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The Medical Treatment of Autism Disorders

Katarina Dodig-Ćurković, Mario Ćurković and
Josipa Radić

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1. Introduction

Autism is one of a group of pervasive developmental disorders and is characterised by qualitative impairments in communication and social interactions and by stereotyped behaviours and interests. Abnormal development is present before the age of 3 years. A quarter of affected children show developmental regression with loss of acquired skills. One third of children with autism have epilepsy and three quarters have mental retardation. Only 15 % of adults with autism lead independent live. Twin and family studies suggest that most cases of autism occur because of combination of genetics factors [1]. Concept of autism has been broadened the last few years from early infantile autism to an autistic spectrum and related communication disorders are grouped together under pervasive developmental disorders or autistic spectrum disorders. People with an autistic disorder have severe difficulties in the integration of perceived in social stimuli into a meaningful entity. More than two people with autistic disorder are also mentally retarded. Autism cannot be cured but adequate intervention can significantly improve the quality of life people with this disorder [2].

The American Psychiatric Association's last version of the Diagnostic and Statistical manual of Mental Disorders identifies within pervasive developmental disorders five subgroups:

- a. autistic disorder,
- b. Rett syndrome
- c. childhood disintegrative disorder
- d. Asperger's disorder and
- e. pervasive developmental disorder.

Prenatal exposure to infection and subsequent inflammatory responses have been implicated in the etiology of autism and schizophrenia [3]. Children with autism are vulnerable to anxiety. Also, higher levels of repetitive behaviours were associated with more anxiety [4]. Autism is a pervasive developmental disorder characterised by impairment in social interaction and communication, with unusual behaviour [5].

From the previous 4 per 10,000 people, today's prevalence estimates range from 0.6 to around 1% [6].

The onset of autistic disorder is before the age of 3 years and is four to five times more frequent in boys than in girls. Girls with autism are more likely to have more severe mental retardation. The causes of autism spectrum disorders are unknown, although genetic and environmental influence have been implicated. There is increasing evidence that people with autism spectrum disorder have abnormalities in the serotonergic system [7].

There are limited options for pharmacological therapeutic interventions in children with autism disorders and some studies showed that risperidone as an atypical antipsychotic may be effective for the treatment of people with autism and intellectual disabilities [8].

The primary models of treatment are non pharmacological interventions that include intervention models such as applied behaviour analysis and developmental and structured teaching. The main role of pharmacological interventions is limited to treating symptoms that may be interfering with a child's ability to learn or function within a particular environment [9].

The prevalence of prescription medications for children with autism is high. Survey indicates that one-half to two-thirds are prescribed at least one medication of any type and about 45% are prescribed at least one psychotropic medication [10-11].

The most commonly prescribed psychotropic medications are antidepressants, stimulants and antipsychotics. The reported prevalence of anticonvulsant medications is approximately 5% among children with autistic disorders and 11-13% among individuals across the life course [12-13].

Atypical neuroleptics have been shown to be useful in the treatment of behavioral symptoms in autism. Attention deficit and hyperactivity disorder medications may be effective for countering the additional features of hyperactivity and short attention span. Antiepileptic drugs for epilepsy and bipolar disorder (Valproate etc.) and selective serotonin reuptake inhibitors have shown promising results for depression [14].

One of the most frequently reported behavioral concerns among children with autism spectrum disorder is high rates of activity and inattention, symptoms that are often associated with attention deficit hyperactivity disorder [15]. The most studied antipsychotic drugs include haloperidol and risperidone [8].

In low dosages, they have been shown to reduce repetitive behaviours (stereotypes) and social withdrawal, as well as a number of related symptoms, such as hyperactivity, aggression, self-abuse behavior, lability of mood and irritability. All the listed symptoms have

appeared in adult patients with schizophrenia, where also with the application of atypical antipsychotics may affect on described clinical picture [16].

70 % of children have mild to moderate learning disability, the remaining 30 % with normal IQ are classified as either high-functioning autism (with language difficulties) or Asperger's syndrome (with normal language). 1-2 % of those with autism have a normal life; 5 to 20 % of those with autism have a borderline prognosis; but 70 % are totally dependent upon support [17].

