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Review Article

Management of Aggressive Behaviors in Neurodevelopmental Disorders - Role of α 2 Agonists

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Abstract

Neurodevelopmental Disorders (NDD) are associated with high rates of comorbid behavioral problems leading to increased need for crisis interventions, ER visits and health care spending. These patients often end up with polypharmacy of multiple psychotropic medications and complexities secondary to the associated side effects, which may often be irreversible. Not having a proper guideline also makes it difficult for physicians to select appropriate medications. Due to underlying sympathetic over activity, many of this group of patients can get easily dysregulated, making it difficult for their caregivers to care for them. A common practice of pharmacological management of behavioral problems in NDD is to use antipsychotics and other psychotropic medications, often without any primary psychiatric disorder. Much less attention has been given to medications like α 2 agonists. Researches in the past couple of decades have found these medications much effective in behavioral management, with added benefit of lower long term side effects.

Keywords: Aggressive Behaviors; Neurodevelopmental Disorders; α 2 Agonists

Introduction

Neurodevelopmental disorders are a group of complex multifactorial disorders impacting growth of the central nervous system in an individual, which may present as intellectual disability, speech and language disorders, ADHD, autism, specific learning disorders as well as Motor disorders (e.g. tics, Tourette's syndrome). Diagnostic and Statistical Manual 5 defines NDD as "a group of conditions with onset in the developmental period. The disorders typically manifest early in development, often before the child enters grade school, and are characterized by developmental deficits that produce impairments of personal, social, academic, or occupational functioning" [1].

According to a recent Study in America 1 in 4 publicly insured and 1 in 9 privately insured children in the US received a diagnosis of neuro-developmental disorder, with a considerably higher risk in males [2]. People with NDD has a higher rate of behavioral problems e.g., verbal and physical aggression, aggression towards property, leading to increased ER visits. A population based study in Ontario found that repeat ER visits by intellectual disability patients with or without psychiatric disorders within 30 days, is much higher than the general adult population [3].

The prevalence of aggressive behaviors in people with intellectual disability and autism is reported to be between 9 to 31%, with a median of 20% [4].

According to a study in England, Rate of emergency admissions to hospitals in intellectually disabled people is nearly 3 times higher than among their matched counterparts [5].

The challenges of caring for these individuals have resulted in frequent use of antipsychotic medications, often in high doses, although their efficacy has not been proven clinically. It is also very common to see multiple psychotropic medications being administered at the same time, in an attempt to reduce aggressive behav-

iors and leading to polypharmacy. There are significant long-term side effects of these medications which increases the need for ongoing medical management [6-9].

Neurobiology of aggression

- **Role of Prefrontal cortex:** Prefrontal cortex (PFC) plays an important role in an individual's day to day life and is like a GPS system that helps a person navigates safely in today's complex world. It controls the highly synchronised functions of the brain, by inhibiting the unwanted signals through very complex network system. Through networks with other brain regions, mainly basal ganglia, parietal cortex, thalamus, motor and sensory cortex and cerebellum, PFC is responsible for delivering executive function (e.g., working memory, impulse control, attention, mental flexibility, planning and organization) [25]
- Aggression is an outcome of failure of top down control of the PFC to modulate the lower order neurons e.g. in the limbic area. The imbalance between the PFC function and the hyperactive and hypersensitive limbic area causes aggressive behaviors in a person [10].
- Sub cortical imbalance in Glutamatergic and GABAergic systems plays a key role in chronic aggressive behaviors.
- Underdevelopment of the PFC in NDD population causes chronic autonomic dysregulation with sympathetic overdrive, resulting in aggressive behaviors. Poor PFC function causes disorganization, impulsivity, distractibility and poor working memory.
- Sensory perceptual problems in this population also contribute to aggression, as individuals may perceive the external sensory responses in a much higher potency. High sensory sensitivity towards loud noise can trigger an individual even in a normal environment and may lead to the perception of being yelled at and abused, leading to aggressive responses. Bright lights may bother them easily making them irritable. Similarly, an individual may get triggered by a normal but unanticipated touch or hug leading to anger.
- Problems with comprehension and other prefrontal cortical deficits are important causes of aggression in individuals especially with NDD.
- Emotion recognition and Reading facial expressions are difficult with people with NDD and various other psychiatric disorders which can easily trigger aggressive behaviors.

