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Pharmacotherapy in Autism Spectrum Disorder: How, When and Why

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Abstract: *Psychiatric comorbidities are more frequent in ASD population if compared to neurotypical development peers. Several studies reported that nearly three-quarters of children and adolescents with ASD also have another psychiatric condition that contributes to worsen their clinical condition and has a negative impact on the quality of life of the entire family. The treatment of ASD symptoms and comorbidities is based on a multimodal approach of behavioural, educational and pharmacological treatments. Pharmacotherapy is employed when other therapies are unable to control the symptoms and are often useful to increase the patient's compliance with other psychoeducational treatments. About 50% - 60% of children with ASD undergo drug therapy to reduce behaviour problems and comorbidities, and polypharmacy is common in about 30%-40%. The use of drug therapy increases with age and antipsychotics, psychostimulants and antidepressants are among the most widely used drugs. Despite the high frequency of psychotropic medication in this population, there is scarce evidence in the literature, supported by studies often limited by a low sample size, a heterogeneous population and without a control group. Large RCT on more commonly prescribed psychotropic drugs in ASD children are needed for a better evaluation of risks and benefits in ASD pediatric patients.*

Keywords: *ASD; comorbidities; pharmacotherapy.*

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Introduction: Autism Spectrum Disorder, prevalence and DSM-5 classification

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder, characterized – according to DSM-5 criteria – by persistent deficits in social interaction and communication, and a limited and stereotypical pattern of interests (American Psychiatric Association, 2013). The causes of this condition, which currently has a prevalence of 1 in 59 children (Baio et al, 2018) are still under study. Genetics play a key role in its aetiology, together with environmental factors affecting early neurodevelopment (Yenkoyan et al., 2017). Given their atypical neuronal development, ASD patients may present peculiar cognitive profiles, characterized by aspects of executive dysfunction and changes in perception and information processing (Lai et al., 2014). Developmental atypia lead to compromised communicative, socio-relational, and behavioral skills - often independent from one another -, with different levels of complexity and severity, and variable clinical presentation (Carter et al., 2005). The word "spectrum" emphasizes the idea that the symptoms in the clinical presentation of ASD are distributed based on a continuous severity gradient, allowing us to group together very different clinical cases (Ring et al., 2008). With this in mind, we can include that high-functioning autism (HF-ASD) and Asperger Syndrome (AS) (American Psychiatric Association, 2000) – currently both classified as ASD with severity level 1, according to the DSM-5 – are among the most complex and multifaceted phenotypes. These two forms are characterized by fluent but pragmatically defective language, and normal cognitive development (IQ≥70). Even with normal linguistic and cognitive skills, these individuals show deficits in social functioning (Covalciuc, 2019) due to difficulties with Theory of Mind (ToM), identification and interpretation of emotions, and empathy (Baron-Cohen et al., 1985; Tine & Lucariello, 2012; Peterson et al., 2016).

Psychiatric Comorbidities in Autism Spectrum Disorder

Psychiatric comorbidities are more frequent in ASD population if compared to neurotypical development peers. Several studies reported that nearly three-quarters of children and adolescents with ASD also have another psychiatric condition that contributes to worsen their clinical condition and has a negative impact on the quality of life of the entire family (Joshi et al., 2010; Hansen et al., 2018). There are extremely heterogeneous neuropsychiatric conditions that can be found in association with ASD,

including attention-deficit hyperactivity disorder (ADHD), anxiety disorder, bipolar disorder, depression, gender dysphoria, non-verbal learning disorder, obsessive-compulsive disorder (OCD), schizophrenia, sensory problems, sleep disorders, and Tourette syndrome and tic disorders (Sharma et al., 2018). Moreover, several studies reported an association between ASD and internalizing symptoms, in particular, emotional dysregulation, mood deflection, worries and anxiety.

