UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: PSIQUIATRIA
DISSERTAÇÃO DE MESTRADO

CORRELAÇÃO ENTRE OS NÍVEIS PERIFÉRICOS DE FATOR NEUROTRÓFICO DERIVADO DO CÉREBRO E VOLUME DE HIPOCAMPO EM CRIANÇAS E ADOLESCENTES COM TRANSTORNO BIPOLAR

TATIANA LAUXEN PERUZZOLO

Orientador: Prof. Dr. Cristian Patrick Zeni

Agosto de 2014.

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SUMÁRIO

LISTA DE SIGLAS E ABREVIATURAS

BDNF: Brain-Derived Neurotrophic Factor (Fator neurotrófico Derivado do Cérebro)

CDRS: Children's Depression Rating Scale

Digit Span IO: Escore da Ordem Inversa do Subteste de Dígitos

Digit Span TS: Escore Total do Subteste de Dígitos

DSM-IV: Manual Diagnóstico e Estatístico de Transtornos Mentais 4º Edição

K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children/ Present and Lifetime Version

NOS: Not Other Specified

TB: Transtorno Bipolar

TBP: Transtorno Bipolar Pediátrico

TDAH: Transtorno de Déficit de Atenção e Hiperatividade

VHD: Volume de Hipocampo Direito

VHE: Volume de Hipocampo Esquerdo

VHT: Volume de Hipocampo Total

WISC-III: Wechsler Intelligence Scales

YMRS: Young Mania Rating Scale

LISTA DE TABELAS

1. **ARTIGO 1**

2. **DEMAIS ARTIGOS – ARTIGO 2**

RESUMO

INTRODUÇÃO

O Transtorno Bipolar Pediátrico (TBP) é um transtorno mental grave que afeta o desenvolvimento e o crescimento emocional dos pacientes acometidos. O Fator Neurotrófico Derivado do Cérebro (Brain-Derived Neurotrophic Factor – BDNF) é reconhecido como um dos possíveis marcadores do quadro e de sua evolução. Esta neurotrofina tem reconhecido papel na sobrevivência, diferenciação e crescimento neuronal durante a infância e a idade adulta, atuando em áreas cerebrais envolvidas na patogênese dos transtornos de humor, como a amígdala e o hipocampo. Anormalidades na sinalização do BDNF no hipocampo poderiam explicar o declínio cognitivo visto em pacientes com TB.

OBJETIVOS

O estudo de possíveis correlações entre BDNF sérico e volume do hipocampo em pacientes com transtorno bipolar pode trazer importantes contribuições para a compreensão da neurobiologia do Transtorno Bipolar (TB). Assim, nosso objetivo com este estudo é avaliar possíveis mudanças no volume do hipocampo em crianças e adolescentes com TB e avaliar sua associação com os níveis séricos do BDNF. Além disso, avaliamos o desempenho de pacientes com TB em tarefas cognitivas relacionadas ao hipocampo e verificamos se houve correlação com os fatores mencionados acima, ou com o tempo de duração da doença.

MÉTODOS

A amostra incluiu 30 pacientes com idade de sete a dezessete anos, participantes do ProCAB (Programa para Crianças e Adolescentes com Transtorno Bipolar).

Processo de avaliação: Pacientes e seus familiares passaram por uma triagem com os critérios do DSM-IV para TB, uma entrevista semi-estruturada, (K-SADS-PL), e finalmente por uma avaliação clínica seguida da aplicação de escalas para mensuração de sintomas de humor. Dos pacientes com diagnóstico confirmado de TB foram coletadas amostras de sangue para avaliação dos níveis do BDNF, e realizada a ressonância magnética do encéfalo.

RESULTADOS

A média observada (mm3) dos volumes de hipocampo direito e esquerdo foi, respectivamente, de 41910.55 e 41747.96. A média dos valores encontrados de BDNF periférico foi de 19.58pg ⁄ µg proteína, com desvio-padrão de 6,33. Não foram encontradas correlações estatisticamente significativas entre os níveis periféricos de BDNF e volume de hipocampo. Também não foram encontradas correlações significativas entre o desempenho cognitivo e volume de hipocampo, nem entre os demais fatores e duração da doença.

CONCLUSÃO

Ao contrário do que é observado em estudos de adultos com TB, não foram encontradas correlações entre os níveis periféricos de BDNF e volume de hipocampo. O mesmo ocorreu em relação à memória de trabalho e duração da doença. Acreditamos que a ausência de correlação observada neste estudo se deve ao curto tempo de evolução do TB em crianças e adolescentes. Além de estudos com maiores tamanhos amostrais para confirmar os

presentes achados, investigações longitudinais, avaliando o desenvolvimento cerebral tendo um grupo de controles, e incluindo pacientes em diversos estados de humor, virgens de tratamento podem auxiliar no esclarecimento do papel do BDNF nas alterações cerebrais decorrentes do TB.

ABSTRACT

INTRODUCTION

Pediatric Bipolar Disorder (PBD) is a serious mental disorder that affects the development and emotional growth of affected patients. The Brain Derived Neurotrophic Factor (Brain-Derived Neurotrophic Factor - BDNF) is recognized as one of the possible markers of the framework and its evolution. This neurotrophin has recognized role in the survival, differentiation and neuronal growth during childhood and adulthood, acting on brain areas involved in the pathogenesis of mood disorders, such as the amygdala and the hippocampus. Abnormalities in BDNF signaling in the hippocampus could explain the cognitive decline seen in patients with TB.

OBJECTIVES

The study of possible correlations between serum BDNF and hippocampal volume in patients with bipolar disorder can provide important contributions to the understanding of the neurobiology of Bipolar Disorder (BD).Thus, our aim with this study was to evaluate possible changes in hippocampal volume in children and adolescents with BD, and associate them to serum BDNF. Additionally, we evaluated the performance of cognitive tasks related to the hippocampus and verified if they presented a correlation with the factors mentioned above, or disease duration.

METHODS

Subjects included 30 patients aged seven to seventeen years from the ProCAB (Program for Children and Adolescents with Bipolar Disorder).

Evaluation process: Patients and their families underwent a screening in which are applied the DSM-IV criteria for TB, and a semi-structured interview (K-SADS-PL).Finally, the patients underwent clinical evaluation, followed by the application of scales to measure mood symptoms. Of the patients with confirmed diagnosis of TB blood samples were collected to evaluate the levels of BDNF and performed magnetic resonance imaging.

RESULTS

We observed mean right and left hippocampal volumes of 41910.55 and 41747.96 mm^3, respectively. The mean value found for peripheral BDNF levels was 19.58 pg/µg protein, with a standard deviation of 6.33. No statistically significant correlations between peripheral BDNF levels and hippocampal volumes were found. Also no significant correlations between cognitive performance and hippocampal volume, or between other factors and disease duration were found.

CONCLUSION

We believe that the lack of correlation observed in this study is due to the short time of evolution of BD in children and adolescents. Besides studies with larger sample sizes to confirm the present findings, longitudinal assessments, addressing brain development versus a control group, and including drug-naive patients in different mood states may help clarify the role of BDNF in the brain changes consequent from BD.

1.INTRODUÇÃO

O Transtorno Bipolar (TB) é um transtorno mental grave, caracterizado por alterações de humor durante as quais uma pessoa tem pelo menos um episódio maníaco, hipomaníaco ou misto, habitualmente acompanhados por um episódio depressivo. Episódios maníacos podem ser marcados por grandiosidade, euforia, irritabilidade, aumento das atividades dirigidas a objetivos ou agitação psicomotora, além de diminuição da necessidade de sono, pressão da fala, fuga de idéias, distração, hipersexualidade, envolvimento excessivo em atividades prazerosas e perda do julgamento crítico. Episódios depressivos caracterizam-se pela presença, por um período mínimo de 2 semanas, de humor deprimido ou perda de interesse ou prazer por quase todas as atividades. Além disso, os indivíduos devem apresentar alterações no apetite ou peso, sono e atividade psicomotora, diminuição da energia, sentimentos de desvalia ou culpa, dificuldades para pensar, concentrar-se ou tomar decisões, bem como pensamentos recorrentes sobre morte ou ideação suicida, planos ou tentativa de suicídio. Em crianças e adolescentes, o humor pode ser irritável ao invés de triste. (1)

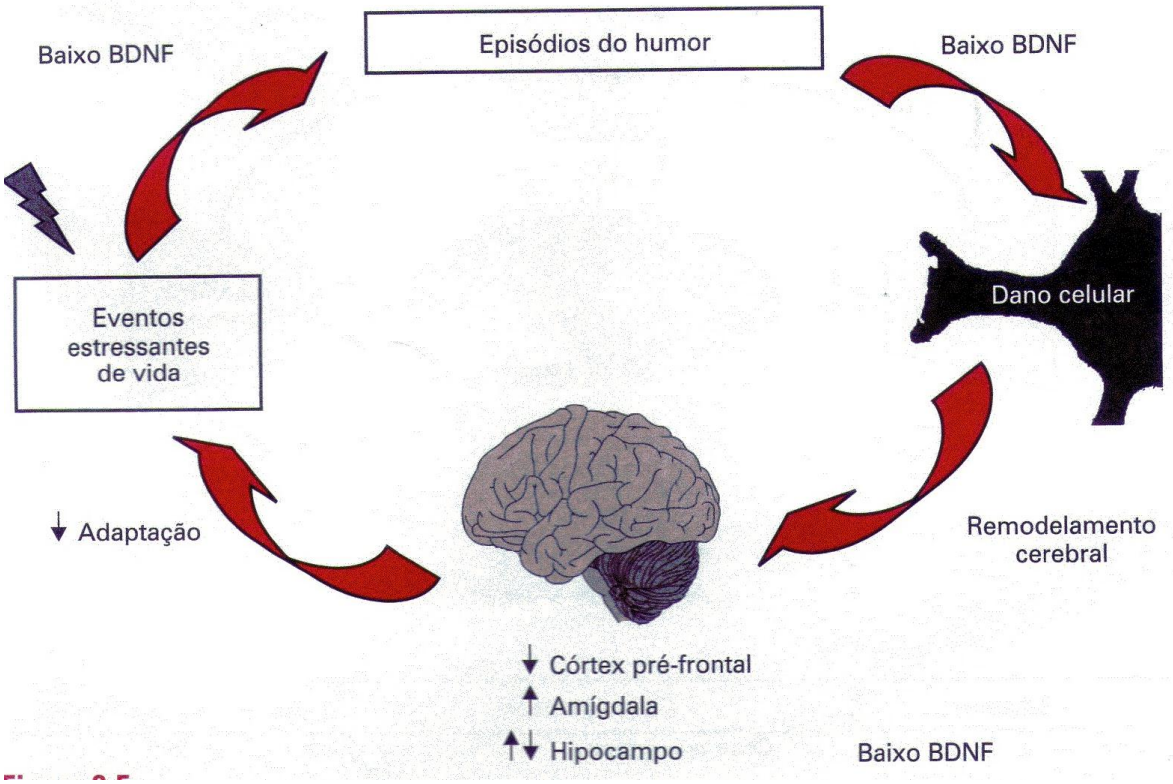
O TB ocorre em aproximadamente 0,4 a 1,6% dos adultos. (2) Opiniões de especialistas, combinadas com resultados de estudos realizados em adultos mostrando que o início da doença ocorre durante a infância, sugerem que o transtorno tem uma prevalência de 1% a 2,9% em crianças e adolescentes. (3-5) Ele está associado a altas taxas de tentativas de suicídio, dificuldades escolares, comportamento de alto risco, como promiscuidade sexual e abuso de drogas, bem como dificuldades nas relações interpessoais, problemas legais e várias hospitalizações. (6, 7)

Além das consequências citadas acima, estudos mostram que crianças e adolescentes com TB apresentam déficits em várias áreas cognitivas. Entretanto, não foi estabelecido se as

mudanças cognitivas percebidas ocorrem concomitantemente com o estabelecimento dos sintomas, ou devido à evolução do quadro. De qualquer modo, o TB perturba o desenvolvimento cognitivo normal, com potencial impacto de reduzir a capacidade funcional dos indivíduos ao longo da vida. (8) Os resultados mais consistentes foram encontrados em relação a prejuízos na memória verbal, além de outros domínios cognitivos tais como memória de trabalho, atenção, funções executivas, flexibilidade cognitiva, aprendizagem reversa, velocidade de processamento e memória visuo-espacial estejam deficitários. (9)

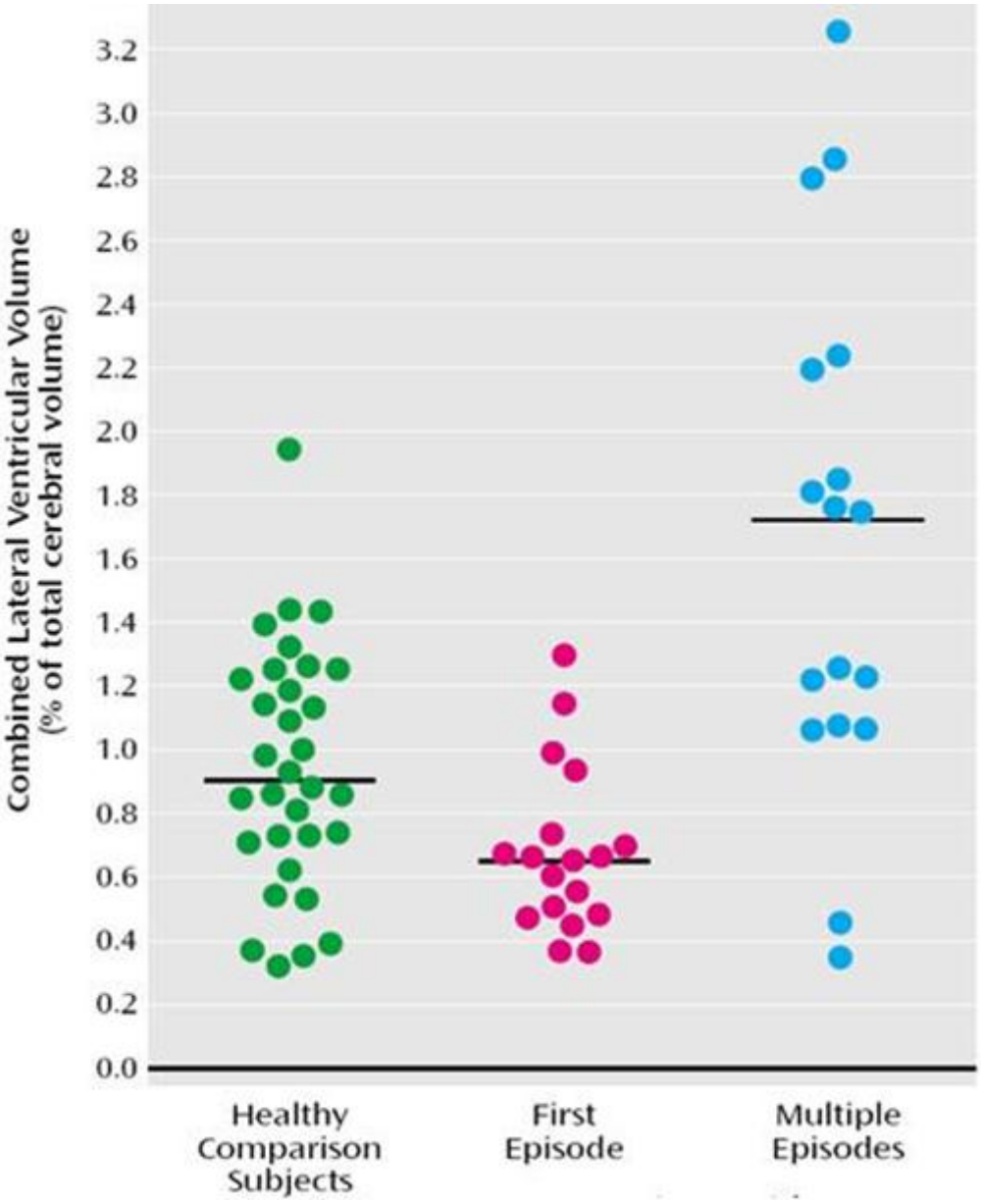
Muitos avanços foram feitos nas pesquisas sobre os fatores causadores do TB, aventando-se que sua etiologia seja multifatorial, provavelmente incluindo fatores orgânicos e psicossociais. (10) Dados de pesquisas em adultos sugerem que neurotrofinas, particularmente o fator neurotrófico derivado do cérebro (Brain-Derived Neurotrophic Factor - BDNF), além de marcadores de inflamação e estresse oxidativo podem estar relacionados com a etiologia do TB. (11, 12)

