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PHARMACOTHERAPY OF CHALLENGING BEHAVIOURS IN CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER

FARMAKOTERAPIA ZACHOWAŃ TRUDNYCH W SPEKTRUM ZABURZEŃ AUTYZMU U DZIECI I MŁODZIEŻY

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Abstract

Purpose: The article attempts to answer the question whether a drug-therapy of challenging behaviours in paediatric patients with autism is warranted. If so, how should it be implemented, including mainly the choice of agent, dosage, length of therapy and drug's expected efficacy and safety.

Views: Challenging behaviours (CB) are common problems in discussed population that additionally aggravate the level of individual functioning. When a drug-therapy of CB is concerned, there is an alarming tendency of increasing antipsychotic use and polypharmacy which exceeds the body of evidence. Out of many agents studied, only risperidone and aripiprazole exhibit established evidence for effectiveness and safety during a short-term use. Research shows comparable efficacy of these drugs and several particularities in secondary outcomes profile. It is established that in pedopsychiatric patients with autism and challenging behaviours both agents equally increase body weight in a statistically significant way; however, risperidone is associated with bigger risk of metabolic changes and extrapyramidal symptoms than aripiprazole. In addition, risperidone significantly augments the risk of hyperprolactinaemia while aripiprazole exhibits no such an action. Aripiprazole, on the other hand, is linked with higher frequency of sedation.

Conclusions: Drug-therapy of CB in autism should be considered only as an addition to comprehensive interventions when behavioural and psychosocial measures lack effectiveness. The safety/efficacy profile in long-term use remains undetermined and needs further studies.

Key words: autism, pharmacotherapy, challenging behaviours.

Streszczenie

Cel: Artykuł stanowi próbę oceny zasadności farmakoterapii zachowań trudnych w autyzmie u dzieci i młodzieży. Omawiane są w szczególności wybór leku i dawkowanie, długość terapii i jej potencjalna skuteczność oraz profil działań niepożądanych.

Poglądy: Trudne zachowania są często obserwowane u dzieci i młodzieży, u których rozpoznano autyzm. Dane dostępne w literaturze wskazują, że są one przyczyną wzrostu zastosowania leków przeciwpsychotycznych i polifarmakoterapii. Badania kliniczne z udziałem pacjentów z trudnymi zachowaniami w przebiegu autyzmu dotyczyły wielu leków. Jednak dotychczas tylko w przypadku arypiprazolu i risperidonu udowodniono w sposób zgodny z zasadami medycyny opartej na dowodach skuteczność i bezpieczeństwo. Dane wskazują na podobne wyniki obu leków w zakresie odpowiedzi na leczenie, a także na kilka różnic dotyczących skutków działań niepożądanych. Ryzyko znaczącego przyrostu masy ciała u dzieci i młodzieży z rozpoznaniem autyzmu i zachowaniami trudnymi w wyniku terapii zarówno arypiprazolem, jak i risperidonem jest porównywalne. Risperidon jednak częściej niż arypiprazol wywołuje zaburzenia metaboliczne i objawy pozapiramidowe. Dodatkowo w sposób istotny statystycznie zwiększa stężenie prolaktyny w omawianej populacji pacjentów. Arypiprazol jest natomiast związany z częstszym występowaniem sedacji.

Wnioski: Farmakoterapia trudnych zachowań w autyzmie u dzieci i młodzieży powinna być rozpatrywana jedynie jako forma dodatkowego wsparcia wielokierunkowego podejścia terapeutycznego. Jej zastosowanie wydaje się zasadne tylko wtedy, gdy inter-

wencje behawioralne i ukierunkowane na trening umiejętności społecznych wykazały niedostateczną skuteczność. Efektywność i skutki uboczne podczas długoterminowych terapii arypiprazolem i risperidonem nie zostały określone zgodnie z medycyną opartą na dowodach i wymagają dalszych badań.

Słowa kluczowe: autyzm, farmakoterapia, trudne zachowania.

