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Editorial

Advances in the pharmacological management of autism spectrum disorders

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Autism spectrum disorders are a group of neurodevelopmental disorders characterized by impairment in socialization, communication and stereotyped behaviour. The disorders included under autism spectrum disorder are – Autism, Asperger's syndrome and pervasive developmental disorder- not otherwise specified (PDD- NOS) [1]. Rett's syndrome and childhood disintegrative disorder are also considered close to this spectrum; hence put under the same umbrella in the international classification of diseases, 10th edition (ICD-10). In this article the terms autism and autism spectrum disorder mean to the same entity as these terms have been frequently interchangeably used in literature, due to their similar clinical characteristics and common target symptoms of treatment.

Autism causes significant morbidity and impairment of socio-occupational functioning. Patients with autism often have various psychiatric morbidities, which further add to the disability. Children and adolescents with autism spectrum disorder often display range of abnormal behaviors in the form of aggression, irritability, tantrums and self-injurious behavior [2]. The prevalence of such behavioural problems in children and adolescents suffering from autism are approximately 50% and in 30% cases the problem is found to be severe [3].

Management of core symptoms of autism and psychiatric co-morbidities associated with it can be done through psychological interventions as well as pharmacological interventions. In this article, the conventional pharmacological management, its limitations and new avenues of pharmacological management of autism are discussed. Pharmacotherapy in autism often recommended, when there is/ are definite target symptom(s) or there is a co-morbid psychiatric disorder [4].

Target symptoms of autism spectrum disorder that needs pharmacological intervention are [4]–

- Restricted and repetitive patterns of behavior
- Social withdrawal
- Challenging (aggressive behavior)
- Hyperactive symptoms
- Sleep disturbances

Recent evidences suggest that antipsychotic medications are increasingly used in patients with autism [5]. Evidences suggest that at least 50% of individuals with autism spectrum disorder receive some form of psychotropic medication treatment across their life span [6]. More than one third of persons with autism receive psychotropic poly-pharmacy as found in a study [7]. Existing evidences suggest that non-pharmacological management is the mainstay treatment of autism; however high-risk (challenging) behaviors in autism need additional pharmacological intervention [5]. Children and adolescents with autism may display aggressive behaviour, self-harm behaviour, persistent irritability and tantrums, which may need pharmacological intervention [2,

8]. Among the pharmacological agents, atypical antipsychotics (risperidone, aripiprazole, olanzapine, quetiapine, ziprasidone, clozapine) are usually preferred; risperidone and aripiprazole are approved by US Food and Drug Administration (FDA) for treatment of such behaviours in youth with autism [2, 3]. Antipsychotic medications are also effective in reducing hyperactivity symptoms, repetitive behavior and social withdrawal [9]. Atypical antipsychotics (clozapine, olanzapine, risperidone) have the propensity to cause weight gain, increased appetite and disturbances in glycemic control, which need to be monitored regularly. Extrapyramidal side effects are also commonly reported with antipsychotics (more with typical antipsychotics than atypical ones), which may limit its use. A recent systematic review describes aripiprazole as a well-tolerated and effective medication (comparable with autism) in the management of behavioural symptoms of autism [10, 11].

Alpha 2 adrenergic agonists like – clonidine and guanfacine has been studied in children and adolescents with autism and found to have beneficial role in reducing the symptoms of impulsivity and hyperactivity [3]. Clonidine is also useful in reducing the irritability. Side effects reported are – sedation (with both clonidine and guanfacine), fatigability (with clonidine) and increased irritability (with guanfacine) [3].

Similarly some initial research evidences suggest that beta- adrenergic antagonist – propranolol have some role in improving the cognitive abilities like – verbal problem solving [12], conversational reciprocity, non-verbal communication [13], working memory and inhibitory control [14]. Propranolol had also improved anxiety and autonomic dysregulation in patients with autism spectrum disorder. Further studies are required to understand the clinical utility of propranolol in autism spectrum disorders.