Another documented association is with OCD symptoms, although it is difficult to discriminate whether the obsessive-repetitive behaviours are more likely to be the expression of a separate comorbidity, or rather should be addressed as an integral part of the core symptoms of ASD. An association between ASD externalizing symptoms such as irritability, aggressiveness, disruptive behaviour and conduct disorders (CD) have been also frequently reported. (Bauminger et al., 2010). All these conditions may be present from the early years of life; externalizing symptoms such as hyperactivity-impulsivity, irritability, self and hetero-aggressiveness, oppositional and problematic behaviours are very common in preschool children, and seem particularly associated with a severe level of autism. The subjects with high functioning ASD may instead experiment frequently internalizing symptoms, with the development of anxiety and depression because of the severe impairment of social, individual and interpersonal development, difficulties in communication, language, empathy, emotion recognition and management of personal autonomy, all affecting interpersonal relationships (Morie et al., 2019; Orinstein et al., 2015). Especially during preadolescence and adolescence, ASD individuals can incur a worsening of the issues caused by the disorder due to normative stress-inducing factors associated to this specific developmental stage.

ADHD

With the new DSM-5 revision of diagnostic criteria, it is now possible to diagnose ASD and ADHD in comorbidity. The two disorders have a comorbid rate from 30% to 50% based on different studies. Patients with ASD are frequently associated with attention problems, impulsivity and hyperactivity, and also subjects with a diagnosis of ADHD have a higher frequency of autistic traits than the general population. Diagnosis is usually made in preschool with prevalence in males compared to females (Leitner et al., 2014).

Tic disorders and Tourette Syndrome

Tourette Syndrome and other tic disorders have been found in comorbidity with ASD. A study found that 22% of a children with ASD showed chronic motor tic symptoms (Canitano & Vivanti, 2007). The diagnosis is often difficult, given the presence of clinical overlap between tics and motor stereotypies.

Anxiety Disorders

Anxiety disorder is reported in up to 80% of subjects with ASD especially in adolescents with Asperger Syndrome or High Functioning ASD (Van Steensel et al., 2011). A recent study reported that in a pediatric population with ASD, the prevalence of separation anxiety disorder was 38%, generalized anxiety was 35% and social phobia was 30%. (Leyfer et al., 2006). The presence of an anxiety disorder can have a negative impact on the quality of life in children and adolescents, and further reduces relationship with peers and school attendance.

Depression

The presence of a depressive disorder was reported in 10% -50% of young patients with ASD and it seems that the depressive symptomatology is more intense and prolonged as well as more frequent than in the general population. It can often be underdiagnosed for masking depressive symptoms with the typical social withdrawal of individuals with ASD. The prevalence of comorbid depression seems to correlate with higher functioning forms of ASD and increasing age (Simonoff et al., 2008; De Filippis, 2018).

Pharmacological and non-pharmacological therapies

Despite the advances in early diagnosis and intervention, no therapy has proven effective in completely reducing the core symptoms of autism. The treatment of ASD symptoms and comorbidities is based on a multimodal approach of behavioural, educational and pharmacological treatments. Among non-pharmacological treatments, cognitive-behavioural therapy is the one that has shown more evidence on the reduction of both behavioural problems and psychiatric comorbidities. Greater benefits of behavioural therapy occur when started early and if accompanied by adequate psycho-educational support to parents. Other types of intervention include speech therapy, psychomotor therapy, occupational therapy and

alternative treatments such as music therapy and others art therapies. Pharmacotherapy is employed when other therapies are unable to control the symptoms and are often useful to increase the patient compliance with other psychoeducational treatments (Rossignol et al., 2009; Lamy & Erickson, 2018).

About 50% - 60% of children with ASD undergo drug therapy to reduce behaviour problems and comorbidities, and polypharmacy is common in about 30%-40%. The use of drug therapy increases with age and antipsychotics, psychostimulants and antidepressants are among the most widely used drugs. Despite the high frequency of psychotropic medication in this population, there is scarce evidence in the literature, supported by studies often limited by a low sample size, a heterogeneous population and without a control group.

