** Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by inattention, impulsivity and hyperactivity. Recently, increases in ADHD prevalence and methylphenidate use have been reported. There is evidence that children and adolescents use ADHD medication only during the school year.

Objectives: To investigate trends in methylphenidate dispensing over a period of 3 years (2010–2012) at the monthly level and to investigate whether there is any monthly variation, especially during the summer season.

Methods: The database of Clalit Health Services (the largest of the four health funds in Israel) was used to identify (i) patients aged 6–17 years with a diagnosis of ADHD, and (ii) methylphenidate dispensation during the period 2010–2012.

Results: Among children aged 6–17 years diagnosed with ADHD, 43% were treated with methylphenidate. For the period 2010 to 2012 there was an annual drop in methylphenidate dispensing, beginning in June and continuing through the 2 months of summer vacation, with a 2.5-fold reduction from July as compared to May. This decline was consistently followed by a rise in medications dispensed starting August. A similar small drop was observed during the Passover school vacation. The summer drop decreased over the years.

Conclusions: Our findings showed a decrease in the number of methylphenidate prescriptions dispensed during the summer months and Passover as compared to the rest of the year. However, this phenomenon appears to be decreasing. Given that ADHD is a chronic disease state that can effectively be managed with pharmacotherapy, discontinuation of treatment may be harmful for patients and should be considered only on a patient-by-patient basis.

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ways and to varying extents, with the consequences of the condition greatly impacting patients, their families and those around them. Treatments and interventions for ADHD differ, with the focus mainly on psychological therapies and pharmacological treatment [1–3]. Over the last decade, increases in ADHD prevalence and use of ADHD prescription medications have been reported in many countries, including Israel [4,5]. In Israel, when drug treatment is considered appropriate for the patient, the central nervous system stimulant methylphenidate is recommended as the first-line therapy in children aged 6 years and older [4,5]. Consistent with the increasing trends in prevalence, a recent study showed that the consumption of ADHD drugs in Israel doubled between 2005 and 2012 [4].

The risks of untreated ADHD can include under-achievement at school, impaired relationships with family members, teachers and friends, increased rates of criminality and accidents, and the development of co-morbid psychiatric symptoms including oppositionality, anxiety, depression and substance abuse [6]. Most of the evidence suggests that the benefits of pharmacological treatments in managing ADHD outweigh the potential for adverse events or side effects from the medications, e.g., appetite suppression and growth delay [7]. However, there is considerable individual variation in physician management of these side effects, the most debated being the issue of “medication holidays” [8]. There is some evidence that many children and adolescents use ADHD medication only during the school year [9]. Cascade et al. [9] demonstrated a significant seasonality, with the total volume of monthly prescriptions falling between 22% and 29% from May to July, depending on the year [9]. Further research comparing adherence during the school year to adherence year-round found that adherence levels are higher during the school year than over the entire year [10], suggesting an effect of seasonality associated with ADHD medication use. The extent of methylphenidate discontinuation during summer school vacation in Israel is unknown. The aim of this study was to investigate the trends in monthly levels of methylphenidate dispensing over a 3 year period (2010–2012), including whether there are seasonal or monthly variations and whether these trends are changing.

In Israel, there are differences between cultural and socioeconomic groups in educational frameworks, as well as in awareness about behavioral disorders. This can affect the avail-

Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder characterized by the symptoms of inattention, impulsivity and hyperactivity. It occurs in approximately 8% of children and youth [1]. ADHD is a disorder that affects children and adolescents in multiple

ability of adequate medical services for diagnosis and access to certain treatments. In the north of the country this gap was shown to result in differences in diagnosis and treatment rates of ADHD [11]. Increases in ADHD diagnosis and treatment with methylphenidate have been particularly notable among girls [5]. In this study different population groups such as Arab and ultra-Orthodox will be studied separately to provide additional knowledge on ADHD-related trends.

SUBJECTS AND METHODS

Clalit Health Services is Israel's largest health fund which serves as an insurer and health care provider, covering 53% of Israel's population and supplying most of the health care services within its system. In Clalit, children are predominantly treated at community primary care clinics by board-certified pediatricians, non-board-certified pediatricians, and general practitioners. Membership in one of four health funds is mandatory and, while transferring is simple, members rarely switch health funds in Israel (~1% per year), thus enabling long-term case histories. All of Clalit's primary and secondary care physicians and pharmacies use an advanced electronic medical records system which feeds into the central database of the organization. This database contains over a decade of patient-level data including sociodemographic, clinical, health care utilization, and drug purchasing data.

