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CLINICAL EXPERIENCE OF LONG-TERM TREATMENT WITH ARIPIPRAZOLE (ABILIFY) IN CHILDREN AND ADOLESCENTS AT THE CHILD AND ADOLESCENT PSYCHIATRIC CLINIC 1 IN ROSKILDE, DENMARK

BEATA DIOMŠINA[1,2]*, PERNILLE DARLING RASMUSSEN[3] and VITA DANILEVIČIŪTĖ[4]

[1]Clinic of Psychiatry, Medical Faculty, Vilnius University, Lithuania
[2]Child and Adolescent Psychiatric Clinic 1 in Roskilde, Region Zealand, Denmark
[3]Child and Adolescent Psychiatric Clinic in Holbaek, Region Zealand, Denmark
[4]Clinic of Psychiatry, Medical Faculty, Vilnius University, Lithuania

Abstract: The aim of this paper is to share the clinical experience of the treatment of aripiprazole (Abilify) in children and adolescents. The authors have done a cross-sectional study about Abilify's treatment in children and adolescents with severe conduct problems (high impulsivity, aggression, outward reaction, physical cross-border behavior), high restlessness with ADHD, psychotic and psychosis-like symptoms with autistic disorders, psychosis, and intensive tics with Tourette's syndrome. The authors studied and described patients at the Child and Adolescent Psychiatric Clinic 1 in Roskilde, Denmark, who were treated with Abilify and were patients of the clinic in June 2013. The target group consisted of 33 patients, aged 9-18 years, which were in Abilify treatment during this time. Indications for the treatment and effectiveness of Abilify, Abilify's common doses used in children and adolescents, and the most common adverse effects of Abilify are presented.
Abilify was found to be effective, well tolerated and safe for children and adolescents. The dose depends on the complexity of diagnosis (higher doses used in cases of complex diagnosis), on the age (higher doses used in older children, but only in the case of noncomplex diagnoses). Statistical analysis shows that in cases of complex diagnoses, dosage does not depend on age but depends on other factors. It also shows that the effect of treatment is better for those who did not gain weight.

Keywords: Abilify, conduct disorder, autism

Second-generation antipsychotics are being used more often than ever before in children and adolescents with both psychotic disorders and a wide range of non-psychotic disorders. Several second-generation antipsychotics have received regulatory approval for some pediatric indications in various countries, but off-label use is still frequent (1).

Aripiprazole (Abilify) is an atypical antipsychotic partial agonist at dopamine D_2 and 5-HT_{1A} receptors and is an agonist at 5-HT_2 receptors. It has been described as a dopamine system stabilizer as, in high levels of dopamine production, it will act as an antagonist; and where dopamine activity is low, it will act as an agonist (2).

In Denmark, aripiprazole (Abilify) is licensed for treatment of schizophrenia, and treatment and prevention of recurrence of mania only for adults. In the USA, it was licensed by the Food and Drug Administration (FDA) in 2002 for the treatment of symptoms associated with autistic spectrum disorders in children and adolescents.

Although in Denmark, treatment of children and adolescents with Abilify is, as in many other European countries, as off-label use, this second generation, atypical antipsychotic is widely used in the treatment of psychiatric conditions in children and adolescents.

Starting around 2008, the Child and Adolescent Psychiatric Clinic 1 in Roskilde has used Abilify more widely and has gathered experience with it.

After five years of prescribing Abilify for children and adolescents, the authors have decided to share their experience and to describe patients who have undergone treatment with Abilify.

* Corresponding author: beatadiom@gmail.com; phone: +45 51 43 96 48 and +37069815218; fax: +45 46 32 30 51; postal address: Lille Strandvej 12 A, 3.th 2900 Hellerup, Denmark

The aim of our study is to share the clinical experience of the treatment of children and adolescents with Abilify.

MATERIALS AND METHODS

The authors have made a cross-sectional study about Abilify's treatment in children and adolescents. The authors have studied and described patients at the Child and Adolescent Psychiatric Clinic 1 in Roskilde, Denmark, who have tried treatment of Abilify and were patients of the clinic in June 2013. The patients received outpatient treatment at the clinic.