As neurotrofinas são neuropeptídeos essenciais para o desenvolvimento do sistema nervoso. No cérebro adulto, atuam na plasticidade sináptica. (13, 14) De todas as neurotrofinas, o BDNF é o mais abundante no cérebro e tem sido implicado em processos neuronais como a neurogênese, sobrevivência neuronal, plasticidade sináptica e crescimento dendrítico. (15) Há evidência consistente relacionando seus níveis séricos e atividade da doença no transtorno bipolar em pacientes adultos(16), sugerindo-se que a viabilidade neuronal possa ser afetada pela redução persistente das neurotrofinas (17), como mostra a figura extraída de Kapczinski et al.(2009).(18)



Kauer Sant'Anna e colegas descobriram que os níveis de BDNF são mais baixos em pacientes que tiveram vários episódios da doença, o que levou à hipótese de que uma modulação por neurotrofinas episódio-relacionada poderia explicar algumas das mudanças estruturais no cérebro, observadas em pacientes bipolares. (19)Além disso, o BDNF é altamente expressado no córtex e hipocampo, áreas do cérebro conhecidas por regular funções complexas, como memória e emoção. Anormalidades na sinalização do BDNF no hipocampo poderiam explicar o declínio cognitivo visto em pacientes com TB.(17, 20)

Há também um crescente corpo de dados que demonstram reduções regionais no volume cerebral acompanhadas por atrofia/perda celular no TB. Assim, estudos de imagem estruturais demonstraram volumes reduzidos de substancia cinzenta em áreas do córtex orbital e medial pré-frontal, estriado ventral e no hipocampo, bem como ampliação de terceiros ventrículos nos pacientes com TB, em relação aos controles saudáveis. Não se sabe se esses déficits constituem anomalias de desenvolvimento que poderiam conferir vulnerabilidade a episódios anormais de humor, mudanças compensatórias para outros processos patogênicos, ou sequelas de episódios afetivos recorrentes. (17)



Strakowski SM et al. Am J Psychiatry 2002.(21)

Resultados de estudos de neuroimagem estruturais e funcionais em TBP geralmente convergem com estudos em adultos, implicando estruturas frontolímbicas(17), tamanhos menores de amígdala (22) e hipocampo (23, 24). Uma correlação negativa significativa entre o volume do hipocampo direito dos adolescentes com TB e duração da doença foi relatada. Dentre estas investigações, Frazier et al. (2005) avaliaram 43 jovens com idade entre 6-16 anos com transtorno bipolar de acordo com o DSM-IV (YMRS=24.8±8), com comorbidades, em uso de psicofármacos no momento da coleta de dados e compararam a 20 controles saudáveis, semelhantes em idade e sexo, e observaram que os indivíduos com TB apresentavam menor volume de hipocampo quando comparados com os controles.(25) Blumberg et al. (2003) avaliaram 14 pacientes com TB com idade entre 10-22 anos, em diferentes episódios atuais no momento da coleta (não descrevem escores obtidos nas escalas de avaliação de sintomas maníacos ou depressivos), não medicados e 23 controles saudáveis para investigar volume da amígdala e do hipocampo. Eles encontraram uma redução de volume significativo tanto da amígdala, quanto do hipocampo em pacientes com TB em relação aos controles. (26) Outra pesquisa de Baykara et al. estudou as alterações do hipocampo após o tratamento em 17 pacientes com TB (medicados, eutímicos no momento da coleta de dados, com comorbidades) e 12 controles. (27) Não houve diferença significativa entre os volumes de hipocampo direito e esquerdo de ambos os pacientes com transtorno bipolar e do grupo controle. Além disso, percebeu-se que os meninos tendiam a ter volumes do hipocampo direito significativamente maiores do que as meninas em ambos os grupos. Houve uma correlação negativa significativa entre o volume do hipocampo direito dos adolescentes com TB e a duração da doença.

Por outro lado, dois outros estudos mostraram que não havia nenhuma diferença em relação ao volume do hipocampo de pacientes com TB e os pacientes no grupo de controle. (28, 29) Chang et al. (2005) avaliaram 20 crianças e adolescentes (idade média: 14.6 anos;

YMRS=15.4±8.7) medicados no momento da coleta de dados, com comorbidades, e 20 controles saudáveis, pareados por sexo, idade e QI, não encontrando diferenças significativas entre os volumes de hipocampo entre os grupos. Volumes reduzidos de amígdala nos pacientes com TB foram encontrados. (28) Dickstein et al. (2008) avaliaram 20 pacientes com diagnóstico de TB (idades de 7 a 17 anos; YMRS=7.6±6.3), medicados no momento da coleta, com comorbidades, e 20 controles saudáveis pareados por sexo e idade, observando uma redução do volume da amígdala esquerda e do núcleo acumbens esquerdo em pacientes com TB, mas não do volume de hipocampo.(29)

Embora estes resultados sejam preliminares devido ao relativo pequeno tamanho amostral e diferenças metodológicas (os estudos utilizaram diferentes softwares de análise das imagens), o comprometimento do hipocampo como uma resposta à redução dos níveis periféricos do BDNF seria uma explicação congruente com os déficits cognitivos vistos nos pacientes. Além disso, até o presente momento, nenhum estudo prévio abordou, ao mesmo tempo, a correlação dos níveis séricos de BDNF com volume de hipocampo e escores em testes neurocognitivos.

2.OBJETIVOS

2.1. OBJETIVOS GERAIS:

Nosso objetivo com este estudo é avaliar, em crianças e adolescentes com TB, possíveis associações entre o volume de áreas cerebrais (hipocampo) e níveis séricos de BDNF. Adicionalmente, avaliaremos se o desempenho em tarefas cognitivas ligadas ao hipocampo apresenta correlação com os fatores citados acima, ou com a duração da doença.

2.2. OBJETIVOS ESPECÍFICOS:

a) Avaliar volumes do hipocampo em crianças e adolescentes com TB.
b) Mensurar os níveis de BDNF periférico nestes pacientes.
c) Avaliar a memória verbal por meio de testes neuropsicológicos - WISC-III (Wechsler Intelligence Scales) e o subteste de dígitos no WISC-III.
d) Correlacionar o volume do hipocampo com os níveis periféricos de BDNF e memória de trabalho para verificar eventual comprometimento.
e) Correlacionar esses achados com a duração da doença.

3.HIPÓTESE

Nossa hipótese é que os pacientes com menores níveis periféricos de BDNF tendem a apresentar menores volumes de hipocampo e pior desempenho cognitivo (memória de trabalho reduzida). Ao mesmo tempo, acreditamos que menores níveis periféricos de BDNF serão encontrados em pacientes cuja doença possui maior tempo de duração.

4.JUSTIFICATIVA

Devido ao envolvimento de BDNF no TB e sua abundância e influência sobre a neurogênese na região do hipocampo cerebral, avaliamos a correlação entre os níveis periféricos de BDNF e medidas volumétricas do hipocampo em pacientes com TB.

Além disso, com base em estudos anteriores que mostram: (1) a relação entre a sinalização anormal de BDNF no hipocampo e declínio cognitivo em pacientes com TB, especialmente em relação à memória verbal e memória de trabalho; e (2) níveis de BDNF são mais baixos em pacientes com múltiplos episódios; iremos avaliar a memória de trabalho dos pacientes por meio de testes neuropsicológicos, comparando pacientes em relação ao seu tempo de doença.

5.RELEVÂNCIA

O estudo de possíveis correlações entre os níveis séricos de BDNF, memória de trabalho e as mudanças volumétricas do hipocampo em pacientes com TB através de neuroimagem pode trazer importantes contribuições para a compreensão da neurobiologia deste transtorno, o que pode aumentar a possibilidade de eficácia de intervenções que impeçam/retardem algumas das modificações atróficas. Estas podem ter um grande efeito benéfico sobre o curso e a trajetória da TB em crianças e adolescentes.

6.CONSIDERAÇÕES ÉTICAS

Crianças, adolescentes e seus pais foram devidamente informados sobre o objetivo do projeto e aceitaram participar do protocolo e utilização de dados anonimamente para publicações. Este projeto foi registrado sob número 07641, tendo sido aprovado pelo Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre. Uma Declaração de Consentimento Livre e Esclarecido foi fornecida para os pais ou responsáveis, além de ser solicitado assentimento verbal por parte do paciente, para a participação em cada etapa do trabalho (avaliação clínica e exames de imagem).

7.MÉTODOS

Este foi um estudo transversal, no qual crianças e adolescentes com TB tipos I, II, ou SOE (Sem Outra Especificação) avaliadas no ProCAB (Programa para Crianças e Adolescentes com Transtorno Bipolar) do Hospital de Clínicas de Porto Alegre, foram convidados a participar. Os critérios de inclusão foram: idade entre 7 e 17 anos; ambos os sexos; ter recebido diagnóstico de TB tipos I, II, ou SOE, de acordo com o DSM-IV. Os critérios de exclusão foram: presença de esquizofrenia, transtorno invasivo do desenvolvimento, abuso de substância ativa, e contraindicações para a realização de Ressonância magnética.

7.1.AVALIAÇÃO E DIAGNÓSTICO:

Todos os pacientes foram submetidos a um procedimento de três etapas para fins de diagnóstico. a) Em primeiro lugar, uma entrevista de triagem, pesquisando sintomas de TB, bem como história familiar de transtornos mentais, foi realizada por um psiquiatra da infância e adolescência com pais e filhos juntos; b) Quando o diagnóstico de TB era suspeitado, os pacientes e os pais passavam, a seguir, por uma entrevista semi-estruturada com o Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL), conduzida por um assistente de pesquisa; c) Após a confirmação do diagnóstico, uma avaliação realizada por um segundo psiquiatra da infância e adolescência, que recebeu todas as informações a partir de consultas anteriores, era conduzida. Pacientes com diagnóstico de TB tipos I, II, ou SOE foram

submetidos à avaliação neuropsicológica, coleta de sangue para determinação do nível de BDNF e de ressonância magnética.

7.2.AVALIAÇÃO NEUROPSICOLÓGICA E NEUROCOGNITIVA:

Para fins de determinação do QI (Quociente de Inteligência) e memória de trabalho, foram aplicados nos pacientes os subtestes de Vocabulário e Blocos da Escala de Inteligência Wechsler para Crianças - terceira versão (WISC-III), além do subteste de Dígitos do WISC-III (escore total e ordem inversa). De acordo com estudos anteriores, a Ordem Inversa do subteste de Dígitos é mais diretamente correlacionada com a memória de trabalho. (30)

7.3.EXAMES DE NEUROIMAGEM:

7.3.1. Aquisição das Imagens:

As imagens de ressonância magnética foram adquiridas no scanner de corpo inteiro de 1.5 T Philips Achieva no Hospital de Clínicas de Porto Alegre, com uso de bobina de crânio de oito canais para recepção do sinal. Foram adquiridas imagens estruturais baseadas em T1 com a sequência SPGRE (Spoiled Gradient Recalled Echo) que propicia a obtenção de imagens anatômicas estruturais de crânio-total com resolução espacial isotrópica de 1 mm cúbico num tempo total de exame de 6 minutos e 33 segundos. Essa aquisição teve 170 fatias contíguas com uma matriz de imagem de 232x256 (leitura e fase), além dos seguintes parâmetros de imagem: TR=8.70; TE=4.0; TI=1000ms; Flip Angle=8o. Possíveis movimentos da cabeça foram minimizados com a colocação de almofadas de espuma dentro da bobina de crânio.

A segmentação volumétrica e medição foram realizadas com o pacote de análise de imagem do Freesurfer, o que é documentado e disponível gratuitamente para download online (http://surfer.nmr.mgh.harvard.edu/). O processamento de imagem foi realizado com o apoio do Centro Nacional de Supercomputação (CESUP), Universidade Federal do Rio Grande do Sul. (31) FreeSurfer v 5.3 foi instalado no cluster com o servidor do sistema operacional 11-SP1 Novell SUSE Linux Enterprise. Cada conjunto de dados dos sujeitos foi alocado a um núcleo de processamento e incluído no script de processamento de envio. O tempo de processamento total para todo o conjunto de dados foi de aproximadamente 20 horas.

7.3.2. Processamento das Imagens:

A reconstrução volumétrica e segmentação cortical foram feitas com o pacote de análise de imagem do Freesurfer, o que é documentado e disponível gratuitamente para download online (http://surfer.nmr.mgh.harvard.edu/). Resumidamente, este processamento inclui a correção de movimento e a obtenção da média de múltiplas imagens volumétricas ponderadas em T1 (quando mais de um estivesse disponível), remoção de tecido não-cerebral; (32) transformação automatizada para espaço Talairach; segmentação de massa branca subcortical e estruturas volumétricas profundas de massa cinzenta; normalização da intensidade; tesselação dos limites das bordas entre massa cinzenta e branca; (33) correção automatizada de defeitos topológicos; deformação da superfície para formar a fronteira entre massa branca e massa cinzenta e a fronteira entre massa cinzenta e líquido cefalorraquidiano; inflação da superfície; registro da imagem para o atlas esférico que utiliza o padrão individual de circunvoluções do córtex para parear a geometria cortical entre os diferentes sujeitos a serem comparados; parcelamento do córtex cerebral em unidades baseadas na estrutura dos giros e sulcos corticais; (34) e geração de uma variedade de dados baseados nessas superfícies

analisadas, incluindo mapas corticais sobre a curvatura cerebral, profundidade de sulcos, volume de diversas áreas cerebrais e cálculo da espessura do córtex de todas as regiões do mesmo. (35, 36)

7.4.DETERMINAÇÃO DOS NÍVEIS SÉRICOS DE BDNF

Os níveis séricos de BDNF foram medidos através do método de ELISA, utilizando um kit comercial de acordo com as instruções do fabricante (Millipore, USA). Resumidamente, placas de microtitulação (96 poços de fundo plano) foram revestidas durante 24 horas a 4 ° C, com as amostras diluídas a 1:100 em diluente de amostra e curva padrão variando de 7,8-500 pg de BNDF. As placas foram então lavadas quatro vezes com tampão de lavagem, seguido pela adição de anticorpo monoclonal de BDNF biotinilado anti-humano de ratos (diluído a 1:1000 em diluente da amostra), incubadas durante 3 horas à temperatura ambiente. Depois da lavagem, uma segunda incubação com uma solução de conjugado de estreptavidina-peroxidase de rábano (diluído a 1:1000) durante 1 hora a temperatura ambiente foi realizado. Após a adição de substrato e de solução de paragem, a quantidade de BDNF foi determinada (absorvância definido em 450 nm). A curva padrão demonstra uma relação direta entre a densidade óptica (DO) e concentração de BDNF. A proteína total foi medida pelo método de Bradford (amostras diluídas 1:200) utilizando albumina de soro bovino (BSA) como padrão.

