New treatment for bipolar disorder in children and adolescents: learning from adult studies

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Nuevos tratamientos para la enfermedad bipolar en niños y adolescentes: aprendiendo de los estudios en adultos

Summary

Introduction. *Up to 45% of bipolar patients fail to respond adequately to or do not tolerate treatment with standard antimanics (lithium, valproate, carbamazepine, or olanzapine). Several new potential normothymic and antimanic treatments are under study. However, there is less literature available on new treatments for bipolar disorder in children and adolescents, but many youths with manic symptoms are treated with mood stabilizers. Our goal was to review the current literature on alternatives to lithium, valproate and carbamazepine in the treatment of bipolar disorder in children, adolescents and adults, focusing on the potential uses of these drugs in youth.*

Methods. *In a comprehensive computerized and manual literature search in Medline, we identified articles, abstracts and book chapters describing new treatments for bipolar disorder in children, adolescent, and adults. We also manually searched the abstracts in recent APA, AACAP and ECNP Annual Meetings.*

Results. *There are very few studies on the treatment of youths with bipolar disorder. The strongest evidence of antimanic action in this age group is on lithium, valproate, and recently on olanzapine, and adjunctive risperidone. Evidence on new antiepileptics and other novel treatments is very limited or none.*

Conclusion. *More controlled studies on the treatment of children and adolescents with bipolarity are needed. Lithium, valproate, olanzapine and risperidone are probably the drugs with more evidence as antimanic efficacy in children and adolescents, but potential risks and benefits of treatment versus no treatment must be discussed with parents.*

Key words: *Bipolar. Mania. Children. Adolescents. Treatment. Lithium. Valproate. Antipsychotics.*

Resumen

Introducción. *Hasta un 45% de los pacientes con enfermedad bipolar no responde adecuadamente o no tolera el tratamiento con los estabilizadores del humor habituales. Actualmente se encuentran en estudio varios tratamientos potenciales con propiedades normotímicas y antimaníacas. Sin embargo, aun cuando muchos jóvenes con síntomas maníacos son tratados con estabilizadores del humor, hay poca literatura disponible respecto a nuevos tratamientos para la enfermedad bipolar en niños y adolescentes. El objetivo de este artículo es revisar la literatura disponible sobre alternativas al litio, valproato y carbamazepina en el tratamiento de la enfermedad bipolar en niños, adolecentes y adultos.*

Método. *A través de búsquedas en Medline y manuales identificamos artículos y capítulos que describían nuevos tratamientos para la enfermedad bipolar en niños, adolescentes y adultos. También revisamos manualmente los abstracts de las reuniones anuales más recientes de la APA, AACAP y ECNP.*

Resultados. *Hay muy pocos estudios que se refieran al tratamiento de jóvenes con enfermedad bipolar. Litio, vaproato y recientemente olanzapina y risperidona muestran la mayor evidencia de acción antimaníaca en este grupo en estudios abiertos no controlados. La evidencia respecto de nuevos antiepilépticos y otros tratamientos noveles es muy limitada o nula.*

Conclusión. *Se necesitan más estudios controlados en el tratamiento de niños y adolescentes con enfermedad bipolar. Litio, valproato, olanzapina y risperidona son probablemente los fármacos con más evidencia de eficacia antimaníaca en niños y adolescentes.*

Palabras clave: *Bipolar. Manía. Niños. Adolescentes. Tratamiento. Litio. Valproato. Antipsicóticos.*

INTRODUCTION

Lithium and the antiepileptic drugs valproate and carbamazepine are effective in the treatment of mania, with 60%-70% response rates in adults[1]. Verapamil also seems to be an effective antimanic agent, although no multicenter studies are available up to the present date[1]. In the year 2000, the atypical antipsychotic agent olanzapine was approved by the U.S. Food and Drug Administration (FDA)

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for the treatment of acute mania in a highly and rapidly changing commercial atmosphere. Up to 45% of the patients who suffer this disease do not respond to the usual mood stabilizers[2] or do not tolerate treatment. Furthermore, the action mechanisms of the normothymics are still being studied. There is considerable interest in the potential use of other drugs in the treatment of bipolar disease, and there are several recent studies on the potential benefits of new epilepsy drugs, noval antipsychotics, drugs such as inositol reuptake inhibitors, proteinkinase-C inhibitors (PKC) (such as tamoxifen), and procedures such as repeated transcranial magnetic stimulation (rTMS). Finally, several drugs (lithium, valproate, carbamazepine, beta-blockers, atypical antipsychotics) are apparently effective in the treatment of some adults with irritability and pathological aggressivity[3].

