

The role of pharmacists in the management of autism spectrum disorder: A survey to determine the knowledge and perception of the parents

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ABSTRACT

Autism spectrum disorder (ASD) is one of the neuropsychiatric disorders of childhood and has many causes including genetic, neurobiological, environmental, as well as other risk factors that can trigger the disorder. The aim of this survey is to determine the knowledge of the families about ASD, the most prescribed medications, their side effects and the alternative therapies used besides to the pharmacological treatment. This study was survey-based and conducted among parents of children with ASD (N=50). Risperidone, aripiprazole, and valproate were the most prescribed drugs (64%) and weight gain (n=14), increased aggressive behavior (n=11) and drowsiness/sedation (n=11) were reported as the main side effects. Besides to pharmacological therapy, most of ASD children have used complementary and alternative medicine like gluten and casein-free diet (n=23) or the sugar diet (n=15), as well as omega-3 (n=43), multivitamins (n=40), heavy metal chelation agents (n=27), vitamin B12 (n=18), zinc (n=17) vitamin D (n=9), and probiotics (n= 7). It is revealed that pharmacists should be able to inform the parents about the general characteristics of ASD, and new treatment approaches, and provide a rational use of prescribed drugs in children with autism.

Keywords: Autism spectrum disorder, pharmacist role, pharmacological therapy, complementary and alternative medicine

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder, which is characterized by persistent deficits in social communication and social interaction, limitations and deviations in verbal and nonverbal skills, repetitive patterns of behavior, interests or activities. The worldwide prevalence of ASD has been steadily increasing in recent decades. In 2016, the USA National Health Center for Health Statistics reported that ASD could be found in 1 out of 36 children (Christensen et al. 2016; Sharma et al. 2018). Due to the large variation in deficiencies and the deviations in symptoms between patients, the diagnosis of ASD can be quite difficult. Therefore, it is necessary to distinguish ASD from other neuropsychiatric disorders, and use appropriate evaluation methods to diagnose correctly in order to improve the clinical management of the disease (National Institute of Mental Health 2018; Baumer and Spence 2018).

Recent studies have shown that multiple genetic factors play a role in the development of ASD (Lovato 2019). Siblings of ASD children also carry a higher risk of developing ASD (Bolton et al. 1994). It is reported that genetic and chromosomal abnormalities, such as Down's syndrome or fragile X syndrome, can be found in 10% of the children with ASD (DiGuseppi et al. 2010; Hall et al. 2008). In addition, parental history of psychiatric disorders, premature birth and fetal exposure to psychotropic drugs, toxins, heavy metals and insecticides have been linked to the pathophysiology of ASD (Cattane et al. 2018; Sharma et al. 2018). With the emergence of possible etiologic causes, new therapy approaches may be introduced in the treatment of ASD (Emberti Gialloreti et al. 2019).

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The current treatment options of ASD include nonpharmacological (behavioral, psychosocial, and educational therapy, food supplements, dietary interventions, etc.) and pharmacological therapies (Goel et al 2018; Baumer and Spence 2018). Pharmacological therapy includes different classes of drugs such as psychostimulants, antipsychotic drugs, antidepressants, NMDA receptor antagonists, alpha-2 adrenergic receptor agonists, cholinesterase inhibitors and antiepileptics (Aman et al 2008; Sharma et al. 2018). Although core symptoms of ASD may improve with appropriate pharmacological therapy, there is currently no appropriate cure. Many families of children with ASD use conventional as well as complementary and alternative (CAM) therapies (Goel et al 2018; DeFilippis 2018). Treatment should be individualized according to the patient's symptoms and family's needs, and also, should be closely monitored by the healthcare team, including the pharmacists. Pharmacists play an important role in the follow up of new treatment approaches, in providing the correct use of the prescribed drugs and over the counter medications (OTC), as well as the education of ASD families. Unfortunately, pharmacists are rarely included in the team of health professionals who routinely provide care to children with ASD (Shafiq and Pringsheim 2018; Breik et al. 2018; Wongpakaran et al. 2017; Luleci et al 2016).