Irritability and aggression – Second generation antipsychotic medications

Antipsychotic medications are among the most studied and used in children with ASD and are frequently employed to reduce behavioural symptoms such as irritability and aggression and for treatment of comorbid schizophrenia and other psychotic disorders. The most prescribed are risperidone, aripiprazole, ziprasidone, quetiapine and olanzapine but only risperidone and aripiprazole are FDA approved. Several RCT and subsequent open-label extension studies showed improvements in externalizing behaviour such as aggression and irritability. A large multicenter RCT trial, conducted by RUPP Autism Network, showed a greater reduction in irritability in ASD children with respect to control (57% versus 14%). In addition, treatment with risperidone is associated with significant improvements in tantrums, aggressive episodes and self-injurious behaviours (McCracken et al., 2002). Risperidone was FDA approved in 2006 for irritability in children and adolescents with ASD aged 5-17 years. Adverse events associated with risperidone treatment included rapid weight gain, appetite increase, fatigue, dizziness, anxiety, cardiac effects, hyperprolactinemia and gynecomastia.

Several randomized double blind placebo-controlled trials showed improvements in irritability in ASD children with aripiprazole. A large RCT trial in ASD children aged between 6-17 years, aripiprazole therapy reduce irritability compared with placebo (Marcus et al., 2009). Aripiprazole was FDA approved in 2009 for irritability in ASD children aged 6-17 years.

For risk increase of cardiovascular and metabolic side effects, metabolic screening and monitoring are strongly recommended for all the patients who received antipsychotic medication.

Mood disorders, anxiety and repetitive behaviour – SSRI

Antidepressant drugs, such as fluoxetine, sertaline, fluvoxamine, citalopram and escitalopram, specifically SSRI, are widely prescribed to ASD children and adolescents (Nadeau et al., 2011). Several RCT clinical studies have been conducted to compare fluoxetine with placebo in ASD children with anxiety symptoms and repetitive behaviours, with contrasting and inconclusive results (Hollander et al., 2005; Autism Speaks, 2009). Only one open label study was conducted for sertraline, fluvoxamine and escitalopram therapy that showed some benefits. A RCT study for citalopram therapy showed no efficacy over placebo, and also revealed a higher incidence of side effects.

Attention deficit/hyperactivity disorder (ADHD) - Psychostimulants

Methylphenidate has been well studied in children with ASD in comorbidity with ADHD. A large crossover RCT (RUPPA Network, 2005) showed a reduction in hyperactivity and impulsivity in patients with ASD and ADHD (50% of 72 patients aged 5-14 years). This improvement remains, nonetheless, lower than in children with ADHD only. Methylphenidate showed no benefit in other symptoms such as irritability and repetitive behaviors.

Conclusions

Children and adolescents with ASD frequently exhibit behavioural symptoms and psychiatric comorbidities that impact their quality of life. Currently, no medication is FDA approved for core symptoms of ASD. Among antipsychotic drugs only risperidone and aripiprazole are FDA approved for ASD-related irritability and aggression. There is also evidence for ziprasidone, olanzapine, paliperidone and clozapine in reducing irritability. For significant metabolic side effects a strongly monitoring is required of all patients on antipsychotic drugs. Methylphenidate is commonly used for ADHD treatment in ASD children with proven effect in reducing symptoms; however, the efficacy is lower with respect to ADHD only. Evidence for use of SSRI in children and adolescents with ASD is limited. The use of SSRI may be associated with side effects such as behavioural activation. Currently, the literature on pharmacological therapy

in ASD children is often limited by studies with a low sample size, a heterogeneous population and without a control group, and there are no large placebo-controlled trials. Large RCT on more commonly prescribed psychotropic drugs in ASD children are needed for a better evaluation of risks and benefits in ASD pediatric patients.

