ADVERSE DRUG REACTION BULLETIN

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Safety of psychotropic drug prescribed for attention-deficit/ hyperactivity disorder in Italy

P. Panei[a], R. Arcieri[a], M. Bonati[b], M. Bugarini[a], A. Didoni[b] & E. Germinario[a]

[a]Italian National Institute of Health (ISS), Department of Therapeutic Research and Medicines Evaluation, Rome and [b]'Mario Negri' Institute for Pharmacological Research, Mother and Child Health Laboratory, Milan, Italy

Correspondence to Pietro Panei, Senior Researcher, Clinical Research Unit, Department of Therapeutic Research and Medicines Evaluation, Italian National Institute of Health, Viale Regina Elena, 299, 00161 Rome, Italy

E-mail: pietro.panei@iss.it

Summary

The drugs prescribed to treat attention-deficit/hyperactivity disorder, one of the most prevalent psychiatric disease affecting children and adolescents, may risk causing harm. Recently, the U.S. Food and Drug Administration (FDA) has warned about liver and cardiovascular risks, and the European Medicines Agency (EMEA) had performed an assessment of risk–benefit ratio of psychostimulants. Pharmacovigilance in an Italian population aged 6–17 years suggests that atomoxetine is more likely to be reported as causing harm than methylphenidate.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most prevalent childhood developmental disorder. It affects 1–8% of school-aged children, with wide differences between countries. ADHD is characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity, which often give rise to serious impairments in academic performance and social adaptive and behavioural functioning, both inside and outside the home.[1,2]

Treatment of the patient with ADHD requires long-term multimodal, multidisciplinary management and consists in the majority of cases in the combination of behaviour therapy and pharmacological medication.[3,4] Psychosocial intervention not only aims to improve psychosocial and educational functioning in affected children and adolescents[5–8] but also helps to control symptoms. Pharmacological treatments are not curative. Such treatment should only be undertaken by specialists. Methylphenidate (Ritalin - Novartis, Switzerland), a psychostimulant, is the oldest utilized drug and is usually the first choice of pharmacological treatment.[9–13] Other stimulants and atomoxetine (Strattera - Eli Lilly, USA), a selective noradrenaline reuptake inhibitor, are currently used to treat ADHD in children.[14–16]

The available data suggest that children and adolescents are at higher risk than adults for experiencing adverse effects during treatment with psychotropic drugs, and adverse reactions are observed with all pharmacological treatments in children with ADHD.[17] Concern has been expressed about the effects of central stimulants on growth rate when they are used to treat hyperactivity in children[18,19], as palpitation and changes in blood pressure and pulse rate (both up and down), angina and cardiac dysrhythmias can occur. Some safety concerns do exist for atomoxetine and methylphenidate, with respect to the very rare risk for QT prolongations[20], which can have severe consequences. Depression and suicide attempt are listed as potential adverse effects, in particular, during treatment with a few methylphenidate products (such as Concerta - Janssen-Cilag, Belgium), thus their use is contraindicated in patients with a history of depression and suicidal ideation.[21] Nervousness and insomnia are the most common adverse reactions reported with methylphenidate even if they are usually controlled by reducing the dosage and omitting the drug in the afternoon or evening. Dizziness, drowsiness, headache and dyskinesia may occur. Hyperactivity, seizures, muscle cramps, choreoathetoid movements and psychotic episodes including hallucinations have been reported. They subside when methylphenidate was discontinued. Symptoms of visual disturbances have

Table 1 Characteristics of population come out in adverse drug reactions during atomoxetine or methylphenidate treatment