The aim of this survey is to determine the knowledge of the families about ASD, the most prescribed medications, their side effects and the alternative therapies used besides to the pharmacological treatment. These findings may give a perspective to strengthen the role of pharmacist in the management of ASD therapy.

MATERIALS AND METHODS

This is a survey-based study which was developed by the authors and conducted among parents of children and ado-

lescentse (2.5-18 years old) with ASD (N=50). Parents completed questionnaires during interviews scheduled at OÇEM (Autistic Children Education Centre) in Istanbul and Sakarya in Turkey. The first part of the survey consisted of demographic characteristics (i.e., age, sex, profession of parents, status of intermarriage, family history of ASD, Alzheimer's disease and dementia), knowledge and perception of parents regarding ASD (such as delayed reply to name, failure to show an interest to other children, repetitive, stereotypic movements, limited social interaction). In the second part of the survey, currently used therapies, such as pharmacological (stimulants, antipsychotics) and non-pharmacological (OTC medications, food supplements, dietary interventions etc.) therapies, presence of concomitant disorders, physicians' visit intervals and social care service support were assessed. The inclusion criteria of the study were: children and adolescents having a confirmed diagnosis of ASD; parents being able to read, understand and fill in the forms properly. All participants provided informed consent, and the study was approved by the Ethics Committees of Istanbul University Cerrahpasa Faculty of Medicine (Number:83045809/5563).

Statistical analysis

The statistical analysis was performed by GraphPad Prism software (version 6). Chi-square and Fisher's test were performed to show association between variables. Mean and standard deviation (SD) were calculated for demographic data and anthropometric measurements.

RESULTS AND DISCUSSION

In this study, a survey was conducted with the parents of children and adolescents with ASD aged between 2.5 and 18 years (N=50). The demographic data of the patients with ASD and their special family characteristics which may be associated with ASD are listed in Table 1. Studies have shown that the prevalence of ASD is four- to five-fold higher in boys than girls (Christensen et al. 2016). A similar male / female ratio was observed in the current study. Among the parents interviewed, the majority of the mothers (66%) were housewives and a special etiological link in terms of an occupational risk of toxicity was not determined.

ASD is known to have a genetic component (Lovato et al. 2018). Thus, we evaluated the genetic risk factors of the ASD patients. It was found that 20% of the parents enrolled in this study were consanguineous. In addition, 14% of the ASD parents have other relatives with ASD, and 28% of them had Alzheimer's and dementia in their families (Table 1). Indeed, due to the small sample size, these available data may not be sufficient for questioning the genetic origin of autism (Lovato et al. 2018; Gyawali and Patra 2019). Most of the ASD parents do not have an ASD association membership, however, 36% of them receive social care services called home care fees.

ASD symptoms in children are often first recognised by their parents and teachers (National Institute of Mental Health 2018; Baumer and Spence 2018). In this study, we determined that parents visit the physicians when they notice the symptoms,

Table 1. Demographic variables of ASD patients and their families

	N	Percentage (%)
• Age		
<7 years	15	30
7-15 years	28	56
15-18 years	7	14
• Gender		
Female	10	20
Male	40	80
• Status of intermarriage		
Yes	10	20
No	40	80
• Family history of autism		
Yes	7	14
No	43	86
• Family history of neurodegenerative brain disorders (Alzheimer's disease and dementia)		
Yes	14	28
No	36	72

such as delay in speaking and deficiency in eye contact (n=45), lack of facial expression and social communication (n=35), recurrent and stereotypic hand, finger, whole body movement (n=12) and lack of developing friendships (n=21). The age when families mostly recognise ASD symptoms in their children is generally around 3 years (Figure 1), which is consistent with the mean age for ASD diagnosis in children (4.3 years) in the USA (Baio et al 2018).

