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PHARMACOLOGY OF BIPOLAR DISORDER IN CHILDREN AND ADOLESCENTS

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Abstract

Bipolar disorder (BPD) is a condition characterized by extreme behavioral and mood changes that affect adults as well as children and adolescents. Diagnosing pediatric BPD frequently presents a challenge for clinicians, due to a wide range of symptom expression, high rate of comorbid disorders, developmental differences which are not a factor adults and various diagnostic criteria. Pharmacological intervention has proven to be most effective in the treatment of BPD amongst children and adolescents. Evidence based on multiple research studies strongly supports the use of mood stabilizers and/or atypical antipsychotic agents depending on symptom presentation. However, adverse effects associated with these medications call for attentive care of young patients. Psychosocial methods are also reccomended as adjunctive treatment.

KEYWORDS: atypical antipsychotics, bipolar disorder, children and adolescents, diagnostics, mood stabilizers, pharmacotherapy

INTRODUCTION

Bipolar disorder (BPD) in children and adolescents can cause severe disturbances in global functioning of children and their families. Children with BPD struggle with academic success and interpersonal relationships, while having a greater risk for substance abuse, hospitalizations and increased suicidal behavior.[1] Growing evidence from clinical and epidemiological studies around the world indicates that BPD often first manifests in adolescence or earlier, while its prevalence is approximated to 1%.[2,3] Patients in a manic episode frequently present with euphoric, expansive or irritable mood, and also present with pressured speech, impulsivity, racing thoughts, increased energy, hypersexuality, grandiosity and increased goal-directed activity.[2] Grandiosity and euphoria in children usually present with behaviors such as argumentativeness, bossiness and attitudes of superiority, i.e. that they are stronger or smarter than others including adults. More commonly, symptoms of irritability, rage, "affective storms," and aggression are prominent.[1] Along with these symptoms, high rates of suicidal ideations have been documented among youth with BPD, with its rate up to 30%.[4] Children and adolescents with BPD are also documented to have a high rate of comorbidity with other psychiatric disorders, especially attention deficit/hyperactivity disorder (ADHD).[5] Other comorbidities associated with bipolar youth include anxiety disorders, disruptive behaviour disorders and substance abuse disorders. In addition, evidence indicates that these comorbidities negatively affect the symptomatology, clinical course and the global functioning of BPD patients.[6]

ETIOLOGY

Currently, the etiology of BPD is unknown but appears to be due to an interaction of genetic, epigenetic, environmental and neurochemical factors. BPD is amongst the most heritable psychiatric diseases with its heritability of 80-85%, and with a nearly ten times higher recurrence risk in first-degree relatives of BPD patients.[7] Moreover, an association has been made between at least 30 genes and an increased risk of the condition.[8] Although it is difficult to establish causation between life events and the development of BPD, childhood maltreatment, particularly emotional abuse or neglect, as well as early parental loss have been linked to the later development of the condition.[9] Evidence also supports a strong genetic component and an epigenetic contribution. Human studies have shown changes in brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) in patients with BPD, indicating that neurotrophic signaling is a molecular mechanism associated with decreased neuroplasticity.[10] Neurochemical factors involved in producing symptoms of mood disorders involve imbalances in systems associated with monoaminergic neurotransmitters, particularly

dopamine and serotonin, as well as their interaction with deficits in other neurotransmitter systems, such as GABA and Substance P.[11] Lastly, functional MRI (fMRI) studies determined hyperactivation of the amygdala, prefrontal and visual system and hypoactivation of the anterior cingulate cortex in BPD, suggesting reduced control of the limbic regions by the prefrontal areas. This results in a low capacity to regulate emotion and interference in effective planning and goal pursuit.[11,12]

DIAGNOSTICS

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) is the standard classification used by mental health professionals in diagnosing BPD.[13] It divides BPD into five categories; BD-I, BD-II, cyclothymic disorder, specified bipolar and related disorders and unspecified bipolar and related disorders (Table 1). The DSM-V criteria are the same for adults and children, but many investigators have argued that it should be modified for pediatric BPD.

