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TIANEPTINA E NEUROPROGRESSÃO NO TRANSTORNO BIPOLAR

Porto Alegre, 2016

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Tese apresentada como requisito parcial para obtenção de título de Doutor em Psiquiatria à Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento.

Orientador: Profa. Dr. Márcia Kauer-Sant'Anna

Porto Alegre, 2016

FOLHA DE APROVAÇÃO DA BANCA EXAMINADORA
NATALIA SONCINI KAPCZINSKI

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Dissertação apresentada como requisito parcial para obtenção de título de Doutor em Psiquiatria à Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento.

Porto Alegre, ... de ..... de 2016.

A comissão Examinadora, abaixo assinada, aprova a Dissertação "Tianeptina e Neuroprogressão no Transtorno Bipolar", elaborada por Natália Soncini Kapczinski como requisito parcial para a obtenção do grau de Doutor em Psiquiatria e Ciências do Comportamento.

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Prof. Dr. Márcia Kauer-Sant'Anna - Orientadora

AGRADECIMENTOS

À minha orientadora, Prof. Dr. Márcia Kauer-Sant'Anna, pelo constante estímulo e pelo conhecimento ensinado.

Aos pacientes e familiares dos pacientes que, apesar de tantas adversidades, aceitaram participar da pesquisa.

À equipe do Prothabi pelo empenho na realização do ensaio clínico com a tianeptina.

À minha família que me apoiou durante todo o curso desse trabalho.

RESUMO

O curso longitudinal do transtorno bipolar é altamente variável, mas um subconjunto de pacientes parece apresentar uma evolução progressiva associada a alterações cerebrais e comprometimento funcional. Em nosso primeiro artigo, discutimos a teoria da neuroprogressão no transtorno bipolar. Este conceito considera a resposta ao estresse que ocorre nos episódios de humor e déficits no funcionamento e cognição, bem como alterações neuroanatômicas nos estágios tardios da doença. Discutimos também refratariedade ao tratamento que pode ocorrer em alguns casos de transtorno bipolar. Foi executada uma busca na base de dados PubMed para artigos publicados em qualquer idioma até 04 de junho de 2016. Foram encontrados 315 resumos e 87 estudos foram incluídos em nossa revisão. Somos da opinião de que o uso de estratégias farmacológicas específicas e remediação funcional pode ser potencialmente útil em pacientes bipolares em estágios tardios. Novas abordagens analíticas que utilizam dados multimodais têm o potencial para ajudar na identificação de assinaturas de subgrupos de pacientes que irão desenvolver um curso neuroprogressivo.

Com base em nossa hipótese de neuroprogressão, decidimos realizar um ensaio clínico randomizado com o antidepressivo tianeptina como tratamento adjuvante para o transtorno bipolar, a fim de melhorar o comprometimento funcional, desfechos clínicos e aumentar os níveis do Brain-Derived Neurothrofic Factor (BDNF). Tianeptina é um fármaco seguro, que atua sobre o sistema glutamatérgico e tem um efeito antidepressivo. Esse estudo teve como objetivo avaliar a eficácia e tolerabilidade da tianeptina como tratamento adjuvante para a depressão bipolar. Foi realizado um ensaio clínico duplo-cego randomizado de manutenção controlado por placebo com tianeptina 37,5 mg/dia. Os participantes (n = 161) tinham uma pontuação na Montgomery Asberg Depression Rating ≥12 no início do ensaio. Após oito semanas de tratamento com tianeptina na fase aberta, aqueles que responderam a tianeptina foram randomizados para o placebo ou tianeptina adjuvante. Os participantes foram recrutados na rede pública de saúde. Tempo para qualquer intervenção foi o desfecho primário do estudo. Mudanças nos sintomas de humor, funcionamento, ritmos biológicos, qualidade de vida, taxas de virada maníaca e níveis séricos de BDNF foram considerados como desfechos secundários. Houve uma diminuição importante nos sintomas depressivos, assim como melhoras no funcionamento, qualidade de vida e pontuações no ritmo

biológico durante a fase aberta de tratamento com tianeptina por oito semanas. Durante as 24 semanas do ensaio duplo-cego randomizado e controlado por placebo, não houve diferença em relação ao desfecho primário: tempo para qualquer intervenção. Além disso, não houve diferenças significativas entre os grupos em relação aos sintomas de humor, funcionamento e níveis de BDNF. Tianeptina foi bem tolerada e não foi associada a virada maníaca em comparação com o placebo. Estes achados sugerem que tianeptina é um medicamento seguro e pode ser eficaz no tratamento da depressão bipolar aguda. No entanto, tianeptina não mostrou efeitos benéficos na fase de manutenção. Este é o primeiro ensaio clínico duplo-cego randomizado de manutenção e de longo prazo com antidepressivo no transtorno bipolar.

Palavras-chave: transtorno bipolar, neuroprogressão, tianeptina, ensaio clínico randomizado, antidepressivo.

ABSTRACT

The longitudinal course of bipolar disorder is highly variable, and a subset of patients seems to present a progressive course associated with brain changes and functional impairment. In our first article, we discussed the theory of neuroprogression in bipolar disorder. This concept considers the systemic stress response that occurs within mood episodes and late-stage deficits in functioning and cognition as well as neuroanatomic changes. We also discuss treatment refractoriness that may take place in some cases of bipolar disorder. We searched PubMed for articles published in any language up to June 4th, 2016. We found 315 abstracts and included 87 studies in our review. We are of the opinion that the use of specific pharmacological strategies and functional remediation may be potentially useful in bipolar patients at late-stages. New analytic approaches using multimodal data hold the potential to help in identifying signatures of subgroups of patients who will develop a neuroprogressive course.

Based on our hypothesis of neuroprogression, we decided to perform a randomized clinical trial with tianeptine as adjunctive treatment for bipolar disorder in order to improve functional impairment and increase serum Brain-Derived Neurothrophic Factor BDNF levels. Tianeptine is a safe medication that acts on the glutamatergic system and has an antidepressant effect. The present study aimed at assessing the efficacy and tolerability of tianeptine as an adjunctive treatment for bipolar depression. We performed an enriched maintenance multi-center double-blind randomized controlled trial of tianeptine 37•5mg/day. Participants (n = 161) had a Montgomery Asberg Depression Rating Score ≥12 at trial entry. After eight weeks of open-label tianeptine treatment, those who responded to tianeptine were randomized to adjunctive tianeptine or placebo in addition to usual treatment. Participants were recruited from public health services and through advertisement. Time to any intervention was the primary endpoint of the study. Changes in mood symptoms, functioning, biological rhythms, quality of life, rates of mania switch and serum BDNF assessments were considered as secondary outcomes. There was a robust decrease in depressive symptoms along with improvements in functioning, quality of life and biological rhythms scores during the eight-week open-label tianeptine treatment phase. During the subsequent 24-week double-blind controlled phase, there was no difference regarding the primary outcome: time to intervention.

In addition, there were no significant differences between groups in mood symptoms, functioning and BDNF levels. Tianeptine was well tolerated and not associated with mania switch as compared to placebo. These findings suggest that tianeptine is a safe medication and may be effective in the treatment of acute bipolar depression. However, tianeptine did not show beneficial effects in the maintenance phase. This is the first long-term randomized, double-blind maintenance trial of antidepressant augmentation in bipolar disorder.

Keywords: bipolar disorder, neuroprogression, tianeptine, randomized clinical trial, antidepressant.

LISTA DE ABREVIATURAS E SIGLAS

BDNF: *Brain-derived neurotrophic factor* – Fator neurotrófico derivado do cérebro

CREB: *cAMP response element-binding protein* - proteína de ligação ao elemento de resposta cAMP

GLT-1: *Glial glutamate transporter* – Transportador de glutamato da glia

FAST: *Functioning Assessment Short Test* - Teste Curto de Avaliação do Funcionamento

NOS: *not otherwise specified* – Sem outras epecificações

SUMÁRIO

1. APRESENTAÇÃO

O transtorno bipolar afeta cerca de 2% da população mundial [1]. As taxas de suicídio em pacientes com transtorno bipolar são 7,8% em homens e 4,9% nas mulheres [2]. Embora existam várias opções de tratamento para a prevenção e tratamento de episódios de humor, estes são frequentemente ineficazes, e cerca de 60% dos pacientes apresentam recaída em depressão ou mania dentro de 2 anos [3]. Além disso, embora os tratamentos disponíveis conseguem efetivamente reduzir os sintomas transtorno bipolar, eles são menos eficazes na recuperação do funcionamento. Este quadro ilustra as falhas da abordagem de tratamento atual no transtorno bipolar, que se concentra principalmente na estabilização dos episódios de humor e prevenção da recorrência, negligenciando o curso longitudinal da doença e a necessidade de promover a recuperação funcional em muitos casos.

O curso do transtorno bipolar é altamente variável, mas um subconjunto de pacientes parece apresentar uma evolução progressiva associada a alterações cerebrais [4–6]. A noção de que vários episódios e recaídas poderiam levar a uma doença mais grave, além de prejuízo intelectual, tem sido constatada desde o trabalho de Griesinger em 1865 [7]. Além disso, o curso potencialmente progressivo da transtorno bipolar também foi descrito em 1920 por Kraepelin [8]. Mais recentemente, um estudo longitudinal mostrou alterações no córtex frontal e aceleração de episódios em função do número de episódios anteriores [9,10]. Tendo em conta estes resultados, mudanças progressivas na apresentação doença foram englobadas sob o conceito de neuroprogressão [11]. O termo “neuroprogressão” foi proposto como a religação patológica do cérebro que ocorre em paralelo com a deterioração clínica e neurocognitiva no curso do transtorno bipolar [4]. No entanto, as implicações clínicas e fundamentos moleculares da neuroprogressão ainda permanecem incompreendidas, sendo às vezes controversas.

A presente tese se baseou na hipótese da neuroprogressão. Primeiramente, revisamos a literatura relativa a neuroprogressão no transtorno bipolar. Essa busca resultou no nosso primeiro artigo que será publicado na Expert *Reviews Neurotherapeutics* sob o título de *Neuroprogression and illness trajectories in bipolar disorder*. O segundo artigo foi um ensaio clínico duplo-cego multicêntrico randomizado que utilizou tianeptina como terapia adjuvante para o tratamento de manutenção de pacientes bipolares. Em virtude do mecanismo de ação dessa

medicação, elaboramos a hipótese que ela poderia evitar a recaída em um episódio de humor, além de melhorar alguns desfechos relacionados à neuroprogressão, como o prejuízo funcional. O artigo está submetido na revista *The Lancet Psychiatry*.