References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed.). https://doi.org/10.1176/ajp.152.8.1228

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Autism Speaks (2009, Feb 18). Autism Speaks Announces Results Reported for the Study of Fluoxetine in Autism (SOFIA), First Industry-Sponsored Trial for the AutismClinical Trials Network (ACTN). Retrieved from https://www.autismspeaks.org/news

Baio, J., Wiggins, L., ... Dowling, N. F. (2018). Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States. *Surveillance Summaries*, *67*(6), 1–23. https://doi.org/10.15585/mmwr.ss6706a1

Baron-Cohen, S., Leslie, A. M., & Frith, U. (1985). Does the autistic child have a "theory of mind"? *Cognition, 21*(1), 37-46. https://doi.org/10.1016/0010-0277(85)90022-8

Bauminger, N., Solomon, M., & Rogers, S. J. (2010). Externalizing and internalizing behaviors in ASD. *Autism Research, 3*(3), 101-112. https://doi.org/10.1002/aur.131

Canitano, R., & Vivanti, G. (2007). Tics and Tourette syndrome in autism spectrum disorders. *Autism, 11*(1), 19–28. https://doi.org/10.1177/1362361307070992

Carter, A. S., Davis, N. O., Klin, A. & Volkmar, F. R. (2005). Social development in autism. In F. R. Volkmar, R. Paul, A. Klin & D. Cohen (Eds.), *Handbook of autism and pervasive developmental disorders* (3rd ed., vol.1, pp. 312-334). John Wiley & Sons. https://doi.org/10.1002/9780470939345.ch11

Covalciuc, S. (2020). Key issues of medical research ethics. *Eastern-European Journal of Medical Humanities and Bioethics, 3*(1), 11-19. http://dx.doi.org/10.18662/eejmhb.17

De Filippis, M. (2018). Depression in children and adolescents with autism spectrum disorder. *Children, 5*(9), 112. https://doi.org/10.3390/children5090112

Hansen, B. H., Oerbeck, B., Skirbekk, B., Petrovski, B. É., & Kristensen, H. (2018). Neurodevelopmental disorders: Prevalence and comorbidity in children

referred to mental health services. *Nordic Journal of Psychiatry, 72*(4), 285-291. https://doi.org/10.1080/08039488.2018.1444087

Hollander, E., Phillips, A., Chaplin, W., Zagursky, K., Novotny, S., Wasserman, S., & Iyengar, R. (2005). A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. *Neuropsychopharmacology, 30*(3), 582–589. https://doi.org/10.1038/sj.npp.1300627

Joshi, G., Petty, C., Wozniak, J., Henin, A., Fried, R., Galdo, M., Kotarski, M., Walls, S., & Biederman, J. (2010). The heavy burden of psychiatric comorbidity in youth with autism spectrum disorders: A large comparative study of a psychiatrically referred population. *Journal of Autism and Developmental Disorders, 40*(11), 1361-1370. https://doi.org/10.1007/s10803-010-0996-9

Lai, M. C., Lombardo, M. V., & Baron-Cohen, S. (2014). Autism. *The Lancet, 383*(9920), 896-910. https://doi.org/10.1016/s0140-6736(13)61539-1

Lamy, M., & Erickson, C. A. (2018). Pharmacological management of behavioral disturbances in children and adolescents with autism spectrum disorders. *Current Problems in Pediatric and Adolescent Health Care, 48*(10), 250-264. https://doi.org/10.1016/j.cppeds.2018.08.015

Leitner, Y. (2014). The co-occurrence of autism and attention deficit hyperactivity disorder in children - What do we know? *Frontiers in Human Neuroscience, 8*, 268. https://doi.org/10.3389/fnhum.2014.00268

Leyfer, O. T., Folstein, S. E., Bacalman, S., Davis, N. O., Dinh, E., Morgan, J., Tager-Flusberg, H., & Lainhart, J. E. (2006). Comorbid psychiatric disorders in children with autism: Interview development and rates of disorders. *Journal of Autism and Developmental Disorders, 36*(7): 849–861. https://doi.org/10.1007/s10803-006-0123-0

Marcus, R.N., Owen, R., Kamen, L., Manos, G., McQuade, R. D., Carson, W. H., & Aman, M. G. (2009). A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(11), 1110–1119. https://doi.org/10.1097/chi.0b013e3181b76658