However, in spite of these studies in adult patients, the existing literature regarding new treatments for bipolar disease in children and adolescents is scarcer. This can be partially due to the present controversy between experts in relationship even to the existence or non-existence and to the diagnostic criteria of bipolarity in children and adolescents[4]. In spite of this relative lack of data, many children and adolescents with mania or «maniform symptoms» are treated in fact with mood stabilizing drugs[5]. However, those drugs that have been shown to be effective in adults are not necessarily effective in children. It is known that tricyclic antidepressants have not been shown to be effective compared to a placebo in controlled trials in children and adolescents with major depression, which contrasts with its demonstrated effectivity in adults[1]. The objective of this article is to perform an updated review of the literature available regarding the alternatives to the use of lithium, valproate and carbamazepine in the treatment of bipolar disease in children, adolescents and adults, focusing on the potential utility of these drugs in the youngest.

METHOD

Using a Medline and manual search of the literature, we identified the articles, summaries and book chapters that described new treatments for bipolar disease in children, adolescents and adults. Furthermore, we performed a manual search of the summaries of the recent annual congresses of the American Psychiatric Association (APA), American Academy of Child and Adolescent Psychiatry (AACAP) and the European College of Neuropsychopharmacology (ECNP). We describe our findings according to the different pharmacological groups.

RESULTS

Conventional mood stabilizers: lithium, valproate and carbamazepine

In spite of the growing use of mood stabilizing drugs such as lithium, carbamazepine and sodium valproate in children and adolescents with bipolar disease, there are very few controlled, double blind studies on efficacy of any mood stabilizer in children and adolescents with this disease[6]. A recent study randomly assigned 42 out-patients (mean age = 11 years; 20 with Bipolar Disease I, and 22 with Bipolar disease II) to 6 weeks of treatment with lithium, sodium divalproate or carbamazepine. The response indexes (CGI improves at 1 or 2, or > 50% of change on baseline score of the Y-MRS scale) were: divalproate 53%, lithium 38% and carbamazepine 38% ($\chi^2 = 0.85$, $p = 0.60$). There were no significant differences among the 3 groups, the three mood stabilizers were well tolerated and no important side effects were observed[7]. In this study, Kowatch et al (2000) reviewed previous studies with lithium, valproate and carbamazepine, and only found one double blind study on lithium controlled with placebo performed by doctor Geller in 25 adolescents with bipolar disease and comorbid substance abuse. After 6 weeks, the adolescents treated with lithium showed a significant decrease in substance abuse and significant improvement in their score on the general functioning scale (GAF)[8].

As far as we know, the study of the Kowatch group (2000) is the last study published on the use of the anticonvulsivants valproate and carbamazepine in children with bipolar disease. We also found 7 previous publications of non-controlled studies with sodium divalproate in children with bipolar disease: 3 clinical cases[9-11], and 4 series of cases[12-15]. The average number of subjects in these series was 5, and they suggest a wide variety of responses to treatment[7]. Analogously, a recent open study of 2-8 weeks in 40 bipolar children and adolescents (ages: 7-19) with manic, hypomanic or mixed episode found a response of 61% to valproate (> 50% of improvement on the Young mania scale, Y-MRS). However, very few participants were included in the double blind phase for the statistical analysis[16].

In spite of the efficacy of carbamazepine in adults with acute mania as second line treatment, this drug has never been studied in a controlled way in children and adolescents with bipolar disease. Most of the articles on carbamazepine come from children and adolescents with attention deficit and hyperactivity disorder (ADHD) or behavior disorder, some of which also present neurological disorders[7].