The both first and second-generation antipsychotics have shown safety and efficacy in short-term and long-term studies in autism. Safety concerns associated with treatment include the risk of drug-related dyskinesias, which is greater with the first-generation drugs (haloperidol, flufenazin), and the risk of weight gain and associated metabolic problems (increases in glucose and lipids), which is greater with the second generation agents [18-19].

Risperidone has been shown to reduce repetitive behaviours and social withdrawal, hyperactivity, aggression, self-harm behaviour, temper tantrums, lability of mood and irritability [17].

It is also has been proved helpful in treating children and adolescents with autism spectrum disorders behavioural problems, conduct and bipolar disorder, Tourette's syndrome and schizophrenia [20].

Risperidone is a high potency antipsychotic with combined dopamine D2 and serotonin 5-HT₂ receptor antagonist properties, has been used to subdue aggressive or self-injurious behaviours. Several reports have suggested that risperidone is effective in diminishing aggressiveness, hyperactivity and self-injurious behaviour in children with autistic disorder. For children with autism, lower dosages ranging from 0.5 to 4 mg per day are generally used [21].

Treatment with atypical antipsychotic olanzapine also can be beneficial in alleviating some behavioral symptoms (irritability, hyperactivity/noncompliance, lethargy), associated with autism [22].

It is very important careful drug titration, usually start with half ($\frac{1}{2}$) or one (1) mg in the morning, and then gradually increase the dose in order to prevent adverse effects [23].

It is important to educate parents of children about possible side effects of treatment with antipsychotics. Most often side effects are feeling of stiffness, primarily in the neck and spinal muscles, sedation and weight gain, and in rare cases also galactorrhoea.

This approach can help parents to distinguish between symptoms of disorder and adverse drug effects, reduce their anxiety and intimidation, and simultaneously upgrade compliance and trust between parent and child. These medications are usually studied in adult schizophrenic patients, and there are frequent dilemmas on the use of this group of drugs in children. It is important to always take into account the adverse effects of this group of drugs, time to inform parents about them and have continuous monitoring of children. We have noticed that is often required professional assistance to parents of such children, because of

the constant confrontation with difficulties and unpredictable course of illness and fear of the uncertain future of their children.

2. Medical options for children and adolescents

Atypical antipsychotics

Atypical antipsychotics (AAPs) are a group of drugs originally developed to treat psychosis. The group includes compounds brought to the market over the past 10 years as safer and better tolerated alternatives to the existing „typical“ antipsychotics. In this group are: *clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole*. The target symptoms for pharmacotherapy with AAP typically include aggression, self-injury, property destruction or severe tantrums. Those drugs have lower risk of inducing neurological side effects such as parkinsonism in the short-term and perhaps tardive dyskinesia in the long-term. These newer compounds have been also reported to improve the negative symptoms of schizophrenia (abulia, avolition, flat affect) there is an interest in the notion that this may be relevant to the social withdrawal and lack of spontaneous interaction in autism. The reduced occurrence of dyskinesias and the improvement in negative symptoms of schizophrenia may be related to the dual action of five-hydroxytryptamine (5-HT) to dopamine (DA) receptor blockade [24]. The lower use of *clozapine* in autism probably reflects concerns about the risk of blood dysplasia and seizures that are associated with the drug. Additionally, frequent blood tests should be required to monitor for agranulocytosis, which can be challenging in children with autism [25]. *Risperidone* has high affinities for DA D2-D4, 5HT2A, 5-HT2C receptors [26].

