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Attention Deficit Hyperactivity Disorder Treatment Practice in Turkey

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ABSTRACT:

Attention deficit hyperactivity disorder treatment practice in Turkey

Objective: To determine the factors associated with type of ADHD prescription and re-admission of the cases to the outpatient clinics between January-July 2013.

Method: The Ministry of Health prescription database, which included prescriber, region, age and gender data and contained almost 20% of IMS data.

Results: A total of 73,189 prescription were prescribed to a total of 41,341 (30,014 males; 72.7%) patients. 38645 (93.5%) of the patients were between 6 and 18 years of age. The most frequently prescribed drug was OROS methylphenidate (MPH, 59.7%) followed by IR MPH, atomoxetine and combination of drugs. There were several regional differences in prescription practice. Treatment choice changed significantly with age and gender. Rate of repeated prescription was highest among 6-18 year-old male subjects receiving combination treatment.

Conclusions: ADHD treatment choice seemed to be heavily influenced by official regulations. Age, gender and drug of choice were important factors associated with treatment adherence.

Keywords: ADHD, treatment, OROS, methylphenidate, atomoxetine

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INTRODUCTION

Studies from several countries have indicated that there is a significant increase in the use of Attention Deficit Hyperactivity Disorder (ADHD) drugs[1-9]. Besides possible side effects, there is a concern that ADHD drugs are misused and diverse. In fact, some studies reported that millions of stimulants might be misused[10,11]. Most of these misused and diverse drugs originate from prescriptions to patients with ADHD[10]. Therefore, it is important to control the use of stimulants, reflected by the restrictive regulations of use in several countries. On the other hand, particularly in developing countries, underdiagnosis is an important issue which may go hand in hand with overdiagnosis[12,15]. Although the long-term effects of ADHD treatment is far from clear, it has been known that there are several serious outcomes of untreated ADHD[16,17]. Besides, ADHD may persist in adulthood, and it

must be treated appropriately in the adult population[18]. Transition from child/adolescent psychiatry to adult psychiatry services may also be problematic for some cases, since ADHD may not be as familiar to adult psychiatrists as to child/adolescent psychiatrists.

The aims of the present study were to provide descriptive data on ADHD prescriptions in Turkey between January-June 2013, to determine the association between prescriptions and gender, age, regions, and prescribing physicians and to examine the association of age, gender, and drug with re-admission of the cases to the outpatient clinics during the study period in a selected sample. In Turkey, all ADHD drugs are indicated only for this disorder, and prescriptions are closely regulated by health authorities: adult psychiatrists are not allowed to prescribe atomoxetine, while other physicians, including pediatrists and family medicine physicians are not allowed to prescribe methylphenidate, at the time of the study. Besides, reimbursement policies change with age; long-acting methylphendaite is reimbursed for patients younger than 25 years of age, atomoxetine for patients younger than 18 years of age, and immediate release methylphenidate for all ages. Therefore, it gives a unique opportunity to examine the effects of regulations on prescriptions practice. In the present study, our hypothesis were that the prevalence of ADHD treatment was higher in males and school-aged individuals, that there were significant regional and prescriber differences, and that re-admission to hospital was associated with age, gender, and drug of choice.

METHODS

Prescription Data

Data was obtained from Ministry of Health Database. The prescription database included prescriptions from hospitals from all Turkey. Data was retrieved by using three-digit anatomical therapeutic chemical (ATC) codes of ADHD drugs available in Turkey. However, the data did not include all prescriptions since reports were incomplete, although it is mandatory to report the data to the central database. We compared the number of boxes reported in the Ministry of Health (MoH) database with the IMS data. This comparison revealed that MoH database included almost 20% of IMS data. Nevertheless, MoH data included prescriber, region, age and gender, which were not available in the IMS data.

Data Analysis

First, descriptive data on all prescriptions were presented. Second, cases were defined. Based on these cases, descriptive data including age, gender, prescribed drugs and drug combinations, prescription from different regions of Turkey, which were defined due to international statistical procedures, and speciality of the prescribers were provided. Third, crosstabs indicating the association between age, gender, drugs, regions and prescribers were presented. Fourth, limited to prescriptions in January and February and to those patients who were prescribed less than 4 boxes of the drug (% of the sample), re-admission of the patient to a hospital until June was examined in terms of drug, age, and gender. Fifth, logistic regression analysis were computed to analyze odds of having Osmotic Release Oral System (OROS) methylphenidate (MPH), immediate release (IR) MPH, atomoxetine or combination treatments; independent variables were gender and age. Another logistic regression analysis were performed to examine odds of having a repeated prescription with age, gender, and drug as dependent variables. All p values were two-sided and $p<0.01$ was considered as statistically significant.

