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Review article

Aripiprazole in treatment of Gilles de la Tourette syndrome – New therapeutic option

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ABSTRACT

Aripiprazole is a dopamine D2- and serotonin 5-hydroxytryptamine $(5\text{-HT})_{1A}$ receptor partial agonist and 5-HT_{2A} receptor antagonist primarily used for the treatment of schizophrenia, bipolar disorder or depression with psychotic ideation. However, recently a number of new possible indications have been suggested, among them Gilles de la Tourette syndrome (GTS). In two randomized, double-blind, placebo-controlled studies in children and adolescents with GTS has been confirmed the efficacy of aripiprazole in tic reduction. In comparison to other neuroleptics, aripiprazole seems to be similarly effective. What is more, the number and profile of possible adverse effects is also favorable. As a consequence, aripiprazole had been registered by Food and Drug Administration (FDA) for the treatment of tics and represents new therapeutic option in treatment of GTS.

1. Introduction

Gilles de la Tourette syndrome (GTS) is a neuropsychiatric disorder affecting children and adults. The number of children aged 5–18 with GTS in Poland is estimated to be around 50 000. The main symptoms of this disease are motor and vocal tics. Tics are sudden, non-rhythmic, repetitive involuntary movements or vocalizations. Tics are found in all GTS patients. 80–90% of individuals with GTS are diagnosed with psychiatric comorbidities, the most frequent are: attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety disorders, depression, autism spectrum disorders, behavioral disorders and oppositional defiant disorder (ODD). The exact cause of the disease is unknown, but genetic causes seem to play the main role. Therefore, only symptomatic treatment is available. Nevertheless, the majority of patients do not require any therapeutic intervention, because symptoms are benign. Only if tics are affecting significantly everyday life and social functioning, behavioral or pharmacological treatment is introduced. The most commonly used drugs are first-generation antipsychotics (haloperidol, pimozide, fluphenazine) and second-generation antipsychotics (aripiprazole, sulpiride, tiapride, risperidone, ziprasidone), clonidine, topiramate, tetrabenazine. Behavioral interventions based on the habit reversal technique (HRT) or exposure prevention response therapy are treatment of choice, but due to limited access they are not always available. Rescue and still experimental therapy remains operation of deep brain stimulation (DBS).

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2. Influence of aripiprazole on tics

Efficacy of aripiprazole among children and adolescents with GTS was confirmed in two randomized, double-blind, placebo-controlled studies published in 2013 and 2017 [1,2]. In both studies drug efficacy was proved by significant tic reduction in Yale Global Tic Severity Scale – Total Tic Score (YGTSS-TTS, range: 0–50) and Clinical Global Impression Scale (CGI). TTS is used to evaluate tic severity during the last week before clinical examination and it contains the following parts: number, frequency, intensity, complexity and interference with daily activities (all items ranged 0–4; total range: 0–25 for motor and vocal tics). CGI measures global improvement rated on a 7-point scale. CGI scores from 1 (very much improved) through to 7 (very much worse) and describe the change or improvement (if any) in different aspects of global functioning. Sallee et al. investigated the effect of aripiprazole among 133 patients aged 7–17 with at least moderate tics affecting daily life (TTS ≥ 20). Patients were randomized to three therapeutic groups: low-dose (<50 kg – 5 mg/day; >50 kg – 10 mg/day), high-dose (<50 kg – 10 mg/day; >50 kg – 20 mg/day) and placebo. The study lasted for 8 weeks. Both low and high drug doses were effective in tic reduction in TTS, accordingly for 6.3 and 9.9 (after adjustment to placebo effect), in comparison to placebo group. This change was statistically significant already in the first week of treatment. Tics were reduced in average by half (45.9% in low-dose group and 54.2% in high-dose group). This effect was pronounced both for motor and vocal tics and impact on daily functioning (YGTSS Impairment of Global Functioning Scale). The vast majority of patients improved much or very much (CGI, 69% from low-dose group, 74.3% from high-dose group) that was also adequate to TTS results surpassing 25% tic reduction. In approximately 50% of cases improvement higher than 50% was reported (YGTSS-TTS: 40.5% and 57.1% of patients). The use of aripiprazole leaded to 5–6 higher dose-dependent chance of clinical improvement in comparison to placebo therapy. NNT, number needed to treat, in high-dose group was 3 and in low-dose group 5. In all study endpoints the efficacy of drug was dose-dependent and higher in high-dose group compared to low-dose group [1].

The second randomized, double-blind, placebo-controlled, multicenter study was conducted in South Korea and included 61 children and adolescents aged 6–18 with TTS ≥22 [2]. The average tic reduction in TTS (combined motor and vocal tic score) after 10 weeks of treatment was of 5.3, after adjustment to placebo-effect (with average tic reduction by 52.9% comparing to baseline TTS). Nevertheless, the reduction of motor tic severity subscale was not statistically significant. Group treated with aripiprazole improved much or very much in CGI as to placebo group (66% vs. 45%). Differently to study from 2017, drug-dose was not previously established, but was evaluated in relation to clinical response. The average dose of aripiprazole used in this trial was of 11.0 mg/day [2].

3. Efficacy of aripiprazole in comparison to other therapeutic options

In both studies tics were reduced for more than 50%. This gives even better clinical outcome than on treatment with other widely-used, symptomatic drugs (haloperidol, pimozide, risperidone, ziprasidone, clonidine, guanfacine), which efficacy was evaluated in randomized, double-blind, placebo-controlled studies. The main tic reduction achieved in those trials ranged between −25.8% and −39.0% [3–9]. In one randomized, head-to-head trial, the goal was to compare the efficacy of aripiprazole and risperidone. The study was carried out among 60 children and adolescents younger than 18 and similar efficacy was registered for both drugs [10]. It can therefore be concluded, that aripiprazole is at least as efficient as other neuroleptics used in the treatment of tics.