INTRODUCTION

Autism spectrum disorder (ASD) encompasses the range of neurodevelopmental chronic disorders. Affected individuals exhibit impaired development of relations, impaired communication skills and restricted, repetitive behaviours. Its prevalence has been suggested to increase lately, estimating about 1% worldwide. It is more common in male individuals and associated with a substantial co-morbidity (> 70%) and the occurrence of non-core symptoms (53%) [1, 2] (Tables 1 and 2).

Preceding classifications, i.e. International Statistical Classification of Diseases and Related Health Problems,10th Revision, and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, require the presence of three core symptoms before the age of three for the diagnose of an autistic disorder and include it between Pervasive Developmental Disorders along with, for example, Asperger Syndrome [3, 4]. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and International Statistical Classification of Diseases and Related Health Problems, 11th Revision, comprise the aforementioned conditions in a single diagnose of broad clinical presentation, i.e. Autism Spectrum Disorder. It is characterised by the duet of symptoms: impaired social development (inseparably connecting communication and socialisation) and the limitation of spontaneous activities which do not necessarily need to be visible in early childhood [5, 6]. In presented paper terms autism and ASD are used interchangeably and refer to DSM-V diagnosis whereas autistic disorder stands for the diagnosis in accordance with DSM-IV (TR). Despite classification evolvement and differences, an emerging need to recognise and treat co-existing psychiatric symptoms seems to be essential [2, 7].

To date, no drug-therapy of autism core symptoms has been proven to be effective [8]. Available guidelines recommend instead parent-mediated, behavioural and psychosocial interventions to be implemented as early as possible [7]. However, research shows increasing rates of psychotropic use (64%) and simultaneous use of multiple psychotropic agents (35%) among children with ASD [9]. It is noteworthy that antipsychotics out of other drug classes used in autistic population are associated with the highest numbers of days treated (2/3 of the year on average) and are one of the most commonly prescribed drugs (Table 3) [10]. Meanwhile, their safety profile in de-

Table 1. Selected psychiatric co-morbidities (of note in paediatric and adult population with autism spectrum disorder (ASD)) (10-17)

Mental health condition	Prevalence in population with ASD
Attention deficit hyperactivity disorder	38-60%
Anxiety disorder	19-40%
Conduct disorder	7-15%
Intellectual disability	14-47%
Bipolar disorder	7%
Epilepsy	9-22%
Schizophrenia	2-35%
Depression	1-30%

Table 2. Frequent (reported ≥ 3 times a week) problems in children and adolescents with autism spectrum disorder (ASD) (2)

Symptom	Prevalence in paediatric population with ASD
Eating problems	58%
Sensory issues	57%
Temper tantrums	48%
Sleep problems	45%
Hyperactive periods	43%
Anxiety	43%
Toileting problems	31%
Aggression to others	22%
Reluctance to separate	15%
Self injury	14%

Table 3. Use prevalence of selected psychotropic medication by class (of note, in paediatric and adult population with autism spectrum disorder (ASD)) (10)

Drug class	Use prevalence in population with ASD
Antidepressant	31%
Stimulants	31%
Antipsychotics	30%
Anxiolytics	15%
Hypotensive agents	12%
Anticonvulsants	10%

veloping population is considered most detrimental and distal health outcomes still poorly understood [18, 19].

CHALLENGING BEHAVIOURS IN AUTISM

"Challenging behaviours" (CB) is the term designed to describe culturally abnormal behaviours in children with learning disabilities that threaten the health of the person or others [20]. National Institute for Health and Care Excellence (NICE) guidelines include CB as possible co-existing symptoms of autism comprising, for example, self-injurious behaviours, aggression towards others (screaming, shouting, kicking, biting) and inappropriate sexualised behaviour [7]. In the pharmacological research literature of autism, these behaviours are referred to as "irritability" or "aggression." This is based on one of the most commonly used drug research measures, i.e. Aberrant Behavioural Checklist – Irritability subscale (ABC-I). The scale includes, among others, mood changes, inappropriate crying and screaming, temper tantrums, self-injurious behaviours (SIB) and aggression towards others [21].