2. INTRODUÇÃO

2.1. Neuroprogressão

O transtorno bipolar tem uma prevalência ao longo da vida de cerca de 2% [1]. As taxas de suicídio em pacientes com transtorno bipolar são de 7,8% em homens e de 4,9% nas mulheres [2]. Os pacientes bipolares apresentam episódios de humor agudos que podem potencialmente levar a comportamentos auto-lesivos, tais como o abuso de drogas e suicídio [2]. Menos apreciado, entretanto, é a evidência emergente que sugere que o transtorno bipolar, como muitas doenças crônicas, pode apresentar um curso progressivo com deficiência e alterações neuroanatômicas.

Os consensos de tratamento atuais sobre transtorno bipolar centram-se principalmente na estabilização de episódios de humor agudos e prevenção de recorrência, negligenciando a necessidade de promover a recuperação funcional [12]. Nesse sentido, parece existir um subgrupo de pacientes com transtorno bipolar que apresentarão prejuízo do funcionamento. Um recente estudo transversal mostrou que 42% dos pacientes eutímicos com transtorno bipolar apresentaram funcionamento global prejudicado quando avaliados pela FAST [13]. Os fatores de risco que predisseram mau funcionamento nos pacientes com transtorno bipolar foram inteligência verbal, controle inibitório, sintomas depressivos residuais, e o número de episódios de humor [14]. Além disso, um estudo relatou alterações funcionais progressivas em pacientes com transtorno bipolar [15].

Estudos transversais e longitudinais sugerem que os casos mais graves podem apresentar reorganização cerebral patológica progressiva em função do número de episódios de humor [9,16]. Um estudo transversal mostrou uma associação negativa entre o volume do hipocampo e o número de episódios maníacos em pacientes com transtorno bipolar [17], enquanto outro estudo encontrou a mesma associação negativa mas com o volume do corpo caloso [18]. Um estudo que utilizou técnicas de *machine learning* relatou alterações nas regiões do sistema fronto-límbico em função do número de episódios maníacos [16]. Além disso, um estudo longitudinal de 6 anos demonstrou diminuição do volume frontal cortical no grupo de pacientes que tiveram pelo menos um episódio maníaco [9]. Essas conclusões estão em linha com o trabalho pioneiro de Strakowski e colaboradores, que relatou aumento do

volume dos ventrículos em pacientes com transtorno bipolar e múltiplos episódios em comparação àqueles que tiveram apenas um episódio [19].

O termo neuroprogressão se refere ao prejuízo do funcionamento e alterações neuroanatômicas que ocorrem em alguns casos de transtorno bipolar [20]. Neuroprogressão é conceituado, portanto, como a religação patológica do cérebro que ocorre em paralelo com o deterioro clínico e funcional presente no curso de transtorno bipolar [20]. Além disso, parece que as alterações em alguns biomarcadores periféricos (estresse oxidativo, marcadores inflamatórios e neurotrofinas) estão associados com neuroprogressão.

2.2. Tianeptina como um agente neurotrófico

A tianeptina se destaca como um agente terapêutico com propriedades únicas, que abordam a maior parte das alterações encontradas no transtorno bipolar [21,22]. Notavelmente, nenhum dos medicamentos atuais disponíveis para o tratamento do transtorno bipolar apresentam todas estas características: 1) a tianeptina exerce efeitos opostos ao estresse crônico nos neurônios, aumentando os fatores neuroprotetores que podem ajudar a extinguir o ciclo de aceleração de episódios de humor do transtorno bipolar e evitar a deterioração neural; 2) a tianeptina afeta a neuroplasticidade no hipocampo e aumenta o comprimento dos dendritos; 3) a tianeptina aumenta os níveis de BDNF na amígdala; 4) a tianeptina atenua a liberação de glutamato induzida por estresse na amígdala; 5) a tianeptina tem propriedades anticonvulsivantes via receptores A1 adenosinérgicos; 6) a tianeptina tem efeitos analgésicos. Como descrito acima, os pacientes com transtorno bipolar 1) são particularmente vulneráveis aos efeitos do estresse; 2) apresentam atrofia de diferentes regiões do cérebro, incluindo o hipocampo; 3) apresentam diminuição dos níveis de BDNF; 4) apresentam ativação da amígdala alterada; 5) apresentam alteração no sistema adenosinérgico; 6) muitas vezes apresentam sintomas somáticos na depressão [21,22].

Especificamente, os efeitos da tianeptina na plasticidade neuronal foram demonstrados por Magarinos e colaboradores que observou que tianeptina, mas não a fluoxetina, preveniu o encurtamento induzida pelo estresse do comprimento dos

dendritos em neurónios do hipocampo [23]. Subsequentemente, o estudo de Czeh e colaboradores relatou que a tianeptina preveniu a atrofia do hipocampo induzida por stress e aumentou a neurogênese hipocampal e o N-acetil-aspartato *in vivo*, um marcador de integridade neuronal [24]. Por outro lado, Reagan e colaboradores demonstrou que o tratamento crônico com tianeptina preveniu o aumento da expressão induzida pelo stress do GLT-1, sugerindo que tianeptina normaliza a transmissão de glutamato excessiva [25]. Lucassen e colaboradores relataram que a tianeptina reduzia a apoptose celular induzida pelo stress no giro denteado e córtex temporal, o que sugere um efeito positivo da tianeptina na sobrevivência neuronal [26]. Reagan e colaboradores também relataram que a tianeptina parece diminuir concomitantemente o pCREB enquanto aumenta a expressão do BDNF na amígdala de ratos [25]. Em conjunto, estes estudos sugerem que tianeptina aumenta a neuroplasticidade e a sobrevivência neuronal, prevenindo a toxicidade induzida por estresse pelo glutamato e a atrofia celular. Estes estudos pré-clínicos, portanto, proporcionam uma interessante hipótese para testar os efeitos da tianeptina sobre o funcionamento e desfechos clínicos de pacientes bipolares, sobretudo aqueles que desenvolverão um curso neuroprogressivo.

3. JUSTIFICATIVA

Observamos que diversos estudos vem corroborando a hipótese da neuroprogressão. Eles mostram que um subgrupo de paciente bipolares apresentaram prejuízo funcional além de um curso clínico mais grave da doença com mais recaídas e hospitalizações.

Diante disso, executamos dois trabalhos. O primeiro foi uma revisão sobre o conceito de neuroprogressão focando nos achados relativos ao funcionamento, alterações neuroanatômicas e de biomarcadores periféricos de pacientes com transtorno bipolar. O segundo foi um ensaio clínico duplo-cego e randomizado com tianeptina no tratamento de manutenção do transtorno bipolar. O desfecho principal desse ensaio clínico era o tempo para qualquer intervenção bem como a melhora do prejuízo funcional.

4. OBJETIVOS

4.1 OBJETIVO GERAL

Determinar a eficácia da tianeptina no tratamento de manutenção do transtorno bipolar.

4.2 OBJETIVOS ESPECÍFICOS

a) Revisar a literatura relacionada com as mudanças no funcionamento, neurocognição e neuroimagem apresentadas no transtorno bipolar.
b) Investigar a eficácia e tolerabilidade de tianeptina 37,5 mg/dia como uma medicação adjuvante para o tratamento de manutenção na depressão bipolar.
c) Avaliar as taxas de virada para mania com tianeptina.
d) Avaliar a eficácia da tianeptina durante a fase aberta do ensaio clínico.
e) Examinar os efeitos da tianeptina sobre os níveis de BDNF periférico e funcionamento psicossocial nas fases aguda e de manutenção do ensaio.

5. CONSIDERAÇÕES ÉTICAS

Esta pesquisa foi desenvolvida com base em parâmetros éticos, de acordo com a resolução 196/96 do Conselho Nacional de Saúde, que exige a anuência por escrito dos participantes, mediante explicação completa e pormenorizada da natureza da pesquisa e dos possíveis incômodos ou benefícios que podem ocorrer em decorrência da mesma. De tal modo, todos os participantes foram esclarecidos dos objetivos da pesquisa, participaram de maneira voluntária e assinaram o Termo de Consentimento Livre e Esclarecido. A pesquisa foi aprovada pelo Comitê de Ética com Seres Humanos da Universidade Federal do Rio Grande do Sul (HCPA/UFRGS). O presente estudo também foi registrado no ClinicalTrials.gov sob o número de registro NCT00879372.

6. ARTIGOS

6.1. ARTIGO 1

6.1.1. Carta de submissão

30-Aug-2016

Dear Dr Passos,

Your manuscript entitled "Neuroprogression and illness trajectories in bipolar disorder" has been successfully submitted online and is presently being given full consideration for publication in Expert Review of Neurotherapeutics.

Your manuscript ID is ERN-2016-0110.R2.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to Manuscript Central at https://mc.manuscriptcentral.com/ern and edit your user information as appropriate.

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Thank you for submitting your manuscript to Expert Review of Neurotherapeutics.

Sincerely,
Joseph Walsh
joseph.walsh@informa.com

6.1.2. Manuscrito

Neuroprogression and illness trajectories in bipolar disorder

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Contributors

All authors contributed to the study design. NSK, ICP, BM, RMC, DLG, and MBB did the scientific literature search. NSK, ICP and BM were responsible for the figures. NSK, BM, RMC, DLG, MBB, MKS, FK and ICP participated in the writing of the manuscript. All authors approved the final version of the manuscript.

Declaration of Interest

FK has received grants or research support from AstraZeneca, Eli Lilly, Janssen-Cilag, Servier, NARSAD, and the Stanley Medical Research Institute; has been a member of speakers' boards for AstraZeneca, Eli Lilly, Janssen, and Servier; and has served as a consultant for Servier. Márcia Kauer-Sant'Anna is on speaker or advisory boards for, or has received research grants from NARSAD, Stanley Medical Research Institute, and Eli-Lilly. All other authors report no competing interests. All other authors declare no competing interests.

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Abstract

Introduction: The longitudinal course of bipolar disorder is highly variable, and a subset of patients seems to present a progressive course associated with brain changes and functional impairment.

Areas Covered: We discuss the theory of neuroprogression in bipolar disorder. This concept considers the systemic stress response that occurs within mood episodes and late-stage deficits in functioning and cognition as well as neuroanatomic changes. We also discuss treatment refractoriness that may take place in some cases of bipolar disorder. We searched PubMed for articles published in any language up to June 4th, 2016. We found 315 abstracts and included 87 studies in our review.

Expert Commentary: We are of the opinion that the use of specific pharmacological strategies and functional remediation may be potentially useful in bipolar patients at late-stages. New analytic approaches using multimodal data hold the potential to help in identifying signatures of subgroups of patients who will develop a neuroprogressive course.

Keywords: bipolar disorder, neuroprogression, allostatic load, machine learning, big data

1. **Introduction**

Bipolar disorder has a prevalence of about 2%, and subclinical variants affect another 2% of the population [1]. The rates of completed suicide in patients with bipolar disorder are 7.8% in men and 4.9% in women [2]. Bipolar patients present acute affective episodes that can potentially lead to self-deleterious behaviors such as drug abuse, self-harm, and suicide [2]. Less appreciated is the emerging evidence suggesting that bipolar disorder, like many chronic illnesses, may present a progressive course with functioning impairment and neuroanatomical changes.