7.5.ANÁLISE ESTATÍSTICA:

A análise dos dados foi realizada por meio da correlação de Spearman, devido ao fato de que as variáveis independentes (volume do hipocampo) e dependentes (níveis periféricos de BDNF) tiveram distribuição assimétrica. Também foram realizadas correlações entre o

volume do hipocampo, os níveis de BDNF, memória de trabalho e duração da doença. SPSS 20 para Windows foi utilizado para análises estatísticas. Todos os testes estatísticos foram bicaudais com um alfa 0,05. Devido à pequena amostra em estudos anteriores, uma estimativa do tamanho da amostra não foi possível. Assim, foram incluídos todos os pacientes que foram encaminhados para tratamento em nosso centro e preencheram os critérios de inclusão, durante 2012-2013.

8.ARTIGO

Correlation Between Peripherals BDNF Levels and Hippocampus Volume in Children and Adolescents with Bipolar Disorder

Artigo submetido para o Neural Plasticity

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Abstract

Pediatric Bipolar Disorder (PBD) is a serious mental disorder that affects the development and emotional growth of affected patients. The Brain Derived Neurotrophic Factor (Brain-Derived Neurotrophic Factor - BDNF) is recognized as one of the possible markers of the framework and its evolution. Abnormalities in BDNF signaling in the

hippocampus could explain the cognitive decline seen in patients with TB. Our aim with this study was to evaluate possible changes in hippocampal volume in children and adolescents with BD, and associate them to serum BDNF. Subjects included 30 patients aged seven to seventeen years from the ProCAB (Program for Children and Adolescents with Bipolar Disorder).We observed mean right and left hippocampal volumes of 41910.55 and 41747.96 mm^3, respectively. No statistically significant correlations between peripheral BDNF levels and hippocampal volumes were found. We believe that the lack of correlation observed in this study is due to the short time of evolution of BD in children and adolescents. Besides studies with larger sample sizes to confirm the present findings, longitudinal assessments, addressing brain development versus a control group, and including drug-naive patients in different mood states may help clarify the role of BDNF in the brain changes consequent from BD.

1. Introduction

Bipolar Disorder (BD) is a severe mental disorder characterized by mood swings during which a person has distinct periods of impairing elevated (mania) or decreased (depression) mood and energy.(1) It occurs in approximately 0.4 to 1.6% of adults, and in 1% in children and adolescents. (3, 4)In the early-age onset presentation (Pediatric Bipolar Disorder – PBD), difficulties in interpersonal relationships, academic functioning, and negative outcomes such as multiple hospitalizations and high rates of suicide attempts are observed. (6, 7)

Despite the devastating effects of BD on child development, little is known about the causes of this disorder. Its etiology is probably multifactorial, including biological and environmental factors. (10)Studies in adults with BD suggest that neurotrophins, particularly brain-derived neurotrophic factor (BDNF), inflammatory markers, and oxidative stress may be related to the etiology of this disorder.(11, 12) BDNF is the most abundant neurotrophin in the brain, and it has been implicated in neuronal processes such as neurogenesis, neuronal survival, dendritic growth, and synaptic plasticity.(15) It has been suggested that neuronal viability might be affected by neurotrophins persistent reduction. (17)Kauer Sant'Anna and colleagues found BDNF levels were lower in patients who had multiple episodes of the disorder, which led to the hypothesis that episode-related reduction neurotrophins could explain some of the structural changes in the brain observed in bipolar patients. (19) Besides that, BDNF is highly expressed in the cortex and hippocampus, areas of the brain known to regulate complex functions such as memory and emotion.

Structural and functional neuroimaging studies of pediatric BD generally converge with adult studies in implicating frontolimbic structures (23), Smaller sizes of amygdala(24) and hippocampus (25, 26), and a significant negative correlation between the volume of the right hippocampus of adolescents with BD and disease duration have been reported. Although these findings are preliminary due to relatively small sample sizes, hippocampal commitment is consistent across several investigations.

Altogether, these findings suggest that abnormalities of BDNF signaling in the hippocampus could be an explanation to the cognitive deficits observed in PBD and brain alterations present in adults after multiple episodes (17, 20)The most consistent associations between PBD and cognitive deficits were reported for impairments in working memory, verbal memory, attention, executive function, response flexibility, reversal learning, processing speed, set shifting and visuospatial memory.(9)

Due to the involvement of BDNF in BD, its abundance and influence on neurogenesis in the hippocampus, we evaluated the correlation between peripheral levels of BDNF and hippocampal volumetric measurements in children and adolescents with BD. Furthermore, based on previous studies showing (1) early cognitive deficits in PBD, we evaluated the working memory of patients with PBD. We also hypothesized that patients with longer disease duration would present lower serum BDNF levels, poorer neurocognitive performance, and reduced hippocampal volumes.

2. Methods:

This was a cross-sectional study. Children and adolescents with Bipolar Disorder I, II, or NOS evaluated in the ProCAB (Pediatric Bipolar Disorder Outpatient Program) of the Hospital de Clínicas de Porto Alegre, were invited to participate. Inclusion criteria were: ages 7-17 years; both genders; Bipolar Diagnosis I, II, or NOS according to DSM-IV. Exclusion criteria were: presence of schizophrenia, pervasive developmental disorder, active substance abuse, and contraindications to MRI.

2.1. Diagnostic Issues

All patients underwent a three-step procedure for diagnosis ascertainment. a) First, a child and adolescent psychiatrist performed BD symptom and family history of mental disorders screening with parent and children together; b) When the diagnosis of BD was suspected, patients and parents went through a semi-structured interview with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL), conducted by a research assistant; c) Clinical evaluation conducted by a second child and adolescent psychiatrist, that received all information from previous queries.

Patients diagnosed with BD I, II, or NOS underwent neuropsychological assessment, blood sampling for BDNF level determination, and MRI.

2.2. Neuropsychological or neurocognitive assessment

Full scale IQ was determined using the Vocabulary and Block Design subsets of the Wechsler Intelligence Scale for Children – Third Version (WISC-III), and the Digit Span of the WISC-III (total score and inverse order). According to previous studies, Digit Span Inverse Order is more directly correlated with working memory. (30)

2.3. Neuroimaging Assessment:

2.3.1. Images Acquisition:

All patients underwent a 1.5 T Philips Achieva magnetic resonance imaging (MRI) using an eight channels head coil. The structural images were acquired using a sagittal 3D T1 weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (repetition time = 8.7 ms, echo time = 4.0 ms, inversion time = 1000 ms flip angle = 8°). Possible head movements were minimized by placing foam pads inside the head coil. The volumetric segmentation and measurement were performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The image processing was carried out with support from the National Supercomputing Center (CESUP), Federal University of Rio Grande do Sul.(31) FreeSurfer v 5.3 was installed in the cluster with Novell SUSE Linux Enterprise Server 11-SP1 operating system. Each data set subject was allocated to one processing core and included in the submission queue processing script. The total processing time for all the data set was approximately 20 hours.

2.3.2. Processing of Structural Images

Cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Briefly, this processing includes motion correction and averaging of multiple volumetric T1 weighted images (when more than one is available), removal of non-brain tissue using a hybrid watershed/surface deformation procedure,

automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles)(37, 38) intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. Once the cortical models are complete, a number of deformable procedures can be performed for in further data processing and analysis to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (35).

2.4. BDNF Serum Levels Determination

BDNF serum levels were measured with sandwich-ELISA, using a commercial kit according to the manufacturer's instructions (Millipore, USA). Briefly, microtiter plates (96-well flat-bottom) were coated for 24h at 4 °C with the samples diluted 1:100 in sample diluent and standard curve ranging from 7.8 to 500 pg of BNDF. Plates were then washed four times with wash buffer followed by the addition of biotinylated mouse anti-human BNDF monoclonal antibody (diluted 1:1000 in sample diluent), which was incubated for 3h at room temperature. After washing, a second incubation with streptavidin- horseradish peroxidase conjugate solution (diluted 1:1000) for 1h at room temperature was carried out. After addition of substrate and stop solution, the amount of BDNF was determined (absorbance set in 450 nm). The standard curve demonstrates a direct relationship between optical density (OD) and BDNF concentration. Total protein was measured by Bradford's method (samples diluted 1:200) using bovine serum albumin (BSA) as a standard.

2.5. Statistical Analysis:

Data analysis was performed using the Spearman correlation, due to the fact that the independent (hippocampal volume) and dependent variables (peripheral levels of BDNF) had asymmetric distribution. Correlations between hippocampal volume, BDNF levels, working memory, and duration of disorder were also performed.

SPSS 20 for Windows was used for statistical analyses. All statistical tests were two-tailed with a set at 0.05.Due to the small sample in previous studies, a sample size estimation was not possible, so that we included all patients who were referred to treatment in our center and fulfilled inclusion criteria during 2012-2013.

2.6. Ethical Issues

Children, adolescents, and their parents were properly informed about the goal of the project, and accepted participating in the protocol and use of data anonymously for publications. This project was approved by the Ethics Committee in Research of the Hospital de Clínicas de Porto Alegre. A Statement of Informed Consent was provided by the parent or guardian, and verbal assent by the patient.

3. Results:

From the 30 patients available for the protocol, twenty-seven patients completed the entire evaluation. Two patients did not undergo MRI due to the use of dental braces, and one patient did not show up for the final assessment session. Demographic data of the subjects are described in Table 1. The final sample was composed of 27 subjects. Fourteen were male and 13 were female, their mean age was 13.8 years. The age of onset of bipolar disorder among patients ranged from 3 to 15 years old. Intelligence Quotient (IQ) in the subjects ranged from 105.77 ± 14.05. The majority of subjects presented Bipolar Disorder Type I diagnosed (66.6%). Three point seven percent of subjects were diagnosed as Bipolar Disorder Type II, and 18.6% as Bipolar Disorder NOS. Disease duration varied from zero to 14 years (average: 4.74; SD: 3.38). Most subjects (77.7%) were taking a number of psychiatric medications: lithium or valproate monotherapy: (n=4; 14.8%); atypical antipsychotics monotherapy (n=4, 14.8%); combined lithium plus anticonvulsants/antipsychotics (n=6, 22.2%); combined anticonvulsants/antidepressants (n=1, 3.7%); multiple combination therapy(n=5, 18.5%); concomitant use of stimulants (n=7, 25.9%).The mean number of psychoactive medications for children in this group was 1.74.

INSERT TABLE 1 HERE

Table 2 shows right hippocampus volume (RHV) and left hippocampus volume (LHV), respectively 41910.55 (mm^3) (SD=4163.04), and 41747.96 mm^3 (SD=5067.43). Peripheral BDNF levels varied from 19.58 ± 6.33(pg／μg protein). The average Digit Span Total Score was 6.66. The average Digit Span Inverse Order was 4.48.

INSERT TABLE 2 HERE

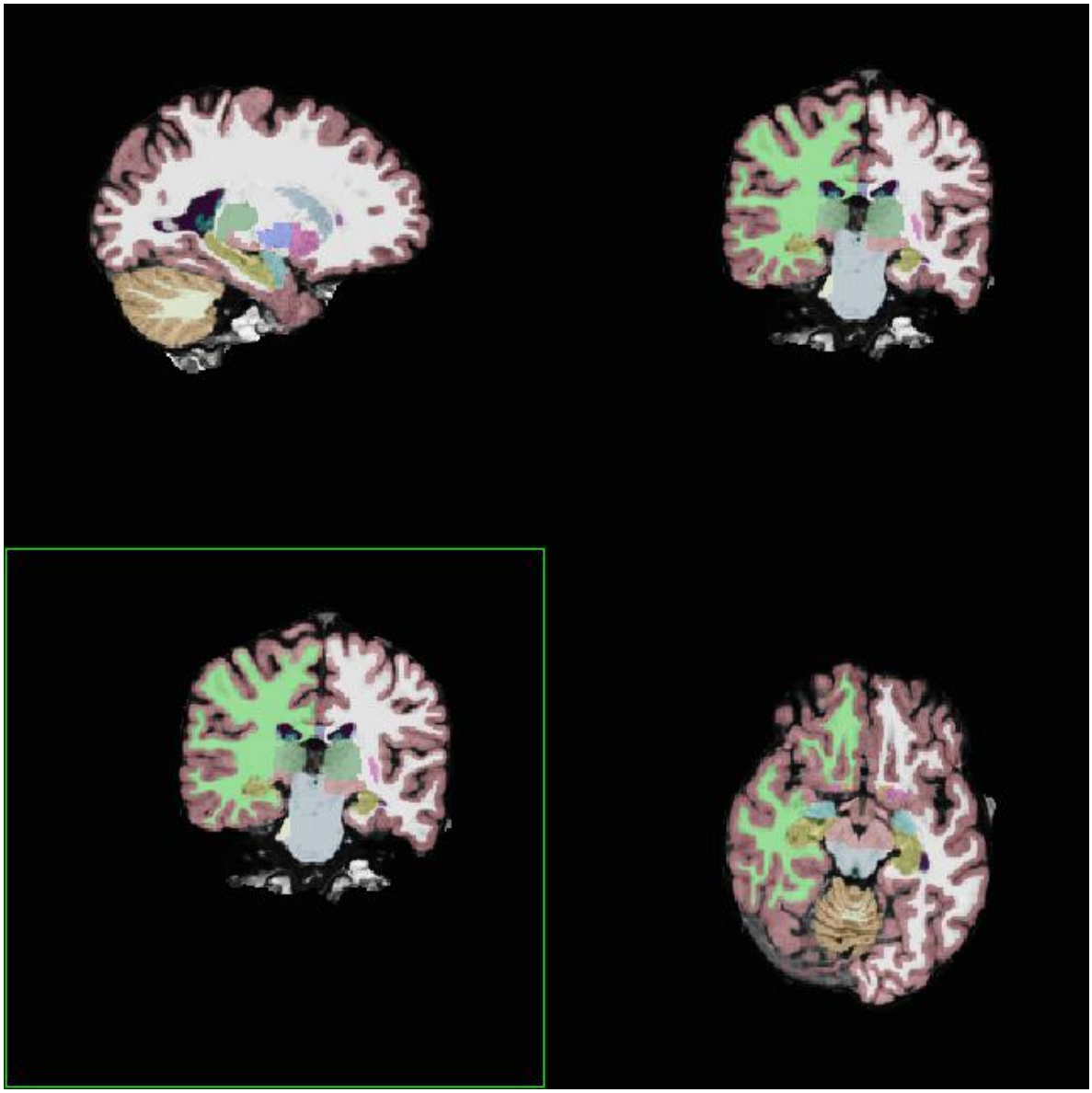

Image 1: Left Hemisphere: left hippocampus (image obtained from a subject MRI).