Use of psychotropic medications for aggression in NDD

Psychotropic medications have been used off level for management of aggressive behaviors in NDD, for a long period of time often without a primary psychiatric diagnosis [6,7,9,12]. The effectiveness of psychotropic medications for managing aggressive behaviors in NDD have been inconclusive and are not supported by much evidences [6,7,11,13]. According to studies some antipsychotic medications are effective in reducing challenging behaviors in children however, these benefits are short lasting and long term use of these medications is associated higher risks than benefits [14]. Risperidone was found to be effective in a 8 week study, in treatment of children with autism and extreme behavioral problems [14]. The effect lasted for 6 months and discontinuation caused return of symptoms [15].

Aripiprazole was found to be effective in treatment of irritability in patients with autism in a 8 week double blind RCT [16]. These medications have been widely used in NDD children, adolescents and adults for behavioral management, often for very long periods of time, which come with high side effects profile [6,17]. Much of the research findings on effectiveness of antipsychotic medications for behaviors management in adults have mixed or inconsistent outcomes [6-9].

There is also some increased risk of unexpected sudden death among children and youth using antipsychotic medications according to study [18]. A study done on the NDD population in New York State found in their study group, 58% adults received one or more psychotropic medication, 6% received typical and 39% received atypical antipsychotics. Uses of other medications for impulse control were minimal- α 2 agonist or β -blockers, stimulant medications and hypnotics were only 1- 2%. 50% antipsychotic medication use was for treatment of a major comorbid psychiatric disorder. 13% were for behaviors control and 38% were for both. Antidepressant use was 23% (SSRIs) and mood stabilizers - 19% [19]. A study done in residential facilities in the UK found higher uses of antipsychotic medications, up to 56% in the NDD population [20].

Receptors	Actions
α 1	Constriction of vascular smooth muscle, radial muscle of eye, vas difference.
α 2A	CNS- mostly at PFC, but also LC, amygdala , hippocampus and Septum pellucidum – Decrease release of NE from presynaptic neuron, Sedation via LC, reduce pain via dorsal horn of spinal cord
α 2B	vascular smooth muscles
α 2C	CNS- striatum, hippocampus and PFC (not on cell surface)

Table 1: Function of α Adreno receptors.

The α-adrenoreceptors

- Are classified as α -1 and α -2.
- The α -1 -receptors work mainly on vascular smooth muscles.
- α 2 receptors are a group of G- protein coupled receptors, classified as α 2A, α 2B and α 2C.
- Epinephrine and Norepinephrine are endogenous agonists and has similar affinities towards all 3 types of receptors- α 2A, α 2B and α 2C.
- All 3 types of α 2 receptor stimulation can suppress an enzyme adenyl cyclase which in turn reduces Cyclic AMP, most importantly in the Locus Coeruleus (LC) nuclei [21].
- Cyclic AMP reduction suppresses neural firing, by potassium efflux through Calcium activated channels and preventing the Calcium ions to enter the nerve terminals, causing reduced sympathetic response and help reduce anxiety, agitation and aggression [21].
- α 2A and 2C act mainly on the CNS and α 2B works on vascular smooth muscles.

α 2 Adrenoreceptor agonists

Following medications fall in this category

- Clonidine
- Dexmedetomidine
- Guanabenz
- Guanfacine
- Tizanidine

In this article we will focus on the use of Clonidine and Guanfacine as these have been used most to treat various psychiatric disorders.

α 2 agonist medications for treatment of aggression in NDD-

Figure 1: Mechanism of action of α 1 and 2 receptors.

Clonidine

- Although it was originally discovered as an antihypertensive medicine, Clonidine was later found to have many other benefits. It has been used in psychiatry to treat ADHD, PTSD, aggression and Opioid withdrawal among several other conditions.
- The NE cells in the LC become overactive during opioid withdrawal. Clonidine is effective in lowering this hyperactivity by blocking presynaptic α 2 receptors [22,23].
- Cohen and colleagues first noticed its effects on reducing tics and started using it for Tourette's syndrome in 1979.
- Hunt., et al. studied its impact on TS and ADHD and found it to be helpful in treating ADHD as well.