RESULTS

A total of 73,189 prescriptions were prescribed atomoxetine, IR MPH, OROS MPH or combinations of these drugs, between January and June 2013. These drugs were prescribed to a total of 41,341 (30,014 males; 72.7%) patients. 187 (0.5%) of these patients were 5 years of age or younger, 2509 (6.1%)

Table 1: Regional distribution of attention deficit hyperactivity treatment, corrected for corresponding population (per 100,000 person).

		Total	Male	Female
Istanbul	5-9	169	246	88
	10-14	204	297	107
	15-19	67	85	49
	20-24	7	8	6
	25-29	2	2	2
West Marmara	5-9	344	511	168
	10-14	406	616	182
	15-19	104	150	55
	20-24	12	9	17
	25-29	4	6	2
Aegean	5-9	265	409	111
	10-14	374	569	168
	15-19	153	203	100
	20-24	23	25	22
	25-29	5	7	4
Eastern Marmara	5-9	462	680	231
	10-14	558	815	285
	15-19	195	249	139
	20-24	20	21	18
	25-29	6	7	5
Western Anatolia	5-9	281	434	121
	10-14	386	561	202
	15-19	217	256	176
	20-24	33	33	32
	25-29	10	11	8
Mediterranean	5-9	319	463	168
	10-14	470	225	148
	15-19	189	225	148
	20-24	19	20	18
	25-29	5	7	4
Central Anatolia	5-9	323	462	178
	10-14	338	500	170
	15-19	146	179	112
	20-24	27	27	28
	25-29	8	7	10
Western Black Sea	5-9	316	487	136
	10-14	391	586	188
	15-19	154	211	96
	20-24	21	27	15
	25-29	7	6	8
Eastern Black Sea	5-9	30	44	16
	10-14	33	51	15
	15-19	12	17	6
	20-24	2	2	2
	25-29	0	0	0
Northeastern Anatolia	5-9	60	91	26
	10-14	77	123	29
	15-19	32	43	21
	20-24	2	1	4
	25-29	3	5	1
Middleeastern Anatolia	5-9	53	79	25
	10-14	52	73	30
	15-19	26	24	28
	20-24	16	18	14
	25-29	7	6	8
Southeastern Anatolia	5-9	35	57	12
	10-14	47	70	25
	15-19	23	33	17
	20-24	7	8	5
	24-29	3	3	4

were 19 years of age or older, and 38,645 (93.5%) were between 6 and 18 years of age. Age distribution was skewed to the left, with a median age of 11 years, 73.6% of the patients were between 7 and 14 years old. Of note, while there were 1,222 patients of 18 years of age, only 572 patients were 19 years old, suggesting more than 50% drop during transition from child/adolescent to adult psychiatry services.

The most frequently prescribed drug was OROS MPH, 24678 (59.7%) of the patients were prescribed this drug with mean dose of 31.5 mg (S.D: 11.9 mg, min-max: 18-117 mg). IR MPH was the second most common drug (10,287, 24.9%). Atomoxetine was prescribed to 4,549 (11.0%) patients with a mean dose of 31.1 mg (S.D: 16.6 mg, min-max: 10-125 mg). 1,827 (4.4%) of the patients were prescribed a combination of drugs: 1,445 (3.5%) were on IR MPH+OROS MPH; 247 (0.6%) were on atomoxetine+OROS MPH and 135 were on atomoxetine+IR MPH (0.3%).

When the regions were investigated; 8,498 (20.6%) of the prescriptions were from Mediterranean region, followed by Eastern Marmara (6,721;16.3%), Aegean (5,759;13.9%), Western Anatolia (5,471;13.2%), İstanbul (4,947;12.0%), Western Black Sea (2,982;7.2%), Central Anatolia (2,805;6.8%), Western Marmara (1,825;4.4%), Southeastern Anatolia (1,120;2.7%), Middleeastern Anatolia (651;1.6%), Northeastern Anatolia (408;1.0%), and Eastern Black Sea (150;0.4%) regions.