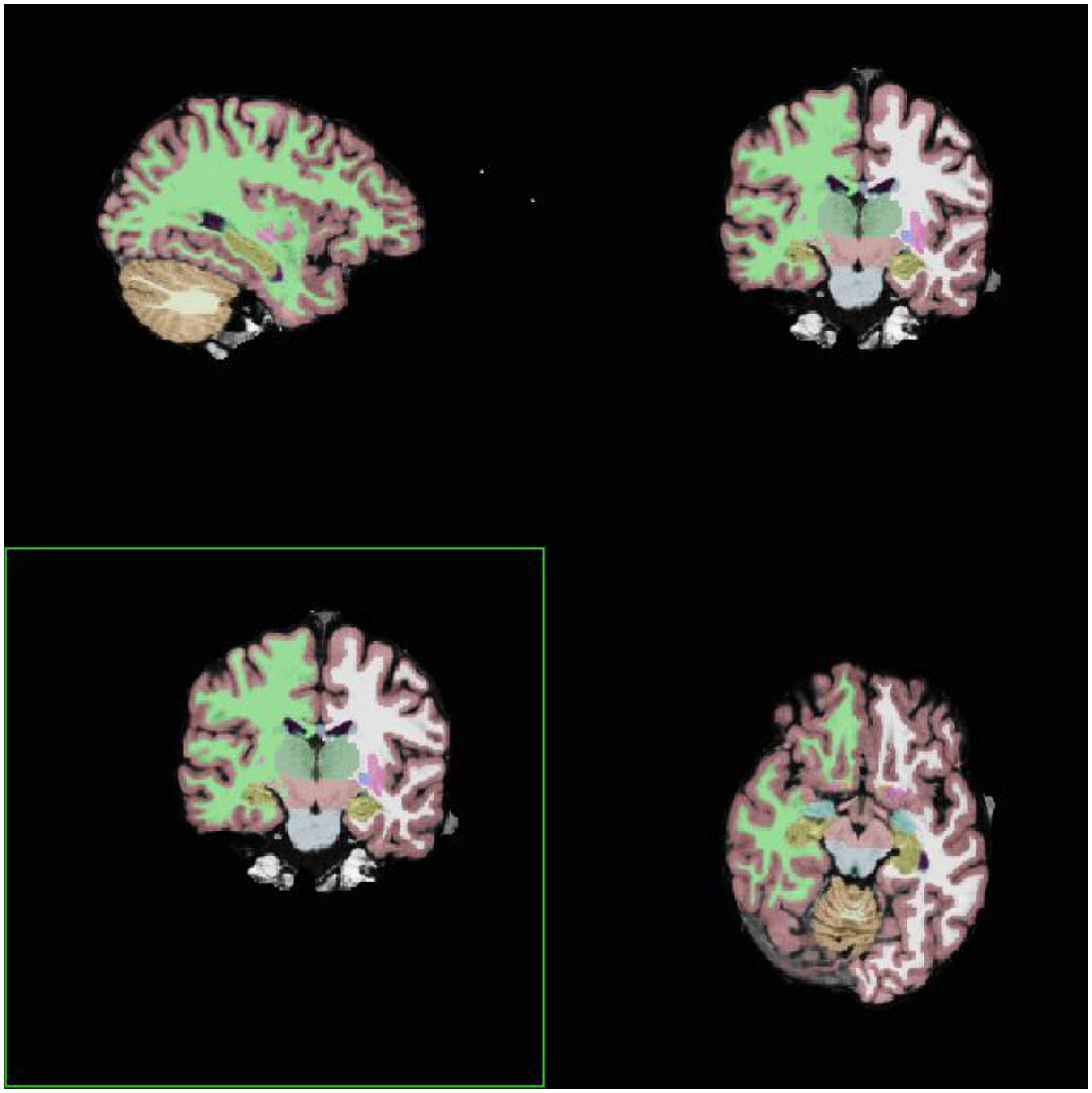

Image 2: Right hippocampus (image obtained from a subject MRI).

3.1. Primary Analysis:

Table 3 shows correlation coefficients of right hippocampus volume, left hippocampus volume and total hippocampus volume with BDNF. Those were, consecutively, 0.148, 0.027 and 0.100, with significance levels of 0.461, 0.892, and 0.621, respectively.

INSERT TABLE 3 HERE

Correlation coefficients between RHV, LHV, THV and the Digit Span Inverse Order were 0.021, 0.097, and 0.045 respectively, and are also presented in Table 3. No correlation was significant.

We did not observe any correlations between BDNF levels and disorder duration, as well as in working memory as measured by the digits inverse order test (Table 4).

INSERT TABLE 4 HERE

4. Discussion:

In our evaluation of hippocampal volume and peripheral levels in children and adolescents with Bipolar Disorder, no statistically significant correlations were detected. The same occurred with respect to working memory, and disease duration.

Although studies in adults have been able to show the relationship between peripheral BDNF levels and hippocampal volume, we hypothesized that the lack of correlation found in this study may represent the short time of evolution of BD in children and adolescents. Usually in adult BD studies, reduced BDNF levels are found in chronic or late-stage individuals with BD, in comparison to patients in early stages of the illness. (19)The same occurs in neuroimaging studies in bipolar disorder, meaning that the effects of systemic toxicity, cognitive and functional impairment, and biological changes seen in BD tend to be cumulative and much more prominent after multiples episodes.(39) Thus, these changes may not yet be found in patients with few years of the disease, as occurs in children and adolescents with BD.

Even diseases that are proven to exert a strong influence on hippocampus morphology and structure, such as epilepsy, may still not reveal changes in neuroimaging exams when in children. For instance, studies of newly diagnosed epilepsy typically fail to find many patients with clear structural subcortical changes at the onset. Zhang et al. compared hippocampus volumes in children with Temporal Lobe Epilepsy (TLE) and healthy controls using magnetic resonance imaging. They have not found hippocampus volume reduction in diagnosed definite/probable TLE children.(40)While there is evidence from adult studies and studies in chronic epilepsy patients that hippocampus atrophy may be a progressive lesion, there is little information regarding hippocampus abnormalities early in the course of epilepsy in patients, particularly in children.(41-43)

Our study was limited, in part, by the fact that most of our subjects were taking psychotropic medications at the time of the assessment, and were euthymic. This is not uncommon given the ethical issues inherent in discontinuing medication in children with severe psychiatric illnesses. Previous investigations demonstrated antimanic and antidepressant agents may influence the effects of BDNF on hippocampus, and that could induce morphological changes in subcortical area in BD, which could also lead to recovery of cognitive function. Due to the cross-sectional design of our study, we cannot state medication use may have influenced the results. Also, we ran additional analyses comparing results for patients who were on and off medication, and no significant differences have risen. (44-47)Another limitation was the lack of a control group, which is a suggestion to future researches. The inclusion of a control group would allow the observation of developmental differences not associated to BD. However, this is the first study addressing brain volumetrics and peripheral biomarkers in PBD, and our exploratory analyses suggest neurobiological underpinnings of BD in children and adolescents may differ from this same disorder in other developmental stage (adult life).

The study of possible correlations between serum levels of BDNF, working memory and hippocampal volumetric changes in patients with BD through neuroimaging can make important contributions to the understanding of the neurobiology of these disorders, such as how and when the course of the disorder would play their effects on brain development. Our findings suggest that in early ages, brain volumetric alterations may not be associated to the BDNF peripheral levels, and cognitive dysfunction. This information raises the possibility that, in children and adolescents, BDNF level changes must not be a priority when attempting to prevent some of the future atrophic modifications.

Despite the lack of significant statistical correlation observed in this study, this is the first study in pediatric bipolar disorder correlating hippocampus volume and BDNF, and no

association between these factors was observed. Replication for result confirmation is crucial, as well as interpretation of these findings in the light of a developmental context. Studies with larger samples, longitudinal studies evaluating normal and disrupted brain development, which include a control group and patients in different mood episodes, may be able to clarify the role of BDNF in brain changes caused by Bipolar Disorder.

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9.CONSIDERAÇÕES FINAIS

Ao contrário do que é observado em estudos de adultos com BD, não foram encontradas correlações estatisticamente significativas entre os níveis de BDNF periféricos e volume do hipocampo. O mesmo ocorreu em relação à memória de trabalho e duração da doença. Embora os estudos em adultos tenham sido capazes de mostrar essa relação, nós levantamos a hipótese de que a ausência de correlação encontrada neste estudo é devido ao curto tempo de evolução do TB em crianças e adolescentes.

Comumente, nos estudos em adultos com TB, níveis reduzidos de BDNF são encontrados em indivíduos em estágio avançado da doença, em comparação com pacientes em estágios iniciais da doença. (14) O mesmo ocorre em estudos de neuroimagem em transtorno bipolar, o que significa que os efeitos da toxicidade sistêmica, cognitivo e comprometimento funcional, bem como as mudanças biológicas vistas no TB tendem a ser cumulativas e muito mais proeminentes após múltiplos episódios. (36) Assim, estes alterações podem ainda não ser encontradas em pacientes com poucos anos de doença, como ocorre em crianças e adolescentes com TB.

Mesmo doenças que comprovadamente exercem uma forte influência sobre a morfologia e estrutura do hipocampo, tais como epilepsia do lobo temporal, podem ainda não revelar alterações nos exames de neuroimagem, de crianças. Por exemplo, estudos de diagnóstico de epilepsia recente normalmente não conseguem encontrar muitos pacientes com alterações subcorticais estruturais claras no início. Zhang et al. comparou volumes do hipocampo em crianças com Epilepsia do Lobo Temporal (ELT) e controles saudáveis, utilizando a ressonância magnética.(40) Eles não encontraram redução de volume no hipocampo de crianças com ELT em relação aos controle saudáveis. Embora haja evidências

de estudos em pacientes com epilepsia crônica que a atrofia de hipocampo pode ser uma lesão progressiva, existe pouca informação sobre anormalidades do hipocampo no início do curso de epilepsia, particularmente em crianças (41-43).

Nosso estudo foi limitado, em parte, pelo fato de que a maioria dos nossos sujeitos estava tomando medicamentos psicotrópicos no momento da avaliação. Isso não é incomum, dadas as questões éticas inerentes à interrupção de medicação em crianças com doenças psiquiátricas graves. A importância disso reside no fato de que muitas pesquisas têm demonstrado que alguns estabilizadores de humor, como o lítio, valproato e alguns antipsicóticos de segunda geração podem influenciar nos níveis de BDNF no hipocampo, induzindo alterações morfológicas na região subcortical, em pacientes com TB, que também podem levar a melhora da função cognitiva.(44-47) Além disso, os pacientes encontravam-se eutímicos no momento da avaliação, diferentemente dos pacientes da maioria dos estudos que exibem como resultado a redução dos níveis periféricos de BDNF em pacientes com TB.

Convém mencionar que análises post hoc foram feitas, dividindo os sujeitos em subgrupos de acordo com a idade (pré-púberes e púberes), tratamento no momento da coleta (com e sem tratamento) e tipo de TB. Também não foram encontradas correlações estatisticamente significativas.

Outra limitação é a ausência de comparação com um grupo de controle, que é uma sugestão para pesquisas futuras. Além disso, os sujeitos exibiram altos índices de comorbidades com outros transtornos, como o TDAH, transtorno desafiador opositivo e transtornos de ansiedade. Por um lado, a inclusão de crianças com TB com comorbidades reflete a apresentação clínica habitual; por outro lado, a inclusão de crianças com apenas TB iria determinar de forma mais precisa a fisiopatologia do TB. No entanto, uma amostra de TB “pura” pode não ser viável, já que estudos mostram que as taxas de comorbidades psiquiátricas em TB variam de 44% a 100%. (23)

Apesar da ausência de correlação estatisticamente significativa entre os fatores estudados, este estudo foi o primeiro onde foram avaliados simultaneamente o volume de hipocampo, os níveis periféricos de BDNF e a memória de trabalho em crianças e adolescentes com transtorno bipolar. A interpretação destes resultados e a comparação com estudos realizados em adultos devem ser feita em um contexto de desenvolvimento. Acreditamos que nossos achados devem-se ao curto tempo de evolução do TB em crianças e adolescentes. Além de estudos com maiores tamanhos amostrais para confirmar os presentes achados, investigações longitudinais, avaliando o desenvolvimento cerebral tendo um grupo de controles, e incluindo pacientes em diversos estados de humor, virgens de tratamento podem auxiliar no esclarecimento do papel do BDNF nas alterações cerebrais decorrentes do TB.

APÊNDICES

DEMAIS ARTIGOS PRODUZIDOS NO PERÍODO

Durante o período de participação no ProCAB (Programa para Crianças e Adolescentes com Transtorno Bipolar), participei de outros trabalhos abordando o tratamento sintomatológico do TB, incluídos nos anexos. Porém, apesar das evidências contundentes do tratamento dos sintomas deste transtorno, continuamos verificando a presença de déficits cognitivos e consequências adversas significativas em nossos pacientes. Essas observações levaram a esta pesquisa. Esperamos que os trabalhos futuros abordem aspectos neuromaturacionais, além da melhora de sintomas maníacos e depressivos, que propiciem a nossos pacientes um desenvolvimento pleno de suas potencialidades.

1. Demais Artigos Produzidos no Período: Artigo 1

Pharmacotherapy for Bipolar Disorder in Children and Adolescents: an Update

Artigo publicado na Revista Brasileira de Psiquiatria

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Abstract

Objective: to review the options for pharmacological acute and maintenance treatment of bipolar disorder in children and adolescents, including the treatment of bipolar depression and the comorbidity with Attention-Deficit/Hyperactivity Disorder.

Methods: literature narrative review through websites PUBMED and PsychInfo of randomized clinical trials and open studies from 2000 to 2012.Series of cases were included when there was not a higher level of evidence.

Results: Published data from Randomized Controlled Trials (RCT) in acute mania/hypomania with significant responses are available for lithium, topiramate, risperidone, olanzapine and aripiprazole. Open trials of lithium and lamotrigine show that these drugs may be effective in the treatment of depressive episodes. SSRIs trials have not been performed. In the treatment of comorbid ADHD, there are encouraging findings with Mixed Amphetamine Salts and atomoxetine; conflicting results are observed with methylphenidate.

Conclusion: Literature from RCTs of traditional mood stabilizers is scarce, but the best available evidence (results from meta-analytic regression) suggests that Second Generation Antipsychotics (SGAs)as a group are more effective in reducing manic symptoms. Risperidone was the only one included in head-to-head comparisons (vs. lithium and divalproex), showing superiority in terms of efficacy, but with more metabolic side effects, also more common in most of the SGAs. There are few studies addressing the treatment of ADHD and depression. Brazilian guidelines for the treatment of pediatric bipolar disorder should also include some of the SGAs as first-line treatment, (especially risperidone and aripiprazole) and those drugs should be provided by public health services.

Introduction

Pediatric Bipolar Disorder (PBD) is a chronic and disabling condition that leads to serious disturbances in the lives of patients and their families. [1] Affected children and adolescents have significantly higher rates of morbidity and mortality compared with healthy children. The impairment in social, family and academic functioning lead to reduced quality of life. [2, 3] In addition, increased rates of suicidal ideation and suicidal behavior are observed. [4]Current data suggest the prevalence of PBD is around 0.1-1%. [5]

In contrast to the robust evidence for pharmacotherapy in adults with bipolar disorder, uncertainties remain regarding the treatment of PBD. [6]As will be seen throughout the text, most of the recent studies have not addressed the classic antimanic agents, but an increase in the evidence of atypical antipsychotics efficacy is observed. However, these drugs have also been associated with significant adverse effects, especially weight gain, loss of glycemic control, dyslipidemia and hyperprolactinemia, making the choice of the drug to be used often difficult. [7]

Another aspect that should be taken into account is the occurrence of high rates of comorbidity with other psychiatric disorders, especially with Attention-Deficit/Hyperactivity Disorder (ADHD), present in more than 40% of patients with PBD in clinical samples and in about 10-15% of children and adolescents in community samples.[8, 9]In a study conducted at the Hospital de Clínicas de Porto Alegre (HCPA - Brazil) in 2003, PBD comorbidity rate with ADHD 58.3% was detected. [8] Earlier studies have found rates of 93% of ADHD in children with Bipolar Disorder (BD), 88% in adolescents who had childhood-onset mania and 59% in adolescents who had adolescent-onset BD.[10]The comorbidity with ADHD determines worse functional outcome and even worse response to treatment. [11, 12]

Considering the issues mentioned above, this study aims to review the options for pharmacological treatment of bipolar disorder in children and adolescents, including the treatment of BD cases with comorbid ADHD.