Most of the patients were still in treatment with Abilify at this point in time, but some of them have stopped Abilify treatment for different reasons (ineffectiveness of the treatment or unacceptable adverse effects).

Most of them started Abilify in the clinic, but some of them started the treatment in other places and later were referred to the clinic. Patients who

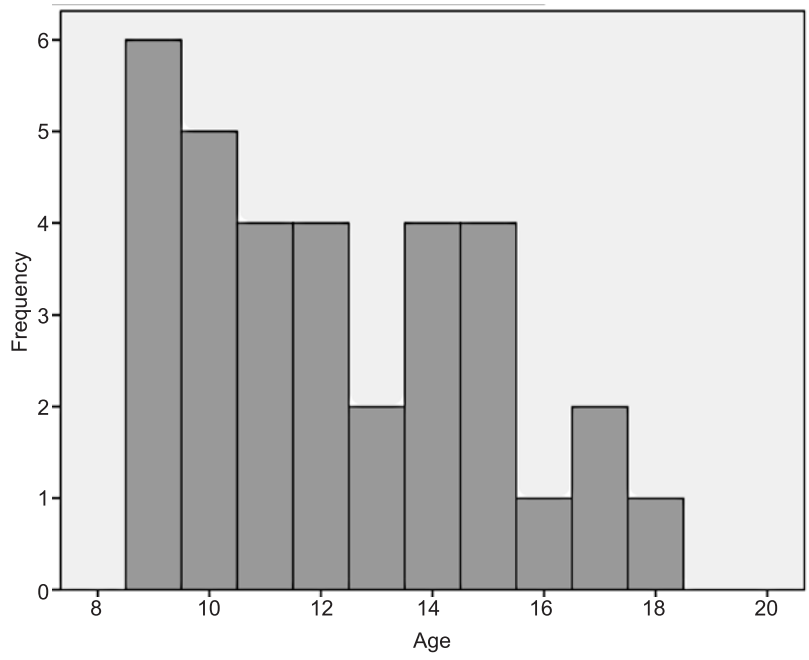

Figure 1. Age distribution in the study group

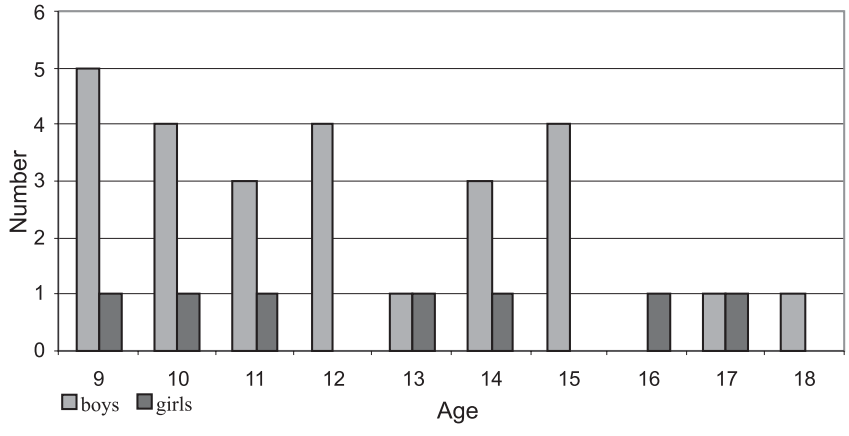

Figure 2. Age and gender distribution in the study group

received Abilify in the clinic starting in August 2008, but were discharged from the clinic at the start of June 2013, are not included in this study.

Another patient is not included in the group because of a short duration of the treatment (only one week). The treatment was interrupted because of intolerable adverse effects in the form of akathisia (the boy suffered inner restlessness, inability to sit still, and remained motionless); the dose and effect were not assessed.

Indications for starting Abilify's treatment for patients were the following:

- severe conduct problems (high impulsivity, aggression, outward reaction, physical cross-border behavior) with autistic disorder and ADHD;
- high restlessness with ADHD;
- intensive anxiety symptoms with autistic disorder;
- psychotic and psychosis-like symptoms with autistic disorders;
- psychosis;
- intensive tics with Tourette's syndrome.