Recent evidences suggest about some role of anticonvulsant (mood stabilizers) in managing the aggressive behavior in autism [3]. In the management of aggressive behavior – lithium, divalproex sodium, lamotrigine and levetiracetam has been tried. The therapeutic effects of levetiracetam and lamotrigine are not better than placebo, whereas some improvement is reported with lithium and divalproex sodium [3].

Individuals with autism spectrum disorders display restricted and repetitive behaviors. Antidepressants have been tried for the management of such behavior. Selective serotonin reuptake inhibitors (fluoxetine, citalopram, escitalopram, fluvoxamine), venlafaxine, clomipramine, desipramine, mirtazapine have been tried in autism spectrum disorders with mixed results [15]. Other than the ritualistic, repetitive behaviors, some improvement in irritability, anxiety and hyperactivity symptoms are also reported with antidepressant treatment.

Stimulants (methylphenidate, atomoxetine) have also been tried in autism spectrum disorders. These medications are effective in controlling the hyperactivity symptoms associated with autism spectrum disorder [15]. Some evidences also exist regarding beneficial role of naltrexone (opioid antagonist) in treating the symptoms of hyperactivity and impulsivity [15]. Cholinergic agents (donepezil, galantamine) and GABA-ergic agents have also been used for treatment of irritability and hyperactivity with positive results [15]; but these preliminary findings need to be evaluated in larger studies. Melatonin is found to be effective in treating the circadian rhythm disturbances in autism spectrum disorder and it is well tolerated by the patients [15]. Antipsychotic drugs used for treatment of aggression and irritability, also improve the sleep disturbances associated in these patients [1].

Poor socialization is a core issue in autism, which was initially believed to be non-responsive to pharmacological intervention; however recent preliminary evidences suggested that intranasal oxytocin having a role in improving social responsiveness [16]. Oxytocin potentiates the neuronal circuits associated with motivation, reward and learning, which are known to be associated with social behavior [17]. Eye to eye contact is an important aspect of social behavior, which is inadequate to absent in autism spectrum disorder. It has been seen that oxytocin have a potential role in improving eye to eye contact by increasing the eye fixation duration [18]. It is well tolerated by the patients. Common side effects associated with use of oxytocin are – increased thirst, constipation, urination [16].

Evidences suggest that patients with autism spectrum disorder have low level of Omega-3 long chain polyunsaturated fatty acid and its supplementation can be beneficial in improving the symptoms, though contrary evidences also exist [19, 20]. Some role of N-acetylcysteine in reducing irritability associated with autism is also evident form recent studies [3]. Role of magnesium, pyridoxine, Vitamin C, Vitamin B12 and D-cycloserine are controversial [20]. However, further robust research evidences are required to understand their clinical utility in autism.

Some early evidences suggest about the potential role of gut microbiota in various psychiatric disorders including autism spectrum disorders. This association opens a window of opportunities for use of new modality of treatment (antibiotics or probiotics) that can alter the gut microbiota in either way, thereby causing improvement in features of autism spectrum disorder [21, 22].

Recent evidences suggest about the neurobiological similarity between schizophrenia and autism spectrum disorder [23]. The evidence based treatment for schizophrenia (e.g: antipsychotic treatment) might be having a potential role in treatment of autism spectrum disorders. Though there are evidences, that antipsychotic drugs are useful in management of challenging (aggressive, disruptive) behavior; there is a need of rigorous study to understand their role in autism spectrum disorders [24]. Dopamine antagonistic drugs exert their role in treatment resistance autism spectrum disorders by brain derived neurotrophic factor (BDNF) stimulation [24]. Low dose loxapine, amitriptyline seems to be useful in management of insomnia, aggression, irritability and gastrointestinal symptoms associated with autism spectrum disorder [24]. A recent study on experimental animals revealed that prenatal maternal administration of vitamin D prevents development of autism spectrum disorder in offspring [25].

Persistence of behavioural problems results in non-involvement of the individuals in psychological training interventional programs; hence pharmacological management of the behavioural symptoms may enable them to participate in those interventional programs. It may be useful to treat the impairing behavioural symptoms pharmacological intervention prior to psychological intervention.

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