Current treatment guidelines in bipolar disorder focus mainly on the stabilization of acute mood episodes and prevention of recurrence while neglecting the need to promote functional recovery. There is an emerging body of knowledge showing functional impairment in a subset of patients with bipolar disorder. A recent large cross-sectional study showed that 42% of euthymic patients with bipolar disorder presented poor overall functioning as assessed by the Functioning Assessment Short

Test (FAST) [3]. Risk factors predicting poor outcome of bipolar disorder were verbal intelligence, inhibitory control, residual depressive symptoms, and number of mood episodes [4]. In addition, one study reported progressive functional changes in patients with bipolar disorder [5].

Both cross-sectional and longitudinal studies suggest that more severe cases may present progressive pathological brain reorganization as a function of mood episodes [6,7]. A cross-sectional study showed a negative association between hippocampus volume and number of manic episodes in patients with bipolar disorder [8] while another study found the same negative association with corpus callosum volume [9]. A machine learning study with a cross-sectional design showed abnormalities in the brain regions covering the fronto-limbic system as a function of number of manic episodes. In addition, a 6-year longitudinal study showed significantly decreased frontal cortical volume (dorsolateral prefrontal and inferior frontal cortex) in the group of patients who had at least one manic episode [6]. These findings are in line with the pioneering work of Strakowski and colleagues, which reported increased ventricle volumes in multiple-episode patients with bipolar disorder compared to those who had only one episode [10].

The term neuroprogression was put forward to account for functioning impairment and neuroanatomical changes that took place in some cases of bipolar disorder. Neuroprogression is thus conceptualized as the pathological rewiring of the brain that takes place in parallel with the functioning and clinical deterioration in the course of bipolar disorder [11]. In addition, it seems that changes in some peripheral biomarkers from oxidative, inflammatory and neurotrophic pathways are associated with neuroprogression. Therefore, the aim of the present work is to review the literature related to the changes in functioning, neurocognition, and neuroimaging presented by a subset of more severe patients with bipolar disorder. Such findings are discussed in the light of the concept of neuroprogression and the peripheral biomarkers changes associated with bipolar disorder. The implication of a neuroprogressive course to treatment strategies in is highlighted. Finally, we propose the use of advanced machine learning algorithms and other predictive analytic techniques in the identification of biological signatures that could potentially identify patients prone to have a neuroprogressive course.

2. Methods

We reviewed the extant literature pertaining to neuroprogression and bipolar disorder. We searched PubMed for articles published in any language up to August 20th, 2016, using the following keywords: ("Bipolar Disorder" OR "Bipolar Disorders" OR "Manic Depressive Psychosis" OR "Bipolar Affective Psychosis" OR "Mania" OR "Manic State" OR "Bipolar Depression" OR "Manic Disorder" OR "Bipolar euthymic") AND ("neuroprogression" OR "staging" OR "illness progression" OR "progression" OR "allostatic load") AND ("treatment response" OR "functioning" OR "cognition" OR "inflammation" OR "oxidative stress" OR "neurotrophins" OR "neuroimaging" OR "Magnetic Resonance Imaging" OR "spectroscopy"). We also searched the reference lists of included studies. Articles met the inclusion criteria if they discussed patients with bipolar disorder and the following outcomes of interest in neuroprogression: treatment response, hospitalization, functioning, cognition, quality of life, suicide, recurrence of episodes, inflammation, oxidative stress, neurotrophins, brain changes. We found 247 abstracts and included 76 studies in our narrative review.

3. Peripheral Biomarkers

A recent study revealed that serum of patients with bipolar disorder, mainly those sera from patients at late stage, induced a decrease in neurite density and cell viability in neuronal cultures [12]. These findings highlight the potential implications of increased oxidative stress and low-grade inflammation in neuronal and glial plasticity [13]. Accordingly, it seems that serum of patients with bipolar disorder, mainly those at the late stage of the illness, may contain chemicals that could be toxic to neural cells, as proposed by the systemic toxicity hypothesis [14]. Abnormalities in both inflammatory and oxidative stress markers may play an important role in this process given the emerging evidence of derangement in these systems as a function of illness progression [15,16]. For example, there seems to be changes in IL-6 and TNF-α levels as patients progress into more severe stages [15]. In addition, one study reported that late stage bipolar disorder patients have increased activity of glutathione reductase and glutathione S-transferase, enzymes critical to the reduction-detoxification pathway [17]. Late stage bipolar disorder patients also have been found to have increased levels of C-C motif ligand (CCL)-11, and C-X-C motif ligand 10 (CXCL10) chemokines [18]. These are pro-inflammatory cytokines which

rely on the PI3K-Akt pathway for signaling [18].

It is worth mentioning that the interpretation of the heightened levels of inflammatory and oxidative stress markers in bipolar disorder is a matter of debate. For instance, it is not clear whether these signaling molecules can cross the blood-brain barrier (BBB). A recent study, however, proposed a model of disruption of BBB integrity and increased permeability to these signaling molecules, that could trigger neuroinflammation [19]. Adding to this, a recent Positron Emission Tomography (PET) scan study of euthymic bipolar patients found distinct signatures of neuroinflammation and microglial activation within the hippocampus [20]. Thus, emerging evidence suggests a connection between peripheral markers of inflammation and oxidative stress and neuroinflammation.

A recent study suggested that damage-associated molecular patterns (DAMPs) serve both as the trigger and as an amplifier of immune activation leading to systemic toxicity in bipolar disorder [21]. This study showed that patients with bipolar disorder presented higher serum levels of the following DAMPs: circulating cell-free (ccf) nuclear (n)DNA, HSP70, and HSP90α as compared to healthy subjects [21]. DAMPs exist in a variety of forms - sugars, metabolic byproducts, lipids, RNA, and DNA - yet they share a commonality in that they have binding affinity with specific Toll-like receptors (TLRs) [22]. TLRs activate signaling cascades within the innate immune system producing an inflammatory response, regardless of whether the ligand was bacterial, viral, parasitic, or non-infectious in origin. Thus, DAMP activation of TLR signaling cascades provides the link between an initial cytotoxic insult (drug abuse, high stress, or affective episode) and a subsequent sterile systemic inflammatory response [14].

Lastly, regarding the interaction of disruption in biological pathways and genetics, a recent study showed that the expression of the early growth response 3 (EGR3) is repressed in patients with bipolar disorder [23]. EGR3 is an immediate early gene transcription factor, which is rapidly activated in the brain in response to environmental stressors and regulates expression of inflammatory modulators. Thus, EGR3 is a potential molecular link between stress and immune activation. Authors hypothesized that dysfunction of EGR3 and its downstream genes facilitate the breakdown of homeostasis leading to a chronic low-grade immune activation that may predisposes individuals to express the bipolar disorder phenotype [23].

4. Neuroimaging findings

There is evidence that patients with bipolar disorder have abnormal brain structures as compared to healthy controls, with patterns indicative of neuronal loss in both cortical and subcortical tissue [24]. White matter pathology has been hypothesized to represent early stage alterations in neuronal activity, whereas gray matter loss associates with more advanced stages of illness [25,26]. This is supported by a recent meta-analysis that showed white matter volume reduction but no gray matter reduction nor whole brain volume reduction among first-episode bipolar disorder patients, [27]. In addition, Strakowski and colleagues studied the lateral ventricles of first episode bipolar patients as compared to those with multiple episodes, identifying significantly enlarged ventricles in the latter group [10]. They suggested that the degree of neuroanatomical atrophy was a function of the number of mood episodes [10]. This same group, later on, reported that bipolar patients with multiple episodes had smaller cerebellar volume than those with a single episode, despite no statistically significant difference in age [28]. This finding is further supported by a recent study that showed an inverse correlation between vermis area V2 volume and the number of previous mood episodes [29].

Our group also found that number of mood episodes, especially the manic episodes, as a potential moderator of brain changes in bipolar disorder. We showed that the posterior corpus callosum [9] and hippocampus [8] were significantly decreased in volume in patients with bipolar disorder as a function of the number of prior number of manic episodes and hospitalizations (figure 1). Moreover, we examined whether structural neuroimaging scans coupled with a machine learning algorithm could distinguish individual patients with bipolar disorder from healthy control subjects [7]. We also investigated the relationship between machine learning–predicted probability scores and clinical characteristics of subjects, such as illness duration and clinical stages. We found that the relevance vector machine algorithm distinguished patients from healthy control subjects with 70.3% accuracy ($p < .005$) using white matter density data and 64.9% accuracy using gray matter density. Multiple brain regions, largely covering the frontolimbic system, were identified as “most relevant” in distinguishing both groups. Furthermore, patients identified by the algorithm with high certainty belonged to the late-stage bipolar disorder group, which

includes patients with >10 total lifetime manic episodes including hospitalizations (figure 2). Furthermore, regarding the interaction of neuroimaging abnormalities and genetics, a recent study showed that brain-derived neurothrophic factor (BDNF) met allele carrier bipolar disorder patients had smaller hippocampal volumes and reduced neurocognitive performance as compared to patients with major depressive disorder and healthy controls [30].

<Figure 1>

<Figure 2>

A limitation of many neuroanatomical studies examining the correlation of brain structure with illness progression is the cross-sectional design. These types of studies preclude any definite conclusions about the direction of the effect. It is possible that these anatomical deficits are responsible for the progression into late stage bipolar disorder, rather than the opposite. Thus, longitudinal studies are crucial to consolidate the knowledge in the field. To this end, a recent 6-year follow-up study in patients with bipolar I disorder demonstrated a decrease in frontal cortical volume (specifically, the dorsolateral prefrontal and inferior frontal cortices) dependent upon the number of manic episodes [6].

Multiple authors have proposed neurodegenerative processes as the putative mechanism responsible for brain structure abnormalities in bipolar disorder [31,32]. Specifically, a defective response in neuroplasticity could result in a reduced number of neurites and intercellular connections [15]. In addition, a recent study of post-mortem brains of individuals with bipolar disorder showed significant increases in pro-apoptotic factors (Bax, BAD, Caspase-9, and Caspase 3) and decreases in anti-apoptotic factors (BDNF, Bcl-2), as well as decrease in synaptic markers (synaptophysin and drebrin) [33].