It is an atypical antipsychotic (serotonin-dopamine antagonist: second generation antipsychotic) and also mood stabilizers. *Risperidone* blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms. They also block serotonin 2A receptors causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms. Interactions at a myriad of other neurotransmitter receptors may contribute to risperidone's efficacy. Alpha 2 antagonist properties may contribute to antidepressant actions. According to Food and Drug Administration, *risperidone* is commonly prescribed for: schizophrenia ages 13 and older, delaying relapse in schizophrenia, other psychotic disorders, acute mania, mixed mania, autism related irritability in children ages 5 to 16, bipolar depression, behavioral disturbances in children and adolescents and disorders associated with problems with impulse control [27]. Usual dosage range is 2 to 8 mg per day orally for acute psychosis and bipolar disorder, but 0.5 to 2.0 mg per day orally for children and elderly. It is the most frequently used atypical antipsychotic in children and adolescents [28].

Research on *risperidone* shows it to be effective in treating aggressive behaviour in patient population. Also, great improvements have been shown on the verbal communication, perception and behavioural symptoms [29].

A large number of papers showed that risperidone is a good choice for autistic children with the behavioral problems and irritability. Treatment with all newer antipsychotics was well

tolerated with low rates of extrapyramid side effects and serious adverse effects. There is evidence that autistic children and adolescents may be even more prone to weight gain with antipsychotic treatment than patients with general psychiatric conditions. This may occur because these individuals often have less autonomy and ability to take control of appetite, food intake and exercise levels to prevent weight gain [30-31]. Risperidone was found to be more effective than haloperidol in the treatment of behavioral symptoms, impulsivity, language skills, and impaired social relations in children with autistic disorders. Comparing two groups children with autism, there was a greater increase of prolactin in the risperidone group, while alanine aminotransferase had further increased in group that was treated with haloperidol. Also sensory motor behaviours and language at the end of the study showed that sensory motor skills and language subscales scores decreased in the group that was treated with risperidone [32]. With use of risperidone in our Department we achieved reduction of psychomotoric symptoms and reduction of hetero-aggressive and self-destructive behaviours and also improvement in contact with his surroundings. Research on the use of risperidone in the treatment of autistic children in Croatia is rare, given the limited use of risperidone in children younger than 15 years, the question arises about the need to expand the scope of application of risperidone in younger age groups (5).

Many studies show the effectiveness of *haloperidol* in a variety of behavioral symptoms in autistic children. Haloperidol is conventional antipsychotic (neuroleptic, butyrophenone, dopamine 2 antagonist) and according to Food and Drug Administration approved for: manifestation of psychotic disorders, tics and vocal ultrances, in second-line treatment of severe behaviour problems in children of combative, explosive hyperexcitability, second-line short-treatment of hyperactive children, treatment of schizophrenic patients who require prolonged parenteral antipsychotic therapy, bipolar disorder, delirium, behavioral disturbances in dementias. Haloperidol blocks dopamine 2 receptors, reducing positive symptoms of psychosis and possibly combative behaviours. It blocks dopamine 2 receptors in the nigrostriatal pathway, improving tics and other symptoms in Tourette's syndrome. There is less evidence on the effectiveness of other typical antipsychotics. Haloperidol treatment often causes side effects such as dystonic reactions and dyskinesia. Because of the risk of extrapyramidal symptoms, the use is limited only for refractory cases. The most often seen side effects are: akathisia, neuroleptic-induced syndrome, parkinsonism, tardive dyskinesia, tardive dystonia, galactorrhoea, amenorrhoea, dizziness, sedation, dry mouth, decreased sweating, hypotension, tachycardia, hypertension, weight gain, tardive dystonia. Haloperidol is not intended for use under age 3. Initial oral dose is 0.5 mg/day; target dose 0.05-0.15 mg/kg per day for psychotic disorders and 0.05 to 0.075 mg/kg per day for nonpsychotic disorders [28]. Risperidone is from 2006. year approved by the FDA for the treatment of children older than 5 years. It helps in reducing the symptoms of irritability, aggression and self-harm. The most frequent side effects are weight gain and sedation. Autism is a disorder that lasts a lifetime. Autistic children with IQ higher than 70 and those that develop language communication ability to the fifth or seventh year have the best prognosis. Research on autistic adults have shown that two-thirds of them remain seriously handicapped in complete or partial dependence on caregivers. Only 1-2 percent of persons are capable for independent life, including employment. Five to twenty percent of persons have nearly nor-

mal life. All study showed also some adverse events or adverse affects by using risperidone such as: weight gain, somnolence, drowsiness, tremor, dyskinesia, rigidity. Also some authors reported a greater rise in prolactin levels in subjects which were treated by risperidone. These results showed that also it was a greater rise in prolactin levels in subjects in the risperidone compared with those in the placebo although they did not report clinical events such as gynecomastia or galactorrhoea, that could be elevated prolactin levels [33].