The patients in the study group were divided into two subgroups: one of them was noncomplex and included patients diagnosed with ADHD, and the other group was complex and included patients with pervasive developmental disorders and psychosis, and patients who had two and more diagnoses.

The study group consisted of 33 children and adolescent psychiatric patients, 7 girls and 26 boys in ages 9-18, which have attended the Child and Adolescent Psychiatric Clinic 1 in Roskilde from August 2008 until June 2013, and have been in treatment with Abilify at least four weeks or longer (the longest period being almost five years).

Patients undergoing Abilify treatment were monitored with clinical psychiatric examinations with their parents. Physical examinations included weight control, blood pressure, blood tests, and EKG both before treatment and after, at approximately four weeks, six months, one year, and later once yearly.

Effectiveness of treatment for the psychiatric symptoms was assessed with only verbal reports from children and their parents about the child's functioning in school, at home, with peer groups, etc. Some of the adverse effects such as fatigue, akathisia, and increased appetite were also evaluated with only verbal reports from children and their parents. However, other possible adverse effects such as increased levels of cholesterol and prolactin were monitored with blood tests, along with other criteria (red and white blood cells, electrolytes balance, liver function tests, cholesterol and prolactin level). Weight gain as an effect of increased appetite was monitored with weight controls.

Finally, based on the data thus acquired, statistical analysis was performed. The following statistical methods were used: descriptive statistics (Figures 1-4, frequency tables 1-5) and inferential statistics (two independent samples *t*-test, Spearman rank correlation coefficient, Mann-Whitney U-test. Statistical package SPSS 21.0 was used for data processing).

Table 1. Diagnosis of the patients.

Diagnosis	Number of cases
Attention deficit hyperactivity disorder	28
Pervasive developmental disorders	13
Psychotic disorders	2
Tourette's syndrome	7
Attention deficit disorder	1
Anxiety disorders	2
Obsessive compulsive disorder	1
Adaptation disorder	1
Mental retardation	4
Inferioritas intellectualis	1
Other disorder of psychological development	1
Attachment disorder	1
Other tics disorder	1

Limitations

1. This study was not designed as a clinical trial, but rather a sharing of real, long-term, clinical experience.
2. The severity of symptoms and the effect of Abilify were not measured with any scale

Table 2. The mean daily dosage of aripiprazole in cases of complex and noncomplex diagnosis.

Complexity of diagnose	Number of patients	Mean daily dosage [mg]	Standard deviation
Noncomplex	11	1.75	1.30
Complex	22	6.27	3.34

Table 3. Adverse effects of Abilify in the study group.

Adverse effect	Number of patients
Only transient fatigue	3
Little tremor of hands in the start of treatment	1
Bothersome fatigue	1
Increase appetite with weight gain	11
Increase appetite with weight gain and transient fatigue	2
Hyperprolactinemia and increase appetite with weight gain	1
No adverse effect	14

Table 4. Adverse effects as a reason to interrupt the treatment.

Adverse effect	Number of patients
Bothersome fatigue	1 (3)
Increased appetite with weight gain	6 (18)
Hyperprolactinemia, increased appetite with weight gain	1 (3)

before or after the start of the treatment, but only with subjective reports about the effects on the symptoms from parents or patients.

3. Most of the patients have been in combined treatment, and in addition to Abilify, have been on the most common ADHD medicines such as methylphenidat and atomoxetin. Some of the patients have been on sertralin for anxiety and depression, and some of them on melatonin for sleep difficulty. Combined treatments were not taken into account.
4. Small sample size, considering number of variables in the study, which was not beneficent for using more sophisticated statistical methods, such like multiple regression analysis.

RESULTS

Description of the study group

Patients' psychopathology

The patients have been diagnosed with attention deficit and hyperactivity disorder (ADHD), pervasive developmental disorders, psychotic disorders, Tourette's syndrome, other tics disorder, anxiety disorders, adaptations disorder, mental retardation, attachment disorders, inferioritas intelectuallis, other disorder of psychological developmental.