New generation anticonvulsivants

Lamotrigine

Lamotrigine inhibits the release of the excitatory neurotransmitter glutamate. Preliminary studies, most of them open but also some controlled ones, show the efficacy of this drug in adults with bipolar disease resistant to treatment, it presenting antidepressive and mood stabilizer effects[17-21]. The principal side effects of lamotrigine are nausea, headache, diplopia, vertigo, ataxia and blurred vision[22]. Risk of a serious cutaneous reaction (3%-4% of incidences), including the Steven-Johnson syn-

drome, associated to the use of lamotrigine is a severe limitation to the potential use of this drug in children and adolescents with psychiatric disorders. In the United States, the use of lamotrigine is not approved in children under 16 years of age. Until more data are available, this drug should not be used in children or adolescents with mania. In any case, careful documentation should be made of an important reason to not follow this general guideline, and of previous failures in studies with other safety drugs[23].

Topiramate

The action mechanism of topiramate includes: potentiation of GABA activity, antagonism of the glutamatergic receptor and sodium channel blockage[24]. Preliminary data in open studies in adults suggests the potential efficacy of topiramate as an antimanic and mood stabilizer/anticycler, in the treatment of bipolar disease[24-31]. However, some patients treated with topiramate experience worsening of their psychotic (3%), depressive (15%) or cognitive symptoms[28,29,32] or developed manic symptoms for the first time[33]. Topiramate is generally well tolerated in children and adolescents with epilepsy and can cause weight loss in some patients[34], which can be desirable at times. Principal side effects include vertigo, drowsiness, psychomotor slowdown, nervousness, paresthesia and ataxia. There is 1%-2% of nephrolithiasis incidence due to inhibition of carbonic anhydrase[22]. Unfortunately, as far as we know, there are no data on its efficacy in children and adolescents with mania.

Gabapentin

Gabapentin is a structural analogue of the GABA that does not interact with GABA receptors. It has a similar structure to that of L-leucine, and interacts with high affinity binding receptors associated with the L-leucine-like amino acid transporter (or similar to L-leucine) of the neuronal cell membrane, causing an increase in turnover of in vivo GABA[35]. Initial open studies indicated the potential efficacy of gabapentin association to other normothymics as antimanic and mood stabilizing drugs in adults[36-39] and adolescents with bipolar disease[35,40]. However, controlled studies that have compared monotherapy of gabapentin with lithium, lamotrigine and placebo have been negative up to now[21,41]. Other studies suggest a potential benefit of gabapentin in the treatment of anxiety disorders[42], alcohol abstinence[43], cocaine dependence[44,45], restless legs syndrome[46] and trigeminal neuralgia[47]. Gabapentin is generally well tolerated, and has a benign profile of side effects and absence of interactions with other drugs. The average dose in the studies published varied from 539 to 3,600 mg/day[22]. Three clinical cases published on patients with epilepsy have described behavioral deinhibition or hypomania in 10 children and one adult, respectively, when gabapentin was associated other antiepileptic drugs[48-50].

Tiagabine and vigabatrin

There are already some studies underway to establish the potential antimanic effect of the competitive inhibitor of GABA reuptake, tiagabine in adults[51]. Its principal side effects are ataxia, nervousness, and tremor[22]. However, we have still not found any studies published on the use of tiagabine in mood disorders. The preliminary results of the use of vigabatrin have not been positive up to now[51]. Up to 10% of the patients in the studies of treatment with vigabatrin develop affective symptoms such as agitation, irritability, and depression[22].

In summary, there is very little data available on the use of the new anticonvulsants gabapentin, topiramate, tiagabine and vigabatrin in children and adolescents with mania. After the preliminary findings in adults, there is very little evidence on the potential use of gabapentin in children and adolescents with bipolar disease at present. The use of topiramate as an antimanic agent in children and adolescents has not been examined up to now and the use of lamotrigine in this group is very limited, given the high incidence of skin rashes, so that its use is generally not recommended or is advised against. There are no data in any age group on the use of tiagabine and vigabatrin in mood disorders. In spite of the increase of clinical use of lithium, valproate and carbamazepine, controlled studies on the use of these drugs in children with mania are necessary.