When the regional distribution was corrected for population, it was evident that the highest prevalence of treatment in children younger than 15 years of age per 100.000 person was in East Marmara region, while the highest prevalence of treatment in 15-30 years group was in West Anatolia region. In all age groups, lowest prevalence rates of treatment were in East Black Sea Region (Table 1).

In 11,258 prescriptions (27.2%), the prescribing physician was not defined by the ministry registration system. 19,006 (46%) prescriptions were issued by child and adolescent psychiatrists. This was followed by adult psychiatry (10,339, 25%), pediatrics (549, 1.3%), family medicine physicians (107, 0.3%), and others (82, 0.2%). This indicated that 97.6% of the defined prescribers were either child and adolescent or adult psychiatrists.

Effects of Age, Gender, Region, and Prescribers

When the prescribers were taken into account, several significant differences were observed (Table 2). First of all, while prescription rates of OROS MPH were relatively similar between adult psychiatrists and child/adolescent psychiatrists (65.9% vs 61.5%), IR MPH was more frequently prescribed by adult psychiatrists (21.2% vs 30.1%), while atomoxetine was more frequently prescribed by child/adolescent psychiatrists (1.1% vs 13.5%). Pediatricians prescribed almost exclusively atomoxetine (86.7%).

Most of the children younger than 6 years of age were treated by child/adolescent psychiatrists (80.4%), followed by adult psychiatrists (15.2%).

Table 2: Prescription rates of OROS MPH, atomoxetine, IR MPH, and combination treatment, per prescriber, gender, and age.

	OROS MPH	ATOMOXETINE	IR MPH	COMBINATION
Prescriber: Child Psychiatry	11684 (61.5%)	2573 (13.5%)	4027 (21.2%)	722 (3.8%)
Adult Psychiatry	6816 (65.9%)	109 (1.1%)	3110 (30.1%)	304 (2.9%)
Others	115 (15.6%)	534 (72.4%)	82 (11.1%)	7 (0.9%)
Gender: Male	18302 (61.0%)	3219 (10.7%)	7186 (23.9%)	1307 (4.4%)
Female	6347 (56.3%)	1326 (11.8%)	3084 (27.4%)	519 (4.6%)
Age: <6 years	29 (15.5%)	12 (6.4%)	145 (77.5%)	1 (0.5%)
6-10 years	9705 (54.8%)	2186 (12.3%)	5355 (30.2%)	459 (2.6%)
11-14 years	9174 (65.7%)	1737 (12.4%)	2332 (16.7%)	727 (5.3%)
15-18 years	4673 (67.0%)	586 (8.4%)	1210 (17.4%)	501 (7.2%)
>18 years	1069 (43.5%)	24 (1.0%)	1229 (50.0%)	138 (5.6%)

MPH (methylphenidate), IR (immediate release)

Table 3: Logistic regression analysis indicating odds of having OROS MPH, atomoxetine, IR MPH, and combination treatment (dependent variable); Independent variables: gender and age.

	OROS MPH	ATOMOXETINE	IR MPH	COMBINATION
Gender: (Wald(df); p) (reference: female)	50.4 (1);<0.001	22.9 (1);<0.001	18.3 (1);<0.001	0.55 (1);>0.45
Male(OR(95%CI);p)	1.18 (1.12-1.22);<0.001	0.85 (0.80-0.91);<0.001	0.90 (0.85-0.94);<0.001	0.96 (0.87-1.1);>0.45
Age: (Wald(df); p) (reference: 6-18 years)	366.6 (2);<0.001	167.6 (2);<0.001	962.2 (2);<0.001	12.4 (2);<0.002
<6 years(OR(95%CI);p)	0.12 (0.08-0.17);<0.001	0.53 (0.29-0.95);<0.005	11.7 (8.3-16.5);<0.001	0.12 (0.02-0.85);<0.05
>18 years(OR(95%CI);p)	0.51 (0.47-0.55);<0.001	0.07 (0.05-0.11);<0.001	3.3 (3.0-3.5);<0.001	1.3 (1.1-1.5);<0.005

MPH (methylphenidate), IR (immediate release)

Table 4: Logistic regression analysis indicating odds of having a repeated prescription (dependent variable). Independent variables: age, gender, and prescribed drug (OROS MPH, atomoxetine, IR MPH, and combination treatment).

