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RESEARCH ARTICLE

TREATMENT OF BIPOLAR DISORDER IN CEREBRAL PALSY: CHALLENGES IN ANTIPSYCHOTIC USE

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Abstract

Cerebral palsy (CP) is a neurodevelopmental disorder that frequently coexists with psychiatric conditions, including bipolar disorder. Treating bipolar disorder in this population poses significant clinical challenges due to the clinical heterogeneity and comorbidities associated with CP. Adverse effects of antipsychotics tend to have a more profound impact on the quality of life in individuals with CP compared to the general population.Therefore, they represent a more serious clinical concern. This article aims to highlight the challenges of choosing antipsychotics for managing bipolar disorder in CP patients.To our knowledge, this topic has not been previously addressed in the literature. We propose that the antipsychotic selection should be guided by individual clinical characteristics, including CP subtype, mobility status, affected limbs, body mass index (BMI), and pre-existing orthopedic conditions. Personalized treatment may help providers better balance the risks of extrapyramidal symptoms and metabolic syndrome, thereby improving therapeutic outcomes and overall quality of life for this overlooked patient population.

Introduction:-

Cerebral palsy (CP) is a severe neurodevelopmental disorder that affects 3 out of every 1,000 live births. In this disorder, an injury to the motor segment of the brain leads to movement disorders in patients. These disorders are classified into three main types: spastic (muscle contractions), dyskinetic (involuntary, uncontrolled movements), and ataxic (poor coordination).

Spastic CP is the most prevalent form, and it affects approximately 80% of patients. Based on which limbs are affected, it can be further categorized as hemiplegic (one side of the body), diplegic (both legs), or quadriplegic (all four limbs). Common clinical features of spastic CP include increased deep tendon reflexes, tremors, hypertonia, muscle weakness, a characteristic scissors gait, and toe walking.

The dyskinetic type, present in about 10–20% of patients, is associated with extrapyramidal symptoms such as athetosis and dystonia. Athetosis is slow, snakelike, writhing movements, particularly in the fingers, which exacerbate during periods of stress. Dystonia is an involuntary, sustained muscle contraction.

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The rarest form is ataxia, which affects 5–10% of individuals with CP. It impairs balance and coordination; patients often exhibit wide-based gait and intention tremors. Some patients may also present with mixed-type CP, displaying features from multiple categories[1, 2]

Depending on the severity of the disorder, various comorbidities may occur: intellectual disability, inability to walk or speak, epilepsy, hip displacement, and incontinence.[3]
Cerebral palsy (CP) is caused by disturbances in fetal brain development. The risk factors associated with CP include placental abruption, uterine rupture, intrauterine infections, prematurity, maternal fever during pregnancy, congenital anomalies, complications related to multiple gestations, and birth asphyxia.

Cortical neurogenesis occurs during early gestation, particularly up to 24 weeks. Disruptions in this developmental process due to genetic abnormalities, intrauterine infections, or exposure to toxic agents can lead to structural brain abnormalities.

In the later stages of pregnancy, myelination, axonal and dendritic growth, and synapse formation occur. At this stage, ischemia and hypoxia contribute to the development of CP. [1]
It is well recognized that having CP significantly reduces individuals' quality of life and leads to considerable psychological distress, resulting in anxiety and depression. Research has shown that the prevalence of psychiatric disorders in CP patients is remarkably higher than in the general population, except for substance use disorders. Having intellectual disability further increases the prevalence of severe psychiatric conditions, such as psychotic disorders and bipolar disorder. On the other hand, among individuals with CP, those without intellectual disability have appeared to have an elevated risk of developing anxiety and depressive disorders.[4]

According to one study, attention-deficit/hyperactivity disorder (ADHD) is the most common psychiatric comorbidity in this population.[5] Other frequently reported psychiatric disorders in individuals with CP include obsessive-compulsive disorder, oppositional defiant disorder, schizophrenia, bipolar disorder, and generalized anxiety disorder.[4, 6] These findings highlight the importance of regular mental health evaluations in individuals with CP. Unfortunately, communication difficulties commonly seen in this population may cause psychiatric symptoms to be overlooked, which can lead to delays in diagnosis and worsening of mental health conditions.

Bipolar disorder is a mood disorder characterized by manic and depressive episodes. A manic episode is defined by an elevated or irritable mood, heightened energy, inflated self-esteem, decreased need for sleep, and racing thoughts lasting for at least a week. In contrast, a depressive episode is composed of feelings of worthlessness, anhedonia, and disturbances in appetite and sleep.[7] Approximately 1.2% of the general population is affected by bipolar disorders. However, it affects 2.1% of the CP patients and 2.7% of the CP patients who also have intellectual disability.[4]
Treatment of bipolar disorder in patients with CP requires special attention due to possibly more severe extrapyramidal and metabolic adverse effects. In this article, we will explore the difficulties and limitations in the management of bipolar disorder in patients with Cerebral Palsy.