CB seem to pose one of the most urgent and difficult tasks to combat in autistic population due to a few reasons. Firstly, CB are relatively common. A study of almost 1400 children diagnosed with ASD reported that ca. 35% were currently demonstrating definite aggression [22]. Secondly, they appear to diminish quality of life to a great extent. Enough to mention, interfering with the course of core symptoms therapy, decreasing the level of family life satisfaction, causing educational withdrawal, being the most common reason for admission to foster care units and finally resulting in potential physical harm to self or others [2, 22]. Moreover, there is no established measure for detection whether aggressive CB are the result of the intrinsic traits of an autistic individual and require biological approach or are rather the consequences of external factors (e.g. changes in the routine, excessive stimulation or inadequate care-givers conduct), demanding counselling and proper adjustments in the patient's life. Eventually, it is still undetermined to what extent these two factors may contribute simultaneously [23]. State recommendations regarding the CB treatment in autism are limited to the possibility of short-term use of risperidone (RIS) when a conduct disorder is diagnosed in children over the age of 5 and adolescents with intellectual disability. British and American guidelines point out that ideally autistic children and adolescents would be treated with non-pharmacological interventions (Table 4). However when CB are too severe to implement behavioural interventions or failed to respond to them and are constituting major interference with family, social or educational functioning, drugs may be recommended as an accessory measure [7, 24].

PURPOSE AND METHODS

The present paper aims to simplify clinical decision making regarding pharmacotherapy targeting CB in children and adolescents diagnosed with autism.

The data was gathered in an informal and subjective manner.

The search of Pubmed/MEDLINE database was conducted using pubmed advanced search option for original papers (Randomised Controlled Trials, open-label and prospective trials), Systemic Reviews and Meta-analysis as well as review of references. Retrospective trials, case series and single case reports were excluded as well as papers which had a full text version in a language other than English. Searched terms included among many others: "autism", "autism spectrum disorder", "autistic disorder", "Asperger syndrome", "drug therapy", "pharmacotherapy", "antipsychotics", "polypharmacotherapy", "irritability", "aggression", "aripiprazole", "risperidone", "adjunctive therapy", "children", "adolescents", "comorbidity". Authors aimed to limit their search to papers published after 2000; however, some exceptions have been made due to the studies' originality.

Table 4. First-line approach for challenging behaviours (5, 15)

No	Step	What to establish?
1	Exclusion of identifiable or curable causes or both	• Health and mental health conditions, environmental problems, behavioural problems
2	Careful assessment of challenging behaviours	• Triggers and patterns of behaviour • Needs that the child attempts to fulfil • Consequences of behaviour. Does maladaptive reinforcement occurs?
3.	Implementation of psychosocial intervention	• Identify target behaviour • Focus on outcomes linked to quality of life • Assess and modify environmental factors • Clearly define intervention strategy that takes into account the developmental level and coexisting problems of the child or young person • Specify timescale to meet intervention goals • Measure systematically target behaviour before and after intervention • Apply interventions consistently in all child's environments • Ensure agreement among parents, carers and professionals in all settings about how to implement the intervention

The search, removal of duplicates and selection of searched papers were conducted manually in a non-systematic fashion. Therefore, numbers of excluded papers on title, abstract and full text level as well as the total number of excluded papers were not elicited.

RESULTS

The majority of trials found featured study design deficiencies, such as small sample design, short study period, subject heterogeneity or, finally, showed a substantial rate of side effects. In consequence, the evidence of haloperidol, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine and naltrexone use in autistic patients was estimated as insufficient. It was recognised that only risperidone and aripiprazol are considered to have established evidence of efficacy and safety, and they are depicted hereafter [25-35].

Risperidone

Risperidone (RSP) is a second-generation antipsychotic acting as a dopaminergic and serotoninergic antagonist. It was suggested that the affinity for serotonin 5-HT_2 receptors is responsible for its efficacy in diminishing aggressive behaviours. Its relative strong affinity to dopamine D2 receptors and serotonin 5-HT_2C receptors probably mediates metabolic and endocrine side effects (SE) [36].

RSP was approved to treat irritability in autistic children and adolescents aged 5-16 years by the Federal Drug Association (FDA) in 2006, supporting its use at a dose range of 0.5-3 mg/day [37]. Several short-term randomised controlled trials demonstrated its efficacy in treating challenging behaviours [38-40].