	Repeated Prescriptions
Gender: (Wald(df); p) (reference: male)	7.7 (1);<0.006
Male(OR(95%CI); p)	1.06 (1.02-1.1)
Age: (Wald(df); p) (reference: 6-18 years)	99.5 (2);<0.001
<6 years(OR(95%CI);p)	0.63 (0.46-0.86);<0.003
>18 years(OR(95%CI);p)	0.65 (0.60-0.71); <0.001
Drug: (Wald(df); p) (reference: OROS MPH)	368.2 (3);<0.001
Atomoxetine	0.82 (0.77-0.87);<0.001
IR MPH	0.65 (0.62-0.68);<0.001
Combination	1.2 (1.1-1.3);<0.001

MPH (methylphenidate), IR (immediate release)

On the other hand, adults were treated almost exclusively by adult psychiatrists (95.9%). Two-thirds of the 6-18 year old subjects were treated by child/adolescent psychiatrists.

Treatment agent changed significantly with age. Both children younger than 6 years and subjects older than 18 years were treated mainly with IR MPH (77.5% and 50%, respectively), while this was 23% among children between 6-18 years. 60.9% of 6-18 year old subjects were treated with OROS MPH. Atomoxetine was almost exclusively prescribed to this age group (99.2%). More than 90% of combined drug treatments were prescribed to 6-18 year olds. Another significant factor was gender: males were prescribed OROS MPH (61.0% vs 56.3%) an girls were prescribed IR MPH (27.4% vs 23.9%) more commonly.

When 6-18 years group was divided into three (6-10, 11-14, 15-18), it was evident that rate of IR MPH prescriptions was highest at 6-10 years group, and atomoxetine prescriptions rate was lowest at 15-18 years group. On the other hand, rate of combination treatment increased in each group.

Logistic regression analysis results were summarized in Table 3. In this analysis, independent variables age and gender; dependent variable was the prescribed drug. Odds of OROS MPH prescription was higher in the 6-18 years age group and males. Odds of having a IR MPH and atomoxetine presciptions were lower in this age group, while OR for having IR MPH prescription was 11.7 in children younger than 6 years. Odds of atomoxetine and IR MPH and atomoxetine prescriptions were higher in females. Odds ratio (OR) for combination treatment was highest in the adult group.

Repeated Prescriptions

Rate of re-prescriptions were investigated among subjects who were prescribed an ADHD drug in January and February. Only subjects who were prescribed fewer than 4 boxes were included in the analysis (n=16,531). 10,569 of these subjects (63.9%) received another prescription in the following 4 months. The highest rate of

re-prescription was among subjects who received combination treatment (74.5%), followed by OROS MPH (67.2%), atomoxetine (61.9%) and IR MPH (52.4%). Rate of re-prescription was also associated with age group (<6: 42.1%; 6-18: 64.8%; >18: 50.1%). Rates were very similar between boys and girls (males:64.5%, females:64.2%). Logistic regression analysis was conducted: independent variables were age, gender and prescribed drug (OROS MPH, atomoxetine, IR MPH, and combination treatment), dependent variable was having a repeated prescription. Logistic regression analysis (n=13,271) indicated that re-prescription was significantly associated with age group (Wald: 99.5, df: 2, p<0.001), drug (Wald: 368.2, df: 3, p<0.001), and gender (Wald: 7.7, df: 10, p<0.001) (Table 4). 6-8 years old male patients who were taking combination medication had the highest odds of re-prescription.

DISCUSSION

The results of the present study revealed several intriguing findings on the prescription practice of ADHD drugs in Turkey. One of the most striking findings was that prescription and reimbursement regulations had a very significant effect on treatment practice. A very substantial majority of the drugs were prescribed by child, adolescent or adult psychiatrists. Age and gender were other important determinants of prescription. Results indicated that children younger than 5 were rarely treated for ADHD with drugs, as adults older than 24 years of age. A very significant majority of the subjects treated for ADHD were between 6-18 years, and there was also almost two times difference between prescription rates in 18 and 19 years of age. This suggested that, several cases might not receive treatment while passing from child/adolescent services to adult services. This result was consistent with previous studies which showed that ADHD treatment rate significantly decline from childhood to young adulthood[19]. It has been suggested that adult psychiatry services felt ill-prepared to deal with ADHD patients and clinicians reported lack of specific knowledge on ADHD[20]. Since ADHD continues to be a significant problem in young adults, this gap between child and adult services may be an important public health problem.