Bipolar Disorder Management in Cerebral Palsy
Bipolar treatments available and approved by the FDA are mainly antidepressants for bipolar depression, as well as antipsychotics and mood stabilizers for mania, depression, and maintenance. Compared with mood stabilizing medications, second-generation antipsychotics have a faster onset of action, making them a first-line treatment for severe acute manic symptoms. Traditional mood stabilizers, such as lithium, valproate, and carbamazepine, are also effective in treating active mania. For long-term treatment, most of the second-generation antipsychotics (except lurasidone and paliperidone), lithium, valproate, and lamotrigine are approved.[8]

Patients with CP may be prone to neurologic adverse effects due to underlying brain conditions, as suggested in various studies. One study shows serotonin syndrome in CP patients with atypical drugs like SSRI monotherapy, lithium, and olanzapine. Serotonin syndrome is characterized by clonus, diaphoresis, hyperreflexia, hypertonia, and hyperthermia, and typically occurs with two or more serotonergic agents. [9] Another study indicated that administering haloperidol to a patient with cerebral palsy (CP) resulted in detrimental motor and cognitive effects. The patient became unresponsive and showed no spontaneous movement. The study suggested that decreased levels of dopamine are observed in animal studies of cerebral hypoxia in the developing brain, and giventhat cerebral

hypoxia is one of the main pathologies of CP, this could lead to significantly reduced baseline dopamine levels in individuals with CP. Consequently, this makes them more susceptible to the effects of pharmacological dopamine blockade. [10]

Also, approximately half of the patients with CP have an intellectual disability. [3]As having an organic brain disorder and intellectual disabilityis a risk factorfor Neuroleptic Malignant Syndrome, when these individuals have an affective disorder, they are at an increased risk for it.[11] Therefore, when prescribing antipsychotics to these patients, it is essential to consider these risks.
Using antipsychotics for patients with cerebral palsy (CP) requires careful consideration. Due to the underlying movement disorder, the risk of experiencing extrapyramidal side effects increases.

Extrapyramidal symptoms (EPS) include akathisia (motor restlessness), dystonia (sustained muscular contraction), parkinsonism (bradykinesia, rigidity, tremor), tardive dyskinesia (late-onset choreiform movements), and tardive dystonia (late-onset dystonia).[12]
CP affects motor control, and EPS can exacerbate movement difficulties, making daily activities even more challenging. The following examples illustrate how EPS may manifest in this population.

Dystonia may increase muscle tone and worsen the already present spasticity in these patients, leading to further stiffness. For patients with ataxic CP, impaired balance combined with EPS symptoms such as parkinsonism could significantly elevate the risk of falls and related injuries.[13]Tardive dyskinesias, including tardive dystonia, are persistent, late-onset adverse effects that may last up to years, and they occur with long-term use of antipsychotics.[12] Tardive dyskinesia mainly affects the orofacial muscles but can also involve the limbs. This limb involvement may contribute to gait disturbances that already exist in CP patients. [3, 14]Tardive dystonia can affect multiple body areas, including neck musculature, trunk, limbs, and oromandibular muscles.[14] Oromandibular dystonia (OMD) is an involuntary contraction of the jaw, tongue, and facial muscles. These issues can worsen speech disorders and swallowing difficulties that are already common in CP patients. Speech disorders in OMD can be summarized by sigmatism (difficulty pronouncing sibilant sounds) and poor phoneme linkage (difficulty connecting speech sounds), which causes reduced fluency. Dysphonia or difficulty in vocalization is also common in OMD. These adverse effects of EPS make social interactions more challenging, causing anxiety in patients.[15] Additionally, having EPS significantly lowers the quality of life[16]and is the direct cause of medication discontinuation for many patients. Along with the fact that psychiatric patients are poor historians, communication problems with CP patients can cause EPS to go undiagnosed.[17] Furthermore, symptoms like akathisia, akinesia, and acute dystonia may resemble common psychiatric symptoms, complicating the diagnosis of EPS. [17]

EPS arises from the dopamine D2 receptor antagonist activity of drugs in the striatum. Research suggests a D2 receptor occupancy rate of 80% or higher is associated with a high likelihood of demonstrating EPS. An occupancy rate between 70% and 80% indicates a moderate probability of EPS, while an occupancy rate below 70% is generally not associated with EPS. Mainly, the goal is to maintain sufficient D2 antagonism to achieve an antipsychotic effect while minimizing injury to the D2 dopamine system to avoid EPS. Second-generation antipsychotics (SGAs) such as aripiprazole, olanzapine, risperidone, olanzapine, and quetiapine typically have a superior EPS profile compared to first-generation antipsychotics (FGAs). High-potency FGAs like haloperidol are more likely to cause EPS due to their highest occupancy rates. Among SGAs, research demonstrates that risperidone has a more unfavorable side effect profile than the other options. In contrast, quetiapine and clozapine have the lowest D2 occupancy rates, so they exhibit the lowest incidence of EPS compared to other SGAs.[17]