The Research Units on Paediatric Psychopharmacology Autism Network (RUPP-AN) trial included 101 participants aged 5-17 years diagnosed with autistic disorder according to DSM-IV. It was divided in three phases. The first one was an 8-week RCT; the second – a 4-month open-label extension phase, and the last one – a 2-month placebo-controlled discontinuation phase. The short-term phase, during which RSP was flexibly dosed from 0.5 to 3.5 mg/day, resulted in a significant decrease in the mean Aberrant Behavioural Checklist – Irritability (ABC-I) subscale and a significant improvement on Clinical Global Impression-Improvement (CGI-I) scale. Authors claim that the RSP-treatment was well-tolerated; most of the SE were mild and resolved within a few weeks. Increased appetite, fatigue, somnolence, dizziness and increased saliva were more common in the RSP group than in the placebo group. Additionally, weight increase was associated with the RSP therapy with an average weight gain of 2.7 kg. Although clinicians' neurological assessment did not reveal treatment-emergent EPS, care takers reported tremor, dyskinesia, rigidity, akathisia and difficulty swallowing in 21 instances, while in a placebo group, it occurred 8 times during the trial [38].

Another 8-week RCT included 79 children aged 5-12 years and included patients diagnosed with any Pervasive Developmental Disorder of DSM-IV classification. The RSP solution (0.01-0.06 mg/kg/day) was administered to intended to treat (ITT) group subjects in a flexible mode. Patients who were taking RSP exhibited a significantly greater mean decrease on the ABC-I subscale. The most frequently reported SE were somnolence, upper respiratory tract infections and increased appetite. It may be worth mentioning that sedation resolved by the end of trial in the majority of patients. EPS were notified by 27% of the RSP treated subjects; however the majority was mild and transient. Finally, control group patients experienced significantly greater weight increase (+2.7 kg vs. +1.0 kg), pulse rate and systolic blood pressure than placebo group [39].

Pandina *et al.* (2007) extracted the data from the study described above solely on patients diagnosed with autistic disorder (DSM-IV). Study supported the results of the stem trial in regard of both efficacy and safety of the RSP treatment [40].

Aforementioned studies used flexible dose pattern of maximum 3.5 mg/day and did not provide information about prolactin (PRL) level changes. A RCT by Kent *et al.* compared the benefit of low-dose RSP (0.125-0.175 mg/day) and high-dose RSP (1.25-1.75 mg/day) adjusted to the participant's weight and found significant change in ABC-I subscale only in a high dose group. It has also depicted the dose-dependency of the following side effects: weight gain, somnolence and prolactin level increase [41].

Data from RUPP trial also enabled to preliminary determine that benefits of the RSP therapy may be expected if the baseline symptom burden ranges from moderate to severe (measured on ABC-I subscale and CGI scale) [42].

Less evidence supports the RSP's efficacy and safety in long-term use. The open label and discontinuation phase of the RUPP study showed the maintenance of positive response. The discontinuation after 6 months was associated with a rapid relapse in most subjects [43]. One open-label 6-month extension study and one naturalistic study (a 21 month follow up of RUPP trial participants) provided preliminary evidence for clinical benefit maintenance or even further improvement during continuation of the RSP treatment. However, weight gain, excessive appetite and enuresis were the biggest concerns [44, 45].

As far as the safety of RSP administration in autistic patients is concerned, there is emerging evidence of remote endocrine and metabolic consequences. For example, asymptomatic hyperprolactinaemia in adolescents with ASD was reported to be associated with diminishing of sexual functioning and decreasing of lumbar spine bone mineral

density [46, 47]. In addition, one prospective study on 168 ASDs patients suggests the association of the RSP long-term treatment with the developing of insulin resistance and increased leptin levels which are known to precede metabolic syndrome and cardiovascular complications. Observed metabolic disorders appeared in a dose- and duration-dependent manner which, along with evidence from other studies, implicates vigilance while prescribing RSP during longer periods [48].

There is also an apparent research tendency to establish the agents which have the potential to augment the RSP therapy in autistic patients. Although replication of results is warranted, several of them showed preliminary efficacy and safety in this matter, i.e. pentoxyfilline, N-acetylcysteine, memantine, pioglitazone, celecoxib and amantadine. However promising, available data do not warrant any clear recommendations of polypharmacotherapy [49-55].