STUDY DESIGN

We conducted a historical cohort study of Clalit children aged 6–17 years old during 2010–2012 (study period) with active diagnoses of ADHD. With the diagnosis – a legal pre-condition for methylphenidate prescriptions – methylphenidate dispensing patterns were analyzed among children diagnosed during the study period. Although there is no confirmation that medications were taken after prescription purchases, those for whom prescriptions were purchased were considered to be treated for the purposes of this study.

Table 1. Demographic characteristics, ADHD diagnoses and treatment by methylphenidate in 2012 among pediatric Clalit members aged 6–17 years

	Population of Clalit pediatric members N	Diagnosed with ADHD N (% among Clalit population)	Treated with methylphenidate N (% among diagnosed)
Total	795,057	105,806 (13.3)	45,516 (43.0)
Age (yr)			
6–11	418,209	50,544 (12.1)	23,097 (45.7)
12–17	376,848	55,262 (14.7)	22,419 (40.6)
Gender			
Male	406,9501	73,275 (18.0)	32,299 (44.1)
Female	388,106	32,531 (8.4)	13,217 (40.6)
Population group			
General	445 003	83 611 (18.8)	39 237 (46.9)
Ultra-Orthodox	42,362	5201 (12.2)	2167 (41.7)
Arab	307,692	16,994 (5.5)	4112 (24.2)

DATA SOURCES AND COVARIATES

Information on ADHD diagnosis was gathered from all Clalit primary care physicians through the Clalit chronic and permanent diagnosis databases (ICD-9 codes 314.00 and 314.01 were included). In the Israeli health care system, only methylphenidate is included in the pharmaceutical reimbursement list for ADHD treatment, hence methylphenidate is the drug of choice for treatment of ADHD. Information on the dispensing of methylphenidate prescriptions summed by month during the entire study period, and summed by week for the months June–September was gathered from the Clalit pharmacy database. The month and the week within a calendar year were taken as variables for the analysis of seasonality changes in methylphenidate dispensing. Other covariates included age (categorized into two groups: 6–11 years and 12–17 years, determined at the start of each calendar year), gender and population sector (a variable taken at the clinic level, indicating whether the clinic is serving predominantly General Jewish, ultra-Orthodox-Jewish or Arab populations). The study was approved by the Clalit community health institutional review board.

STATISTICAL ANALYSIS

The prevalence of ADHD in 2012 was calculated as the number of children with existent diagnoses of ADHD at the beginning of 2012 divided by the total number of children aged 6–17 years in the Clalit database at the same time, using either crude rates or split by age, gender and/or population sector groups. The annual rate of treatment with methylphenidate was calculated as the proportion of children filling at least one methylphenidate prescription during the year among the children diagnosed with ADHD by the beginning of the year. This rate was assessed according to age, gender and population group. The number of children treated by methylphenidate was also calculated on a monthly basis, with analysis comparing the 2 months of summer vacation (July and August) to the rest of the year. These rates were also based on the population at the beginning of the year. In addition, weekly trends were analyzed for the summer vacation period (from the end of June until the beginning of September) to determine the time point of change in the methylphenidate dispensing trend. The rate of stopping treatment was defined as the ratio of the number of children for whom medication was not purchased during July and August over the number of children for whom medication was purchased during May and June. The ratio was calculated separately for every population group and for each year of study. Comparisons were assessed by chi-square test and by ANOVA.

RESULTS

PREVALENCE OF ADHD

A total of 795,057 members aged 6–17 years old were identified in the Clalit database as of 1 January 2012 [Table 1]. Among them, 13.3% (105,806) were diagnosed as having ADHD. Boys comprised 69% of ADHD-diagnosed children, and 79.0% were

from the General Jewish population sector, while ultra-Orthodox patients comprised 4.9% and Arab patients 16.1% (these population groups comprise 56.4%, 5.6% and 38.0% respectively of the entire relevant age group). Hence the General Jewish population had increased risk of being diagnosed with ADHD [relative risk (RR) 1.53, 95% confidence interval (95%CI) 1.49–1.57] compared to the ultra-Orthodox Jewish population, and even more compared to the Arab population (RR 3.40, 95%CI 3.35–4.46). The highest percentage of diagnosed children treated with methylphenidate was observed in the General Jewish group (46.9%), followed by the ultra-Orthodox group (41.7%), and the lowest in the Arab group (24.2%). Thus, Arab children had both lower diagnosis (in the total population) and lower treatment rates (among diagnosed patients) (RR 1.93, 95%CI 1.87–1.98) compared to the Jewish children from the General and ultra-Orthodox groups.