Clozapine and other atypical antipsychotics

Traditional or «typical» antipsychotics (D2 dopaninergic agonists) are effective in the treatment of acute mania and also prevent recurrence of bipolar disease episodes. However, due to the risk of tardive dyskinesia and extrapyramidal symptoms, they are considered a second line treatment[52].

Clozapine

Clozapine has a minimum or null risk of tardive dyskinesia and it is effective in the treatment of acute mania (with or without psychotic symptoms) as well as in the prophylaxis of bipolar recurrences (mood stabilizing effect). One clinical case has been published on a 13 year old child with refractory bipolar disease and obsessive compulsive disorder who responded to a combination of clozapine, clomipramine and lithium[53].

However, given the risk of agranulocytosis associated to clozapine (1% incidence), similar atypical antipsychotic drugs have been developed but without this potentially fatal side effect. In 1998, Toren et al reviewed the clinical experience published with atypical antipsychotics in children and adolescents with any disorder (MedLine 1974-1998). These authors found 5 double blind placebo controlled studies (n = 105), 24 open clinical trials (n = 387), and 33 series of cases (n = 115), that provided data regarding the use of clozapine, risperidone, olanzapine, sulpi-

ride, tiapride, amisulpiride, remoxipride and clotiapine in children and adolescents. Some of these drugs, especially clozapine, risperidone and olanzapine, were shown to be effective in the treatment of schizophrenia, bipolar disease, and generalized disorders of the development of the autistic spectrum. However, they only found 3 studies of cases of clozapine (n = 12), 2 of risperidone (n = 12) and one case of colanzapine (n = 2) in children with mood disorder[54].

Olanzapine

Olanzapine has a profile of affinity to receptors similar to that of clozapine and a better profile of side effects. It has been approved in the United States (2000) for the treatment of acute mania[55,56]. Preliminary open studies indicate the efficacy of olanzapine in the treatment of acute mania in adolescents[57-59]. In these three clinical cases (n = 33; ages 5-17 years), the response rate was «pronounced», 61%, and 71%, respectively, and the dose varied from 2.5 to 20 mg/day. The principal side effects were sedation and weight increase, however, these studies did not report extrapyramidal side effects. The Frazier study (2000) found a significant average change, from the baseline to the end point, in the Y-MRS of -19 + 9 ($p < 0.001$). However, another series of cases in 5 hospitalized children (ages 6 to 11 years) with different diagnoses (bipolar disease, non-specified psychosis, schizophrenia and ADHD) showed improvement in three patients, but the treatment with olanzapine was interrupted in the 5 children within the first 6 weeks of treatment due to adverse effects or lack of clinically significant response. The average duration of the treatment with olanzapine was 32 days (range 2 to 7 weeks) and the average dose was 7.5 mg/day (range = 2.5-10 mg/day)[60].

Risperidone

Risperidone also has a low potential risk of tardive dyskinesia, however (as with olanzapine), it is not as effective as clozapine in the treatment of resistant schizophrenia. Since risperidone has fewer side effects than haloperidol, including fewer negative effects on cognition, some controlled studies on risperidone are presently being carried out in the treatment of mania. There are several cases published that describe the efficacy of risperidone in acute mania and rapid cycling in adults, when this drug has been used as therapy associated to a mood stabilizer[61-64]. However, there are also cases that report worsening of the manic symptoms with treatment with risperidone[56,65]. In a recent open study, risperidone was administered to 26 subjects (24 children: 19 with borderline IQ and 5 with mild mental retardation) from 10 to 18 years of age, who were hospitalized for treatment of a psychiatric disorder associated to aggressive behavior. The risperidone doses varied from 0.5 to 4 mg, for period of 2 to 12 months. Fourteen (54%) of the 26 patients presented a marked reduction in aggressivity, and 10 subjects presented a moderate one. The principal side effects reported were weight increase in 2 subjects and sedation in 7 children who required dose reduction. These results suggest that risperidone can be useful in the treatment of severe aggressive behavior in children and adolescents[66]. A retrospective review of the clinical histories of out-patients (n = 28, average ± SD of age, 10.4 ± 3.8 years) with bipolar disorder (25 mixed and 3 hypomanic) treated with risperidone (average ± SD dose = 1.7 ± 1.3 mg/day; duration: 6.1 ± 8.5 months) found improvement in the aggressive and manic symptoms in 82% of the children and in the psychotic symptoms in 69% of the patients. To define improvement (robust), an improvement of the CGI ≤ 2 (sufficient or much improvement) was used. The authors concluded that, even though it was limited due to its retrospective nature, this study suggests that risperidone can be effective in the treatment of youths with acute mania[67].