5. Functional and Neurocognitive Impairment

The evidence described above suggests an inflammatory process in patients with bipolar disorder. Such inflammation would, in turn, produce changes in the biochemical profile as well as white matter volumetric loss followed by gray matter volumetric loss in the fronto-limbic system and hippocampus [11]. We are of the opinion that the brain changes related to neuroprogression are associated with functional impairment even during euthymia [11]. Functional impairment is highly

prevalent among patients with bipolar disorder [3]. A recent large multicenter study of euthymic outpatients with bipolar disorder reported that 42% of euthymic patients showed poor overall functioning as assessed by FAST [3]. Authors also reported that residual depressive symptoms appeared to have an impact on overall functioning and in nearly all areas of functioning assessed by FAST (autonomy, occupational functioning, cognitive functioning, interpersonal relationships, and leisure time) while residual manic symptoms have an impact on autonomy and financial issues [3]. Another study showed that while almost all patients with first-episode mania had recovery from the syndrome within 2 years, only one third of those patients reached full functional recovery and functional deficits are evident [34]. In addition, it has been shown that patients who have only experienced one mood episode have better functioning than those with multiple episodes in a 1-year follow-up study [35]. It was also reported that the risk factors predicting poor functioning in patients with bipolar disorder were estimated verbal intelligence, inhibitory control, residual depressive symptoms, and number of mood episodes [4]. It is worth mention that age and illness duration were not predictors of functional outcome in this study [4]. In addition, one study reported worsening of functioning in patients with bipolar disorder as they progress to more severe stages of the illness [5].

It was also showed that at least a subset of patients with bipolar disorder has neurocognitive impairments even during euthymic periods [36–38]. Indeed, one prospective study reported that the trajectory of neurocognitive changes begins as early as the prodromal phase [39]. The main neurocognitive domains affected by this process are executive control, verbal learning and memory, working memory, and sustained attention [37,40]. Another study reported an association between the number of previous manic episodes with progressive neurocognitive decline [41]. Our group has also identified similar changes which increase in severity at later stages of the disorder [8]. In this study, patients at late stage with over than ten manic episodes and at least one hospitalization have worse memory performance during immediate recall than either healthy controls or early stage bipolar patients (between whom there was no statistically significant difference) [8] (Figure 1).

The conclusions of these cross-sectionals studies were corroborated in part by longitudinal studies and meta-analyses. For example, a twelve-month prospective study of patients with bipolar disorder identified a continuing, residual deficit in

performance directly proportional to the length of the manic episode [42]. In addition, a three-year follow-up study of older adults with bipolar disorder reported that their rate of neurocognitive decline was greater than expected, even when controlled for age and education [43]. Specific worsening deficits in verbal memory and delayed free recall were identified during a five-year follow-up study [44]. Lastly, a recent meta-analyses showed that number of manic episodes affected performance on Verbal Learning Task Short-Delay, Verbal Learning Task LongDelay, and Trail Making Test, while the number of depressive episodes had no association with cognitive decline [37].

However, some longitudinal studies and also meta-analysis have failed to reproduce a correlation between the number of mood episodes and the level of neurocognitive deterioration [45–47]. These reveal the sensitive and subtle nature of many of these findings; small samples, failure to allow adequate time for a neuroprogressive process, medication status, and the possibility that only a certain subset of bipolar patients experience the progressive form of the disorder all may be confounding factors in the study of bipolar neuroprogression.

6. Treatment implications

The hypothesis of neuroprogression shed light on two important points regarding the treatment of bipolar disorder which are largely neglected by current treatment guidelines: treatment resistance and functional impairment. A recent review suggested that there is an association of number of mood episodes with treatment resistance in patients with bipolar disorder [48]. Accordingly, one study showed that Cognitive Behavioral Therapy was significantly more effective than treatment as usual in those with fewer than 12 previous episodes but less effective in those with more episodes [49,50]. In addition, caregiver psychoeducation was only seen to be beneficial for patients in early stages of the disease (well defined periods of euthymia without overt psychiatric symptoms) [51]. Regarding treatment with psychoactive drugs, a recent study showed that a history of many previous episodes was associated with poor response to lithium but not to divalproex [49,50]. It was also reported that Individuals who are either manic or depressive on hospital admission and have a history of >5 previous episodes have decreased response to olanzapine [52]. Noticeably, a study assessing pharmacological maintenance treatment across

stages of illness found that monotherapy was more frequent in stage 1, two drugs in stage 2, and three or more medications or clozapine at stage 3 and 4 [53]. Lastly, it seems that fewer hospitalizations are a predictor of a positive response to lamotrigine monotherapy [54].

Functional impairment is still a major unmet need in the treatment of bipolar disorder [11]. Recently, functional remediation therapy has arisen as a promising approach to improve functioning in patients with bipolar disorder [55]. A multicenter randomized controlled trial with 239 outpatients with bipolar disorder showed that functional remediation presented significant efficacy in improving functional impairment as compared with treatment as usual for euthymic patients over 21 weeks of treatment [55]. Later on, the same authors showed that improvement in psychosocial functioning is maintained after 1-year follow-up in patients with bipolar disorder receiving functional remediation [56]. In addition, a recent study showed that functional remediation is also effective at improving verbal memory and functioning in a sample of cognitively impaired bipolar patients at 6-month follow-up [57].

Another promising treatment for late-stage bipolar disorder is clozapine [58]. A systematic review that included 15 clinical trials showed that clozapine was associated with improvement in social functioning [58]. The same systematic review also showed that clozapine is associated with improvement in suicidal ideation and aggressive behavior and the number and duration of hospitalizations [58]. It is worth mentioning that clozapine may be also effective for treatment-resistant patients with bipolar disorder [59,60]. A retrospective study showed that long-term clozapine add-on therapy was effective in reducing the number and duration of re-hospitalizations of patients with bipolar disorder resistant to conventional treatment [61]. In the same vein, a three-year follow-up study showed that clozapine reduced psychiatric hospitalization and emergency room visits in patients with bipolar disorder despite regular pre-clozapine treatment for bipolar disorder [62]. However, clozapine has a significant burden associated with its use due to a relatively high frequency of neutropenia and the subsequent requirement of a complete blood count periodically to monitor for this side effect.

The molecular basis of neuroprogression also provides a wealth of new therapeutic drug targets to research. In this same vein, some attempts have been made at curbing the immune system (anti-inflammatory medications and monoclonal

antibodies) and attempts at antioxidant therapy with n-acetyl cysteine therapy. A recent meta-analysis reported that the use of anti-inflammatory agent promotes a moderate antidepressant effect greater than that of conventional therapy [63]. However, future research directions for this field must be developed from a neuroprogressive approach in tighter revaluation of the functional and cognitive impairments.

7. Expert Commentary

It seems that neuroprogression is not a general rule in bipolar disorder. The number of manic episodes seems to be the clinical marker more robustly associated with neuroprogression. Indeed, most of the evidence in our review came from studies with patients with patients with bipolar 1 disorder. Several studies found significant associations between number of manic episodes and brain changes [6,8,9], as well as with neurocognitive impairment [41]. Early trauma and psychiatric and clinical comorbidity also seem to be risk factors associated with a neuroprogressive course among patients with bipolar disorder [64,65]. It is worth noting that two important limitations of the cross-sectional studies included in our review are the inability to confirm causality and the memory bias. Retrospective studies present important limitations to assess number of episodes, history of trauma or when the disorder has begun.

In terms of peripheral biomarkers, BDNF seems to be a marker of illness activity in bipolar disorder [66]. Cross-sectional studies point to a potential role of inflammatory markers as both a biomarker of illness activity and of stage of illness. Longitudinal studies are needed in order to clarify the exact role of inflammation and neuroinflammation in bipolar disorder. The hypothesis that bipolar disorder is associated with progressive changes in the fronto-limbic system as well as in functioning and cognitive domains have been proven by cross-sectional and longitudinal studies [6,7,35]. It is worth mentioning that a recent study proposed a staging model of bipolar disorder based on the progressive neuroimaging changes [67]. Future longitudinal studies would benefit from taking into account medication status. In addition, we believe that systems biology approach will significantly advance this field. Systems biology is the computational and mathematical modeling of complex biological systems. This approach may use machine learning technique

(see Five-Year View) and will assist us in the identification of illness-perturbed ‘networks’ within a patient with bipolar disorder and use these signatures to identify subtypes of bipolar disorder [68].

Finally, we discussed the implications of neuroprogression in treatment resistance in bipolar disorder, presenting potential therapeutic strategies and modalities that may overcome the functional and cognitive impairment related to the neuroprogressive brain. While treatments such as lithium monotherapy, cognitive behavioral therapy, and psychoeducation seem to be better suited to prevent further recurrences within patients with few episodes, complex pharmacological strategies and functional remediation might be considered in more severe patients.

It is worth mentioning that recent evidence shows that the neurotrophin [69], inflammatory [70], and oxidative [71] pathways are also involved in the pathophysiology of unipolar depression. It has been postulated that these systems interact to drive brain structural and neurocognitive alterations in those patients [32]. However, no study compared the neuroprogressive course in patients with bipolar disorder versus patients with unipolar disorder so far. We hypothesized that the neuroprogressive course would be more pronounced in patients with type-I bipolar disorder since some studies have shown the association between manic episodes and brain changes as well as with cognitive impairment [7,8,11].

8. Five-Year View

Big data is a broad term used to denote volumes of large and complex measurements [72]. Beyond genomics and other “omic” fields, big data includes clinical, sociodemographic, administrative, molecular, environmental, and even social media information. Machine learning, also known as pattern recognition, represents a range of techniques used to analyse big data by identifying patterns of interaction among variables [73]. Compared with traditional statistical methods that provide primarily average group-level results, machine learning algorithms allow predictions and stratification of clinical outcomes at the level of an individual subject [74]. These approaches hold great potential for hypothesis generation and testing regarding potential biomarkers, imaging features, clinical descriptors, and demographic data in psychiatric disorders [75]. Further, big data analytics allow the discovery of clinically relevant predictive models of psychiatric disorder treatment response, resistance,

and mortality that will allow targeted therapies to particular subsets of patients [76,77].

Big data analytics approach lends itself to the particular pursuit of identifying risk factors and biomarker alterations of neuroprogression in bipolar disorder. The reasons for this are as follow; machine learning algorithms inherently allow massive multivariate analysis and identify the interactions between multiple measurements (here, neuroimaging results, peripheral biomarkers, functional impairment, and clinical features). This multimodality is necessary, as neuroprogression in bipolar disorder is multifactorial in itself; this is an excellent indication of the need for machine learning techniques, where information from numerous attributes should be considered simultaneously in order to estimate the probability of an outcome [73]. Indeed, a parallel can be made between the use of these techniques in the study of Alzheimer's and multiple sclerosis, where machine learning algorithms are able to 'fuse' or integrate multimodal data to produce meaningful predictions about these disorders [78,79]. Lastly, machine learning is largely atheoretical, explicitly designed to not rely on the preexisting bias when identifying patterns within data sets; these findings are often unexpected, well-hidden, or difficult to observe because of prior biases.