Children with ASD generally experience difficulties in developing social, speech, and behavioral skills. Therefore, pharmacological therapy is the mainstay in ASD therapy, in order to help patients to become functional in their daily activities, which additively needs to be supported by behavioral therapy as well

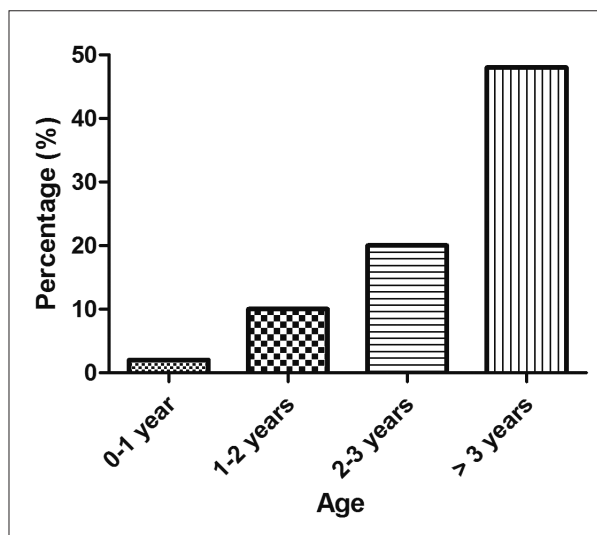


Figure 1. Rates of ASD Diagnosis by Age.

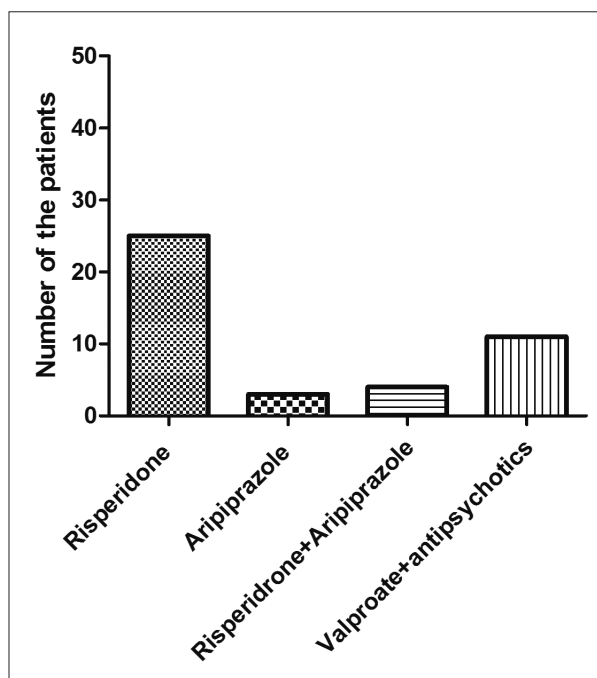


Figure 2. Rates of prescribed drugs for ASD treatment in this study.

(Goel et al. 2018; DeFilippis 2018). Risperidone and aripiprazole, the atypical antipsychotic agents, are the only medications approved by the USA Food and Drug Administration (FDA) to treat irritability and self-injurious and aggressive behaviors in children with ASD (Posey et al 2008, Oshikoya 2019, Wink 2017). In particular, Risperidone is the commonly prescribed antipsychotic with the most comprehensive data in ASD, and is used either alone or in combination with aripiprazole to treat children with ASD (Novaes et al. 2008). In this study, we observed that 36% (n = 18) of ASD children do not use any medication for ASD treatment. Among 50 ASD children, 32 (64%) were either on risperidone, aripiprazole or their combination therapy (Figure 2). 77% of the parents stated that drug treatment was effective. In addition, weight gain (n=14), increased aggressive behavior (n=11) and drowsiness/sedation (n=11) were reported as the main side effects by the parents. In line with our findings, weight gain and associated metabolic risks have been reported with antipsychotic treatment in other ASD patients. Indeed, it's well known that weight gain and drowsiness are the main side effects of risperidone, while sedation occurs especially with the use of aripiprazole (Wink 2017).

In this study, we documented that valproate was prescribed in 11 patients in combination with the antipsychotic agents, risperidone and aripiprazole. Indeed, valproate is an antiepileptic drug which can be added to ASD therapy in relation to the child's functioning and needs (Goel et al. 2018). In accordance with this data, we determined that among these 11 patients who were on combined drug regimen, 9 were also diagnosed with epilepsy along with ASD. Two clinical trials were noticed in the literature that investigated the effect of valproate in reducing the aggression and irritability symptoms of ASD patients. Therein, Hellings et al (2005) showed that there were no differences in the symptoms observed between the placebo and valproate groups following 8 weeks of treatment. However, Hollender et al. (2010) reported that valproate was superior to placebo in 12 weeks of treatment in controlling these symptoms in ASD children.