But only 11 patients from the study group have been diagnosed with only one diagnose ADHD (F 90.0 or F 90.1), and most of the patients (22 patients or 70% of the patients) have been diagnosed with more complex psychiatric disorders such as pervasive developmental disorders or psychotic disorders, or they had ADHD in addition to other disorders such as Tourrette's syndrome, attachment disorder, mental retardation, anxiety disorder or other disorder of psychological development so their psychopathology is more complex. Later, the group was divided into subgroups of complex diagnosis and a subgroup of noncomplex diagnosis.

Age and gender of patients are given in Figures 1 and 2.

Doses used

The mean daily dosage of aripiprazole in the study group was 4.65 mg, standard deviation 3.52, a minimum dosage 0.25 mg and maximum dosage of 12.5 mg.

The mean daily dosage of aripiprazole in cases of complex diagnosis was 6.27 mg, standard deviation 3.34 and in cases of noncomplex diagnosis was 1.75 mg, standard deviation 1.30.

Tolerability, adverse effects and effectiveness of the treatment

There were 14 patients who had no adverse effects. Another 19 patients had such adverse effects as a fatigue, little tremor of hands in the start of treatment, increased appetite with weight gain, hyperprolactinemia.

There were six (18%) patients who complained of fatigue, and five of them (15%) had fatigue as a transient adverse effect. But in one case, fatigue was very bothersome and lasted as long as the boy was in treatment. There was, however, a positive effect on his impulsiveness and his intensive anxiety symptoms, but after five weeks the treatment was interrupted, because the boy was almost always tired and sleepy, making it impossible for him to function optimally.

Increased appetite with following weight gain was observed in 14 patients (42%). Increased appetite is a very serious adverse effect, and often for young people it becomes impossible to continue the treatment. Therefore, treatment was interrupted because of this adverse effect in 6 patients (18%).

Hyperprolactinemia was observed in only one patient. Unfortunately, the patient did not collaborate with a physician to have a blood test, and the boy developed gynecomastia - an obvious symptom

of hyperprolactinemia. His treatment was interrupted because of hyperprolactinemia and increased appetite.

The treatment was interrupted because of adverse effects in eight patients (24%).

However, there were 14 patients (42%) who had no adverse effects. If we put them together with other three patients (9%) who had transient fatigue and one patient (3%) who had little tremor of hands in the start of treatment, we can see that 18 patients could tolerate Abilify treatment and they had no adverse effect or only a very slight adverse effects. The largest part of the patients had good tolerability of Abilify (54%).

To defend Abilify as a safe antipsychotic medicine, it is necessary to point out that no Abilify-treated patient developed dyslipidemia, no patient had a cardiac adverse effect.

Of the patients treated, 21 (64%) had a positive effect, eight (24%) had some effect, only three (9%) did not have an effect, and only one (3%) had a negative effect of treatment (the patient reported deterioration of tics caused by Abilify).

Analyses of data

Correlations of the treatment's effect with used dosage, complexity of diagnosis, age, weight and weight gain were analyzed.

The authors also tried to analyze the factors that determined the doses. Are patients' age and weight or complexity of psychopathology the main determining factors for the choice of dose?