In another open trial, risperidone was administered to a clinically heterogeneous group of 11 children and adolescents (age range 5.5-16 years, average 9.8 years) with affective symptoms (most suggesting bipolar disease), aggressive and violent behavior, and pronounced management problems. These patients had responded inadequately to other normothymic drugs. In our sample of outpatients 8 (73%) of 11 children seemed to present therapeutic response with risperidone. The risperidone doses were low (0.75-2.5 mg/day) and the clinical responses were sometimes observed at a few days of receiving the medication. In 7 of 8 children, improvement was judged to be moderate to important. The principal side effects reported were sedation and weight increase. Seven (87.5%) of the eight responders were taking another concomitant drug (4 of them were receiving mood stabilizers) in subtherapeutic doses. These preliminary findings suggest that risperidone (as monotherapy or associated therapy) can be useful in the treatment of children and adolescents with mood disorders (especially subthreshold bipolar disease) and with aggressive behavior[68].

A retrospective review of the clinical histories in 38 children and adolescents (ages 5-17 years) with different psychiatric disorders treated with risperidone (mean treatment duration: 15 months; mean dose: 2.5 mg/day) found no significant abnormalities in the hepatic enzymes, suggesting that risperidone in short term treatment does not affect the hepatic function in children and adolescents. However, prospective studies on a large scale are necessary to confirm these findings[69].

Quetiapine

Although there are still no controlled studies with quetiapine, there are some studies that describe the use of quetiapine in adults with treatment resistant mania, with low risk of extrapyramidal symptoms[70,71]. An open study (n = 10) of adolescents with schizoaffective disorder (n = 7) and bipolar disorder with psychotic symptoms (n = 3) showed dose dependent pharmacokinetics, absence of serious adverse events and of extrapyramidal symptoms (the most common side effects were insom-

nia and orthostatic hypotension) and improvement in positive and negative symptoms, BPRS *(Brief Psychia - tric Rating Scale)* and CGI. This study was not designed to evaluate improvement of manic symptoms[72]. There is one clinical case published of a 9 year old girl with mania and psychotic symptoms, treated satisfactorily with a combination of quetiapine (450 mg/day) with valproate, after not responding to multiple combinations of mood stabilizers and antipsychotic agents[73].

Ziprasidone

In a recent 3 week double blind study, ziprasidone was more effective than placebo in acute mania in adults[74], however there are no studies in children or adolescents with mania.

In summary, atypical antipsychotic agents are used in the treatment of bipolar disease, generally in acute episodes of mania. There are some data regarding the potential use of olanzapine and risperidone in the treatment of mania in children and adolescents, with a tolerable profile of side effects. Use of risperidone added to mood stabilizer treatment is well tolerated and effective in relieving manic symptoms in adolescents[56]. These drugs are well tolerated and seem to also be effective in depressive episodes. However, cases of tardive dyskinesia or dystonia induced by atypical antipsychotics and also cases of tardive dyskinesia that have improved with the use of atypical antipsychotics have been described[56,75]. To use these drugs in children, we should consider the potential endocrine risks (weight gain, prolactin increase) and neurological ones (extrapyramidal symptoms, tardive dyskinesia) with the potential benefits of the treatment and also the risk associated to no treatment (suicide, hospitalization, etc.).

Future treatments for bipolar disease in adults

Although we have not found data published regarding the use of the following drugs in children and adolescents with bipolar disease, however, we briefly review the preliminary findings in this growing area of investigation in adults with bipolar disease, since it is a potential area for better knowledge on this disease in all the age groups.