	Atomoxetine (n = 781)						Methylphenidate (n = 643)					
ADR	**No. of events**	**Sex**	**Age (years)**	**TI**	**TTO (months)**	**Expected events**	**No. of events**	**Sex**	**Age (years)**	**TI**	**TTO (months)**	**Expected Events**
Suicidal ideation	3	Male	10	Y	9							
		Male	10	Y	5	Y						
		Female	8	Y	6.5							
Psychiatric disorder	5	Male	12	Y	14.5							
		Male	8	Y	9.5							
		Male	8	Y	7	Y						
		Male	10	Y	2							
		Female	7	Y	1							
Change of personality	5	Male	14	N	12							
		Male	10	N	2							
		Male	13	Y	1	Y						
		Male	8	Y	13							
		Male	9	Y	3							
Neurological disease	3	Male	12	Y	17							
		Female	6	N	4	Y						
		Male	12	N	IMLY							
Seizures	2	Male	14	Y	11	Y	1	Male	12	Y	2	Y
		Male	6	Y	7							
Hypomania	1	Male	7	Y	IMLY	Y						
Tics							1	Male	9	Y	6.5	Y
Impotence	1	Male	17	N	15 days	N						
Decreased appetite	2	Male	7	Y	6	Y	2	Male	12	Y	1.5	Y
		Male	8	Y	4			Female	10		2	
Gastrointestinal disease	7	Male	12	Y	IMLY							
		Male	7	Y	1							
		Male	8	N	3	Y						
		Male	6	Y	8							
		Male	6	Y	1							
		Male	8	Y	6							
		Male	9	N	5							
Hyperbilirubinaemia	4	Male	15	N	7							
		Male	13	Y	4	Y						
		Male	7	Y	12							
		Male	13	Y	9							
Lengthened QT interval	1	Male	8	Y	4	Y						
Tachycardia	2	Male	6	Y	1.5	Y	1	Male	10	Y	6 days	Y
		Male	6	Y	IMLY							
Cardiovascular disease	2	Male	11	Y	1.5	Y	1	Male	13	Y	6	Y
		Male	8	Y								
Hypertension	1	Female	16	N	1	Y	1	Male	14	Y	5	Y
Hypotension					3.5	Y	1	Male	13	Y	2	Y
Headache	2	Male	16	N	3	N	1	Male	14	N	IMLY	Y
		Male	7	Y	2							
Decreased platelet production	1	Male	15	Y	5	N						
Aphasia							1	Male	9	Y	44	N
Urticaria	2	Male	6	Y	6	Y						
		Male	9	Y	2							
Neurological bladder	1	Female	7	Y	2	N						
Hypernatraemia	1	Male	11	Y	7 days	N						
Sleepiness	2	Female	11	Y	1.5	Y						
		Male	13	N	1							
Alopecia							1	Male	13	N	3.5	Y
Asthenia	1	Male	8	Y	2	Y						
Proteinuria	1	Male	7	Y	15 days	N						
Dermatological disease	2	Male	10	Y	2	Y						
		Male	12	Y	9							

ADR, adverse drug reaction; IMLY, Immediately; TI, treatment interruption; TTO, time to onset (months).

been reported. The U.S. Food and Drug Administration reported six cases of liver injury in teenagers and adults who had been treated with atomoxetine for several months.[22] The label warns that severe liver injury may progress to liver failure, resulting in death or the need for a liver transplant in a small percentage of people who take atomoxetine. The warning also indicates that the medication should be discontinued in children who develop a yellowing of the skin or whites of the eyes (jaundice) or laboratory evidence of liver injury. Liver dysfunction and hypersensitivity reactions have rarely been reported with methylphenidate exposure. Longer term and larger scale safety monitoring studies in youngsters are needed to inform clinicians about the safety profiles of different compounds. This information is required to evaluate comprehensively the risk-to-benefit profile of individual psychotropic drugs as well as to define more individualized treatment algorithms, in particular, for patients at high risk for the development of more severe adverse events. So far in Europe, no national survey of the 'disease' was carried out. The data available are coming from pharmacovigilance centre or pharmaceutical companies. The outcome of monitoring strategies from the current study should maximize the effectiveness and minimize the adverse outcomes in those vulnerable children who need pharmacological treatment.

Methods

Methylphenidate and atomoxetine prescription in Italy requires a strict diagnostic assessment prior to treatment, and systematic monitoring during treatment. A proper national Registry, which is compiled by local reference centres, is compulsory.[23] Collected data for each child are periodically analysed and findings reported and discussed with all participants in the national network. Regional health authorities are responsible for the accreditation of the reference centres in regional hospitals, which are related with the mental health services (MHS) for children and adolescent located in the local communities. The reference centre is responsible for confirmation of the diagnosis according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria, and for verification of the appropriateness of the therapeutic plan established by the MHS. The reference centre ensures the interface between the family paediatrician and the MHS, and guarantees the monthly visit, and the renewal of the drug prescription, as well as the behaviour therapy carried out by the MHS. Thus, the Italian Registry represents a distinctive instrument, a unique experience in the international context, to assure appropriate care and safety drug use in ADHD children.