As such, pediatric BPD frequently presents a challenge for clinicians, due to a wide range of symptom expression, high rate of comorbid disorders, developmental differences that are not a factor in adults and various diagnostic criteria.[1] A key problem is the transposition of adult diagnostic criteria to define the illness in children and adolescents, since some of the symptoms such as impulsivity, hypersexuality, overspending and grandiose ideas are not experienced in the same way at different ages and have different baselines in youth, if they occur at all. Moreover, feelings of anxiety, low mood, fluctuations in self-esteem and variations in habits such as eating, sleeping and expanding energy are all normal in the development of youth; as such, they are challenging to distinct from an emerging BPD.[14] Lastly, differential diagnosis of BPD includes ADHD, major depressive disorder, anxiety disorders and personality disorders such as borderline personality disorder. It is important to remember that these disorders may coexist; it is estimated that BPD develops in approximately 30% of young individuals with ADHD, and up to 20% of BPD patients also suffer from borderline personality disorder.[1,15]

BASICS AND ACTION MECHANISMS OF PHARMACOLOGICAL AGENTS

Pharmacological agents currently prescribed in treating BPD are mood stabilizers, classified in two generations, alongside antidepressants. First-generation mood stabilizers (FGMSs), such as lithium, valproates, and carbamazepine, were introduced in the 1960s and 1970s.[16] Valproates and carbamazepine are also used as and referred to as anticonvulsants. Second-generation mood stabilizers (SGMSs) started as therapy in 1995, with the discovery of the mood-stabilizing properties of clozapine.[16] The SGMSs include atypical antipsychotics, such as clozapine, olanzapine, quetiapine, aripiprazole, and risperidone, as well as an anticonvulsant drug, lamotrigine. Recently, as a candidate for SGMSs, a novel antipsychotic, lurasidone, has been suggested.[16] Antidepressants are also used in the treatment of BPD, particularly depressive episodes, but are not recommended as monotherapy due to possible conversion to hypomania or mania.[1] Each drug should be trialed for a sufficient time and at a sufficient dosage to determine the effectiveness of the agent. Generally, a 6- to 8-week course of an antimanic agent, at appropriate doses, is recommended before adding or replacing it with another drug.[5]

Lithium is thought to exert multiple neurotransmitter effects, including enhancing serotonergic transmission, increasing norepinephrine synthesis, blocking postsynaptic dopamine, and increasing GABA activity. It also inhibits calcium, glutamate, and G-proteins, all components of the intracellular signaling cascade.[17] Both lithium and valproate inhibit protein kinase C.[1,17] Anticonvulsants have been reported to increase GABA neurotransmission and decrease glutamatergic channels, resulting in a net decrease in neuronal activity.[2] First generation antipsychotics are dopamine-blocking agents that vary in their affinity for the dopamine 2 receptor. Second generation atypical antipsychotics block not only dopamine but certain serotonine receptors as well. They appear to have mood stabilizing as well as antipsychotic effects. Antidepressants alleviate depression primarily through serotonergic, dopaminergic, and noradrenergic mechanisms.[11]

PHARMACOTHERAPY IN CHILDREN AND ADOLESCENTS

Lithium was the first medication to be approved by the US Federal Drug Administration (FDA) for the treatment of mania in BPD for youth aged from 12 to 17 years. It was also shown to be effective in treating acute episodes of depression in adolescents with bipolar I disorder.[18] Common adverse effects associated with lithium include nausea, headache, acne, weight gain, thyroid dysfunction, diabetes insipidus and tremor. Moreover, it is associated with an increased risk of Epstein's anomaly, a congenital defect of the tricuspid valve associated with maternal use during pregnancy.[2] Controlled studies suggest that divalproex sodium may be more effective in the treatment of acute episodes of mania in bipolar disorder, and less effective as a continuation therapy or for prevention of relapse.[18] Recent data also suggest that divalproex sodium may be less effective than atypical antipsychotics when used in the treatment of pediatric BPD.[2] It was also proven to be more effective in combination with quetiapine.[19] Common adverse effects include sedation, headache, gastrointestinal symptoms and weight gain.[2] Furthermore, pancreatitis, hepatotoxicity, alopecia, thrombocytopenia and polycystic ovary syndrome have also been associated with this medication.[2] There is some support for the use of carbamazepine in the treatment of BPD, with improvements seen in symptoms of mania, depression, ADHD and psychosis. However, according to research, the improvements were shown to be modest and of lower efficacy compared to lithium and divalproex sodium.[18]