Aripiprazole

Aripiprazole (ARI) is a second generation antipsychotic, having a unique partial agonistic action at dopamine D2 receptors and serotonin 5HT-1A receptors, and an antagonistic action at serotonin 5HT-2A receptors. It is believed to balance dopaminergic processes and, in consequence, decrease the risk of SE associated with pure blockade of dopamine receptors, such as hyperprolactinaemia and metabolic changes [56, 57].

ARI was registered by the FDA in 2009 to treat irritability in autistic children and adolescents aged 6-17 years, using a dose of 2-15 mg/day [58].

Two pivotal RCTs proved ARI efficacy and safety in treating challenging behaviours in children and adolescents with the diagnosis of autistic disorder according to DSM-IV (TR).

A fixed-dose 8-week study randomly assigned 218 participants to one of the four groups, i.e. ITT groups, which were administered 5, 10 or 15 mg/day, and a control group. All doses administered resulted in a significant change in the ABC-I subscale and GCI-I score at the endpoint. In fact, positive response was observed as early as after the first week of treatment. Dose-dependent efficacy was not reported. Ca. 84% of participants in each group reported at least one SE during the trial. The most common SE were sedation, fatigue and vomiting. Fatigue and sedation showed numerical association with higher dosage, however, without statistical significance.

EPS were observed in about 22% of ITT participants and 12% in placebo group. They were reported to be of mild severity but no data on their natural course and response to treatment were shared. It is noteworthy that all the ARI treatment groups gained body weight to a statistically greater extent than placebo-administered subjects (mean weight change in ITT groups was +1.5 kg vs. placebo group +0.3 kg) [59].

The second 8-week RCT was conducted on 98 patients who were either administered ARI in a flexible dose manner or placebo. As in the previously described study, the significant effect of the ARI treatment in participants who were on active medication was seen already after the first week. At week 8th, both the mean CGI-I and ABC-I subscale scores significantly improved as compared with placebo. The rate of SE was similar as in the previous study. Three most common SE were fatigue, somnolence and vomiting. Participants of the ITT groups exhibited no clinically relevant changes in vital signs or electrocardiogram abnormalities. As in the study by Marcus *et al.*, ARI was associated with a significant weight gain (+2 kg at week 8th on ARI vs. 0.8 kg on placebo) [60].

A pooled analysis of the safety data from these two RCTs revealed that ARI had a minimal effect on lipid and glucose blood levels and was associated with a significant decrease of PRL levels [61]. Short-term studies by Owen et al. and Marcus *et al.* were followed by a 52-week open-label study. It included 330 participants who were prescribed ARI in a flexible mode for a year. They were divided in three groups, i.e.: 1) participants treated with ARI in a short-term trial (prior ARI); 2) participants of control groups (prior placebo); and 3) *de novo* participants. *De novo* and prior placebo groups achieved improvement in the ABC-I subscale early during the study and maintained it to week 52nd. At the endpoint, significant amelioration was observed also in a CGI-I score in these groups (the majority of participants were assessed as much improved or very much improved) in comparison with their condition before therapy. Previously achieved improvement in 'prior ARI' participants was maintained based on the results from both scales. SE occurrence was similar to the antecedent short-term trials (86%). The common SE included increased body weight (which reached a plateau at 3-6 months), vomiting, nasopharyngitis and increased appetite. EPS were present in 14.5% of subjects [62].

The *post-hoc* analysis of previously reviewed trial was conducted in order to establish risk factors for secondary outcomes. It suggests greater susceptibility to pronounced weight gain and somnolence in the individuals who were antipsychotic naïve at the start point. Authors also point out that younger subjects and those with a higher baseline body weight may be prone to gain more weight during ARI treatment [63].

Risperidone vs. aripiprazole

Several studies comparing these agents demonstrated the similarity of their efficacy in the short-term use [64-66]. In general, the tolerability of both active compounds was alike. Somnolence/Sedation effects were the most frequently reported SE [65]. No significant differences between RSP and ARI were observed in treatment-emergent weight gain [64, 65].