Recent machine learning studies in bipolar disorder have focused on distinguishing individual bipolar disorder patients from healthy controls [80,81]. Our own group has used this approach to generate a machine-learning predicted probability score of bipolar disorder based on clinical characteristics of subjects and white and gray matter density data; interestingly, multiple brain regions, specifically the frontolimbic system, were identified as "most relevant" in distinguishing both groups. The algorithm also identified late-stage bipolar disorder with high certainty (those with >10 total lifetime manic episodes and hospitalizations) [7] (figure 2).

Future studies are poised to investigate outcomes related to neuroprogression using multimodal data fusion and machine learning algorithms. For example, a relevant machine learning application in neuroprogression may attempt to predict individual subjects with bipolar disorder likely to have functional impairment in a clinical sample (figure 3). Functional impairment in bipolar disorder is associated with a large range of clinical and biological risk factors associated to neuroprogression, such as number of previous mood episodes, and number of previous

hospitalizations, early trauma, brain changes, and demographic variables. Another interesting line of research in the interface between machine learning and bipolar disorder is to attempt to predict whether a patient with functional impairment will respond to a specific intervention.

<figure 3>

9. Key Issues

- Neuroprogression has been defined as the pathological brain rewiring that takes place in portion with recurrent mood episodes.
- The neuroprogressive course of illness refers to a subset of patients that will develop a progressive course of bipolar disorder characterized by episode acceleration or treatment refractoriness or functional/neurocognitive impairment or suicide attempts.
- Manic episodes, psychiatric and clinical comorbidity and early trauma are associated with neuroprogression in bipolar disorder. These factors may show sensitization to themselves and cross-sensitization to one another leading to faster illness stage progression.
- Patients with bipolar disorder and with high episode counts have a decreased response to cognitive behavioral therapy, lithium and olanzapine.
- Complex medication strategies, clozapine and functional remediation might be useful for patients at the late stage with functional impairment
- Future research in the field of treatment of bipolar disorder may benefit from the concept of neuroprogression and tighter revaluation of the functional and cognitive impairments.

References

1. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch. Gen. Psychiatry. 2007;64:543–52.

2. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. Arch. Gen. Psychiatry. 2011;68:1058–64.

3. Samalin L, de Chazeron I, Vieta E, Bellivier F, Llorca P-M. Residual symptoms and specific functional impairments in euthymic patients with bipolar disorder. Bipolar Disord. 2016;18:164–73.

4. Reinares M, Papachristou E, Harvey P, Mar Bonnín C, Sánchez-Moreno J, Torrent C, et al. Towards a clinical staging for bipolar disorder: defining patient subtypes based on functional outcome. J. Affect. Disord. 2013;144:65–71.

5. Rosa AR, Magalhães PVS, Czepielewski L, Sulzbach MV, Goi PD, Vieta E, et al. Clinical staging in bipolar disorder: focus on cognition and functioning. J. Clin. Psychiatry. 2014;75:e450-6.

* This article provides a staging model based on functional impairment in patients with bipolar disorder

6. Abé C, Ekman C-J, Sellgren C, Petrovic P, Ingvar M, Landén M. Manic episodes are related to changes in frontal cortex: a longitudinal neuroimaging study of bipolar disorder 1. Brain. 2015;awv266.

** This longitudinal study showed that manic episodes were associated with brain changes

7. Mwangi B, Wu M-J, Cao B, Passos IC, Lavagnino L, Keser Z, et al. Individualized prediction and clinical staging of bipolar disorders using neuroanatomical biomarkers. Biol. Psychiatry Cogn. Neurosci. Neuroimaging. 2016;1:186–94.

* This is a machine learning study in which manic episodes were associated with brain changes

8. Cao B, Passos IC, Mwangi B, Bauer IE, Zunta-Soares GB, Kapczinski F, et al. Hippocampal volume and verbal memory performance in late-stage bipolar disorder. J. Psychiatr. Res. 2016;73:102–7.

9. Lavagnino L, Cao B, Mwangi B, Wu M-J, Sanches M, Zunta-Soares GB, et al. Changes in the corpus callosum in women with late-stage bipolar disorder. Acta Psychiatr. Scand. 2015;

10. Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J, et al. Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. Am. J. Psychiatry. 2002;159:1841–7.

* One of the first studies to show that number of mood episodes were associated with brain changes

11. Passos IC, Mwangi B, Vieta E, Berk M, Kapczinski F. Areas of controversy in

neuroprogression in bipolar disorder. Acta Psychiatr. Scand. 2016;

** Systematic review regarding neuroprogression in bipolar disorder

12. Wollenhaupt-Aguiar B, Pfaffenseller B, de Saraiva Chagas V, Castro MAA, Passos IC, Kauer-Sant'Anna M, et al. Reduced Neurite Density in Neuronal Cell Cultures Exposed to Serum of Patients with Bipolar Disorder. Int. J. Neuropsychopharmacol. 2016;In Press.

* This study showed that the blood of patients with bipolar disorder at late stage was associated with reducued neurite density in a neuronal cell culture.

13. Rajkowska G. Cell pathology in bipolar disorder. Bipolar Disord. 2002;4:105–16.

14. Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PVS, Kauer-Sant'Anna M, Klamt F, et al. A systemic toxicity index developed to assess peripheral changes in mood episodes. Mol. Psychiatry. 2010;15:784–6.

15. Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Young LT, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int. J. Neuropsychopharmacol. 2009;12:447–58.

16. Andreazza AC, Kauer-Sant'anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, et al. Oxidative stress markers in bipolar disorder: a meta-analysis. J. Affect. Disord. 2008;111:135–44.

17. Andreazza AC, Kapczinski F, Kauer-Sant'Anna M, Walz JC, Bond DJ, Gonçalves CA, et al. 3-Nitrotyrosine and glutathione antioxidant system in patients in the early and late stages of bipolar disorder. J. Psychiatry Neurosci. 2009;34:263–71.

18. Panizzutti B, Gubert C, Schuh AL, Ferrari P, Bristot G, Fries GR, et al. Increased serum levels of eotaxin/CCL11 in late-stage patients with bipolar disorder: An accelerated aging biomarker? J. Affect. Disord. 2015;182:64–9.

19. Patel JP, Frey BN. Disruption in the Blood-Brain Barrier: The Missing Link between Brain and Body Inflammation in Bipolar Disorder? Neural Plast. 2015;2015:708306.

20. Haarman BCMB, Riemersma-Van der Lek RF, de Groot JC, Ruhé HGE, Klein HC, Zandstra TE, et al. Neuroinflammation in bipolar disorder - A [(11)C]-(R)-PK11195 positron emission tomography study. Brain. Behav. Immun. 2014;40:219–25.

** First study to show microglial activation in euthymic bipolar patients by using PET

scan.
21. Stertz L, Fries GR, Rosa AR, Kauer-Sant'anna M, Ferrari P, Paz AVC, et al. Damage-associated molecular patterns and immune activation in bipolar disorder. Acta Psychiatr. Scand. 2015;132:211–7.
* This study reported a possible trigger for the increased inflammatory markers reported in patients with bipolar disorder.
22. Jounai N, Kobiyama K, Takeshita F, Ishii KJ. Recognition of damage-associated molecular patterns related to nucleic acids during inflammation and vaccination. Front. Cell. Infect. Microbiol. 2012;2:168.
23. Pfaffenseller B, da Silva Magalhães P V, De Bastiani MA, Castro MAA, Gallitano AL, Kapczinski F, et al. Differential expression of transcriptional regulatory units in the prefrontal cortex of patients with bipolar disorder: potential role of early growth response gene 3. Transl. Psychiatry. 2016;6:e805.
24. Hibar DP, Westlye LT, van Erp TGM, Rasmussen J, Leonardo CD, Faskowitz J, et al. Subcortical volumetric abnormalities in bipolar disorder. Mol. Psychiatry. 2016;
25. Lin A, Reniers RLEP, Wood SJ. Clinical staging in severe mental disorder: evidence from neurocognition and neuroimaging. Br. J. Psychiatry. Suppl. 2013;54:s11-7.
26. Gildengers AG, Chung K-H, Huang S-H, Begley A, Aizenstein HJ, Tsai S-Y. Neuroprogressive effects of lifetime illness duration in older adults with bipolar disorder. Bipolar Disord. 2014;16:617–23.
27. Vita A, De Peri L, Sacchetti E. Gray matter, white matter, brain, and intracranial volumes in first-episode bipolar disorder: a meta-analysis of magnetic resonance imaging studies. Bipolar Disord. 2009;11:807–14.
28. Mills NP, Delbello MP, Adler CM, Strakowski SM. MRI analysis of cerebellar vermal abnormalities in bipolar disorder. Am. J. Psychiatry. 2005;162:1530–2.
29. Monkul ES, Hatch JP, Sassi RB, Axelson D, Brambilla P, Nicoletti MA, et al. MRI study of the cerebellum in young bipolar patients. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2008;32:613–9.
30. Bo C, Bauer IE, Sharma AN, Mwangi B, Frazier T, Lavagnino L, et al. Reduced hippocampus volume and memory performance in bipolar disorder patients carrying the BDNF val66met met allele. J. Affect. Disord. 2016;198:198–205.
31. Rao JS, Harry GJ, Rapoport SI, Kim HW. Increased excitotoxicity and

neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. Mol. Psychiatry. 2010;15:384–92.

32. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci. Biobehav. Rev. 2011;35:804–17.

33. Kim H-W, Rapoport SI, Rao JS. Altered expression of apoptotic factors and synaptic markers in postmortem brain from bipolar disorder patients. Neurobiol. Dis. 2010;37:596–603.

34. Tohen M, Hennen J, Zarate CM, Baldessarini RJ, Strakowski SM, Stoll AL, et al. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. Am. J. Psychiatry. 2000;157:220–8.

35. Rosa AR, González-Ortega I, González-Pinto A, Echeburúa E, Comes M, Martínez-Àran A, et al. One-year psychosocial functioning in patients in the early vs. late stage of bipolar disorder. Acta Psychiatr. Scand. 2012;125:335–41.

36. Wu M-J, Passos IC, Bauer IE, Lavagnino L, Cao B, Zunta-Soares GB, et al. Individualized identification of euthymic bipolar disorder using the Cambridge Neuropsychological Test Automated Battery (CANTAB) and machine learning. J. Affect. Disord. 2016;192:219–25.

37. Bourne C, Aydemir Ö, Balanzá-Martínez V, Bora E, Brissos S, Cavanagh JTO, et al. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. Acta Psychiatr. Scand. 2013;128:149–62.

38. Lolich M, Holtzman JN, Rago CM, Vázquez GH. [Neuroprogression and cognition in Bipolar Disorders: A systematic review of cognitive performance in euthymic patients]. Vertex. 26:265–75.

39. Ratheesh A, Lin A, Nelson B, Wood SJ, Brewer W, Betts J, et al. Neurocognitive functioning in the prodrome of mania--an exploratory study. J. Affect. Disord. 2013;147:441–5.

40. Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: A meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. J. Affect. Disord. 2009;113:1–20.

41. Martínez-Arán A, Vieta E, Reinares M, Colom F, Torrent C, Sánchez-Moreno J, et al. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am. J. Psychiatry. 2004;161:262–70.

42. Kozicky J-M, Torres IJ, Silveira LE, Bond DJ, Lam RW, Yatham LN. Cognitive change in the year after a first manic episode: association between clinical outcome and cognitive performance early in the course of bipolar I disorder. J. Clin. Psychiatry. 2014;75:e587-93.

43. Gildengers AG, Mulsant BH, Begley A, Mazumdar S, Hyams A V, Reynolds Iii CF, et al. The longitudinal course of cognition in older adults with bipolar disorder. Bipolar Disord. 2009;11:744–52.

44. Santos JL, Aparicio A, Bagney A, Sánchez-Morla EM, Rodríguez-Jiménez R, Mateo J, et al. A five-year follow-up study of neurocognitive functioning in bipolar disorder. Bipolar Disord. 2014;16:722–31.

45. Martino DJ, Strejilevich SA, Marengo E, Igoa A, Fassi G, Teitelbaum J, et al. Relationship between neurocognitive functioning and episode recurrences in bipolar disorder. J. Affect. Disord. 2013;147:345–51.

46. Gildengers AG, Chisholm D, Butters MA, Anderson SJ, Begley A, Holm M, et al. Two-year course of cognitive function and instrumental activities of daily living in older adults with bipolar disorder: evidence for neuroprogression? Psychol. Med. 2013;43:801–11.

47. Samamé C, Martino DJ, Strejilevich SA. Longitudinal course of cognitive deficits in bipolar disorder: a meta-analytic study. J. Affect. Disord. 2014;164:130–8.

48. da Costa SC, Passos IC, Lowri C, Soares JC, Kapczinski F. Refractory bipolar disorder and neuroprogression. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2015;In Press.

49. Scott J, Paykel E, Morriss R, Bentall R, Kinderman P, Johnson T, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. Br. J. Psychiatry. 2006;188:313–20.

50. Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD. Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. Am. J. Psychiatry. 1999;156:1264–6.

51. Reinares M, Colom F, Rosa AR, Bonnín CM, Franco C, Solé B, et al. The impact of staging bipolar disorder on treatment outcome of family psychoeducation. J. Affect. Disord. 2010;123:81–6.

52. Berk M, Brnabic A, Dodd S, Kelin K, Tohen M, Malhi GS, et al. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and

their implication for the staging model and early intervention. Bipolar Disord. 2011;13:87–98.

53. Goi PD, Bücker J, Vianna-Sulzbach M, Rosa AR, Grande I, Chendo I, et al. Pharmacological treatment and staging in bipolar disorder: evidence from clinical practice. Rev. Bras. Psiquiatr. (São Paulo, Brazil 1999). 37:121–5.

54. Obrocea G V, Dunn RM, Frye MA, Ketter TA, Luckenbaugh DA, Leverich GS, et al. Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. Biol. Psychiatry. 2002;51:253–60.

55. Torrent C, Bonnin C del M, Martínez-Arán A, Valle J, Amann BL, González-Pinto A, et al. Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. Am. J. Psychiatry. 2013;170:852–9.

56. Bonnin CM, Torrent C, Arango C, Amann BL, Solé B, González-Pinto A, et al. Functional remediation in bipolar disorder: 1-year follow-up of neurocognitive and functional outcome. Br. J. Psychiatry. 2016;208:87–93.

57. Bonnin CM, Reinares M, Martínez-Arán A, Balanzá-Martínez V, Sole B, Torrent C, et al. Effects of functional remediation on neurocognitively impaired bipolar patients: enhancement of verbal memory. Psychol. Med. 2016;46:291–301.

58. Li X-B, Tang Y-L, Wang C-Y, de Leon J. Clozapine for treatment-resistant bipolar disorder: a systematic review. Bipolar Disord. 2014;

59. Gitlin M. Treatment-resistant bipolar disorder. Mol. Psychiatry. 2006;11:227–40.

60. Poon SH, Sim K, Sum MY, Kuswanto CN, Baldessarini RJ. Evidence-based options for treatment-resistant adult bipolar disorder patients. Bipolar Disord. 2012;14:573–84.

61. Chang JS, Ha K-S, Young Lee K, Sik Kim Y, Min Ahn Y. The effects of long-term clozapine add-on therapy on the rehospitalization rate and the mood polarity patterns in bipolar disorders. J. Clin. Psychiatry. 2006;67:461–7.

62. Wu C-S, Wang S-C, Liu S-K. Clozapine use reduced psychiatric hospitalization and emergency room visits in patients with bipolar disorder independent of improved treatment regularity in a three-year follow-up period. Bipolar Disord. 2015;17:415–23.

63. Rosenblat JD, Kakar R, Berk M, Kessing L V, Vinberg M, Baune BT, et al. Anti-inflammatory agents in the treatment of bipolar depression: a systematic review and meta-analysis. Bipolar Disord. 2016;18:89–101.

64. Passos IC, Jansen K, Cardoso T de A, Colpo GD, Zeni CP, Quevedo J, et al.

Clinical outcomes associated with comorbid posttraumatic stress disorder among patients with bipolar disorder. J. Clin. Psychiatry. 2016;77:e555-60.

65. Leverich GS, Post RM. Course of bipolar illness after history of childhood trauma. Lancet. 2006;367:1040–2.

66. Fernandes BS, Molendijk ML, Köhler CA, Soares JC, Leite CMGS, Machado-Vieira R, et al. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. BMC Med. 2015;13:289.

67. Frank E, Nimgaonkar VL, Phillips ML, Kupfer DJ. All the world's a (clinical) stage: rethinking bipolar disorder from a longitudinal perspective. Mol. Psychiatry. 2015;20:23–31.

68. Passos IC, Mwangi B, Kapczinski F. Big data analytics and machine learning: 2015 and beyond. The lancet. Psychiatry. 2016;3:13–5.

69. Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biol. Psychiatry. 2008;64:527–32.

70. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol. Psychiatry. 2010;67:446–57.

71. Ng F, Berk M, Dean O, Bush AI. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. Int. J. Neuropsychopharmacol. 2008;11:851–76.

72. Khoury MJ, Ioannidis JPA. Medicine. Big data meets public health. Science. 2014;346:1054–5.

73. Mwangi B, Ebmeier KP, Matthews K, Steele JD. Multi-centre diagnostic classification of individual structural neuroimaging scans from patients with major depressive disorder. Brain. 2012;135:1508–21.

74. Iniesta R, Stahl D, McGuffin P. Machine learning, statistical learning and the future of biological research in psychiatry. Psychol. Med. 2016;46:2455–65.

75. Passos IC, Mwangi B, Kapczinski F. Big data analytics and machine learning in psychiatry. The Lancet Psychiatry. 2016;3:13–5.

76. Wu M-J, Mwangi B, Bauer IE, Passos IC, Sanches M, Zunta-Soares GB, et al. Identification and individualized prediction of clinical phenotypes in bipolar disorders using neurocognitive data, neuroimaging scans and machine learning. Neuroimage. 2016;In Press.

77. Passos IC, Mwangi B, Cao B, Hamilton JE, Wu M-J, Zhang XY, et al. Identifying a clinical signature of suicidality among patients with mood disorders: a pilot study using a machine learning approach. J. Affect. Disord. 2016;193:109–16.

78. Eshaghi A, Riyahi-Alam S, Saeedi R, Roostaei T, Nazeri A, Aghsaei A, et al. Classification algorithms with multi-modal data fusion could accurately distinguish neuromyelitis optica from multiple sclerosis. NeuroImage. Clin. 2015;7:306–14.

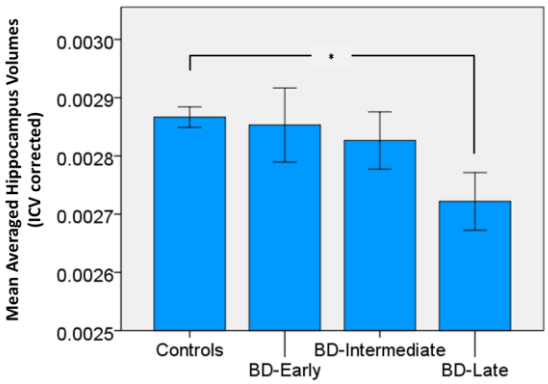
79. Zhang D, Wang Y, Zhou L, Yuan H, Shen D. Multimodal classification of Alzheimer's disease and mild cognitive impairment. Neuroimage. 2011;55:856–67.

80. Redlich R, Almeida JJR, Grotegerd D, Opel N, Kugel H, Heindel W, et al. Brain morphometric biomarkers distinguishing unipolar and bipolar depression. A voxel-based morphometry-pattern classification approach. JAMA psychiatry. 2014;71:1222–30.

81. Mwangi B, Spiker D, Zunta-Soares GB, Soares JC. Prediction of pediatric bipolar disorder using neuroanatomical signatures of the amygdala. Bipolar Disord. 2014;16:713–21.

FIGURES:

A)



B)

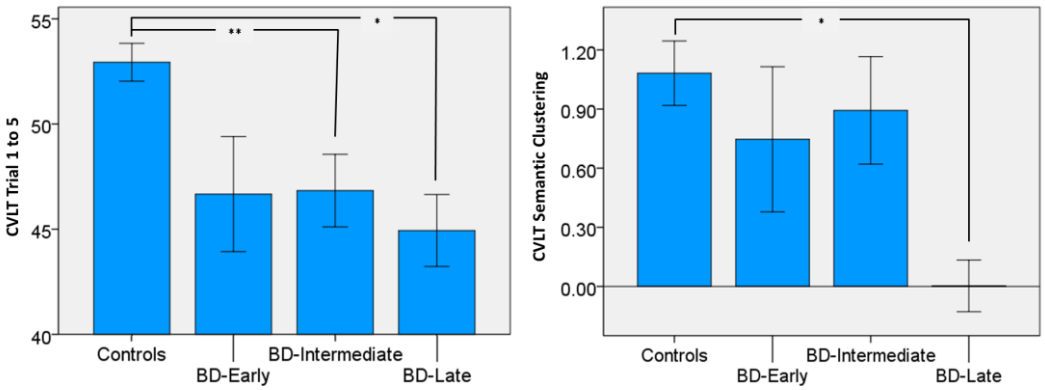


Figure 1. Reduced hippocampal volume and worse memory performance and strategy in patients with bipolar disorder at late stage. **A)** BD-Late subjects showed significantly reduced hippocampal volumes compared to healthy controls. **B)** Both BD-Intermediate and BD-Late subjects showed significantly worse memory recall performance compared to HC, while only BD-Late subjects showed worse semantic clustering score than HC. BD-Early, bipolar disorder type I at early stage; BD-Intermediate, bipolar disorder type I at intermediate stage; BD-Late, bipolar disorder type I at late stage. *p<0.05; **p<0.01.