Additionally, more serious side effects are reported, such as aplastic anemia and Stevens-Johnson's rash.[1]

Recent studies show that atypical antipsychotics, i.e., risperidone, olanzapine, aripiprazole, and quetiapine (also known as second generation mood stabilizers), may be more effective than FGMSs in the treatment of manic and mixed episodes with an improvement rate of 66% as compared to the rate of 38.5% for lithium. At the same time, it is important to emphasize that atypical antipsychotics, despite high efficacy, lead to more metabolic disorders in young people than FGMSs.[21] In an 8-week randomized controlled trial with 279 children and adolescents aged 6 to 15 years, subjects were randomly assigned to receive risperidone, lithium or divalproex sodium.[5] Patients in the risperidone group had a significantly higher response rate (68.5%) than those treated with lithium (35.6%) or divalproex sodium (24%).[5] Adverse effects of risperidone included weight gain, hyperprolactinemia, somnolence, headache and fatigue.[5,12] Olanzapine appears to work quickly and effectively with regard to treating manic and mixed symptoms, but it may not be an optimal first choice for maintenance therapy because of its metabolic adverse effects, such as significant weight gain, akathisia and increases in systolic blood pressure, total cholesterol, fasting glucose, serum prolactine levels and liver enzymes.[2,5] Nevertheless, it has been recommended by the FDA to treat depression in combination with fluoxetine.[1] Aripiprazole has been reported to have less metabolic adverse effects than the latter antipsychotics, whereas somnolence, parkinsonism and akathisia are most frequently reported. It also may be more effective in long-term treatment, and has partial agonist properties on D2 receptors, which makes it useful in treating comorbid ADHD symptoms.[5,12] Ziprasidone has also been reported to have a lower risk of being associated with metabolic syndrome, while proving to be effective in treatment as monotherapy. In a 4-week double-blind, placebo-controlled trial evaluating the efficacy of ziprasidone for mania in bipolar youth aged 10 to 17 years, results showed great improvement in manic symptoms and overall functioning in the ziprasidone group compared to the placebo group, while showing no greater risk of weight gain compared to placebo.[2] The most frequent side effects among patients are dystonia, headache, and sedation.[2,5] Quetiapine is indicated by the FDA for treating manic episodes as monotherapy or adjunctive therapy, with adverse effects being orthostatic hypotension and sedation.[2] Clozapine is reserved for treatment-refractory cases because of its substantial adverse effect profile; agranulocytosis, increased risk of myocarditis, arrhythmias, seizures and diabetes.[2,5] Less is known about the efficacy of topiramate in treating pediatric BPD, with some trials reporting a small improvement of symptoms and a lower remission rate, as well as trials reporting effectiveness as adjunctive therapy for reducing manic symptoms. Frequent adverse effects associated with topiramate include decreased appetite, cognitive impairments, weight loss, nephrolithiasis and paraesthesias.[2,18]

Several studies suggest that lamotrigine is effective as maintenance therapy and possibly for the treatment of depressive episodes, symptoms of mania, psychosis and ADHD. One open-label trial, which included 46 youths aged 8 to 18 years with BPD, found a response rate of 72% for manic symptoms and 82% for depressive symptoms.[18] However, it received a black-box warning for those under age 16 due to an increased incidence of Steven-Johnson's rash in youth.[1,2,18] Lurasidone was also shown to be effective in decreasing depressive symptoms in bipolar youth.[12] The use of selective serotonin reuptake inhibitors (SSRIs) in bipolar depression is suggested only in addition to mood stabilizers, due to the risk of manic episode development. However, a study conducted by Leverich et al. has shown that even combination therapy has rates of conversion to hypomania or mania up to 11% in acute and up to 21% in continuation trials.[1,5] Furthermore, in a review of six studies evaluating SSRIs in children with major depression, the rate of switching to mania/hypomania was between 2 and 6%. Pharmacological agents proven to be most effective in maintenance therapy are aripiprazole, lamotrigine, lithium and divalproex (Table 2). It is important to emphasize that although monotherapy is generally recommended for the management of pediatric BPD, combination therapy is often implemented due to partial response to treatment with a single agent. Nevertheless, drug benefit should always be weighed with the adverse effect profile, taking into account that combination therapy may lead to exacerbation of adverse effects.[2,5,12]