McCracken, J. T., McGough, J., ... McMahon, D. (2002). Risperidone in children with autism and serious behavioral problems. *The New England Journal of Medicine, 347*(5), 314–321. https://doi.org/10.1056/nejmoa013171

Morie, K. P., Jackson, S., Zhai, Z. W., Potenza, M. N., & Dritschel, B. (2019). Mood disorders in high-functioning autism: The importance of alexithymia and emotional regulation. *Journal of Autism and Developmental Disorders, 49*(7), 2935-2945. https://doi.org/10.1007/s10803-019-04020-1

Nadeau, J., Sulkowski, M. L., Ung, D., Wood, J. J., Lewin, A. B., Murphy, T. K., May, J. E., & Storch, E. A. (2011). Treatment of comorbid anxiety and autism spectrum disorders. *Neuropsychiatry, 1*(6), 567–578. https://doi.org/10.2217/npy.11.62

Orinstein, A., Tyson, K. E., Suh, J., Troyb, E., Helt, M., Rosenthal, M., Barton, M. L., Eigsti, I. M., Kelley, E., Naigles, L., Schultz, R. T., Stevens, M. C., & Fein, D. A. (2015). Psychiatric symptoms in youth with a history of autism and optimal outcome. *Journal of Autism and Developmental Disorders, 45*(11), 3703-3714. https://doi.org/10.1007/s10803-015-2520-8

Peterson, C., Slaughter, V., Moore, C., & Wellman, H. M. (2016). Peer social skills and theory of mind in children with autism, deafness, or typical development. *Developmental Psychology, 52*(1), 46–57. https://doi.org/10.1037/a0039833

Research Units on Pediatric Psychopharmacology Autism Network/RUPPA. (2005). Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. *Archives of General Psychiatry, 62*(11), 1266-1274. https://doi.org/10.1001/archpsyc.62.11.1266

Ring, H., Woodbury-Smith, M., Watson, P., Wheelwright, S, & Baron-Cohen, S. (2008). Clinical heterogeneity among people with high functioning autism spectrum conditions: Evidence favoring a continuous severity gradient. *Behavioral and Brain Functions, 4*(1), 11. https://doi.org/10.1186/1744-9081-4-11

Rossignol, D. A. (2009). Novel and emerging treatments for autism spectrum disorder: A systematic review. *Ann Clin Psychiatry, 21*(4), 213-236. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19917212#

Sharma, S. R., Gonda, X., & Tarazi, F. I. (2018). Autism spectrum disorder: Classification, diagnosis and therapy. *Pharmacology & Therapeutics, 190*, 91–104. https://doi.org/10.1016/j.pharmthera.2018.05.007

Simonoff, E., Pickles, A., Charman, T., Chandler, S., Loucas, T., & Baird, G. (2008). Psychiatric disorders in children with autism spectrum disorders: Prevalence, comorbidity, and associated factors in a population-derived sample. *Journal of the American Academy of Child and Adolescent Psychiatry, 47*(8), 921–929. https://doi.org/10.1097/chi.0b013e318179964f

Tine, M., & Lucariello, J. (2012). Unique theory of mind differentiation in children with autism and Asperger syndrome. *Autism Research and Treatment, 2012*, 1–11. https://doi.org/10.1155/2012/505393

Van Steensel, F. J. A., Bögels, S. M., & Perrin, S. (2011). Anxiety disorders in children and adolescents with autistic spectrum disorders: A meta-analysis. *Clinical Child and Family Psychology Review, 14*(3), 302–317. https://doi.org/10.1007/s10567-011-0097-0

Yenkoyan, K., Grigoryan, A., Fereshetyan, K., & Yepremyan, D. (2017). Advances in understanding the pathophysiology of autism spectrum disorders. *Behavioural Brain Research, 331*, 92-101. https://doi.org/10.1016/j.bbr.2017.04.038