Transcranial magnetic stimulation (rTMS)

Electroconvulsive therapy (ECT) is effective in the treatment of mania and depression[76]. Given the similar properties of ECT and rTMS, there are preliminary studies of rTMS in the treatment of mania. Recent studies show that the stimulation of the right prefrontal cortex by rTMS has antimanic properties with a duration of 14 days after 10 treatments. Left prefrontal cortical stimulation produces an antidepressive effect. Parameters such as frequency of magnetic stimulus, its intensity and site are still under study. The advantages over ECT are that the rTMS has no endocrine or cognitive side effects and does not require general anesthesia. Given these advantages, maintenance treatment with rTMS is probably preferable to maintenance ECT[51]. We found only one study that described the clinical case of a 28 year old female patient with bipolar depression who did not present clinical response according to the Hamilton scale for depression, after 10 sessions of rTMS on the right dorsolateral prefrontal cortex[77].

Inositol reuptake inhibitors

Inositol is a polyol with a key role in the phosphoinositol-phosphate (PIP) cycle. The PIP cycle is the origin of two important second messengers: IP3, responsible for producing an increase of free calcium in the cytosol, and DAG that activates the proteinkinase-G (PKG). These second messengers are important in the function of the cholinergic (muscarinic), noradrenergic (αl), serotonergic (5-HT2a and 5-HT2c) receptors, and in other neurotransmitter systems. In the PIP cycle, the enzymatic degradation of IP3 is inhibited by lithium, reducing the availability of intracellular inositol and thus reducing the ability of the cell to react to the effect of the interaction between the neurotransmitters and their receptors. Depletion of the inositol levels by inhibition of the PIP cycle is the present hypothesis on the therapeutic effect of lithium in mood disorders[78]. Based on the hypothesis of depletion of inositol by lithium the efficacy of the inositol reuptake inhibitors (L-fucose and nordidemnin) is under study in adults with mood disorders. Preliminary results show that these drugs strengthen the action of lithium and can be useful in adults who are non-responding or partially responding to lithium, however, up to now, there are no studies in children and adolescents[78,79].

Proteinkinase-C inhibitors (PKC)

Recent studies on the antimanic action mechanism of lithium and valproate indicate that lithium (via reduction of inositol) and valproate also inhibit the action of PKC. Lithium and valproate affect the PKC action in the gene activation in the DNA through this inhibition of PKC. Tamoxifen is a drug used in the treatment of hormone dependent breast cancer, with an antiestrogen action based on the competitive binding to estrogen receptors. Tamoxifen is a potent inhibitor of PKC, and preliminary studies indicate that it has an antimanic action in adults. In the future, the PKC inhibitors can be useful in the treatment of bipolar disease, however, there are no studies published in children and adolescents[79,80].

Omega-3 fatty acids

There is considerable interest in this field after the preliminary double blind placebo controlled study with omega-3 fatty acids in the treatment of adults with bipolar disease that was positive[81], however we have not found any data regarding this treatment in adolescents and children.

CONCLUSIONS

Literature on bipolar disease treatment in children is scarce. Even the use of traditional mood stabilizers such as lithium, valproate, carbamazepine and classic antipsychotics is not based on controlled studies up to the present date. Presently, the drugs having the most available data supporting their antimanic effect in children are lithium and valproate. Furthermore, data are emerging in relationship to the role of new atypical antipsychotics such as risperidone, olanzapine, and probably quetiapine in the treatment of mania in children or adolescents. There are no data up to now regarding ziprasidone in young people with mania. Regarding new epilepsy drugs, there are only some articles on the use of gabapentin in this population, however, due to its poor results in adults, gabapentin will probably remain as an associated treatment and not monotherapy in any case. There are no data regarding the use of topiramate in children with bipolar disease and the use of lamotrigine is very limited given its potential risk of rash and Stevens-Johnson's Syndrome. The rTMS, inositol reuptake inhibitors and PKC inhibitors are still being studied and can represent a new era in the treatment of bipolar disease due to their intervention on specific intracellular targets.

As always, we should be careful in the use of new drugs in children and consider the potential risks of undesired effects in relationship to the risks of traditional treatments and the risk of not treating the child. It is essential to discuss these risks and benefits with the parents so that they can give their informed consent for the treatment. Finally, it is clear that more controlled studies on the pharmacological treatment of children and adolescents with bipolar disease are needed.

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