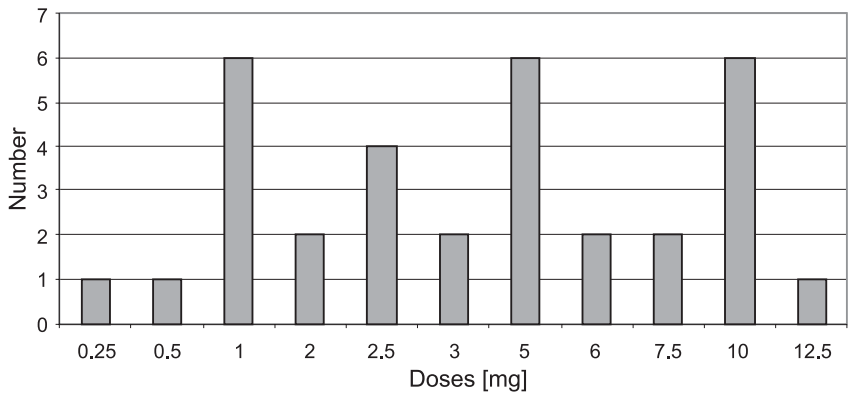

Figure 3. Doses used in the study group

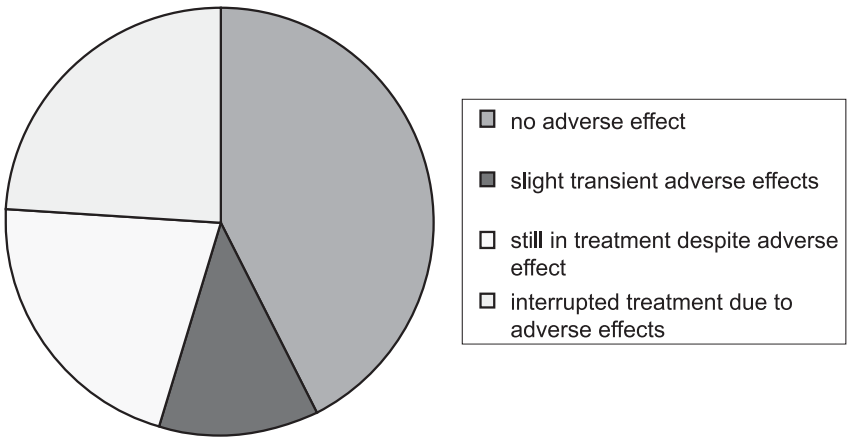

Figure 4. Tolerability of the treatment in the study group

Table 5. Diagnosis, ages, genders of the patients, doses used, and effects of the treatment in the study group.

No.	Complexity of psychopathology	Diagnosis	Doses [mg]	Effect	Age	Gender	Adverse effects	Still in treatment (blank) or reason of interruption of treatment
1	1	F 84.5	10	++	11	G	Fatigue	
2	1	F 90.0 F 84.0	6	+	11	B	Weight gain, increased appetite, fatigue	
3	1	F 20.9	10	++	10	B	Weight gain, increased appetite, fatigue	
4	1	F 90.0 F 84.5	5	++	17	G	Fatigue	
5	0	F 90.0	0.25	++	9	G	no	
6	1	F 90.0 F 70 F 43.23	10	++	18	B	no	
7	1	F 90.1 F 84.0	3	+	9	B	no	
8	0	F 90.0	2.5	+	12	B	Weight gain, increased appetite	Interrupted weight gain
9	1	F 90.1 F 84.5	5	++	15	B	Little tremor of hands in the start of treatment	
10	0	F 90.0	1	+	10	B	no	
11	0	F 90.1	1	++	9	B	no	
12	0	F 90.0 F 95.8	2.5	-	14	B	Weight gain, increased appetite	Interrupted weight gain ineffectiveness of treatment
13	1	F 84.0 F 42.0 F 90.0	5	0	13	B	Weight gain, increased appetite	Interrupted weight gain ineffectiveness of treatment
14	0	F 90.0	2	++	14	G	Weight gain, increased appetite	Interrupted weight gain
15	0	F 90.0	1	+	11	B	Weight gain, increased appetite	
16	1	F 90.0 F 95.2 F 84.5 F 41.1 F 40.2	12.5	++	9	B	no	
17	1	F 90.0 F 84.1	2.5	++	12	B	Strong annoying fatigue	Interrupted fatigue
18	1	F 90.1 F 88	5	+	14	B	Weight gain, increased appetite	Interrupted weight gain

Table 5. cont.