Methods

This narrative review was conducted searching the PubMed and PsycInfo websites crossing the following keywords, individually, and two by two: bipolar disorder, adolescent, child, pediatric, juvenile, early-onset, mania, treatment, pharmacotherapy, lithium, valproate, divalproex, carbamazepine, oxcarbazepine, topiramate, lamotrigine, gabapentin, atypical antipsychotics, risperidone, paliperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, combined therapy and augmentation. Two reviewers (TLP and CPZ) conducted the search independently. When any discrepancies were detected, results were combined. We also assessed the references of the other literature reviews. The study included review articles, meta-analyses, randomized clinical trials and open trials published between 2000 to 2012 in Portuguese, Spanish and English. Unpublished studies available from other sources, such as the FDA website or symposia annals, were also included. Unpublished data did not undergo peer-reviewing and this should be considered a possible limitation for these studies. Series of cases and case reports were not included when a higher level of evidence was present. References for series of cases and case reports are available in Supplemental Online Material.

Results

The studies found in the review were divided as follows: 1. Treatment of mania/hypomania; 2. Treatment of bipolar depression 3. Maintenance treatment and 4. Treatment of comorbid ADHD. Within these divisions, they will be categorized according to the strength of scientific evidence in the area: a. Randomized controlled trials and meta-analyses; b. Open, retrospective or follow-up studies.

1. Treatment of mania/hypomania/mixed states

1 .a Randomized controlled trials/ Meta-analyses

By the time this review was conducted, we detected 15 randomized controlled trials [13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 24, 26, 28, 29, 31] and 2 meta-analyses. [27, 32]

Geller et al. conducted the first randomized controlled trial in PBD.[13]Adolescents with BD I or II or major depressive disorder and supposed predictors of bipolarity (delusions, switching to mania during tricyclic antidepressant treatment, marked psychomotor retardation and BD in a first-degree relative)with comorbid substance use disorder were assessed in a 6-week randomized double-blind, placebo-controlled trial (DBPCT) using lithium (0.9-1.3mEq/L) (n=25; age: 16.3±1.2 years). They found that lithium was more effective than placebo in improving functioning scores according to the Children Global Assessment Scale (CGAS). Also, the analysis of urine drug assays was significantly different for the lithium (n = 13) versus the placebo (n = 12) groups, but there was no difference between groups on measures of mood symptoms according to the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS) mood items. There were limitations in the study due to the fact that the diagnosis of BD was made in a flexible way, allowing the entry into the protocol of patients with clinical depression and predictors of future bipolarity. Polyuria was the most frequent adverse effect.

Kowatch et al. conducted an 8-week RCT of divalproex, lithium or placebo (unpublished, presented at an AACAP meeting) in 153 subjects aged 7 to 17 years with BD I in manic or mixed episode.[14] Response was defined as Clinical Global Impressions-Improvement scores of 1 or 2 (very much or much improved). Response rates were: 54% for divalproex; 42% for lithium; and 29% for placebo. Lithium showed a trend toward efficacy but did not clearly separate from placebo. Effect sizes for lithium and divalproex were moderate.

Wagner et al. evaluated the efficacy of divalproex ER as monotherapy for PBD during a DBPCT in 150 patients (manic or mixed episode, aged 10-17 years).[15]Divalproex was given to a maximum dosage of 35 mg/kg/day (serum levels:80 to 125 µg/mL) during 4 weeks. Concomitant use of antipsychotics, antidepressants or other mood stabilizers was not allowed. Participants were assessed with the Young Mania Rating Scale (YMRS), the Clinical Global Impression – Severity scale (CGI-S), the Clinical Global Impression – Improvement scale (CGI-I) and the Children's Depression Rating Scale – Revised (CRDS-R). There was no significant difference between placebo and divalproex ER in YMRS total score (-8.8 against -7.9, respectively, $p = 0.604$) or in secondary measures. Divalproex was similar to placebo in the incidence of adverse effects, except for weight gain, which was higher in group using Divalproex ER. The most common adverse events were headache and vomiting.

A 6-week double-blind, randomized trial of risperidone (0.25mg-2mg/day) plus placebo vs. divalproex (60-120µg/mL) plus placebo was conducted by Pavuluri et al. in 66 patients aged 8-18 years.[16] Reduction in YMRS scores was the primary efficacy measure. The secondary measures were the CDRS-R, the CGI-BP, the Overt Aggression Scale (OAS), and the Brief Psychiatric Rating Scale for Children (BPRS-C). Response rates were defined as ≥50% improvement in YMRS for mania and ≥50% improvement in CDRS-R for depression. The rates achieved for manic symptoms were 78.1% for risperidone vs. 45.5% for divalproex ($p<0.01$); and for depressive symptoms, 65.6% for risperidone, and 42.4% for divalproex ($p< 0.1$). The remission rates (YMRS ≤12 and CDRS-D ≤ 28) were 62.5% with risperidone vs. 33.3% with divalproex ($p<0.05$). There were no significant differences in weight gain. There were 24% drop outs in risperidone group and 48% in divalproex group, mostly due to increased irritability.

Another divalproex DBPCT was performed in 30 adolescents (12-18 years) with bipolar I manic or mixed episode by DelBello and colleagues. [17] Patients received an initial

dose of divalproex 20 mg/kg and were randomized to receive adjunctive quetiapine (maximum dose of 450 mg/day) or placebo, for 6 weeks. The primary efficacy measure was change in YMRS scores. The quetiapine group demonstrated greater reduction in YMRS scores compared with the placebo group ($p = 0.03$). In addition, the response rate of YMRS was significantly higher in divalproex + quetiapine group than in the placebo + divalproex group (87% versus 53%, $p = 0.05$). Sedation was the main adverse effect, significantly more common in the quetiapine group.

A DBPCT investigated the use of oxcarbazepine monotherapy in 116 youths with BD in manic or mixed episode.[18] The patients were recruited to receive flexible doses of oxcarbazepine (maximum dose 900–2400 mg/day) or placebo during 7 weeks. The primary efficacy measure was the mean change from baseline to endpoint in the YMRS. Oxcarbazepine monotherapy (mean dose = 1515 mg / day) did not significantly improve YMRS scores at endpoint compared to placebo. The oxcarbazepine group reported the occurrence of dizziness, nausea, somnolence, diplopia, fatigue and rash with an incidence at least twice that of the placebo group.

A pilot DBPCT with 56 children and adolescents (6-17 years) with a diagnosis of bipolar I disorder receiving topiramate ($n = 29$) or placebo ($n = 27$) was conducted to analyze the efficacy of topiramate monotherapy for acute mania in children and adolescents.[19] Efficacy measures included the YMRS, BPRS-C, CDRS, the CGAS and the CGI-I. However, the study was discontinued prematurely when trials on the use of topiramate in adults with mania showed no efficacy. In the short period in which the study was conducted, the only statistically significant differences observed were the variation in the YMRS ($p = 0.003$) and BPRS-C ($p = 0.048$). Adverse events of topiramate included decreased appetite, nausea, diarrhea and paresthesia.

A DBPCT including 169 children and adolescents (ages 10-17 years) diagnosed with bipolar I disorder, experiencing a manic or mixed episode, in which participants were randomized to placebo (n=50), risperidone 0.5-2.5 mg / day (n = 61) or risperidone 3-6 mg / day (n = 58) during 3 weeks, was conducted by Haas et al. [20] Subjects were assessed using the YMRS, the CGI-I, the Clinical Global Impression–Bipolar (CGI-BP) scale and the BPRS-C. Significant improvement in the YMRS score was observed in both risperidone groups compared to placebo ($p < 0.001$). Twenty-six percent of subjects receiving placebo achieved a clinical response, compared with 59% in the 0.5–2.5 mg risperidone group ($p = 0.002$) and 63% in the 3–6 mg risperidone group ($p<0.001$). Adverse events most commonly associated with risperidone were somnolence, headache and fatigue (dose dependent increase of percentage), as well as average weight gain. The study results suggest that the lower dose range is associated with a better safety profile.

An 8-week randomized controlled trial was developed by Geller et al. with 279 children and adolescents aged 6 to 15 years.[21] Subjects were randomly assigned to receive risperidone (4 to 6 mg), lithium (1.1-1.3 mEq/L) or divalproex sodium (111-125 μg/mL). The primary outcome measure was the Children Global Impressions for Bipolar Illness Improvement–Mania (CGI-BP-IM). Patients were also assessed with the Modified Side Effects Form for Children and Adolescents and the K-SADS - Mania Rating Scale (KMRS). The risperidone group had significantly higher response rate than those treated with lithium (68.5% vs. 35.6%; $p<0.001$) and those treated with divalproex sodium (68.5% vs. 24.0%; $p<0.001$). There was no significant difference in response rates between the lithium and the divalproex groups. The mean weight gain was significantly greater with risperidone than lithium (3.31 vs. 1.42 kg; $p<0.001$) and divalproex sodium (3.31 vs. 1.67 kg; $p<0.001$). Higher increases in Body Mass Index and hyperprolactinemia were detected in subjects treated with risperidone.

A 3-week multicenter DBPCT was conducted by Tohen et al. with 161 adolescents aged 13-17 years with an acute manic or mixed episode. [22, 23] Subjects received either olanzapine in flexible doses (2.5-20 mg/day [n=107]) or placebo (n=54). There was a significantly greater reduction in the YMRS scores for patients receiving olanzapine than in the placebo group (-17.65 vs. -9.99; $p \leq 0.001$). The mean weight change was significantly greater for patients receiving olanzapine relative to patients receiving placebo (3.7 kg versus 0.3kg; $p \leq 0.001$) as was the frequency of other side effects such as drowsiness and sedation. Furthermore, in the olanzapine group, significant increases of systolic pressure ($p=0.001$), fasting glucose ($p<0.002$), total cholesterol ($p<0.001$) as well as serum prolactin levels ($p<0.001$) and liver enzymes (AST: $p<0.002$; ALT: $p<0.003$) were reported.

The effectiveness of quetiapine in the treatment of acute manic episodes associated with BD in children and adolescents aged 10 to 17 years was demonstrated in a 3-week DBPCT (unpublished,http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/psychopharmacologicdrugsadvisorycommittee/ucm164280.pdf).[24, 25]Patients were randomized to quetiapine 400 mg/day (n = 95), quetiapine 600 mg/day (n = 98) or placebo (n = 91). Quetiapine 400 mg/day and 600 mg/day were statistically superior to placebo, according to changes in YMRS scores ($p <0.001$ for both doses versus placebo). Improved functioning according to the CGAS scores was also observed.

A 4-week, DBPCT (unpublished, http://www.fda.gov/downloads/AdvisoryCommittees/Committees-MeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisory-Committee/ UCM170736.pdf) was designed by DelBello et al. to evaluate the efficacy of ziprasidone compared to placebo in 238 children and adolescents aged 10-17 years with BD-I.[26, 27] The target dose was 80-160 mg/day for subjects weighing >45 kg and 40-80 mg/day for children weighing <45 kg. The

primary efficacy measure was the change in YMRS total score. A reduction >50% in YMRS was achieved in 62% of the subjects in the ziprasidone group, compared to 35% of the subjects in the placebo group ($p<0.001$). Difference from placebo was only achieved at week 4.Patients using ziprasidone 40-80mg/day showed less improvement than the group using 80-160mg/day, but it was unclear if it's due to the dose or weight effect, since the dosing mechanism is related to the weight. The most frequent side effects among patients treated with ziprasidone were dystonia, headache and sedation.

Aripiprazole demonstrated statistically significant superiority over placebo in the treatment of acute mania or mixed states in a 4-week DBPCT (n=296). [22, 28]Patients were randomized to use aripiprazole 10mg, aripiprazole 30mg or placebo during an acute phase of four weeks and, then, continued their treatments for over 26 weeks. Reduction in YMRS total score of at least 50% at week 4 was achieved by 44.8%, 63.6%, and 26.1% of subjects in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo groups, respectively ($p < 0.01$ for both doses vs. placebo). Adverse events were mild to moderate for the two subgroups using aripiprazole, and somnolence, parkinsonism and akathisia were most frequent.

A DBPCT conducted at the Department of Child and Adolescent Psychiatry at the HCPA (n=43, 8-17 years) included patients with BD in manic/mixed episode comorbid with Attention-Deficit/Hyperactivity Disorder (ADHD). [29]Patients were randomized to receive placebo or aripiprazole monotherapy to the maximum dose of 20mg/day for 6 weeks. The aripiprazole group had a greater reduction in outcome parameters (YMRS, Children Mania Rating Scale – Parent version [CMRS-P] and CGI-S), higher rates of response and remission and, also, a significant reduction in ADHD symptoms despite no use of concomitant stimulant medication. The most common adverse events reported by the group using aripiprazole were somnolence and drooling.

Regarding alternative treatments, a 16-week, double-blind, placebo-controlled trial of flax oil was conducted using flax oil for 51 subjects with BD aged 6-17 years.[30, 31] Patients had a previous failure in stabilizing symptoms and/or were intolerant to lithium and/or valproate and/or atypical antipsychotic therapy, or desired participation in a study without conventional treatment. The oil contained the omega-3 fatty acid α-linolenic acid (α-LNA). Patients were randomly assigned to receive supplementation with flax oil, containing 550 mg α-LNA per 1 gram (maximum dosage: 12 capsules/day) or an olive oil placebo adjunctively or as monotherapy. No difference between flax oil or placebo was detected in the measures of mood symptoms and global functioning (YMRS, CDRS-R and CGI-BP).

No double-blind placebo controlled trials were available in our literature review regarding carbamazepine, lamotrigine, gabapentin, paliperidone or clozapine. A summary is presented in Table 1.

INSERT TABLE 1 HERE

Biederman et al conducted a meta-analysis comparing open label studies and randomized placebo-controlled trials to evaluate the accuracy of information provided by open studies as predictors of the findings of RPCTs. [27]Fourteen studies were included (19 observations: 11 open trials and 8 randomized placebo controlled trials) of second generation antipsychotics and mood stabilizers. Similarities between the effects of treatment of open studies and RPCTs were found, suggesting open studies may predict treatment safety and efficacy. It was also described that a higher YMRS result difference was found for risperidone in RPCTs than in open studies. There were no other significant differences between open label studies and RPCTs with other individual medications evaluation.

Liu et al conducted a systematic review of available literature on the effectiveness of agents for the treatment of mania, depression and ADHD in children and adolescents.[32] The review included 29 open-label studies and 17 RPCTs covering 2666 individuals and

evaluated mood stabilizers, second-generation antipsychotics (SGA) and naturopathic compounds (flax oil and omega-3). Modest effects were reported for traditional antimanic agents, such as lithium carbonate, divalproex sodium and carbamazepine, when used as monotherapy. The SGAs as a group were significantly more effective than mood stabilizers and naturopathic compounds, in the meta-analytic regression of RCTs. No significant difference was observed between risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole (to which RPCTs are available). However, SGAs are also related to increased rates of weight gain and somnolence.

By reviewing the available literature, it's observed that risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole have a large effect in reducing YMRS scores. Literature from RPCTs of traditional mood stabilizers is scarce, but the best available evidence (results from meta-analytic regression) suggests SGAs are more effective in reducing manic symptoms. Correll et al (2010) conducted a comparative analysis of randomized, placebo-controlled trials of SGAs and mood stabilizers. [33] Nine RPCT in youth were found (5 evaluating SGAs and 4 about mood stabilizers). The results of the study show that SGAs may be more effective in reducing manic symptoms than mood stabilizers. Head-to-head comparisons are scarce. The two available studies suggest risperidone is more effective than lithium and divalproex, but more metabolic adverse events were associated to risperidone use. In those studies, divalproex seemed to be more effective than lithium.