United Kingdom guidelines recommended maximum daily doses of between 2 and 3.5 mg for children weighing under and over 45 kg, respectively. In practice many authorities recommended using very small doses starting at 0.25 mg and increasing very slowly if required.

Aripiprazole is the most recent addition to the list of available AAPs. Studies in adults with schizophrenia have shown it to be an effective antipsychotic with a low risk of side effects and causing reduced levels of weight gain [34]. Aripiprazole is dopamine partial agonist (dopamine stabilizer, atypical antipsychotic, third generation antipsychotic) and commonly prescribed for: schizophrenia ages 13 and older, maintaining stability in schizophrenia, acute mania/mixed mania ages 10 and older, bipolar maintenance, depression, autism-related irritability in children ages 6 to 17, bipolar depression, other psychotic disorders, disorders associated with problems with impulse control, behavioral disturbances in children and adolescents. Theoretically increases dopamine output when dopamine concentrations are low, thus improving cognitive, negative and mood symptoms. After treatment with aripiprazole, children showed less irritability, hyperactivity, and stereotypes (repetitive, purposeless actions).

Notable side effects must be considered, however, such as weight gain, sedation, drooling, and tremor (35).

By blocking alpha 1 adrenergic receptors it can cause dizziness, sedation and hypotension. Partial agonist actions at dopamine 2 receptors can also cause nausea, occasional vomiting and activating side effects. Mechanism of any possible weight gain is unknown; weight gain is not common with aripiprazole and may have a different mechanism from atypical antipsychotics for which weight gain is common or problematic. Usual dosage range is 15-30 mg/day, but children and patients which not acutely psychotic may need to be dosed lower (2.5 -10 mg /day) in order to avoid akathisia and activation and for maximum tolerability. Aripiprazole was efficacious in children and adolescents with irritability, associated with autistic disorder and was generally safe and well tolerated. Also, it has been shown to be efficacious and generally well tolerated in children and adolescents with schizophrenia and bipolar mania [36-37]. Aripiprazole is approved for use in schizophrenia ages 13 and older, manic/mixed episodes ages 10 and older and irritability associated with autism ages 6 to 17. Clinical experience and early data suggest aripiprazole may be safe and effective for behavioral disturbances in children and adolescents, especially at lower doses. Children and adolescents using aripiprazole may need to be monitored more often than adults and may tolerate lower doses better. Also, may be more risk of weight gain in children than in adults [28]. Data in youth with autism and disruptive behaviour disorders, available only for some antipsychotics, suggest greater weight gain, possibly due to less prior antipsychotic expo-

sure. Metabolic effects differ among second-generation antipsychotics, despite significant weight gain with all studied agents, suggesting additional, weight-independent effects. Pharmacological work indicates that antipsychotics polypharmacy increases the risk for obesity or any other cardiovascular, cerebrovascular or hypertensive adverse event [38].

Serotonin reuptake inhibitors (SRIs)