No.	Complexity of psychopathology	Diagnosis	Doses [mg]	Effect	Age	Gender	Adverse effects	Still in treatment (blank) or reason of interruption of treatment
19	1	F 98.8 F 95..2	2.5	++	17	B	no	
20	1	F 90.0 F 60.3	10	0	16	G	no	
21	1	F 90.0, F 84.0. F 95.2., F 70	5	++	14	B	no	
22	1	F 84.0 F 90.0 F 95.2	3	+	9	B	no	
23	0	F 90.0	1	++	10	B	no	
24	1	F 84.8 F 90.0 F 70.0	10	++	15	B	no	
25	1	F 84.0 F 90.1 F 95.2	10	++	12	B	no	
26	1	F 90.0 F 71	0.5	++	9	B	no	
27	0	F 90.0	1	++	10	G	Fatigue	
28	0	F 90.1	5	++	12	B	Weight gain increased appetite	
29	0	F 90.0	1	++	10	B	Weight gain, increased appetite	
30	1	F 90.0, F 95.2	7.5	0	15	B	Weight gain, increased appetite	Interrupted weight gain and ineffectiveness of treatment
31	1	F 28, F 94.1 R 41.8	6	++	11	B	Weight gain, increased appetite	
32	1	F 84.5	2	++	13	G	Weight gain increased appetite	
33	1	F 90.0, F 95.2 F 70	7.5	+	15	B	Weight gain increased appetite, hyperprolactinemia	Interrupted weight gain and hyperprolactinemia

++ positive effect, + some effect, 0 no effect, – negative effect, B = boy; G = girl

Statistical analyses of used doses show the following results:

1. Dose depends on the complexity of diagnosis. Higher doses are used in cases of complex diagnosis. Independent sample *t*-test shows that the mean dose is greater in cases of complex diagnoses ($p < 0.001$), standard deviation of dose is also greater for complex diagnoses ($p = 0.002$). Mann-Whitney U-test confirms results of the *t*-test, $p < 0.001$ (see Table 2).
2. Dose depends on age. Higher doses are used in older children. Spearman rank-correlation coefficient 0.42 shows that dose increases with an increase of age, $p = 0.015$ (statistically significant relationship).

   After separate statistical analysis of cases of complex diagnoses and noncomplex diagnoses, it appears that in cases of simple diagnoses, the dose depends almost exclusively on age ($p < 0.001$, Spearman coefficient 0.88), but in cases of complex diagnoses, dose does not depend on age ($p = 0.645$, Spearman coefficient 0.11) . It seems that dose depends on other factors.
3. Statistical analyses show that the effect of treatment is better for those who did not gain weight ($p = 0.040$, Spearman coefficient 0,11).

There were 84% cases with good effect for those who didn‘t gain weight; only 46% for those who did.

It seems that no weight gain gives better compliance and predicts a better result of the treatments.

DISCUSSION

As we mentioned before in the section of the limitations of the study, our study was not designed as a clinical trial. However, we observed the patients for a longer period of treatment than is done in a clinical trial, which usually lasts several weeks. Some of our patients have been in Abilify treatment for almost five years. Therefore, the observation of the patients for a longer period of treatment could be considered an advantage of our study.

The indications for starting Abilify's treatment for our patients have been similar as in other studies. In Ercan's study (3), there were: inattention, hyperactivity/impulsivity, delinquency, aggressive behavior, conduct disorder, oppositional defiant disorders.

In the study by Valicenti-McDermott and Demb (4), there were diagnoses within the autistic spectrum, mental retardation, attention-deficit/hyperactivity disorder/disruptive behavior disorders, mood disorders, reactive attachment and sleep disorders. Target symptoms included aggression, hyperactivity, impulsivity, and self-injurious behaviors.

In the study of of Masi et al. (5), target symptoms were Tourette's disorder and co-morbid ADHD.

As one can see, in our study group of 33 children and adolescents aged 9-18 years, we observed a positive effect in 64% of the patients. These are approximately the same results as in the studies by Ercan et al. (3). They conducted a study to determine the effectiveness and safety of aripiprazole in children and adolescents with both attention deficit/hyperactivity disorder and conduct disorder. In their eight-week, open-label study with 20 children and adolescents ranging in age 6-16 years they observed very much or much improvement with regard to inattention, hyperactivity/impulsivity, delinquency, aggressive behavior, conduct disorder, and oppositional defiant disorders in 63.1% of the patients.

Valicenti-McDermott and Demb (4) observed much improvement in regard to target symptoms in 56% of the patients in their study groups.