To assess the safety of drug treatment in ADHD in the Italian paediatric population, collected registry data into the national registry were analysed, and we report the results below.

Table 2 Adverse drug reactions classified to system organ class

System organ class	Atomoxetine (%)	Methylphenidate (%)
Psychiatric disorders	14/52 (27)	
Nervous system disorders	8/52 (15.4)	3/11 (27.2)
Gastrointestinal disorders	9/52 (17.3)	2/11 (18.2)
Cardiac disorders	6/52 (11.5)	4/11 (36.4)
Skin disorders	4/52 (7.7)	1/11 (9.1)
Hepatic disease	4/52 (7.7)	
Others	7/52 (13.4)	1/11 (9.1)

Results

After 30 months, 1424 children with ADHD receiving methylphenidate or atomoxetine were enrolled in the Italian Registry. Median age of population was 10.8 years (range 6–18 years): male children 1261 (88.6%), female children 163 (11.4%). The majority of children (1187, 83.3%) were diagnosed with ADHD combined (inattentive and hyperkinetics), 166 (11.7%) with ADHD inattentive and 71 (5.0%) with ADHD hyperkinetics.

Atomoxetine was the drug taken by 781 (54.8%) children and adolescents, and 643 (45.2%) were prescribed methylphenidate. The average dose was 18.5 mg per day for methylphenidate and 38.7 mg per day for atomoxetine.

Sixty-three patients experienced serious adverse events (Table 1), 52 receiving atomoxetine and 11 methylphenidate; 49 (77.8%) of these children stopped treatment. Fourteen children with normal ECG before treatment showed ECG abnormalities at check after about 6 months of treatment. Eight of these children had received atomoxetine and six had received methylphenidate.

There were three cases of suicidal ideation and all these occurred in children who had received atomoxetine. Four cases of hyperbilirubinaemia as a proxy of hepatic toxicity, seven cases of gastrointestinal diseases, five cases of psychiatric disorders and five cases of change of personality were also associated with atomoxetine use. One female experienced a neurological bladder with failure of micturition and hospitalization. Cases of aphasia, tics, alopecia and hypotension were reported in children who were taking methylphenidate.

The cardiovascular risk was assessed with ECG before the start of pharmacological treatment and every 6 months thereafter.

The rate of serious adverse reaction of any kind is higher in the atomoxetine recipient, 52 out of 781 (6.6%), than in methylphenidate recipient, 11 out of 643 (1.7%). The relative risk for adverse reaction is 3.57 [95% confidence interval (CI) 1.92–6.64] for atomoxetine compared with methylphenidate. The odds ratio to discontinue the treatment in atomoxetine recipient compared with methylphenidate is 2.10 (95% CI 1.54–2.85). The common adverse events are more frequent in children who have taken atomoxetine (734 patients) compared with those taking methylphenidate (445 patients). The results are shown in Tables 1 and 2. Not all of the adverse reactions identified are noted in the summary of product characteristics for atomoxetine and methylphenidate.

In the UK's Yellow Card database of spontaneous adverse reaction reports, 63% of the reports for atomoxetine and 42% of the reports for methylphenidate are in the system organ classes psychiatric disorders, nervous systems disorders and gastrointestinal disorders.[24,25]

Conclusion

The multimodal treatment is held to be the best approach to manage ADHD. The scientific community reached a wide agreement on this matter. All the same, the drugs prescribed in Italy for the multimodal treatment showed several problems related to risk–benefit profile. Particularly, atomoxetine is associated with important systemic reactions such as neurological, psychiatric, gastrointestinal, cardiac and hepatic. Although no drugs can be totally well tolerated, a systematic monitoring is

mandatory to assess the safety of drug treatment in ADHD children.

The results we report come from a registry, not from a randomized trial. It is, therefore, impossible to exclude potential biases in the assignment of treatments. Furthermore, we cannot calculate from the data the person-time at risk in each group. Our results should, therefore, be viewed cautiously.

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