Repetitive behaviours are a core symptom domain in autism that has been linked to alterations in the serotonin system. While the selective serotonin-receptor inhibitor fluvoxamine has been shown to be effective in adults with autism, as yet no published placebo controlled trials with these agents document safety and efficacy in children with autism. Trials with SRIs suggest benefits in adults with autism spectrum disorders. In the only double-blind study of SRIs in adults with autism to date, McDougle et al. conducted a placebo controlled study on fluvoxamine and found that 53% patients were responders compared to placebo group. Significant improvements in repetitive thoughts and behaviour, maladaptive behaviour, aggression, social relatedness and language usage were reported. In contrast to this adult trial of fluvoxamine, a subsequent trial in children and adolescents with autism conducted by the same group found poor response to fluvoxamine, only one of 18 responded, while 14 had adverse effects [39]. To control the depressive symptoms are commonly used fluoxetine, fluvoxamine and sertraline. These act to reduce repetitive, ritualized behaviours and improvement in social skills. SRIs are prescribed for the treatment of co-morbidity associated with autistic spectrum disorders such as depression, anxiety and obsessive-compulsive behaviours [40]. Several studies suggested that children may respond better to low doses of SRIs specifically fluoxetine, than they did to fluvoxamine. Some of the FDA approved drugs used to treat symptoms of autism that can be administered to children above the age of seven include fluoxetine, fluvoxamine, sertraline and clomipramine. Serotonin reuptake inhibitors (SRIs) such as *clomipramine, fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram and escitalopram* that inhibit the uptake at the presynaptic site.

Fluoxetine is selective serotonin reuptake inhibitor often classified as an antidepressant but it is not only antidepressant. It is commonly prescribed for: major depressive disorder ages 8 and older, obsessive-compulsive disorder ages 7 and older, premenstrual dysphoric disorder, bulimia nervosa, panic disorder, bipolar depression, treatment resistant depression in combination with *olanzapine*, social phobia and posttraumatic stress disorder. Usual dosage range is 20-80 mg for depression and 60 to 80 mg for bulimia. In children it is approved for obsessive-compulsive disorder and it could be helpful in some autistic children with stereotypical reactions. Adolescents often receive adult dose, but doses slightly lower for children. *Fluvoxamine* is also selective serotonin reuptake inhibitor and commonly prescribed for obsessive-compulsive disorder, social anxiety disorder, depression, panic disorder, generalized anxiety disorder, posttraumatic stress disorder and it was helpful for compulsive behaviour and aggression as well as increased prosocial behaviour, in adults with autism, who participated in a double-blind placebo controlled study [41].

In children fluvoxamine is approved for ages 8 to 17 for obsessive-compulsive disorder in initial dose of 25 mg/day at bedtime, increase by 25 mg/day every 4 to 7 days. *Mirtazapine* is an atypical antidepressant in that it possesses both serotonergic and adrenergic activity.

Study suggested that it can be helpful for some children with autism for symptoms including aggression, self-injury, irritability, hyperactivity, anxiety, depression and insomnia. Adverse effects were minimal and included increased appetite, irritability and transient sedation [42]. Although SRIs may demonstrate therapeutic benefits in autism spectrum disorders, many studies suggest the need for additional randomized controlled trials. Also, given the increased awareness of the dangers associated with SRIs induced activation and agitation, the presence of these side effects in the autistic population warrants closer attention to dosage, titration and subject selection issues [43].

No specific SRIs or dose range has been shown to improve a specific autistic symptom although some patients have demonstrated improvements. Benefits with these drugs in treating functional impairments in autism have been observed. Response to therapy and adverse effects are individualized. Current evidence does not support selection of one SRIs over another for any impairment associated with autism [44].

Tricyclic antidepressants

Autistic spectrum disorders is associated with restricted and/or stereotyped interests or behaviours. Tricyclic antidepressants block noradrenaline and serotonin reuptake. Increasing the availability of these neurotransmitters in the central nervous system. Through their impact on serotonin tricyclic antidepressants have been used in the treatment of autistic symptoms and comorbidities in individuals with autism.

Clomipramine is a tricyclic antidepressant that inhibits the reuptake of both norepinephrine and serotonin. It is commonly prescribed for obsessive-compulsive disorder, depression, severe and treatment-resistant depression, anxiety, insomnia, neuropathic pain/chronic pain. It boosts neurotransmitters serotonin and noradrenaline, blocks serotonin reuptake pump, presumably increasing noradrenergic neurotransmission. Notable side effects are: blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhoea, heartburn, unusual taste in mouth, weight gain, fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness, sexual dysfunction, sweating [28]. Clomipramine has been shown to reduce irritability, hyperactivity, inadequate eye contact and inappropriate speech but also further research is required before tricyclic can be recommended for treatment of autistic children [45]. In children and adolescents it is important to monitor patients, particularly during the first several weeks of treatment, also not recommended for use in children age 10.