The most commonly prescribed drug for ADHD was OROS MPH before 18 years of age, OROS MPH has been reported to be used increasingly in ADHD treatment in other countries[3,9]. However, IR MPH were more commonly prescribed to adults. While stimulants appear to be more effective than non-stimulant treatments in adults with ADHD, there were no significant differences between short and long acting stimulants[21]. A very small minority of adults with ADHD were on atomoxetine, again reflecting the strong influence of reimbursement policies on prescription practice. Adult psychiatrists did not prescribe atomoxetine, while other physicians, including pediatrists and family medicine physicians did not prescribe methylphenidate. All these results showed that the regulations on prescription clearly worked very well and as intended by the reimbursement and health autorities. However, the rationale of these regulations, when the benefit of patients were taken into account, was not as clear. There is no scientific rationale for any adolescent patient to stop taking atomoxetine and switch to methylphenidate, after turning to 19, when the patient is benefiting from the treatment.

Results showed that there was a very heterogenous prescription practice among different regions of Turkey. A 10 to 14 years old boy had almost 16 times higher chance of being on ADHD treatment, if he lived in Eastern Marmara, when compared with Eastern Black Sea region. This reflected, in part, the distribution of mental health specialists, particularly child and adolescent psychiatrists in Turkey. On the other hand, although there is a more balanced distribution of adult psychiatrists, there were significant regional differences in rate of adult ADHD treatment. The regional differences in child and adult treatments were not parallel in every case. Since we did not have a control drug to compare, it was not possible to comment on whether these regional differences in ADHD drug use were reflected in the use of other

psychotropic drugs. Regional differences in ADHD drug use have been reported in several countries[4,6,22]. While socioeconomic status, treatment preferences, prescribing habits, clinical experience were suggested as possible causes of regional discrepancies, a definite explanation could not be provided by the researchers. Whatever the cause, since there is no obvious reason for significant regional differences in ADHD prevalence between various regions within the same country, these significant discrepancies may lead to important public health problems. On the other hand, it must be kept in mind that since the data did not involve all prescriptions and the rate of reported prescription from each region was not determined, the figures might reflect reporting biases. Our data also did not include the number of child psychiatrist and adult psychiatrist in each region.

Logistic regression analysis indicated that there were significant differences in rates of repeated prescriptions in terms of gender, age and drug. 63.9% of the patients received another prescription in the following 4 months. 6-18 years and younger than 6 years groups had the highest and lowest rates of repeated prescription, respectively. Highest rate of repeated prescription were among patients who used a combination of drugs, which might reflect both increased severity and specialist care. Indeed, almost all patients treated with combination of drugs had their prescriptions from a child or adult psychiatrist. Previous studies have shown that treatment adherence increases with speciality care, increased severity of symptoms and use of long-acting formulations[23]. Our finding that rate of repeated prescription was higher in patients who were on OROS MPH than IR MPH was consistent with previous reports. Lower rate of repeated prescription in preschool children might reflect lower effect size of stimulants in this group[24]. It can also be speculated that the belief among parents that symptoms are not a disorder is more common in this age group. In adults, lower rates of repeated prescriptions might reflect more complex emotional and behavioral problems comorbid with ADHD in this age group. Another reason might be diagnostic issues; a thorough examination of childhood symptoms are necessary for precise diagnosis of adult ADHD, which is not a simple task in crowded outpatient clinics.

Most important limitation of the present study was that the data did not involve all prescriptions. Although the data reflected a significant amount of prescriptions, it was impossible to determine the reporting rate in in different regions and among different specialists. Other limitations included a relatively short time-period to assess repeated drug use; lack of standard diagnosis, which was inevitable; lack of data on the number of child and adult psychiatrist in each region, and lack of data on prescribing physician in almost a third of cases. Nevertheless, we believe that this study is important for it provides data on ADHD drug use from a developing country with a different culture.

In summary, our results indicated that there were several factors associated with ADHD treatment, in Turkey. Region, age, gender, prescribed drug and prescribing physician were all important factors. Future studies examining the possible causes of differences and discrepancies are necessary to have a better understanding of ADHD treatment practices and factors associated with treatment adherence.

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