Interesting is comparison of aripiprazole and behavioral therapy with regard to tic reduction. CBIT, comprehensive behavioral intervention for tics, mostly based on HRT, when compared to control therapy (psychoeducation and support therapy), reduced tics by 4.1 after adjustment to placebo effect (7.6 vs 3.5). 53% of children and adolescents and 38% of adults reported much or very much tic reduction in (CGI) [11,12]. Although no clinical trials were conducted in order to compare directly aripiprazole with behavioral therapy, the medication seems to be slightly more beneficial in tic reduction than behavioral interventions based on CBIT/HRT.

4. Placebo effect

It is worth mentioning the sound placebo effect present in GTS. In study by Sallee et al. placebo resulted in tic reduction of 7.1 according to TTS that corresponded to an average of 23.1%. 54.8% of patients experienced amelioration higher than 25%, while 16.7% reached and upswing higher than 50% (TTS) and 38% of patients reported very pronounced or pronounced positive outcome (CGI) [1]. In the study by Yoo et al. placebo effect leaded to tic reduction by 9.6 (TTS) and in average 32.6% in comparison to baseline rating, in 44.8% of patients therapeutic effect was estimated to be good or very good (CGI, score 1 or 2). Although partially those results could be explained by natural waxing and waning nature of tics, the significance of placebo effect in GTS patients should be taken into great consideration in the treatment of tics. Practical implications are that results of open, uncontrolled studies should always be interpreted critically, bearing in mind the placebo effect.

Likewise, clinically significant seems to be nocebo effect. Adverse events of placebo were registered in 71.4% [2] and 40.9% of patients [1] in study conducted by Yoo et al. Total number of adverse events was even higher in placebo group than in those receiving aripiprazole (57 vs 56) [2].

5. The influence of aripiprazole on psychiatric comorbidities

Sallee et al. detected positive impact of aripiprazole on symptoms of ADHD, but only in the high-dose group. Better results in SNAP-IV Scale (Swanson, Nolan and Pelham Questionnaire-IV) were reached in terms of concentration, hyperactivity and impulsivity. No significant impact was registered when it comes to OCD (Y-BOCS Scale, Yale-Brown

Obsessive Compulsive Scale), depression (CDRS-R Scale, Children's Depression Rating Scale Revised) and the level of anxiety (PARS Scale, The Pediatric Anxiety Rating Scale). The results of this randomized, double-blind, placebo-controlled trial are contrary to the study conducted in Germany, that showed significant positive influence of aripiprazole on OCD and tendency to improve depression, anxiety and ADHD symptoms. However, this was an open, uncontrolled study, that was carried out on a small group of patients ($n = 44$) and only among adults [13]. In study by Yoo et al. no evaluation of psychiatric comorbidities was conducted [2].

6. Side effects

Sallee et al. came to the conclusion, that use of high dose of aripiprazole lead to 5.5 higher risk of adverse event that cause drug dechallenge, while administration of low doses is not related to such risk. In group of patients treated with aripiprazole 12 patients were not able to finish the study (8 of them due to adverse events), the vast majority of which were children with body mass <50 kg and receiving high dose of the drug, 10 mg/day. In study by Yoo et al., none patient dropped out of the study as the consequence of side effects. The majority of patients experienced at least one side effect (65.9% and 75.6% [1], and 75.0% [2]). The most common ones were: sedation, sleepiness, tiredness and increased appetite [1], moreover, nausea, headache, infections of upper respiratory tract, weight gain [2]. In contrast to other neuroleptics, aripiprazole did not provoke hyperprolactinemia what is probably related to partial agonistic impact of aripiprazole on dopaminergic receptors [2]. The majority of adverse events were mild or moderate, no severe side effect or death was detected. Extrapyramidal complications were rare or clinically insignificant [2] and were dose-dependent [1]. Sallee et al. reported them in 13.3% of high-dose group and the most frequent symptom was akathisia [1].

7. Dosing scheme

During the first two days aripiprazole is administered in dose 2 mg/day, during the days 2–7 the dose is increased to 5 mg/day and then, depending on clinical response, the dose could be increased 5 mg/week [1,2]. It is estimated, that an average effective dose is 5 mg for children with body mass <50 kg and 10 mg >50 kg. The maximal dose used in controlled trials was 20 mg/day [1,2]. In open studies, however, the dose up to 30 mg/day was used [13].

8. Summary

1. The efficacy of aripiprazole in GTS was confirmed in two short-term, randomized, placebo-controlled, multicenter clinical trial conducted among children and adolescents.
2. Aripiprazole reduces tics by 50% in average in approximately half of patients.
3. 2/3 of patients with GTS improve much or very much.
4. The most frequent side effects are sedation, sleepiness, tiredness and increased appetite.

9. Conclusions

1. Aripiprazole is an efficient drug reducing tics in GTS among children and adolescents.
2. Aripiprazole has level B recommendation and from 2014 is registered by FDA in the treatment of GTS.
3. Aripiprazole is safe and well-tolerated drug in tic treatment.

Conflict of interests

Piotr Janik – paid expert testimony for Adamed company to register aripiprazole for the treatment of tics in Gillesa de la Tourette syndrome.

Natalia Szejko – none.

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