Anticonvulsants

Anticonvulsants are commonly used in clinical practice in the treatment of autistic children and adults. One in four people with autistic pervasive developmental disorder also have a seizure disorder and usually treated with anticonvulsants such as carbamazepine, lamotrigine, valproic acid. *Lamotrigine* is an anticonvulsant, mood stabilizer, voltage-sensitive sodium channel antagonist and mostly prescribed for: maintenance treatment of bipolar disorder, partial seizures in adults and children age 2 and older, bipolar depression, major depressive disorder, etc. One of the common side effects is rash especially in children ages under 12 and in children taking valproate. Very slow titration may reduce the incidence of

skin rash. A study of lamotrigine in 28 children with autism showed no separation between active drug and placebo on measures of stereotypes, lethargy, irritability, hyperactivity, emotional reciprocity, sharing pleasures and in language and communication, socialization and daily living skills noted after 12 weeks [46-47].

The goal of treatment is to alleviate symptoms and improve functioning. If it starts early intensive programs of education and behavioral therapy, can achieve for the child reaches a certain level of independence and gain some social skills. Available pharmacotherapeutic agents are not sufficiently effective for the treatment of the basic symptoms of autistic spectrum. These can help in alleviating comorbid symptoms as a support to the educational, behavioral and cognitive measures. Commonly treated pharmacologically, are the attention deficit, hyperactivity, mood disorders, (anxiety, depression), obsessive-compulsive symptoms, irritability, aggression, propensity for self-harm and sleep disorders. British study from 2004. year by authors Emerson E. and Hatton C, (from Institute for Health Research, Lancaster University, Lancaster UK), conducted on 68 adults with autism diagnosed before the 1980., with an IQ above 50 is shown following: twelve percent achieved a higher level of independence, ten percent have some friends and are generally employed, but they need support to some extent, nineteen percent have some independence, but generally live at home and they need significant support with the supervision of daily life, forty-six percent require professional, residential care in the specialized institutions for autistic spectrum disorder, with high levels of support and very limited autonomy, while twelve percent have a need for high levels of hospital care.

Electroconvulsive therapy /ECT

ECT is considered as a safe, effective and life-saving treatment in people mainly adults who suffer from affective disorders, acute psychosis and catatonia. There are recent speculations that certain types of autism may be the earliest expression of catatonia and that both disorders have identical risk factors. ECT may improve autism and if started early enough, may prevent further development of autistic symptoms in some children. Researched area that may support the hypothesis that ECT is effective in autism should be pursued [48]. Electroconvulsive therapy should be considered a potentially useful intervention in cases with autistic disorder and a severe comorbid affective disorder.

Acupuncture

Acupuncture which involves the use of needles or pressure to specific points on the body, is used widely in Traditional Chinese medicine and increasing within a western medical paradigm. Also, it has been sometimes used as a treatment aimed at improving autism spectrum disorders symptoms and outcomes. Adverse effects noted included bleeding, crying due to fear or pain of life [49].

Neurofeedback

Behaviour therapy improves communications and behavioral functioning in children with autistic symptoms. Neuro-feedback is a noninvasive approach shown to enhance neuroregulation and metabolic function in autistic spectrum disorder [50].

Biological therapies

There are, so called biological therapies (“somewhat controversial”) such as secretin, oxytocin, gluten and casein free diet, vitamin B6, magnesium, dimethylglycine, hyperbaric oxygenation therapy, *melatonin*. Melatonin administration in autistic spectrum disorders is associated with improved sleep parameters, better daytime behaviour and minimal side effects. Commonly used doses are 1-9 mg at night [51]. Vitamin B6 is being tested as a drug to stimulate brain activity. It has been suggested that impairments associated with autism spectrum disorders (ASD) may be partially explained by deficits of omega-3 fatty acids, and that supplementation of these essential fatty acids may lead to improvement of symptoms [52].