1 .b Open label studies

We were able to detect 20 open-label, retrospective or follow-up studies available in the literature at the time the review was concluded. Data are synthesized in Table 2. [34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53]

Kowatch et al conducted an open study of lithium, divalproex sodium or carbamazepine (n=42) for 6 weeks. [52]All three drugs were found effective. There were no significant differences between the three drugs.

In an open trial of carbamazepine (788 ± 252mg daily, n=27, eight weeks), 16 (59%) children completed the study, and treatment with carbamazepine was associated with statistically significant, but modest levels of improvement in the mean scores of the YMRS (10.1±10.2, p <0.001), suggesting lack of complete resolution of mania. [53]

Biederman et al. conducted a 12-week, open-label, prospective trial with 39 subjects (6-17 years old) using lamotrigine monotherapy at doses ranging from 160.7 ± 128.3mg/day in subjects <12 years (N = 22) to 219.1 ± 172.2 mg/day in children 12–17 years old (N = 17). [38]Patients were assessed with the YMRS, the CGI-I, CDRS and BPRS. The response rates, defined as a reduction in YMRS scores ≥30% or improvement of mania in CGI-I (≤2), was 66%; 54% of the subjects had a reduction in YMRs scores ≥50% (p<0.001). Lamotrigine was also associated with improvement in depressive, ADHD and psychotic symptoms, but 25% of the patients discontinued the trial due to adverse events, being dermatologic side effects the most common.

Regarding combination treatment open trials, risperidone as an augmentation agent in patients using lithium with poor response (n=38) was effective and well tolerated, with response rates of 85.7% (defined as a decrease in the YMRS≥50%). [45] Divalproex sodium plus risperidone or lithium plus risperidone in 37 patients promoted significant improvement in the YMRS, the CDRS-R, and the CGI-BP (p<0.001). There were no significant differences between groups in terms of efficacy, safety or tolerability.[46]

Wozniak et al. conducted an open trial evaluating 40 patients aged 6 to 17 years, comparing olanzapine monotherapy with the combination of olanzapine plus topiramate. [48]The group using topiramate presented a reduced weight gain, but did not showed superiority to olanzapine monotherapy in reducing manic symptoms.

Biederman et al. evaluated the use of olanzapine (6.3 ± 2.3 mg/day) or risperidone (1.4 ± 0.5mg/day) monotherapy in 31 preschool children (ages 4-6 years) in an 8-week open trial. [47] The primary efficacy measures were a reduction ≥ 30% in the YMRS and improvement in the CGI scale. Both antipsychotics proved to be effective in reducing manic symptoms. There was no difference in rate of response between risperidone and olanzapine (69% vs. 53%, p=0.4). Weight gain was observed with the two drugs. Significantly higher prolactin serum levels were observed with risperidone.

Masi et al. assessed the effect of clozapine in 10 subjects (12 to 17 years-old). [49]Improvements measured with CGI-I, YMRS, BPRS, CGA and CGAS were significant ($p < 0.001$). The average dosage of clozapine was 75-300 mg/day. The most common side effects were increased appetite, sedation, enuresis and sialorrhea. There was an increase of body weight of 10.7%.

Rucklidge et al. researched the effect of the intake of a micronutrient formula, basically with vitamins and minerals (EMPower), for 3-6 months in 120 subjects aged 7-18 years with BD. [51] Around 80% of these patients were in use of psychiatric medication and 24% reported comorbidity with ADHD. The data were obtained from the formula company's database. Clients should complete a daily symptom checklist derived from the DSM-IV and send it to the company through internet, FAX or phone. About 46% of patients experienced BD symptoms improvement > 50%, but 38% of the sample kept on using psychotropic medication.

Regarding treatment of mania/mixed states, case reports and series of cases were not included in the text due to the presence of a higher level of evidence.

The open studies evaluating treatment options for mania exhibit similar results to those found in RCT. The SGAs show to be effective in reducing effect measures. The same seems to happen with most mood stabilizers, with the exception of topiramate and carbamazepine. Open studies on alternative treatments exhibit modest results.

INSERT TABLE 2 HERE

2. Treatment of bipolar depression

2 .a Randomized controlled trials/ Meta-analyses

By the time this article was performed, there was only one RCT about treatment of bipolar depression. DelBello and colleagues conducted a double-blind, placebo-controlled trial of quetiapine in 32 subjects (12-18 years) with BD in a current depressive episode. [54] Subjects underwent a 300-600mg trial of quetiapine or placebo for 8 weeks. Treatment response was defined as a reduction in CDRS-R ≥50%. There was no statistically significant difference in changes in CDRS-R scores from baseline to endpoint between the placebo and quetiapine groups ($p = 0.89$), or in response rates (placebo =67% versus quetiapine = 71%) or in secondary efficacy measures changes. The most frequent side effect of quetiapine was dizziness.

2.b Open label studies

Three open label studies were found. [55, 56, 57]A 6-week open label study of 27 adolescents aged 12 to 18 years with bipolar I disorder experiencing an acute depressed episode was performed by Patel et al. to examine the effectiveness of lithium in decreasing depressive symptoms. [55] The subjects received lithium 30 mg/kg, which was adjusted to

achieve a therapeutic serum level of 1.0-1.2 mEq/L. Response rates, defined as a reduction in CDRS-R score ≥50%, occurred in 48% of the subjects. Thirty percent of the patients achieved remission (CDRS-R score ≤ 28 and a CGI-BP Improvement score of 1 or 2) with lithium monotherapy. The most common side effects were headache (74%), nausea/vomiting (67%), stomachache (30%), and abdominal cramps (19%).

An 8-week open-label trial of lamotrigine was performed by Chang et al. with 20 adolescents (ages 12-17 years) with bipolar disorder experiencing a depressive episode, using lamotrigine in monotherapy or with other mood stabilizer and/or with a stimulant drug (if ADHD was diagnosed). [56] The primary measures of response were improvement on the CGI at week 8 and a decrease of at least 50% in the CDRS-R scores, which were achieved in 84% and 63% of the subjects, respectively. Significant decreases in the YMRS (p=0.001) and the Overt Aggression Scale-Modified scores (p=0.001) were observed. No significant adverse effects were reported during the trial.

A retrospective review of medical records of 59 patients with PBD was conducted by Biederman et al. evaluating the use of Selective Serotonin Reuptake Inhibitors (SSRI) and mood stabilizers in bipolar depression. [57] It was observed that SSRIs were associated with significant improvement of bipolar depression, but increased the chances of recurrence of manic symptoms. Furthermore, it was found that the use of mood stabilizers improved manic symptoms, but did not change the course of bipolar depression. SSRIs did not modify the improvement of manic symptoms obtained with mood stabilizers. In conclusion, this study suggests that treatment of bipolar depression in children and adolescents can be performed with an SSRI, since it is preceded by adequate control of manic symptoms with mood stabilizers. Prospective studies are urgently needed to confirm this finding.

There are few studies regarding bipolar depression in children and adolescents and all the available trials have limitations, such as small sample sizes, and the lack of a placebo

group. Based on current studies, lithium (monotherapy) and lamotrigine (monotherapy or adjunctively) seem to be effective treatments. SSRIs may be an alternative to treat depressive symptoms, but current studies suggest their use only combined to antimanic agents. Studies are urgently needed on this topic.

3. Maintenance treatment

3.a Randomized Controlled Trials

Three RCT about maintenance treatment were found.

In the continuation of the open study of lithium developed by Kafantaris et al., a double-blind placebo-controlled trial phase was conducted.[58] Adolescents who initially responded to lithium were randomly assigned to lithium or placebo for 2 weeks. The results indicated that both lithium and the placebo had similar rates of exacerbation of symptoms (52.6% lithium; 61.9% for placebo). Despite promising results in the open label study phase, a large treatment effect for lithium was not found in the maintenance phase.

From one hundred and thirty nine subjects aged 5-17 years who were initially treated with lithium combined with divalproex, 60 patients were randomly assigned to discontinue one of the agents for 76 weeks, while the others were kept on combination therapy (Findling et al). [59]There was no difference in time for recurrence of symptoms between lithium and divalproex monotherapy groups. Receiving both drugs again promoted remission rates of 89.5%.

As a continuation of an open label study of aripiprazole in monotherapy with 96 subjects (4-9 years-old), Findling et al. conducted a double-blind, placebo-controlled trial with 60 patients from the initial study who achieved remission and stabilization. [60] These patients were randomly assigned to use aripiprazole (mean dose: 6.4±2.1 mg/day) or placebo during 72 weeks and the primary outcome measure for this phase of the trial was time to

discontinuation due to a mood event. The median weeks to discontinuation was higher with the aripiprazole group (6.14, SE ± 11.88 weeks; p=0.005) than with placebo (2.29, SE ± 0.38 weeks; p=0.003), leading to the conclusion that aripiprazole may be a more effective long-term treatment than placebo. The most common side-effects with aripiprazole were stomach pain, increased appetite and headaches.

3.b Open label studies

Three open label studies were detected.

A prospective open-label 8-week trial was conducted by Findling et al in 38 patients aged 5 to 17 years with BD I or II who remitted with combination therapy of lithium and divalproex. [(61)] The main issue raised by the authors was whether there was benefit in receiving more than one drug during long-term treatment for patients who stabilized on combination drug therapy. For this purpose, patients subsequently discontinued one of the agents. Those who became symptomatic during maintenance monotherapy with lithium or divalproex presented an 89.5% remission rate when treated with the same combination, according to the YMRS, CDRS-R, CGAS, and CGI-S.

An 11-week open trial was performed by Tramontina et al with 10 patients (11-17 years) who were previously in use of a single mood stabilizer or an antipsychotic presenting weight gain over 5%. [(62)] The subjects were enrolled to switch their medication for topiramate. The main hypothesis was that topiramate in monotherapy would be able to maintain mood stabilization and reduce body weight at the same time. There was a significant reduction in YMRS scores ($p<0.01$) and also in body weight ($p<0.01$).

A 48-week open prospective study was conducted by Duffy et al with 18 patients meeting DSM-IV lifetime criteria for bipolar disorder type I, II or NOS, with age between 13 to 20 years. [(63)] Initially, during 8 weeks, patients used quetiapine in increments of 50 mg daily to a maximum of 800 mg/day according to improvement of clinical symptoms. At the

same time, other psychotropic drugs previously in use were discontinued if possible. Concomitant use of clonazepam or zopiclone for insomnia was allowed. Five patients needed combination therapy. In that trial, quetiapine was effective and well tolerated. The CGI-S scores were reduced along the trial ($p < 0.01$). The most common side effects were somnolence and flu-like symptoms.

Maintenance treatment is mandatory due to the high recurrence rates in PBD. The effect of combined therapy of lithium and divalproex sodium is controversial: in the open label trial, it seemed effective, but this result was not replicated in the RCT. Topiramate showed effectiveness in reducing YMRS and weight after mood stabilization with other agents. Quetiapine has also demonstrated a positive response. However, high-level evidence is scarce. Most drugs were not assessed in long-term treatment trials. The studies where even one of the agents was discontinued evidenced faster recurrence of symptoms. Expert suggestion is maintenance of the same medication and dosage the patient was initially stabilized, and comorbidity control.

4. Comorbidity with ADHD

4.a Randomized controlled trials

Three RCT were found discussing the comorbidity with ADHD.

Scheffer et al. conducted a 2-stage trial, where patients with their moods stabilized with divalproex sodium, but without significant improvement of ADHD symptoms were invited to join a 4-week randomized, double-blind, placebo controlled crossover trial of Mixed Amphetamine Salts (n=30, age range 8-17 years-old). [64] Significant improvement in ADHD symptoms was observed in the MAS group, while no significant between-group change in the YMRS was detected. Mixed Amphetamine Salts were considered safe and effective without promoting destabilization of BD.

Findling et al. conducted a 4-week double-blind, placebo controlled crossover trial of methylphenidate in 16 children and adolescents with BD+ADHD previously in use of mood stabilizers, with residual ADHD symptoms.[65] Best dose week of treatment (5mg-10mg-15mg) was compared to placebo and a significant difference was observed between medicated and non-medicated groups in the ADHD rating scale-IV (ARS-IV) and Conners Parent Rating Scale. No significant difference was observed in the changes in scores of the YMRS and the CDRS-R.

Zeni et al. [11] conducted a randomized crossover trial with methylphenidate and placebo (2 weeks each) in children and adolescents with BD+ADHD previously stabilized with aripiprazole (n=16; 8-17 years-old). No significant differences between the effects of methylphenidate and placebo were detected in ADHD (p=0.97) or manic (p=0.34) symptoms. Significant improvement in depressive symptoms was observed in the methylphenidate group (p=0.01). One patient discontinued the trial due to the onset of a severe mixed episode. No other significant adverse events were observed.

4.b Open label studies

Twelve patients (6–17 years) with BD+ADHD underwent an 8-week open trial of atomoxetine, combined to at least one mood stabilizer or antipsychotic.[66] A significant decrease in the ADHD Rating Scale-IV (ADHD-RS-IV) was observed, and no significant changes were detected in the YMRS or CDRS-R. Response (≥ 25% decrease in the ADHD-RS-IV) was seen in 8 subjects (67%) and remission (≥ 40% decrease in the ADHD-RS-IV), in 6 patients (50%). Two subjects were discontinued early due to worsening of mood symptoms. Placebo-controlled studies are needed to clarify the role of atomoxetine in this population.

Treatment of the comorbidity with ADHD has also been understudied. The current data suggests the use of a stimulant (MAS or methylphenidate) or atomoxetine, after mood stabilization. Methylphenidate does not seem to be effective in reducing ADHD symptoms when combined to aripiprazole. Although all agents were safe and well tolerated, and mood destabilization is exception, caution should be taken when stimulants and/or atomoxetine are introduced in the therapeutic regimen.

Discussion

Studies on the treatment of bipolar disorder in children and adolescents have increased in recent years, especially those directed to the use of SGA. However, many uncertainties remain. Current algorithms suggest starting with monotherapy and then progressing to a combined treatment of two different classes of drugs. [68] Data from RPCTs from traditional mood stabilizers are scarce. The efficacy of some atypical antipsychotic agents (risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole) has been well demonstrated, especially for aripiprazole and risperidone. Aripiprazole showed efficacy in at least two published RCTs. [28, 29]Risperidone also showed higher efficacy than divalproex sodium in two different studies. [16, 20]Although no specific SGA has proved to be more effective than others, available meta-analysis and comparative studies of RPCTs suggests SGAs are more effective than traditional mood stabilizers. Also, a head-to-head comparison of risperidone vs. lithium and divalproex showed that risperidone demonstrate superiority in terms of efficacy, but with more metabolic side effects. [21] Paliperidone, quetiapine and ziprasidone data from RPCTs have not been published to date. Also, there are no large studies evaluating clozapine in children and adolescents in the literature, except for series of cases. In clinical practice, clozapine is reserved for cases refractory to treatment because of its side effect profile, so investigations with greater methodological value need to be performed.