SUMMER DISCONTINUATION OF METHYLPHENIDATE TREATMENT

From 2010 to 2012 there was a clear downward annual drop in the dispensing of methylphenidate during the 2 months of summer vacation (July and August), beginning in June and continuing into August. Medications were dispensed in July at a rate that was 2.5-fold lower than in May (range 2.4–2.6 during 2010–2012). A smaller but similar drop was observed in the spring seasons of March 2010 and April 2011 and 2012, corresponding to shorter holiday vacation breaks [Figure 1]. When examining the drop in medications dispensed during the summer at higher temporal resolution (by week), the drop begins annually during the two last weeks of June and continues during July and early August [Figure 2]. During the last 2 weeks of August, dispensing increases. In 2012, this elevation was sharpest (in this particular year the school year started 1 week earlier). Overall, a drop of 38% was observed in the last week of June (range 31%–44%), 57% in the third week of July (range 54–59%), and a drop of 64% (range 62–65%) in the second week of August, all relative to the first week of June. The same analysis was conducted separately for children aged 6–11 years and those 12–17 years old, and for boys and girls. Similar annual patterns were observed in these subgroup analyses, indicating a decrease in drug issuing during the summer vacation months.

We conducted a separate analysis to study the discontinuation of treatment during July and August among children who were treated during May and June [Table 2]. Overall, the percentage of children stopping treatment in July and August declined over the 3 year period: 37.0% in 2010, 30.0% in 2011 and 24.0% in 2012 (*P* value for trend < 0.0001). This downward trend in stopping treatment during the summer months was consistent and significant among all subgroups. A comparison of demographic characteristics of children who were untreated during the 2 months of summer vacation shows that the frequency of stopping treatment was slightly lower among boys (vs. girls), aged 6–11 (vs. aged 12–17) and among ultra-

Orthodox Jews (vs. the Arab group and General Jewish groups), as depicted in Table 2.

Figure 1. Number of children aged 6–17 treated with methylphenidate by month and year

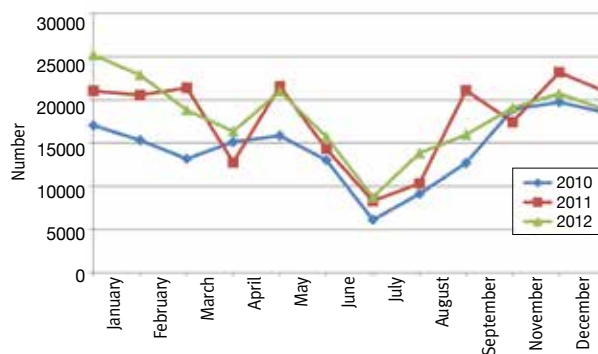


Figure 2. Number of children aged 6–17 treated with methylphenidate end of June–beginning of September, by week

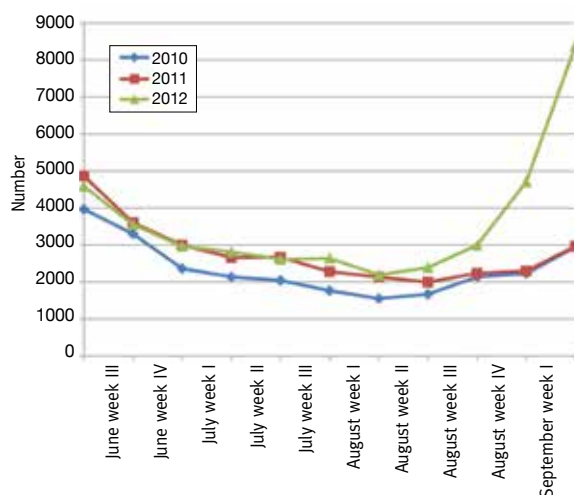


Table 2. Percentage of children who were not treated with methylphenidate during summer vacation (July and August) among those treated in previous May and June, by gender, age and population group, by year

	2010	<i>P</i> value χ^2 test	2011	<i>P</i> value χ^2 test	2012	<i>P</i> value χ^2 test	<i>P</i> for trend
Gender							
Boys	36.1	0.005	29.0	0.002	23.1	0.001	< 0.0001
Girls	40.2		33.4		27.0		< 0.0001
Population group							
Arabs	38.0	< 0.0001	36.2	< 0.0001	27.5	< 0.0001	0.004
Ultra-Orthodox	22.3		16.3		14.5		0.006
General	37.8		30.4		24.6		< 0.0001
Age group							
6–11	35.9	< 0.0001	28.2	< 0.0001	22.5	< 0.0001	< 0.0001
12–17	40.5		33.9		26.8		< 0.0001

DISCUSSION

The prevalence of ADHD in the Israeli pediatric population found in this study (13%) is similar to previously reported prevalence statistics among schoolchildren worldwide (2%–17%) [12], with a higher prevalence of the disorder among boys. The prevalence of medication prescribed to those diagnosed in this study (43%) matches rates of treatment in other developed countries (32–71%) [13,14].