Results of a study by Findling et al. also suggest a clinically meaningful effect. Their study provides valuable safety and tolerability information regarding the long-term use of aripiprazole in the treatment of pediatric patients with irritability associated with autistic disorder (6). Moyal et al. showed a positive effect of Abilify for irritability and on quality of life (3).

We would also like to emphasize that mean daily dose in our study group is much lower than in Ercan's study (4.65 mg *versus* 8.55 mg).

Our results show that a higher dose is used in older children, which is also described in the study by Blumer et al. (8). Based on the results of the pharmacokinetic study, Blumer and colleagues (8) have proposed following weight-based dosing for pediatric patients: 1 mg for patients < 25 kg, 2 mg for patients between 25 and 50 kg, 5 mg for those between 50 to 70 kg , and 10 mg for patients with weight greater than 70 kg. It seems that larger doses for older children can be a consequence of their higher weight.

We can also see that the mean dose is greater in cases of complex diagnoses than in cases of noncomplex diagnoses. It could appear very logical: older children and those with more severe pathology need a higher dose of medications. However, our results also show that in cases of noncomplex diagnoses, the dose depends almost exclusively on age; but in cases of complex diagnoses, dose does not depend on age. It could be, that in cases of complex psychopathology, clinical dose depends more on the severity of pathology as well as on individual fac-

tors. It is well known that factors influencing choice of a treatment dose in a clinical situation can be many, they are inter-related, sometimes not easily measured, and therefore more sophisticated experiments and more advanced statistical methods (such like regression analysis) are desirable in order to explain treatment decisions of a physician. However, such methods require using considerably larger patient samples and possibly other research designs. This was not feasible in our situation.

In the studies of Ercan (3) and Masi et al. (5), no patient was excluded from the study because of adverse drug effects, but in our group, 24% of patients interrupted treatment because of adverse effects. We must take into account that there were patients who received treatment much longer that the patients from Ercan's eight-week, open-label study and Masi's 12-week open-label study.

Most studies report adverse effects from Abilify in the form of weight gain, increased appetite, fatigue, and tremors. We observed the same adverse effects.

Valicenti-McDermott and Demb (4) report adverse effects in 50% of the patients - almost the same as our results, where we observed adverse effects in 58% of the patients. As shown in their study, mean body mass index (BMI) rose significantly from 22.5 to 24.1. This is one of the most bothersome adverse effects, which complicated treatment with Abilify. In our study, increased appetite was observed in 42% of the patients.

In our study, the effect of treatment is significantly better for those who did not gain weight. It seems that no weight gain gives better compliance and predicts a better result of the treatments.

Many studies report that Abilify is a well tolerated, effective medicine with minimum extrapyramidal effects (9). Abilify does not show any adverse effect on QTc interval. Aripiprazole is not associated with increased prolactin or with dyslipidemia (10).

Our results show that there was only one patient in the study group, who had little tremor of hands in the start of treatment. During five years of the treatment, no Abilify-treated patient developed dyslipidemia, and only one patient developed prolactinemia. There were no patients who had a cardiac adverse effect.

Our experience and results should encourage clinicians to use Abilify in children and adolescents.

CONCLUSIONS

1. Abilify is found to be effective for child and adolescent psychiatric disorders (64% of the patients had positive effects, and 21% of them had some effects from the treatment).
2. Abilify is found to be well tolerated in children and adolescents. Fifty seven percent of the patients could tolerate Abilify treatment, and they did not have any side effects or had a very slight adverse effect.
3. Abilify is found to be safe. No Abilify-treated patient developed dyslipidemia or a cardiac adverse effect. Hyperprolactinemia and akathisia are seldom adverse effects of Abilify.
4. Increased appetite and weight gain are the most common adverse effects of Abilify. Increased appetite and weight gain were observed in 42% of patients.
5. The dose depends on the complexity of diagnosis and on the age. Higher doses are used in cases of complex diagnosis. Higher doses are used for older children, but only in the case of noncomplex diagnoses. Statistical analysis shows that in cases of complex diagnoses, dosage does not depend on age.
6. Statistical analysis shows that the effect of treatment is better for those who did not gain weight.

Declaration of interest

The authors do not have any interests to declare.

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