Children and adolescents with BD end up using several medications without success before getting proper mood stabilization. [13] A study of children and adolescents with BD from community samples showed that patients were treated, on average, with 3.4 ± 1.5 medications and underwent the use of about 6.3 ± 3.7 psychotropic drugs previously. [69, 70] The drug associations are commonly seen and combinations of second-generation antipsychotics are becoming more frequent. A study by the Florida Mental Health Institute evaluating the medical records of 12.764 children (484 of them diagnosed with BD) and 10.419 adolescents (823 of them diagnosed with BD) of Florida's Medicaid over five years, showed that 7% of children and 8% of adolescents were using more than one antipsychotic drug, although the evidence indicating the efficacy of antipsychotic combination in children with BD is limited to reviews of medical records. [71, 72] Some data of studies in adults suggest that side effects of SGAs may be exacerbated when used in combination.[73] Based on this information, we believe that combination antipsychotic therapy should be reserved to cases where patients had multiple failures on several monotherapies, including clozapine. Controlled studies on polypharmacy of antipsychotics in Pediatric Bipolar Disorder are needed to determine the risks versus benefits of this treatment option.

The use of each drug should be performed in sufficient time and dosage to determine the effectiveness of the agent. Generally, a course of 6-8 weeks of an antimanic agent is recommended, using appropriate doses, before adding or replacing it with another drug. [5, 74, 75, 76]

The lack of replicated results of randomized placebo controlled trials and head-to-head comparisons of different psychopharmacologic therapeutic approaches prevent the designation of any treatment as having stronger evidence for the treatment of bipolar disorder in children. However, we call attention to the fact that, in Brazil, the only drugs provided by the Brazilian public health system (Sistema Único de Saúde - SUS) are lithium,

carbamazepine and valproate. Lithium effect has not been adequately studied in RPCTs of PBD. The studies with valproate suggested it was not different from placebo and no RPCT is available for carbamazepine. The only comparison of these agents vs. risperidone detected risperidone was more effective than lithium or valproate. The SGAs (except paliperidone and clozapine), in spite of larger documentation of efficacy, are not provided by the government for the treatment of bipolar disorder, being reserved only for proven cases of schizophrenia. This further limits the choice of the most suitable drugs for treating pediatric patients with bipolar disorder. We suggest the inclusion of risperidone and aripiprazole as a standard treatment of PBD, due to the level of evidence and the risk-benefit profile. The cost of other SGAs, which reduces access to most of the population, adds significant and unnecessary suffering and impairment for children, adolescents and their families. Our hopes are that future Brazilian guidelines include evidence-based treatment for these patients.

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2. **Demais Artigos Produzidos no Período: Artigo 2**

Avoiding Stimulants May Not Prevent Manic Switch: a case report with atomoxetine

Artigo publicado no ***The Journal of Neuropsychiatry and Clinical Neurosciences***

Letter to the Editor

Tatiana Lauxen Peruzzolo, Silzá Tramontina, Luis Augusto Rohde, Cristian Patrick Zeni.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) affects 5.3% of children and adolescents worldwide, and it is associated with significant impairment in academic and social functioning. Stimulants are first-choice treatment for the disorder.(1)However, this psychoactive drug may promote psychotic and manic-like symptoms in approximately 0.25% of children with ADHD. (2) In the presence of Bipolar Disorder, current guidelines suggest mood stabilization with antimanic agents before treatment of ADHD. Nonetheless, when subthreshold or family history of manic/hypomanic
symptoms are present in patients with ADHD, guidelines fail to provide clear and
evidence-based data to orient treatment. Current indications are a close follow-up and adequate treatment of ADHD. Other options are use of antimanic agents, which has not yielded significant positive results, or the use of atomoxetine or other nonstimulant agents. (3)

Atomoxetine, a selective inhibitor of norepinephrine reuptake has demonstrated to improve ADHD symptoms. It promoted a significant response in both children and adolescents according to two recent meta-analyses. Although a small percentage of subjects have experienced symptoms of hostility and aggression, the rate of manic switch has not been determined. (4)

We describe a case of a 14 year-old patient who presented manic symptoms after the use of atomoxetine. We also take the opportunity to discuss the recent studies of manic symptoms after ADHD treatment.

Kate is a 14-year-old female teenager. When she was in preschool, she was

diagnosed ADHD by a child neurologist. Parent training was indicated at preschool, instead of medication. During school years, her notebooks were incomplete, she daydreamed, avoided repetitive activities, or activities where concentration was required. She was very disorganized. Also, she was hyperactive, constantly "on the go", dancing and jumping all the time. She was stubborn and did not obey orders (only at home). She was easily frustrated and annoyed, sometimes slammed her bedroom`s door, but in school she could control those behaviors. Conduct issues were not present. She was retained two grades (1st and 2nd grade).

Sometimes she became "silly". She laughed easily, her thought was accelerated, she was more generous than usual with her friends. Most moments of excessive happiness preceded parties, or times when receiving gifts. However, these periods would never last more than a couple of hours, and neither the parents nor the patient see any impairment in these changes. No hypersexuality, increased energy or decreased need for sleep were reported. She said she also felt sad every day, would not see fun in everyday life, but did not report this to impair her life. She feared horror movies, nighttime, darkness, and would not be home alone. No developmental or medical abnormalities were reported. Her mother had a chronic treatment resistant depression, and her brother had a multiple substance use disorder.

Previous treatment trials included carbamazepine (which was reported to increase her irritability), oxcarbazepine (no response), risperidone (due to oppositional behavior towards parents, without clinical response), methylphenidate (short and long acting formulations, without clinical response, and small increase in irritability).

Inattention, impulsivity, and mood instability persisted, with significant impairment in academic and interpersonal functioning. Although at baseline assessment some indicators of BD were observed, parental assessment of mania according to the Child Mania Rating Scale (CMRS) for Parents score was 10, and CMRS for Teachers score was 6. ADHD symptoms, according to the SNAP-IV scores were: inattention: 2.44; hyperactivity 1.77; opposition 0.25; total score: 1.53 by her parents assessment. In school, scores were: inattention: 2.22; hyperactivity 0.11; opposition 0.25; total score:0.88.

Due to the absence of response do methylphenidate, atomoxetine 25mg (0,4mg/kg/day), her inattention and hyperactivity presented a partial improvement. No mood complaints were reported. When atomoxetine was raised to 25mg bid (0,8mg/kg/day), the patient had a significant improvement in inattention, hyperactivity, oppositional symptoms and school performance, but she turned to be very irritated, thought

that her classmates were “childish” and bragged on them. She spent around U$500,00 on cell phone calls to her friends and boyfriend. She became very suspicious of her boyfriend. She was increasingly more scared of sleeping alone, needing lights on. No visual or auditory hallucinations, and no suicidal thoughts or ideation were present. Risperidone was started and raised to 1mg, and paranoid thoughts and irritation decreased, but she cried easily, increased symptoms of separation anxiety, would not even sleeping alone. Lamotrigine was started and titrated to 50mg/day. Due to significant weight gain, risperidone was switched to aripiprazole. The patient is currently stable, using aripiprazole 15mg, lamotrigine 50mg, and atomoxetine 25mg. Current CMRS scores for Parents score is 15, and CMRS for Teachers score is 1. Current SNAP-IV scores: inattention: 20/27 1.22; hyperactivity 12/27 0.77; opposition 9/8 1.00; total score: 1.00 41/26 by her parents assessment. In school, scores are: inattention: 0.89; hyperactivity 0; opposition 0; total score: 0.31.

Discussion

The main purpose of this report is to illustrate a manic episode onset with the use of atomoxetine, an effective agent for the treatment of ADHD. In addition, we would like to remind clinicians on the need of close observation and consideration of risks and benefits when treating patients with subthreshold mood symptoms.

The symptoms discussed here are common in clinical practice; ADHD symptoms are clearly observed, and mood instability can be detected, but a diagnosis of BD-NOS (Not Otherwise Specified) may not be ascertained since duration criterion is not present. Manic/hypomanic symptoms may be easily confounded with ADHD (in this case, represented by impulsivity, event-related mood changes).

Although ADHD and BD are highly comorbid (11–22% of co-morbidity with BD have been mentioned in subjects with ADHD, and 40-89% of ADHD in samples of BD), (5) treatment options for ADHD in this context are not well-defined. Studies regarding stimulants, considered the first line medication intervention for ADHD, exhibit controversial results. Current data suggest the use of stimulant agents as safe and

well tolerated, and mood destabilization is an exception (but not rare), with low rates of manic symptoms development. However, it remains a concern that the use of

stimulants may hasten the onset of BD. Atomoxetine, considered a second line agent for the treatment of ADHD, has shown a moderate efficacy. (1) In the presence of BD or ADHD with subsyndromal BD, it could be considered as a pharmacological option due to smaller risk of manic switch.

However, this case and a few studies have shown otherwise. Most published trials have reported the occurrence of aggression and irritability. (4) In double-blind, placebo controlled trials previously conducted, irritability and mood swings were reported in 8% and 2% of subjects respectively. 4 However, a history of mood symptoms was an exclusion criterion for these studies. Thus, the occurrence of these adverse events should most likely be higher in general practice. Mania and hypomania are also reported as possible events.

Due to the high rates of comorbidity with BD and all the risks inherent to a

manic episode onset, monitoring mood symptoms is crucial when starting children and adolescents with ADHD on atomoxetine. This care should be emphasized when

personal or family history of mood disorders or symptoms are present, although mood worsening may not happen exclusively in the context of these risk factors.

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3. Termo de Consentimento Livre e Esclarecido 1:

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Nome: Número do protocolo:
Pesquisadores: Luis Augusto Rohde e Cristian P. Zeni

Esta é uma pesquisa para identificar substâncias que podem estar alteradas no sangue de indivíduos portadores de Transtorno de Humor Bipolar. Você está sendo convidado para participar com seu filho como um controle, ou seja, por não apresentar este Transtorno. Sua participação será através do preenchimento de alguns questionários e da coleta de uma amostra de sangue. O sangue coletado será armazenado e essas substâncias serão avaliadas em conjunto com alguns dados coletados de pacientes.

Os riscos envolvidos são um mal-estar passageiro ou manchas roxas no local da coleta de sangue. Como seu filho já estará realizando um exame de sangue, nenhuma coleta adicional será necessária, apenas a coleta de 5 ml de sangue adicionais e o respondimento de alguns questionários. Os pais também terão que fazer uma coleta de sangue. Seu nome e seus dados serão mantidos em sigilo pelos pesquisadores do Serviço de Psiquiatria da Infância e Adolescência, sendo estes dados utilizados somente para pesquisa.

Eu,_____, fui informado(a) dos objetivos especificados acima e da justificativa desta pesquisa, de forma clara e detalhada. Recebi informações específicas sobre cada procedimento no qual estarei envolvido, dos desconfortos ou riscos previstos, tanto quanto dos benefícios esperados. Todas as minhas dúvidas foram respondidas com clareza e sei que poderei solicitar novos esclarecimentos a qualquer momento. Além disso, sei que terei liberdade de retirar meu consentimento de participação na pesquisa de acordo com essas informações, sem que isto me traga prejuízos. Em caso de qualquer outra dúvida quanto ao estudo e o que ele envolve e sobre os seus direitos, você deverá contatar os médicos Luis Augusto Rohde ou Cristian Zeni pelo telefone (051)21018094.

ACORDO EM PARTICIPAR DO ESTUDO:
Nome do voluntário:_____
Nome do Responsável Legal do voluntário_____Parentesco:_____
Médico Supervisor:_____

Assinatura do voluntário:_____ Data: __/__/__

Assinatura do responsável pelo voluntário:_____Data: __/__/__

4.Termo de Consentimento Livre e Esclarecido 2

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

"PROGRAMA PARA CRIANÇAS E ADOLESCENTES COM TRANSTORNO BIPOLAR - ProCAB" - Diferenciação dos Transtornos de Humor em Crianças e Adolescentes Através de Estudos de Neuroimagem

Nome: Data de Nascimento:
Pesquisadores Responsáveis: Luis Augusto Rohde, Flavio Kapczinski, Silzá Tramontina, Cristian Zeni

Antes de participar deste estudo, que faz parte do estudo de acompanhamento que você e seu filho já participam, gostaríamos que você tomasse conhecimento do que ele envolve. Damos abaixo alguns esclarecimentos sobre dúvidas que você possa ter. Em caso de qualquer outra dúvida quanto ao estudo e o que ele envolve e sobre os seus direitos, você deverá contatar o Dr. Cristian Zeni pelo telefone (051) 3359-8094.

Qual o objetivo desta pesquisa?
Conhecer características clínicas dos pacientes com Transtorno de Humor Bipolar e Desregulação Grave de Humor, e fazer uma comparação da estrutura e funcionamento do cérebro através de exames de neuroimagem. Isso é feito com um exame chamado Ressonância Magnética. É um exame seguro, que não envolve o uso de radiação, e tampouco há injeção de substâncias para a sua realização. Porém, esse exame é contraindicado em pessoas que tenham implantes metálicos ou eletrônicos, quaisquer tipos de próteses permanentes, fragmentos metálicos no corpo, stents, piercings, tatuagens recentes, aparelhos ortodônticos, cirurgias recentes ou gravidez, seguindo o protocolo do Serviço de Radiologia Hospital de Clínicas de Porto Alegre. Nenhum exame será cobrado dos participantes. Além disso, queremos ver as mudanças que ocorrem no cérebro após o tratamento e ao longo do desenvolvimento até a vida adulta.

O que acontecerá neste estudo?
As crianças e adolescentes farão o exame de Ressonância Magnética no Serviço de Radiologia do HCPA, com acompanhamento do pesquisador responsável. Esse exame dura cerca de 25 minutos, e não será utilizado nenhum tipo de medicação para este exame.

Quais os benefícios em participar deste estudo?
A sua participação neste estudo poderá proporcionar, no âmbito pessoal, a identificação de algum problema não antes conhecido com posterior encaminhamento para atendimento, e no âmbito coletivo, poderá ajudar no desenvolvimento de maior conhecimento do Transtorno Bipolar e da Desregulação Grave de Humor, principalmente em relação às causas das doenças, como elas funcionas, e como evoluem.

Quais são os direitos dos participantes?
Os pesquisadores deste estudo podem precisar examinar os seus registros, a fim de verificar as informações para o objetivo deste estudo. No entanto, os seus registros médicos serão sempre tratados confidencialmente. Os resultados deste estudo poderão ser enviados para publicação

em um jornal científico, mas você não será identificado por nome. Sua participação no estudo é voluntária, de forma que caso você decida não participar, isto não afetará a sua avaliação e encaminhamento.
Você terá acesso aos resultados dos exames, podendo ter cópia dos laudos e imagens.

Quais são os riscos que envolvem este estudo?
Não são conhecidos riscos na realização do estudo. Durante o exame de Ressonância Magnética, você ouvirá um barulho parecido com batidas, como num jogo de videogame. O aparelho de Ressonância parece um tubo, onde você ficará dentro durante todo o exame. Isso pode gerar algum desconforto. Entretanto, o técnico vai lhe dar protetores de ouvido para reduzir o barulho e o desconforto.

Quais são as responsabilidades dos participantes?
Os participantes deste estudo comprometem-se a comparecer aos exames agendados ao longo do estudo.

Declaro que entendi os objetivos, riscos e benefícios de minha participação na pesquisa, bem como meus direitos e responsabilidades, e concordo em participar.

Em caso de dúvida, poderão ser contatados os pesquisadores e o Comitê de Ética em Pesquisa (3359-8304).

Este documento será entregue em duas vias, sendo uma via entregue para o participante.

Porto Alegre, _____ de _____ de 20_____ .