However, substantial variances in favour for ARI were calculated for the occurrence of hyperglycaemia, EPS and hyperprolactinaemia [65, 66].

Side effects of the agents described above are in accordance with prevailing knowledge on their pharmacodynamics in children and adolescents with the exception of equal body weight gain during the ARI and RIS short-term treatment. The reason for this outcome remains yet to be established [67, 68].

Assessment

Although RSP and ARI seem to be agents with the biggest evidence supporting their efficacy and safety in the treatment of CB in autistic children and adolescents, data depicted above should be interpreted with caution. Most studies are short-term trials, which can result in the underestimation of SE. Both RCTs of ARI and a RCT by Shea *et al.* of RSP were industry-funded. Moreover, a substantial overlap of participants in studies by Marcus *et al.* and Owen *et al.* cannot be excluded. Longer-term studies followed-up participants from short-term RCTs who showed good tolerability and response to treatment. This has a potential to bias the secondary outcome profile as the sample was lacking individuals who developed treatment-emergent symptoms. In addition, longer-term trials used open-label method, which is questionable for establishing drug efficacy.

Furthermore, the majority of RCTs included patients with the diagnosis of autistic disorder according to DSM-IV (TR) with the exception of patients with other pervasive developmental disorders which are presently encompassed in one diagnose of ASD. Clinicians encounter scarce literature describing the use of second generation drugs in patients with Asperger syndrome or high-functioning autism [69].

Taking the aforementioned doubts into consideration, this paper underscores concerns regarding side effect profile of antipsychotics used in the therapy of CB in paediatric autistic population. It seems that the body of evidence does not support chronic and common use of antipsychotics in these cases. The urgent need for further studies, preferably carried out independently of pharmaceutical companies, to determine distal risks of these medications and their therapeutic value is therefore prominent. Additional trials may be also helpful to establish clinical and genetic risk factors for side effects and drug-refractoriness. More research is also necessary to establish safety and efficacy profile in different clinical presentations on the autism spectrum, which would correspond to current diagnostic classification.

LIMITATIONS

Although the authors' intention was to provide an extensive review of the available data, this paper is limited by the non-systematic fashion of search and only one database searched.

CONCLUSIONS

1. Challenging behaviours are common and cause burdensome problems among children and adolescents with autism. The first-line approach includes managing possible environmental factors and treating co-existing conditions, careful assessment, psychosocial and behavioural interventions.
2. If first choice approach is insufficient or impossible to implement due to symptom severity, time-limited drug-therapy should be considered.
3. It is recommended that pharmacotherapy are used in conjunction with a total treatment programme (behavioural, psychosocial) as it is not curative and relapse is expected at discontinuation.
4. Risperidone and aripiprazole appear to be agents of the strongest evidence of efficacy and safety. In view of their similar efficacy, the choice between these two drugs should be driven by clinical consideration of patient characteristics and needs.
5. There is not yet an established evidence of the efficacy or safety for any form of augmentation of the aforementioned drugs.
6. The following steps are recommended in executing pharmacotherapy (adapted from NICE, 2013):

- Identification of the target behaviour and decision on the measure to monitor effectiveness;
- Discussion on the potential benefit, side effects and course of the treatment with a patient and his/her parents or care-givers;
- Baseline investigations: weight, height, waist and hip measurements, pulse and blood pressure, fasting blood glucose, glycosylated haemoglobin, blood lipid and prolactin level, assessment of nutritional status, diet, assessment of any movement disorder and level of physical activity;
- Start-up with a low dose, slowly titrating upwards, and usage of minimal effective dose (CAVE studied doses did not exceed 3.5 mg/day and 15 mg/day for risperidone and aripiprazole respectively);
- Routine and proactive monitoring of compliance, effectiveness and secondary effects including clinical (weight, EPS, etc.) and biological (glucose, lipids, prolactin, etc.) assessments;
- Revision of the effects after 3-4 weeks and discontinuation if there is no clinically important response at week 6th;
- Preparation of a plan for stopping treatment (including a relapse plan) after week 8th.

Conflict of interest/Konflikt interesu

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