In order to reduce this occupancy, some medications that indirectly augment dopamine activity through serotonin antagonism (high 5-HT2/D2 ratio) and partial D2 agonism are being tested. While these diminish EPS liability, they do not eliminate EPS altogether. Both risperidone and ziprasidone exhibit strong serotonin antagonist activity; however, this is insufficient to prevent EPS in the case of risperidone. For ziprasidone, this assertion is valid to a lesser extent. Patients who switched from conventional antipsychotics or risperidone to ziprasidone experienced fewer EPS after six weeks of ziprasidone treatment. That said, the EPS risk of risperidone below the doses of 6 mg per day is low. Across a therapeutic dose range of 0.5–16 mg per day, there is a significant linear correlation between the dose of risperidone and the incidence of EPS, which is still associated with fewer adverse effects than high-potency FGAs.

Both quetiapine and clozapine have significant 5-HT2A antagonism, but they also possess unique properties that reduce D2 antagonism.
Aripiprazole has a very low EPS liability despite having a striatal D2 occupancy rate between 80% and 90%. This phenomenon can be attributed to the partial agonist properties of aripiprazole. Specifically, the agonist activity is 30%, which is sufficient to maintain normal dopaminergic motor activity.[17, 18]

According to a meta-analysis on EPS associated with antipsychotics, quetiapine is associated with the least incidence of dystonia (1.4%), paliperidone is associated with the least incidence of akathisia (3.3%), while clozapine is associated with the least incidence of parkinsonism (3.7%) and tremor (0.2%). Haloperidol shows very high rates of these side effects, ranging from 16% to 24%.[19] Clozapine is typically reserved for treatment-resistant patients due to the serious side effects of agranulocytosis. However, some studies suggest that clozapine may lead to symptom resolution for tardive dyskinesia, especially in cases of tardive dystonia.[12, 16]

Children with disabilities face a higher risk of obesity compared to the general population of children. Patients with diplegic or quadriplegic CP may be wheelchair-bound, and the adverse effects of antipsychotics, such as metabolic syndrome and weight gain, should be considered more seriously in this population. Reduced mobility, restricted social participation, and an increase in depressive symptoms significantly contribute to weight gain within this group.[2, 20, 21]

In patients with limited mobility, the incidence of pressure ulcers increases. Although being obese may provide some protection against pressure ulcers, extremely obese individuals (BMI>40) have higher rates of pressure ulcers compared to patients with a normal weight. Overall, both being underweight and extremely obese are risk factors for developing pressure ulcers.[22]

Studies indicate that individuals with cerebral palsy (CP) who carry excess weight around the belly experience gait problems, resulting in slower walking speeds, shorter step lengths, and reduced ranges of joint motion. They also exhibit decreased moments and powers during movement.[23] Furthermore, 36% of CP patients are affected by hip disorders. Spasticity can contribute to hip pain and dislocation. As individuals gain weight, the compressive and shear forces on the hip during walking increase. This additional load on the hip joint raises the risk of developing hip pain and related pathologies. [3, 24] Moreover, increased weight can heighten the need for caregiver assistance in daily activities, making their responsibilities more challenging.[20]

A meta-analysis examining weight gain as an adverse effect of antipsychotics indicates that olanzapine is associated with the most clinically relevant weight gain within six weeks of treatment, affecting 24.1% of patients compared to 1.4% on placebo. Following olanzapine,risperidone results in weight gain for 16.8% of patients, compared to 2.9% on placebo, while aripiprazole shows a 16.8% weight gain versus 7% on placebo. Quetiapine is associated with weight gain in 12.5% of patients compared to 6% on placebo. [25]

In another comprehensive study, clozapine and olanzapine were identified as having the highest risk of weight gain, with olanzapine at the top of the list. Mid-risk antipsychotics include asenapine, risperidone, paliperidone, and quetiapine. The antipsychotics associated with the lowest risk of weight gain are aripiprazole, lurasidone, and ziprasidone. Haloperidol is also noted to cause less weight gain than second-generation antipsychotics (SGAs). [26, 27]

Conclusion:-

We aimed to demonstrate how these adverse effects of antipsychotic medications impact the lives of cerebral palsy patients and which medications carry a higher risk. Also, we sought to highlight that the treatment of bipolar disorder in patients with cerebral palsy should be customized by considering their specific clinical characteristics. These characteristics can include the subtype of CP (spastic, ataxic, or dyskinetic), which limb is affected, wheelchair dependency, the presence of pre-existing hip disorders, and their Body Mass Index (BMI). By considering the patient profile, physicians can better prioritize whether to be more cautious about extrapyramidal or metabolic adverse effects of antipsychotics. This approach will help choose the most appropriate medication and optimize outcomes for this population. To our knowledge, this topic has not been addressed previously in the literature, and further research is essential to guide clinical decision-making in this overlooked group.

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