_____
Nome do Paciente

_____ _____

Representante Legal **Nome do Representante**

_____

Pesquisador responsável (nome e assinatura)

TABELAS

1. Tabelas de Resultados Do Artigo

Tabela 1:Dados Demográficos (N=27)

	Média	**DP**
Idade (anos)	13,8889	2,97856
Idade de início (anos)	9,1852	3,79308
Tempo de doença (anos)	4,7407	3,38086
YMRS	7,51	8,86
CDRS	28,11	11,31
QI	105,77	14,05

DP: Desvio padrão; YMRS=Young Mania Rating Scale;
CDRS=Children's Depression Rating Scale.
QI=Quociente de Inteligência.

Tabela 2: Resultados das avaliações (N=27)

	Média	DP
VHD[a] (mm^3)	41910,55	4163,04
VHE[b] (mm^3)	41747,96	5067,43
VHT(mm^3)	83658,51	9015,84
BDNF (pg/µg protein)	19,58	6,33
Digit Span TS[d]	6,66	1,83
Digit Span IO[e]	4,48	1,90

VHD=Volume de Hipocampo Direito; VHE=Volume de Hipocampo Esquerdo;
VHT=Volume de Hipocampo Total; BDNF=Brain-Derived Neurotrophic Factor;
Digit Span TS=Subteste de Dígitos, escore total;
Digit Span IO=Subteste de Dígitos, ordem inversa.

Tabela 3: Correlações entre níveis de BDNF, volumes de hipocampo e variáveis neuropsicológicas.

	VHD		VHE		VHT	
	ρ (Rô)	**P**	**ρ (Rô)**	**P**	**ρ (Rô)**	**P**
Tempo de Doença	.107	.595	.251	.207	.217	.276
BDNF	.148	.461	.027	.892	.100	.621
QI	-.009	.963	.065	.749	.045	.825
Digit Span TS[f]	-.098	.587	.102	.743	.014	.985
Digit Span IO[g]	-.021	.918	.097	.632	.045	.825

ρ: Rô de Spearman;VHD=Volume de Hipocampo Direito; VHE=Volume de Hipocampo Esquerdo;BDNF=Brain-Derived Neurotrophic Factor; QI=Quociente de Inteligência;Digit span TS=Subteste de dígitos, escore total; Digit span IO= Subteste de Dígitos, ordem inversa.

Tabela 4: Correlação entre Níveis Séricos de BDNF e tempo de Doença, YMRS, CDRS, QI e o subteste Dígitos.

	BDNF	
	ρ (Rô)	**P**
Tempo de Doença	.069	.731
QI	.069	.732
Dígitos	.187	.351

BDNF: Fator neurotrófico Derivado do Cérebro; ρ: Rô de Spearman; QI: Quociente de Inteligência.

2. Tabelas de Resultados do Artigo 1

Tabela 1. Randomized Controlled Trials Assessing Pharmacotherapy for Children and Adolescents with Bipolar Disorder

Study/Reference	Medication	Dosage range	Subjects	Duration	Result	Limitations / Observations/ Adverse side-effects*
Geller 1998 [13]	Lithium vs Placebo	0.9-1.3 mEq/L	25	6 weeks	Li=Pc in YMRS Li>Pc in CGAS	Polyuria
Kowatch 2007 [14]	Lithium vs Divalproex vs Placebo	**	153	8 weeks	DVP>Pc Li=Pc	**
Wagner 2009 [15]	Divalproex vs Placebo	35mg/kg/day	150	4 weeks	DVP=Pc	Weight gain
Pavuluri 2010 [16]	Risperidone+Placebo vs Divalproex+Pc	Risp 0.25-2mg/day DVP 60-120µg/mL	66	6 weeks	Risp>DVP	No difference in weight gain
DelBello 2002 [17]	Divalproex+Quetiapine vs Divalproex+Placebo	DVP 20mg/kg/day Quet 450mg/day	30	6 weeks	DVP+Quet>DVP+Pc	Sedation
Wagner 2006 [18]	Oxcarbazepine	900mg-2400mg/day	116	7 weeks	OXC=Pc	Dizziness, nausea, diplopia, somnolence, fatigue and rash
DelBello 2005 [19]	Topiramate	200-400mg/day	56	4 weeks	TPT>Pc	Decreased appetite, nausea, diarrhea and parestesia
Haas 2009 [20]	Risperidone	0.5-2.5mg/day or 3-6mg/day	169	3 weeks	Risp>Pc	Weight gain, somnolence, headache and fatigue
Geller 2012 [21]	Risperidone vs Lithium vs Divalproex Sodium	4-6mg/day 1.1-1.3mEq/L 111-125µg/mL	279	8 weeks	Risp>Li Risp>DVP Li=DVP	Increases in BMI and hyperprolactinemia
Tohen 2007 [22]	Olanzapine	2.5-20mg/ml	161	3 weeks	Olan>Pc	Weight gain, drowsiness, sedation, increases in systolic pressure, fasting glucose, total cholesterol, serum prolactin levels and liver

						enzymes
DelBello 2009 (24)	Quetiapine	400mg/day or 600mg/day	284	3 weeks	Quet>Pc	Sedation, dizziness, headache and fatigue
DelBello 2009 (26)	Ziprasidone	60-80mg/day or 120-160mg/day	238	4 weeks	ZPS>Pc	Dystonia, headache and sedation
Findling 2009 (28)	Aripiprazole	10mg or 30mg/day	296	4 weeks	Arip>Pc	Somnolence, parkinsonism and akathisia
Tramontina 2009 (29)	Aripiprazole	20mg/day	43	6 weeks	Arip>Pc	Somnolence and drooling
Gracious 2010 (31)	Flax oil	12 capsules/day (550mg α-LNA/gram)	51	16 weeks	Flax oil=Pc	14% discontinued due to mood-related issues, 30% due to other clinical issues and 53% for any other reason
Depressive Episode						
DelBello 2009 (54)	Quetiapine	300-600mg/day	32	8 weeks	Quet>Pc	Dizziness
Maintenance treatment						
Kafantaris 2003 (58)	Lithium	0.6-1.2mEq/L		2 weeks	Li>Pc	
Findling 2005 (59)	Lithium vs Divalproex	Li: 0.6-1.2mmol/L DVP: 50-120µg/mL	139	76 weeks	Li=DVP	Increased thirst, emesis and enuresis with lithium. Headache and stomach pain with DVP.
Findling 2012 (60)	Aripiprazole	6.4±2.1mg/day	60	72 weeks	Arip>Pc	Stomach pain, increased appetite, headaches
Comorbidity with ADHD						
Scheffer 2005 (64)	Divalproex+Mixed Amphetamine Salts	DVP: 82.4 µg/ml MAS: 14.5 mg/ml	30	4 weeks	DVP+MAS>DVP+Pc	Abdominal pain, diarrhea, nausea, appetite increase, headache, drowsiness, difficulty falling asleep, irritability, and rash.
Findling 2007 (65)	Methylphenidate	5mg-10mg	16	4 weeks	MPH=Pc	One subject discontinued due to urticaria and vomiting.

						A second subject discontinued due to increases in serum alkaline phosphatase and liver transaminase concentrations
Zeni 2009 [11]	Aripiprazole + Methylphenidate vs. Aripiprazole+Placebo	MPH: 0.3-0.7mg/kg/day Arip: 10-20mg	16	2 weeks with each treatment option	Arip+MPH=Arip+Pc	One patient discontinued the trial due to severe mixed episodes.

*Adverse effects significantly more frequent in the active medication group vs. placebo
**Data not available
Li: lithium; DVP: Divalproex sodium; Risp: Risperidone; Quet: Quetiapine; OXC: Oxcarbazepine; TPT: Topiramate; Olan: Olanzapine; Zps: Ziprasidone; Arip: Aripiprazole; MAS: Mixed Amphetamine Salts; MPH: Methylphenidate; Pc: Placebo.

Tabela 2: Open Label, Retrospective or Follow-up Studies in the Treatment of Mania, Hypomania or Mixed Episodes, Depressive Episode, Maintenance and Comorbidity with Attention-Deficit/Hyperactivity Disorder

Type of study	Study/ Reference	Medication	Dosage range	Subjects	Duration	Result	Limitations / Observations/ Adverse side-effects*
Treatment of manic, hypomanic or mixed episodes							
Open Label	Kafantaris 2003[34]	Lithium	0.6-1.2mEq/L	100	4 weeks	2/3 of subjects responded ¼ achieved remission	Adjunctive antipsychotics were used in 46% of subjects
Follow-up	Pavuluri 2005 [35]	Divalproex Sodium	50-120µg/mL	34	6 months	73,5% of response rate* 52,9% of remission rate	Drop-out rate : 6.4%, due to benign rash
Open Label	Wagner 2002 [36]	Divalproex Sodium	45-125µg/mL	40	2-8 weeks	61% of response rate*	10% used adjunctive therapy with lithium and 53% used other drugs simultaneously
Open Label	Kowatch 2000 [52]	Lithium, Divalproex Sodium and Carbamazepine	Li: 0.8-1.2mEq/L DVP: 85 to 110 µg/L	42	6 weeks	Response rates were as follows: sodium divalproex,	All 3 mood stabilizers were well tolerated,

			CBZ: 7 to 10 µg/L			53%; lithium, 38%; and carbamazepine, 38%*	and no serious adverse effects were seen.
Open Label	Joshi 2010 [53]	Carbamazepine	788 ± 252 mg/day	16	8 weeks	Modest levels of improvement in YMRS scores	Suggests lack of complete resolution of mania
Open Label	Pavuluri 2009 [37]	Lamotrigine	150-200mg/day	46	14 weeks	Response rate: 72% on manic symptoms and 82% in depressive symptoms***	Benign rash in 6.4% of subjects
Open Label	Biederman 2010 [38]	Lamotrigine	160.7 ± 128.3 mg/day(subjects <12 years); 219.1 ± 172.2 mg/day (subjects>12 years).	39	12 weeks	Response rates: 66% (<12 years) and 54% (>12 years)**	25% of subjects discontinued the trial due to adverse events, mostly dermatological
Open Label	Pavuluri 2006 [45]	Lithium + Risperidone	Li: 0.6-1.0 mEq/L Risp: 2mg/day	38	11 months	Response rates: 85.7%*	Weight gain, nausea/vomiting, increased appetite, stomach pain, sedation, polyuria, enuresis, tremor, restlessness, stiffness of muscles, fatigue, cognitive dulling, flu-like symptoms.
Open Label	Pavuluri 2004 [46]	Risperidone + Lithium vs Risperidone + Divalproex Sodium	Risp: 3mg/day; Li: 0.6-1.0mEq/L; DVP: 50-120µg/mL	37	6 months	Response rates (≥50% change from baseline YMRS score at the end of study) were 80% for DVPX+Risp and 82.4% for Li+Risp	Combination therapy was well-tolerated in both the groups. Two subjects discontinued earlier in Risp+Li group due to enuresis and fatigue.
Open Label	Wozniak 2009 [48]	Olanzapine vs Olanzapine + Topiramate	Mon: Olan 8.6±3.4mg/day Comb: Olan 9.9±5.2 and Top: 70.5-30.5 mg/day	40	8 weeks	Statistically significant reduction in YMRS scores with both treatments.	Spacey, tremor, akathisia, dazed, nistagmus, speech deterioratio

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Open Label	Biederman 2005 [47]	Olanzapine vs Risperidone	Olan: 10mg/day Risp: 2mg/day	31	8 weeks	Response rates: 69% for risperidone and 53% for olanzapine**	Preschooler children. Weight gain observed with both drugs. Higher prolactin levels with risperidone.
Open Label	Biederman 2005 [34]	Risperidone	1.25 ± 1.5 mg/day	30	8 weeks	Significant decrease in YMRS (average 14.4 points)	8 dropouts (7 due to lack of efficacy and one due to orthostatic hypotension)
Open Label	Frazier 2001 [40]	Olanzapine	2.5-20mg/day	23	8 weeks	61% of response rate**	Increase of body weight.
Retrospective	Marchand 2005 [41]	Quetiapine	397.4 ± 221.4 mg/day	32	6.1 ± 5.9 months	50% of subjects symptom improvement	14 were in use of quetiapine monotherapy
Open Label	Biederman 2007 [42]	Ziprasidone	57.3 ± 33.9 mg/day	21	8 weeks	Improvement in mean YMRS and CGI-I scores	Sedation, headache and gastrointestinal problems.
Open Label	Tramontina 2007 [43]	Aripiprazole	2-20mg/day	10	6 weeks	Improvement in global functioning scores (p=0.01), manic symptoms (p<0.01), and ADHD symptoms (p<0.01)	Sialorrhea, tiredness, sedation, confusion, depressive symptoms, increased appetite or decreased appetite, sweating, tremors, nervousness, and anxiety
Open Label	Findling 2011 [44]	Aripiprazole	15 mg/day	69	16 weeks	62.5% met response criteria****	Stomachache, headache and increased appetite.
Open Label	Wozniak 2006 [50]	Omega-3 fatty acid	1290 mg 4300 mg/day	20	8 weeks	35%of subjects symptoms improvement (decrease in YMRS≥50%)	Small but statistically significant weight gain.
Open Label	Rucklidge 2010 [51]	Micronutrient formula (EMPowerplus)	15 capsules of micronutrient formula[a]	120	3-6 months	43% decline in PBD symptoms and 40% in ADHD symptoms, evaluated by LOCF*****	The data were obtained from the formula company's database
Depressive Episode							
Open	Patel	Lithium	1.0-1.2 mEq/L	27	6 weeks	48% of response	Headache,

Label	2006 [55]					rate******	nausea/vomiting, stomachache, abdominal cramps
Open Label	Chang 2006 [56]	Lamotrigine	100-200mg/day	20	8 weeks	63% of response rate******	No significant adverse effects.
Review of medical records	Biederman 2000 [57]	SSRI And Mood Stabilzers	*******	59	*******	Significant improvement of bipolar depression with SSRI. Improvement of manic symptoms with Mood Stabilizers.	Recurrence of manic symptoms with SSRI. Mood Stabilizers did not change course of bipolar depression.
Maintenance Treatment							
Open Label	Findling 2005 [61]	Lithium or Divalproex Sodium (monotherapy vs combination)	Li: 0.6-1.0mmol/L DVP: 50-100µg/L	38	8 weeks	Patients who became symptomatic with monotherapy presented 89.5% of remission rate with combined therapy).	Five patients discontinued study participation due to adverse events (alopecia in both groups; increased thyrotropin blood level and thrombocytopenia in DVP group; enuresis in Li group)
Open Label	Tramontina 2007 [62]	Topiramate	50-150mg/day	10	11 weeks	Significant reduction in YMRS scores and also in body weight	Cognitive Impairment
Open Label	Duffy 2009 [63]	Quetiapine	50-800mg/day	18	48 weeks	Effective and well tolerated	Somnolence and flu-like symptoms.
Comorbidity with ADHD							
Open Label	Chang 2009 [66]	Atomoxetine	1.2mg/kg	12	8 weeks	67% of response rate. 50% of remission rate.	To subjects discontinued due to worsening of mood symptoms

a: the ingredients of the formula are listed on the developer's website (Truehope.com)
*Defined as a reduction in YMRS scores ≥ 50%.
**Defined as a reduction in YMRS scores ≥ 30%.
*** Defined as a score less than 12 on the YMRS. Response for depressive symptoms was defined as a score less than 40 on the CDRS-R.
**** Response criteria consisted of 3 of 4 consecutive weeks with (1) CDRS-R <29; (2) YMRS <10; and (3) CGAS >50.
***** Last Observation Carried Forward (LOCF)
******Defined as reduction in CDRS-R scores≥50%.
*******Data not included in table due to the nature of the study.

SSRI: Selective Serotonin Reuptake Inhibitors; Li: Lithium; DVP: Divalproex Sodium; CBZ: Carbamazepine, Risp: Risperidone; Olan: Olanzapine.

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