Medication is frequently used in the clinical management of ADHD, and clinical trials have shown psychostimulants to be highly efficacious, with a $\geq 70\%$ rate of clinical responders [15]. Despite this efficacy, there is evidence that seasonal patterns in ADHD medication usage are related to school year calendars for many children and adolescents [9,16]. The findings of the current study show similar results; in Israel there was a consistent reduction in the dispensing of methylphenidate during June, July and August – 26%, 60% and 43% respectively – as compared to May. A more moderate reduction was also observed during the 3 week Passover school vacation (March 2010, April 2011 and April 2012). With no rise in medication dispensing in June, compared to previous school-year months, over-purchasing of medications (stockpiling) before the summer vacation can be ruled out. This notable shift in treatment emphasizes the need for improved awareness among physicians, patients and their parents regarding the importance of continued treatment for those patients considered to need ongoing, uninterrupted medical treatment. Inconsistent or non-existent treatment of ADHD is quite problematic. When left untreated, the core symptoms of ADHD appear to increase the risk for substance abuse disorders and antisocial behavior. Substance abuse subsequently further negatively affects the core symptoms of ADHD, leading to more functional impairment [9]. A recent observational study reassessed a UK cohort of 126 school-aged children with ADHD 5 years later in adolescence. The research team found that about 70% of the sample met the full criteria for ADHD and that most of the sample exhibited high levels of antisocial and criminal behavior and substance abuse problems in adolescence [17]. Only 10% of the sample appeared to have functionally and symptomatically recovered, some of whom continued to be prescribed medication.

Beyond the public health concern that a high proportion of ADHD pediatric patients do not receive any treatment, many patients receive only intermittent dosing of ADHD medications. Intermittent dosing of ADHD medication can lead to problems from the frequent need to both redevelop initial medication tolerance and re-accommodate to adverse events. Unfortunately, patients' and/or parents' efforts to minimize time spent on ADHD medications require their starting and stopping ADHD medications repeatedly, which may actually have the paradoxical effect of increasing the overall side effect

burden for patients. This repeated starting and stopping by patients or their parents in relation to the school year (and in many cases just for weekends [8]) may initiate stimulant discontinuation-related adverse events.

Barner et al. [18] and Marcus et al. [19] found poor persistence and adherence to ADHD medication over a 1 year period in the Texas Medicaid and California Medicaid systems respectively. Barner and co-authors reported 3.2 to 5.1 months persistence before a 30 day break, and Marcus et al. a 4.7 month period with extended-release methylphenidate and a 3.5 month period with immediate-release methylphenidate, indicating that children did not persist for half a year on therapy. Low adherence rates can be attributed to parents providing medications to their children only on school days, omitting weekends, holidays and summer months. This is supported by Faraone and colleagues [20] who reported that 30.5% of children in their study took “planned medication breaks.”

The strategy of weekend holidays during methylphenidate use is controversial. In the present study, the phenomenon of stopping treatment during summer vacation was slightly more frequent among girls. Prior research found that girls with ADHD may be less disruptive and less impulsive [21] than boys with ADHD, and it is possible that such behavioral differences permit a break in treatment during summer vacation. Additionally, the present study found a higher frequency of treatment breaks among adolescents aged 12–17 years. Prior research found a general alleviation of ADHD symptoms that occurs with age [22], and it is possible that this alleviation may contribute to treatment breaks. Among boys from the ultra-Orthodox group, frequency of stopping treatment in the summertime was lower than among boys from other population groups, probably because of the shorter summer vacation in the ultra-Orthodox male education system, while the frequency of treatment breaks among ultra-Orthodox girls was similar among girls from other population groups, as the length of summer vacation for ultra-Orthodox girls is the same as in the other population sectors. This study shows that this tendency towards discontinuation of treatment during the summer vacation in Israel is in decline.