Stimulant drugs

Stimulants have been shown to reduce hyperactivity and improve focus, but they may cause behavioral worsening, weight loss and stereotypes de novo. Drugs such as methylphenidate are prescribed for attention deficit hyperactivity syndrome and have proven sufficiently component in treating the similar symptoms of autism. Methylphenidate is stimulant commonly prescribed for narcolepsy and treatment-resistant depression and attention deficit hyperactivity disorder in children ages 6 to 17 and in adults. It increases norepinephrine and dopamine by blocking their reuptake. The main goal of treatment of attention-deficit-hyperactivity is reduction of symptoms of inattentiveness, motor hyperactivity, and or impulsiveness that disrupt social, school and occupational functioning. The common side effects are: insomnia, headache, tics, irritability, anorexia, nausea, abdominal pain, weight loss, blurred vision, and sometimes life-threatening or dangerous side effects as psychotic episodes, seizures, palpitations, tachycardia, hypertension, rare neuroleptic malignant syndrome or cardiovascular abnormalities. Usual dosage range is 2.5 to 10 mg twice per day. Use in young children should be reserved for specialist of child and adolescent psychiatry and it is not licensed for children age under 6 years [28].

There is evidence that non-stimulant medication atomoxetine is effective. In both cases adverse events may be increased in this group requiring a slower titration and lower end doses. Atomoxetine is selective norepinephrine reuptake inhibitor commonly prescribed for attention deficit hyperactivity disorder in adults and children over 6 years old. Usual dosage is 0.5 to 1.2 mg/kg per day in children up to 70 kg. Recommended target dose is 1.2 mg/kg per day. It is not licensed for children with structural cardiac abnormalities or other serious cardiac problems [28].

Secretin is a treatment that has received much media attention after reports of efficacy from a small open studies but it controlled studies have failed to show any benefit. In autism also same alternative treatments have been used, but none have shown some benefit [53].

Clonidine is antihypertensive and centrally acting alpha 2 agonist hypotensive agent, nonstimulant for attention deficit - hyperactivity disorder. It is commonly prescribed for attention deficit - hyperactivity disorder, Tourette's syndrome, substance withdrawal, anxiety disorders, menopausal flushing etc. It is not licensed for children and children may be more sensitive to hypertensive effects of withdrawing treatment. Children may be more likely to

experience central nervous depression with overdose and might be even exhibit signs of toxicity with 0.1 mg of clonidine. Usual dosage is 0.1 to 0.4 mg per day in divided doses. Clonidine is moderately prescribed drug for controlling hypertensive behaviour in autistic children [28]. Other treatment options are: stem cells therapy, sensory-motor therapy, auditory integration therapy, sensory integration therapy and music therapy.

3. Conclusion

The decision to use medications early in the treatment plan for children with autism may be a long-lasting good decision.

Antipsychotics as drugs are intended primarily for the treatment of adult patients with psychotic disorders, but showed the favorable effects on the symptoms in autistic children, especially risperidone. Risperidone has been approved by the US Food and Drug Administration for the symptomatic treatment of irritability (including symptoms of aggression toward others, deliberate self-injuries, temper tantrums, and quickly changing moods) in children and adolescents with autistic disorder.

Some studies suggest that the earlier use of antipsychotics in autistic children may have protective effect on IQ, which further justifies the use of these drugs in early childhood [18]. Research on the use of risperidone in the treatment of autistic disorders among children in Croatia are rare, given the limited use of risperidone in children younger than 15 years, the question arises about the need to expand the scope of application of risperidone in younger age groups.

Also, it may be worth to explore some alternative treatments, such as behavioural interventions, to try to avoid long-term medications. Also it is important to know that although these psychotropic medications have many beneficial effects, they all come with some risk in terms of adverse effects. It is well established that the early detection and treatment of side effects helps reduce their long-term adverse effects on health. Family members are the ones most likely to recognize those reactions such as: weight gain or fatigue. Also it is need for psychoeducational programs for families or individuals with autism that teach parents about medications and the signs and symptoms of potential side effects.