It is reported that, three-quarters of children with ASD may also have another medical, psychiatric, or neurological disorder, including attention-deficit hyperactivity disorder, anxiety, bipolar disorder, inflammatory bowel disease, epilepsy, fragile X syndrome, gender dysphoria, intellectual disability, neuroinflammation and immune disorders, non-verbal learning disorder, obsessive-compulsive disorder, schizophrenia, sensory problems, sleep disorders, tuberous sclerosis, Tourette syndrome and tic disorders (Sharma et al. 2018; Tye et al. 2019). In our study, half of the children with autism have intestinal problems, and almost all the children with this problem have also developed fungal infections. The surveyed children mostly (76%) have sleep disturbances. Other diseases determined to be associated with autism include epilepsy (n=9), intellectual disability (n=7) and hyperactivity (n=4) (Table 2). In this relation, children with ASD can use several medications at the same time for the treatment of different symptoms, as well as comorbid disorders (Wongpakaran et al. 2017). Therefore, it is important to consider the effectiveness, adverse effects and interactions of these medications used systemically during ASD therapy. In this regard, pharmacists can

develop systems to monitor these symptoms and provide data about responsiveness to drug therapy and thereby, can play an important role in the improvement of the prognosis and clinical outcomes in ASD patients.

We determined that most of children with autism in this survey study (74%) had undergone heavy metal assessment. As a result of this assessment, heavy metals, particularly mercury and lead, were detected in almost all the children in this study pop-

ulation, and in among 54% of them, the heavy metal chelation agents like 2,3-dimercaptosuccinic acid (DMSA) were preferably used (n=27). Although, there is no evidence of the efficacy and potential side effects of this chelation therapy in ASD, the heavy metal ratio is quite high in ASD patients and thus, it is suggested that there is a relationship between the heavy metals ratio and ASD (Pelch et al. 2019). However, reviewers of the chelation therapy concluded that this treatment is not recommended for individuals with ASD, and that risks associated with chelation therapy outweigh any potential benefits (Davis et al. 2012; James et al. 2015; DeFilippis 2019). Chelation agents can bind ions nonspecifically, and thus cause a decrement in the plasma levels of calcium, iron, and magnesium as well. This may associated with hypertension, hypotension, cardiac arrhythmias, and hypocalcemia, the latter of which can be fatal (James et al. 2015; DeFilippis 2019). In this context, pharmacists can determine and monitor the problems related to the decreased levels of these ions, and can raise the awareness of the patients in relation to the symptoms of these deficiencies. In this survey study, we determined that 38% of the children have anemia. The reason of the anemia might be the decrease in the level of iron due to chelation therapy, but we did not find a statistically significant correlation (p=0,9877).

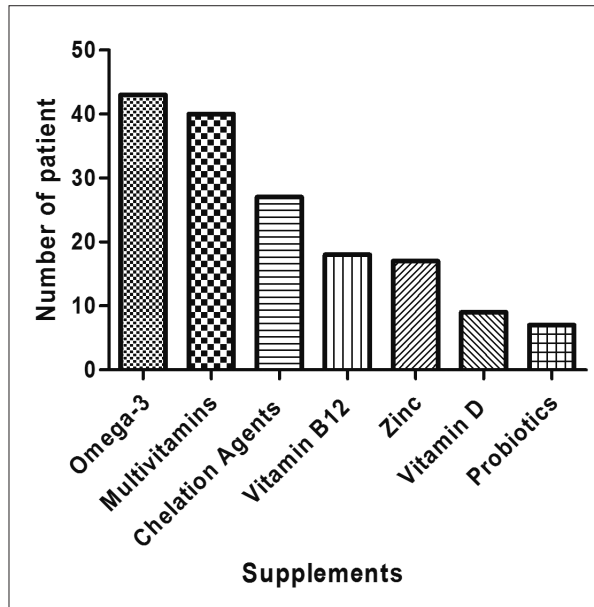


Figure 3. Rates of supplemental therapy used in this study.