- It seems to have a better impact on hyperactivity, impulsivity and aggression than inattention. It has also been beneficial in treatment of aggressive behaviors in NDD patients.
- Clonidine has significant sedative effects and it is thought to be the mechanism behind reducing hyper arousal symptoms in these groups of patients.

Guanfacine

Sustained release formulation of Guanfacine XR has been available since 2009 and was approved by FDA for treatment of ADHD in children. Although it was only approved for children with ADHD, it has been found beneficial in treatment of various other conditions and has been used off label to treat adults with ADHD, PTSD, TBI and other disorders where impulse control or hyper arousal is a problem. It is found to have following pharmacological effects which make it a suitable agent in these conditions.

Reducing NE related excitation

- Guanfacine binds to Specific α 2A auto-receptors in the presynaptic neurons and inhibits NE release to the synaptic cleft. It closes the voltage gated Ca++ channels and depletes Ca++ in the presynaptic neurons. Ca++ is an important factor for exocytosis, without which neurons cannot release NE to the cleft.
- Activation of the somatodendritic α 2A receptors by Guanfacine suppresses the activation of the locus coeruleus. Suppression of locus coeruleus activity helps with calming and sedating effects and this property of Guanfacine helps to treat symptoms of hyper arousal, excitability and aggression.
- Guanfacine suppresses the tonic activation of locus coeruleus, and as a result improves phasic activation of locus coeruleus. This improves stimulus driven activation of LC, improves behavioral response and task performance.

Reducing glutamatergic activation

α 2A receptors are present throughout the brain in non-Noradrenergic neurons. Activation of these has following effects

- Suppresses release of several neurotransmitters including Glutamate. This is likely associated with inhibition of the kindling effect in the limbic area and helpful in emotion regulation. Beneficial for treatment of psychiatric disorders with hyper arousal symptoms e.g., PTSD
- Suppression of spontaneous amygdalar activity by the α 2 adrenergic agonists contributes to their antiepileptic property.
- It also modulates corticothalamic activation by allowing only high frequency transmissions to enter thalamus during arousal state [25], helps to reduce noises/over activity in the brain.
- Reduces Sympathetic outflow from the rostral ventrolateral medulla, which lowers the fight/flight response and helps to have a calming effect.

Role on prefrontal cortex

- The α 2A adrenoreceptor agonists improve working memory and behavioural inhibition. It prevents distractibility by improving top-down control by PFC. It improves attention and reduces aggressive behaviour [27].
- Guanfacine has been used off label to treat aggression in IDD, ADHD, ODD in children as well as aggression in adult as it improves activity in the PFC.

Discussion

Behavioral problems are commonly associated with NDD and are very challenging to treat. Although antipsychotic medications have been in use extensively to control behaviors in these populations, it comes with a high cost. Patients often end up with polypharmacy and develop a host of side effects. Antidepressants and mood stabilizers are also in use for behavioral management. The α 2 agonists have been shown to improve aggressive behaviors by improving PFC function, especially by reducing hyper arousal, impulse control, improving top down control and thereby to reduce aggression.

The α 2 agonists are primarily antihypertensive medications that work centrally by reducing fight flight response and are good alternative for patients who can tolerate it. Side effect profiles for this group of medication are tolerable even by children and both Clonidine and Guanfacine XR are approved for use in children. Polypharmacy in NDD patient have been a ongoing topic of discussion and using these medications that works centrally to reduce aggression can lower use of polypharmacy and as a result reduce side effects related to poly pharmacy.

Conclusion

α 2 agonist drugs are in market for several decades and are proven to be beneficial for aggression in NDD in many patients. Unfortunately, this group of medications is not much promoted and

has not been given enough attention for its potentials in treating aggression, especially in this vulnerable group of NDD patients. It is a much-needed area of research that has significant future promises.

Abbreviations

TS- Tourette's syndrome
ADHD- Attention deficit hyperactive disorder
IDD- Intellectual disability disorder
ODD- Oppositional defiant disorder
PTSD- Post traumatic stress disorder
TBI- Traumatic brain injury
SSRI- Selective serotonin reuptake inhibitor

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