Atypical antipsychotic agents are widely used psychopharmacological interventions for autism spectrum disorders and among them risperidone has demonstrated considerable benefits in reducing several behavioral symptoms associated with autism spectrum disorders. Although risperidone has several adverse effects, most are manageable or extremely rare. An exception is rapid weight gain, which is common and can create significant health problems [54]. Aripiprazole, a third generation of atypical antipsychotics, is relatively new drug that has a unique mechanism of action different from other antipsychotics. After treatment with aripiprazole children showed less irritability, hyperactivity and stereotypes (repetitive, purposeless actions). Notable side effects must be considered such as weight gain, sedation, drooling and tremor [55].

Autism comprises a clinically heterogeneous group of disorders-named „autism spectrum disorders“ ASD. They share common features or impaired social relationships, impaired language and communications, and repetitive behaviours or a narrow range of interests. Management of an autism involves educational, behavioral and medical therapies to promote conversational language and social interactions while mitigating repetitive self-stimulatory behaviours, tantrums, aggression and self-injuries behaviours. Medications, especially atypical antipsychotics can ameliorate specific symptoms such as aggressive or self-injured behaviour. Children treated early can usually be taught, to varying degrees, to communicate, recognize and respond to social interactions, developing imaginative play, and curb all consuming repetitive self-stimulatory behaviors [56]. Although most children with autism are healthy, evidence is mounting that medical disorders have a significant effect on behaviours, level of functioning and response to educational therapies. Sensory issues including a blunted pain response, inability to tell others when they are uncomfortable and poor tolerance of medical evaluations can lead to suboptimal medication care. The use of medications has increased as newer medications, especially the atypical antipsychotics, which affect both serotonin and dopamine systems and serotonin reuptake inhibitors (SRIs) which modulate the serotonin system, have been studied in children. In 1997. year the National institute of Mental Health Research Units on Pediatrics Psychopharmacology Autism Network investigated the safety and efficacy of drugs for treating the behaviours associated with autism. Some of conclusions are: no medications are autism specific, marked differences exist in the efficacy of drugs in adults vs. children, individual antipsychotics medications within the same class may differ with respect to their potency and side effect profile, affected individuals may respond differently to the same medication, medication management should be integrated into family centered, multi-modal behavioral and educational program. Typically, first line treatment for children with autism include psychosocial treatments and educational interventions with the goal of maximizing language acquisition, improving social and communications skills and extinguishing of maladaptive behaviours. Currently there are no available standard medication treatments, addressing the core symptoms of autism. There are no pharmacological treatments currently approved by US Food and Drug Administration for autism. When used, pharmacological interventions usually target specific symptoms, accompanying the core symptoms, and severely impairing the individual's functioning, often not allowing for „first line“ educational and behavioral interventions to take place (aggression, self-injurious behavior, compulsive rituals, low frustration tolerance with explosive outbursts, hyperactivity). The newer psychotropics, especially the atypical antipsychotics and the selective serotonin reuptake inhibitors (SSRIs) have more benign side effects profiles than older agents [57]. Despite increased support for pediatric psychotropic use, there is a need for more long-term safety and efficacy studies of existing medications and newer, safer, and more effective agents with fewer side effects for the pharmacological treatment of all childhood disorders in which aggression is prominent. Prescription of antipsychotics drugs requires careful monitoring because of the safety risks and the likelihood of a long-term use.

Drug administration should be initiated at low dosages and subsequent dosage changes should be based on tolerability and clinical response. Also children using risperidone may need to be monitored more often than adults.

Author details

Katarina Dodig-Ćurković^{1*}, Mario Ćurković² and Josipa Radić³

*Address all correspondence to: katarinadodigcurkovic@gmail.com

1 University Department of Child and Adolescent Psychiatry, University Hospital Center Osijek and Medical faculty in Osijek, Croatia

2 Family medicine Office, Health Center Osijek and Medical faculty in Osijek, Croatia

3 University Department of Internal medicine, University Hospital Center, Split and Medical faculty in Split, Croatia

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