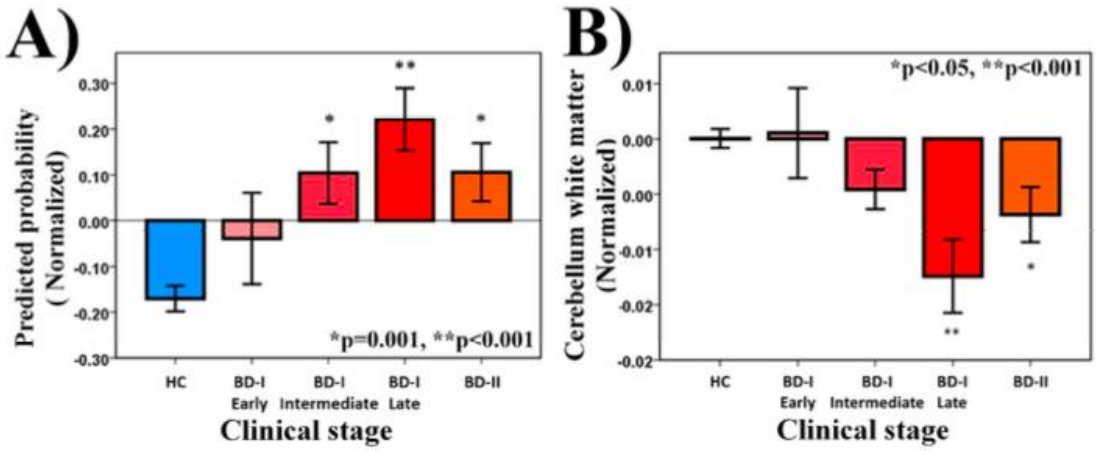


Figure 2. (A) Comparisons of average predicted probability scores between healthy control subjects (HC), patients with early-stage bipolar disorder type I (BD-I Early), patients with intermediate-stage bipolar disorder type I (BD-I Intermediate), patients with late-stage bipolar disorder type I (BD-I Late), and patients with bipolar disorder type II (BD-II). Analysis of variance was performed among groups (F 5 13.54, p , .005). Post hoc tests with Bonferroni multiple comparison corrections were also performed to examine differences among groups. Probability scores of patients with early-stage bipolar disorder type I did not differ significantly from scores of healthy control subjects. Probability scores of patients with intermediate-stage bipolar disorder type I and late-stage bipolar disorder type I were significantly different from scores of healthy control subjects (significantly higher probability scores). Probability scores were normalized by subtracting the "chance level" score (.5) for visualization purposes only. **(B)** Comparisons of average cerebellar white matter density between healthy control subjects and clinical stages. Similar to probability scores, white matter density between healthy control subjects and patients with early-stage bipolar disorder type I did not differ significantly. The progressive white matter density reductions in patients with intermediate-stage bipolar disorder type I and late-stage bipolar disorder type I, which were not observed in patients with early-stage bipolar disorder type I as compared with healthy control subjects, may be an indication of neuroprogression. Analysis of variance statistical tests were corrected for multiple comparisons using the Bonferroni method. White matter density values were normalized by subtracting the average value in the healthy control group for visualization purposes only.

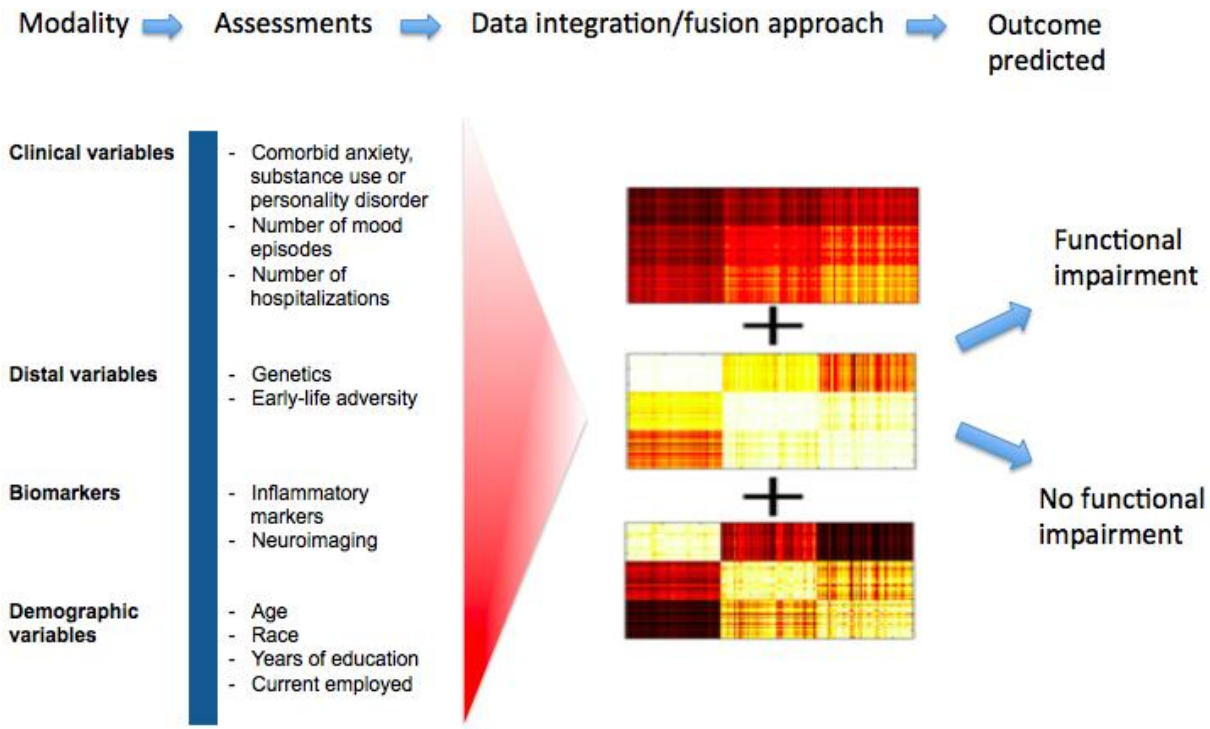


Figure 3. Conceptual model which reports the use of machine learning algorithms to predict functional impairment in patients with bipolar disorder.

6.2 ARTIGO 2

6.2.1 Carta de submissão

Dear Dr Natália S Kapczinski,

You have been listed as a Co-Author of the following submission:

Journal: The Lancet Psychiatry
Corresponding Author: Flavio Kapczinski
Co-Authors: Natália S Kapczinski, MSc; Ives C Passos, MD, PhD; Karen Jansen, PhD; Pedro Magalhaes , MD, PhD; Adam Fijtman; Ana Claudia Loredo-Souza; Aroldo A Dargel; Bianca Wollenhaupt-Aguiar; Bianca Pfaffenseller, PhD; Fernando K Gazalle, MD, PhD; Gabriela D Colpo, PhD; Joana Bucker, PhD; Júlio C Walz; Keila Maria M Ceresér, PhD; Kelen P Bridi, PhD; Lisiane Sória, MSc; Maurício Kunz, MD, PhD; Michele Pinho; Pedro Goi, MD, PhD; Ramiro Reckziegel, MD, PhD; Renan K Burque; Benício N Frey, MD, PhD ; Márcia Kauer-Sant'Anna, MD, PhD
Title: A 24-week Randomized, Placebo-Controlled Trial of Adjunctive Tianeptine in the Maintenance Treatment of Bipolar Disorder

If you did not author this submission, please contact the Corresponding Author of this submission at flavio.kapczinski@gmail.com; do not follow the link below.

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Thank you,

The Lancet Psychiatry

6.2.2 Manuscrito

A 24-week Randomized, Placebo-Controlled Trial of Adjunctive Tianeptine in the Maintenance Treatment of Bipolar Disorder

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Summary

Background: Tianeptine is a safe medication that acts on the glutamatergic system and has an antidepressant effect. The present study aimed at assessing the efficacy and tolerability of tianeptine as an adjunctive treatment for bipolar depression. **Methods**: We performed an enriched maintenance multi-center double-blind randomized controlled trial of tianeptine 37•5mg/day. Participants (n = 161) had a Montgomery Asberg Depression Rating Score ≥12 at trial entry. After eight weeks of open-label tianeptine treatment, those who responded to tianeptine were randomized to adjunctive tianeptine or placebo in addition to usual treatment. Participants were recruited from public health services and through advertisement. Time to any intervention was the primary endpoint of the study. Changes in mood symptoms, functioning, biological rhythms, quality of life, rates of mania switch and serum BDNF assessments were considered as secondary outcomes. **Findings**: There was a robust decrease in depressive symptoms along with improvements in functioning, quality of life and biological rhythms scores during the eight-week open-label tianeptine treatment phase. During the subsequent 24-week double-blind controlled phase, there was no difference regarding the primary outcome: time to intervention. In addition, there were no significant differences between groups in mood symptoms, functioning and BDNF levels. Tianeptine was well tolerated and not associated with mania switch as compared to placebo. **Interpretation**: These findings suggest that tianeptine is a safe medication and may be effective in the treatment of acute bipolar depression. However, tianeptine did not show beneficial effects in the maintenance phase. This is the first long-term randomized, double-blind maintenance trial of antidepressant augmentation in bipolar disorder.

Funding: Stanley Medical Research Institute. Grant reference number: 07TGF-1148.

Introduction

Bipolar disorder affects approximately 4% of the population worldwide.[1] Bipolar depressive episodes are associated with significantly greater psychosocial impairment and suicide attempts compared to manic or hypomanic episodes.[2] Previous studies have reported high rates of lack of response in randomized controlled trials for bipolar depression. Non-response rates of 40% or higher have been reported with first-line treatments such as lithium, quetiapine, lamotrigine, or olanzapine-fluoxetine combination.[3–6] The use of antidepressants as adjunctive treatments to mood stabilizers are helpful in only a quarter of patients with bipolar depression.[7] In addition to that, antidepressants are prescribed very often to individuals with bipolar disorder, but the potential risk of switch to mania and mood destabilization make it a highly controversial topic among experts in the field.[8] Independent meta-analyses showed that short-term antidepressant trials are effective in the treatment of acute bipolar depression.[9] However, one of the key questions that still remains is “for how long should subjects with bipolar disorder be kept on antidepressants after an acute response?” To the best of our knowledge, there are no long-term randomized, double-blind maintenance trials of antidepressant augmentation in bipolar disorder.