Continuation in treatment is generally desirable. There are significant life impairments found in individuals with ADHD. Among young people, difficulties with completion of homework, participation in extracurricular activities, the ability to pay attention while driving and to resist engaging in risky behaviors have been noted, and uninterrupted treatment may help to reduce such difficulties [23]. Furthermore, children and adolescents adhering to consistent medication management for their ADHD treatment may be better able to control their behavior and impulsivity, resulting in less criticism and better feedback from caregivers and peers. Such feedback is likely to bolster the children and adolescents' self-esteem. During their late adolescent years, relationships, self-esteem, substance abuse, work, and other problems are

associated with having had ADHD as a child. Suspending the treatment that improves these conditions is not in a patient's best interests.

Current guidelines suggest that physicians treat ADHD as a chronic medical condition [1,24] and, certainly, consistent treatment of most chronic medical illnesses usually gives patients and those treating them better results than episodic medication management. While school-year-only dosing of ADHD medications may be acceptable for some, the vast majority of children and adolescents do better even in extra-school behavior when they take their ADHD medication regularly [19]. As Findling et al. discuss [25], there are myriad non-school-related activities in patients' lives that may benefit from continued treatment. As such, compulsory medication breaks are not recommended; rather, the need to take such breaks should be considered on a case-by-case basis and should not be implemented as a general rule.

According to Van De Loo-Neus and team [15], there is limited and inconsistent evidence for long-term advantages of medication treatment beyond symptom control, such as improved social functioning, academic achievement, employment status and fewer adverse psychiatric outcomes. In terms of safety, long-term effects of medication on growth, blood pressure and heart rate are limited and the occurrence of suicidal, psychotic and manic symptoms is rare [15]. Therefore, this group recommends that clinical decisions about starting, continuing, and stopping ADHD medication should be made on an individual basis and medication-free periods implemented at regular times to investigate the need for an ongoing benefit of medication [15]. It is worth considering Findling's assertion that child psychiatrists and neurologists generally continue pharmacological treatment of their patients throughout the summer months, while pediatricians tend towards summer breaks in treatment [25]. Clearly, there is a discrepancy in the information dispensed to psychiatrists and neurologists versus that dispensed to pediatricians.

Use of a retrospective prescription database to examine ADHD adherence and persistence patterns has the advantage of examining large populations (such as the present cohort of 105,806 children with a previous or current diagnosis of ADHD, of whom 45,516 were treated with methylphenidate during the study period) and medication prescribing patterns over longer follow-up periods.

LIMITATIONS

This study, while analyzing a large cohort, carries some limitations. To begin with, diagnoses are registered by a physician during a parent-initiated visit to a clinic, in contrast to a survey with psychological evaluation. This may carry the risk of a few causes of bias, under-reporting due to parents' and teachers' lack of attention to the child's behavioral condition or due to parents' intention to avoid blemishing a child's clinical file (two factors

that may partially cause the gender and sector imbalance). In addition, some contacts may be initiated with the intent to receive methylphenidate prescriptions to "calm" disorderly but healthy children. While we have complete data on patient primary care physician visits and drug purchasing, we obviously do not know whether the drugs were consumed immediately or at all; we may, however, assume that most patients will not purchase more chronic medications when they have considerable supplies at home. Thus, incomplete adherence will tend to smooth out over time. On the other hand, the examination of potential early purchases of stocks before summer trips abroad did not suggest an increase in late June–early July before children travel with their parents, but rather indicated a decrease in such purchases. In addition, our database does not allow us to distinguish reliably between subtypes of ADHD which could potentially show different seasonal patterns. This study did not compare written prescriptions with filled prescriptions and thus we cannot differentiate whether low purchase rates are due to physicians' instructions or to low patient compliance.

CONCLUSIONS

The present study determined that, indeed, there is a decrease in the number of methylphenidate prescriptions dispensed in Israel during the summer months and Passover break as compared to the rest of the year. However, it is worth noting that this phenomenon appears to be decreasing on an annual basis. It is possible that such a decrease is related to increased awareness among doctors, parents and patients of the potential harms associated with treatment breaks. Given that ADHD is a chronic disease state that can effectively be managed with pharmacotherapy, discontinuation of treatment may be harmful for patients and should be considered only on a patient-by-patient basis. Because treatment breaks can result in symptom deterioration, it is recommended that providers identify patients with poor adherence and determine the reasons for non-adherence (e.g., side effects, forgetfulness, parent or child opposition, etc.). After doing so, providers may be able to successfully intervene with strategies to address any barriers to medication adherence, which will likely improve patient outcome.

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