	N	Percentage (%)
• Bowel disorders		
Yes	26	52
No	24	48
• Fungal infections		
Yes	23	46
No	27	54
• Sleep disorders		
Yes	38	76
No	12	24
• Comorbid psychiatric or neurological disorder		
Yes	17	34
No	33	66
• Intellectual disability		
Yes	16	32
No	34	68
• Anemia		
Yes	19	38
No	31	62
• Heavy metal assessment (mercury, lead)		
Done (High)	33	89
Done (Normal)	4	11

Another issue that is discussed regarding the children with autism is the elimination diets. Although this is not a proven case, most families apply an elimination diet for their children. We determined that many of the ASD parents that participated in our survey study, applied gluten and casein-free diet (n=23) or the sugar diet (n=15), especially in children with autism who also have fungal infections. Dietary approaches do not treat the symptoms of ASD but they can benefit by normalizing symptoms related to gastrointestinal dysfunction and therefore, improve overall well-being in ASD patients (Kawicka and Regulska-Ilow, 2013). It should be noted that ASD children may have malnutrition risks due to low energy intake, gastrointestinal problems and malabsorption of the nutrients. Thus, ASD children are required to be followed-up for special nutrition by dieticians or doctors in order to evaluate the nutrient status, especially in terms of vitamin D, calcium, potassium, iron and fiber intake (Kawicka and Regulska-Ilow 2013; DeFilippis 2019; Sharma et al. 2018).

In this survey study, we noticed that, besides a pharmacological treatment, 54% of the parents applied psychotherapy to their children. In addition, hyperbaric oxygen therapy is another additional treatment preferred in some of the ASD children in this study. Although 64% (n=32) of the children with autism have pharmacological therapy, 90% (n=45) of the children were preferably given food supplementation such as omega-3 (n=43), multivitamins (n=40) and heavy metal chelation agents (n=27). In addition, vitamin B12 (n=18), zinc (n=17) vitamin D (n=9), and probiotics (n=7) were also used as well (Figure 3). Höfer et al. (2019) recently showed that almost half of the parents of the children with ASD in Germany reported that they use or have used complementary and alternative medicines for their children. It seems that this is a global problem, and pharmacists should be aware of the significant prevalence of the use of these supplementary medicines. In this context,

pharmacists can play a crucial role in informing the caregivers of children and adolescents with ASD about the effectiveness and potential side effects of these supplementary products.

Almost all of the parents in this survey study stated that they received the first information about the use of drugs in ASD from their doctors. Taking into account the long-term use of medicines in children with ASD and the possibility of polypharmacy, the interest of pharmacists in monitoring the patient is very important to ensure maximum benefit from the pharmacological treatment (Wongpakaran et al. 2017, Sharma et al. 2018). It is the responsibility of the pharmacist to inform the family about ASD, to explain the use of drugs in the correct manner, to warn about important side effects of drugs, to emphasize the important points in their nutrition and to inform the parents about the dietary supplements. Pharmacists' responsibility is, in fact, the part of pharmaceutical care provided to the patients and their relatives.

Concerning the families of autistic children, they need to be consulted on the process of this disease, the problems that can accompany the disease, the approach and follow-up to the child, the aim and effectiveness of the drugs and alternative therapies, the possible side effects of these therapies and the precautions to be taken, the route and duration of use of the drugs and alternative therapies (Wongpakaran et al. 2017).

Concerning the role of pharmacists, as a health professionals, they should be informed about the general characteristics and current treatments of ASD, in order to provide early awareness to the families of children who may be autistic, and to direct them to the physician in the proper time. They should contribute to the positive outcomes of the treatment by ensuring the correct use of the drugs prescribed to the children and adolescents diagnosed with autism (Wongpakaran et al. 2017; Luleci et al. 2016).

CONCLUSION

In this study, it was revealed that pharmacists should be able to inform the parents of children and adolescents diagnosed with autism about the general characteristics of ASD, provide an early awareness to their families about the disease, and direct them to the physician in the appropriate time, to inform the parents about new treatment approaches and ensure the rational use of prescribed drugs in children and adolescents with autism.

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