TREATMENT OF BPD AND COMORBID DISORDERS

As mentioned earlier, BPD in youth frequently presents with other comorbid disorders, which often worsen the prognosis of these patients. In treating comorbid BPD/ADHD, current evidence suggests the addition of a stimulant (mixed amphetamine salts or methylphenidate) or atomoxetine after mood stabilization.[5] Lithium and topiramate have shown to be effective in treating comorbid substance abuse in adolescents with BPD.[22,23] A study by Geller et al. evaluated pharmacotherapeutical-only intervention for co-occurring BPD and substance abuse disorder in adolescents. Adolescents receiving lithium had greater reductions in the percentage of urine screens positive for any substance.[23] Psychosocial methods have been recommended to treat other comorbidities as anxiety and disruptive behaviour disorders.[18] Furthermore, the occurrence of psychotic symptoms, present in many of the patients, should be considered in determining treatment options. A combination of second and third generation mood stabilizers has been recommended as an initial approach to these patients.[2]

PSYCHOTHERAPY

Given the complex presentation of symptoms in BPD, the likelihood of comorbid disorders, and the variable efficacy of pharmacological interventions, psychosocial treatments can be critical to improvement and are believed to be necessary as adjunctive treatment. These include focused psychotherapy for adolescents, individual family psychoeducational psychotherapy and

cognitive-behavioral therapy. These methods focus on increasing knowledge and understanding of BPD and its treatment, strengthening problem-solving and communication skills and assisting the family of the patients in the support of and involvement in the treatment process.[1,18]

PROGNOSIS

Despite substantial advances in the pharmacological treatment of BPD, a number of longitudinal outcome studies indicate that the course of this illness remains unfavorable for many patients, with a syndromatic persistence of 48% and functional remission of only 6%.[24] (Figure 1) Patients with total noncompliance or partial noncompliance do not differ significantly in outcome, supporting the general assumption that full treatment compliance is an essential goal of pharmacotherapy for patients with BPD. Treatment noncompliance is also associated with comorbid substance use disorders. Other factors that increase risk of recurrence include early age of onset, severity and family psychopathology.[25,26]

CONCLUSION

BPD in children and adolescents is a serious condition that requires great effort from clinicians as well as patients and their families. SGMSs have been shown to be most effective in treating this disorder, but are associated with many adverse effects that should be taken into careful consideration. Long-term prognosis also highly depends on full treatment compliance. Despite recent developments in the diagnostics and treatment of pediatric BPD, additional research is necessary for better assessment and achievement in this field.

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FARMAKOLOGIJA BIPOLARNOG AFEKTIVNOG POREMEĆAJA KOD DJECE I MLADIH

Sažetak

Bipolarni afektivni poremećaj (BAP) karakteriziran je ekstremnim promjenama u raspoloženju i ponašanju koje pogađaju odrasle kao i djecu i mlade. Dijagnosticiranje BAP-a često predstavlja izazov među liječnicima, s obzirom na širok raspon obrazaca simptoma, visoku stopu komorbiditeta, razvojne razlike u odnosu na odraslu populaciju i raznolike dijagnostičke kriterije. Farmakološka intervencija dokazano je najučinkovitija u liječenju BAP-a kod djece i mladih. Stabilizatori raspoloženja i/ili atipični antipsihotici strogo su preporučeni za uporabu, ovisno o prezentaciji simptoma. Međutim, štetni učinci povezani s ovim lijekovima zahtijevaju pozornu njegu mladih pacijenata. Psihosocijalne metode također su preporučene kao adjunktivna terapija.

KLJUČNE RIJEČI: atipični antipsihotici, bipolarni afektivni poremećaj, dijagnostika, djeca i mladi, farmakoterapija, stabilizatori raspoloženja