Individuals with bipolar disorder are particularly vulnerable to the effects of stress;[10,11] may show atrophy in different regions of the brain, including the hippocampus;[11–13] present decreased levels of brain-derived neurotrophic factor (BDNF) during depressive mood episodes;[14] show altered amygdala activation;[15] and present alterations in the adenosinergic system.[16] In this context, tianeptine may be a good option as an augmentative strategy in bipolar disorder considering its pharmacological profile: tianeptine exerts opposite effects than chronic stress in neurons, increasing neuroprotective factors;[17,18] promotes neuroplasticity in the hippocampus and has been reported to increase dendritic length;[19–21] increases BDNF levels in the amygdala;[22] attenuates stress-induced glutamate release in the amygdala;[23] and has anticonvulsant properties via adenosinergic A1 receptors.[24]

Moreover, its action on the glutamatergic system may be also associated with its antidepressant effect.[25]

In the light of these findings, we set out to conduct the first long-term randomized, double-blind controlled maintenance trial of tianeptine as an adjunctive therapy in bipolar depression. In the first phase, all participants received tianeptine in an open-label manner for two months. Then, treatment responders were randomly assigned to remain on adjunctive treatment with tianeptine or switch to placebo in a double-blind fashion for six months. The primary aim of our study was to investigate the efficacy and tolerability of tianeptine 37•5mg/day as an adjunctive medication for maintenance treatment in bipolar depression. Secondary aims were: 1) assess the rates of switch to mania with tianeptine; 2) assess the efficacy of tianeptine during the open-label phase; 3) examine the effects of tianeptine on peripheral BDNF levels and psychosocial functioning in both acute and maintenance phases.

Methods

Trial design

This is an enriched maintenance randomized controlled trial of adjunctive tianeptine for bipolar depression. In the open-label phase, individuals who met inclusion criteria received 8 weeks of tianeptine 37•5mg/day as adjunctive treatment. The second phase was a 24-week randomized double-blind placebo-controlled trial. The aim of this phase was to assess the efficacy of tianeptine as an adjunctive maintenance treatment to those who recovered from the depressive episode in the open-label phase. The total duration of the trial was 32 weeks. This trial was registered at clinicaltrials.gov (NCT00879372) and was completed between 2008 and 2013. This study was approved by the local research ethics board of all sites and all study participants signed the informed consent before study entry. This study was conducted in accordance with the Helsinki Declaration as revised in 1989.

Participants

The study was carried out in three centers, namely Hospital de Clínicas de Porto Alegre, Hospital de Clínicas de Santa Maria and Hospital Espirita de Porto Alegre. Study participants were mostly recruited from local advertisements and direct contact with health professionals from databases obtained in previous studies. Potential participants were initially screened using a structured interview over the telephone and then in-person screening visits were booked with a study psychiatrist.

Participants were included if they met criteria for bipolar disorder as assessed by trained psychiatrists using the Structured Clinical Interview for DSM-IV (SCID). The inclusion criteria for the open-label phase were as follows: (a) 18 years or older; (b) Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥ 12 and scores on MADRS items 1 (apparent sadness) and 2 (reported sadness) ≥ 2 at screening and baseline; (c) Young Mania Rating Scale (YMRS) total score ≤ 12 at baseline; (d) Regular use of either lithium or valproate at therapeutic levels for at least 4 weeks before baseline; (e) Be able to provide informed consent and to comply with the study procedures; (f) Regular use of an effective contraceptive method in the case of women of childbearing age.

The exclusion criteria were as follows: (a) Current Axis I disorder other than bipolar disorder within 6 months of study entry; (b) History of nonresponse to an adequate treatment period (6 weeks) of ≥ 2 classes of antidepressants during the current episode; (c) History of known nonresponse or intolerance to tianeptine; (d) Current substance dependence or abuse (DSM-IV) except for nicotine; (e) Unstable medical illness; (f) Current serious suicidal or homicidal risk as judged by the investigator; (g) Being pregnant or currently breastfeeding. The withdrawal criteria were as follow: (a) Treatment-emergent mania or hypomania defined as a YMRS total score ≥ 16 on 2 consecutive assessments or an adverse event report of treatment-emergent mania or hypomania requiring intervention; (b) Discontinuation of treatment or patient deemed as non-compliant by the attending physician; (c) Discontinuation of contraceptives or pregnancy; (d) Serious adverse event; (e) Hospitalization; (f) Withdrawal of consent.

Individuals who responded to adjunctive tianeptine (≥50% reduction in MADRS total score) in the open-label phase were eligible for the randomized maintenance phase.

Interventions

Tianeptine or matching placebo was administered orally three times a day. Tianeptine was initiated at 12•5mg/day and was gradually increased every other day until the patient achieved the target dose of 12•5mg TID (37•5mg/day) within five days. Tianeptine has been used for major depression and has proven to be comparable - efficacy and safety - to fluoxetine in a double-blind trial.[26,27] Non-psychotropic medications taken prior to the study entry were allowed. Lithium, valproate, clonazepam and risperidone were only allowed if they were started more than four weeks before randomization. Diazepam was also allowed as a concomitant medication only in case of insomnia or anxiety (maximum dose: 10mg/day).

Outcomes of the open-label phase

Clinical assessments were performed at the screening, week (W) 0 and W08 in the open-label trial phase, including the Young Mania Rating Scale (YMRS)[28] and Clinical Global Impression (CGI-BP).[29] Global Assessment of Functioning (GAF),[30] World Health Organization Quality of Life Questionnaire for Brief Version (WHOQOL-BREF),[31] Biological Rhythms Assessment in Neuropsychiatry (BRIAN),[32] Functioning Assessment Short Test (FAST),[33] and serum BDNF levels were measured at the W0 and W8.

Serum BDNF levels were measured using a commercial kit of sandwich-ELISA according to the manufacturer's instructions (Chemi-Con, USA) as previously described.[14] For this, 5ml of blood were withdrawn by venipuncture into a free-anticoagulant vacuum tube. The blood was immediately centrifuged at 3,000g for 5 minutes, and serum was kept frozen at -80ºC until the biochemical analyzes were performed.

Outcomes of the randomized, maintenance phase

Clinical evaluations were performed at W0, W02, W04, W08, W16 and W24 in the randomized phase. The primary outcome was time to any intervention. Interventions

included initiation of unscheduled meetings due to mood symptoms, initiation of new medication, psychotherapy, hospitalization, electroconvulsive therapy (ECT), discontinuation or dose adjustment of the current treatment. Secondary efficacy measures included changes in the MADRS and YMRS scores. Functioning Assessment Short Test (FAST)[33] were measured at the W0 and W24 and serum BDNF levels were measured at the W0, W16 and W24.

Randomization and Blinding

Participants were randomly assigned to adjunctive tianeptine or placebo in a double-blind fashion for twenty-four weeks of follow-up during the second phase of the study. Randomization was centralized, and randomization numbers were not sequential within any site. No member of the investigational team had access to the randomization scheme during the study. Medication and placebo packaging were identical. Tianeptine is commercially available in Brazil and was purchased and re-packed by the pharmacy of Hospital de Clínicas de Porto Alegre (coordinating site).

Statistical analysis

Sample size calculations were performed in a similar fashion to that described by Berk and colleagues [34] with time to any intervention as the primary outcome. The last visit of the open-label phase (week 8) served as the baseline (week 0) for the maintenance phase of the trial. All randomized participants who had at least one post baseline assessment were included in the analysis. The analysis was performed blind to treatment assignment. Kaplan-Meier estimates and the Mantel-Cox log-rank test were used to evaluate differences in time to intervention for a mood episode between the tianeptine and placebo groups (primary outcome). The proportional hazards assumption was tested and was not violated. The analyses of continuous measures in the first and second phases involved the use of a likelihood-based mixed-effects model repeated measures (MMRM) approach with random intercept and slopes. For the randomized phase, the MMRM model included the fixed, categorical effects of group, time and group-by-time interaction.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 406 subjects were initially screened, 161 patients met DSM-IV criteria for bipolar depression and consented to participate in the open-label tianeptine trial phase. At week 8, a total of 123 patients were assessed (discontinuations = 38). Sixty-nine patients achieved response criteria and were eligible for the 24-week double-blind placebo-controlled randomized trial. Thirty-three patients were randomized to placebo and 36 to tianeptine. There were no significant differences between the two treatment groups with respect to completion rates (tianeptine: 66•7%, n=24; placebo: 69•7%, n=23; p=0•991). Figure 1 depicts the CONSORT flowchart for our study.

Open-label phase

Sociodemographic and clinical features at baseline of the open-label phase are shown in Table 1. Most study participants had bipolar I disorder and moderate/severe depressive symptoms scores (mean MADRS score= 27). The mean age of illness onset was 24 years. In the open-label phase, there was a significant improvement in depressive symptoms as measured by changes in mean MADRS scores from baseline to W8 (26•87±7.58 vs. 13•65±9•44, p<0•001). There were also significant improvements from baseline to W8 in GAF (54•21±10•57 vs. 66•75±14•08, p<0•001), FAST (43•57±13.25 vs. 34•51±15.21, p<0•001), BRIAN (54•86±9•83 vs. 47•58±10•95, p<0•001), and CGI-BP (4•61±0•98 vs. 2•95±1•43, p<0•001) scores. We also found improvement in all quality of life domains: Physical health (34•95±13•65 vs. 48•09±15•47, p<0•001), Psychological health (29•23±15•79 vs. 43•20±18•77,

p<0•001), Social relationships (36•93±18•87 vs. 44•94±20•66, p=0•001) and Environment (44•82±13•66 vs. 51•08±14•98, p<0•001).

We found no baseline to W8 difference in serum BDNF levels (p=0•808). The rate of switch to mania (defined by YMRS ≥ 12) at W8 was very low (n=5; 4•1%).

Randomized maintenance phase

Table 2 shows the demographic and clinical features of study participants at randomization. A total of 22 interventions occurred: 12 in the tianeptine group and 10 in the placebo group. There was no difference between tianeptine and placebo groups in overall event rates (X2=0•073, p=0•787). The 22 individuals who dropped out of the study in the randomized phase did so for the following reasons: one switched to mania, eight had poor adherence, seven withdrew consent, five relapsed into a depressive episode and one developed renal impairment due to sepsis.

None of the participants from the tianeptine group had a manic switch while one participant of the placebo group had a manic episode during the maintenance phase. The average time to any intervention for the tianeptine group was similar (146•4 days, SE=12•2, 95%CI 122•6-170•2) to the placebo group (154•0 days, SE=13•7, 95%CI 127.1-180•8), log rank χ2=0•039, p=0•844 (Figure 2).

No significant group-by-visit interactions were identified in the mixed-effects model repeated measures approach for symptoms or functioning measures: MADRS (p=0•055), YMRS (p=0•218), and FAST (p=0•661). There was no difference in BDNF levels between groups at week 24 (F=0•146; p=0•703).

Discussion

This is the first long-term randomized, placebo-controlled trial of adjunctive antidepressant as a maintenance treatment for bipolar disorder. We found no differences between tianeptine 12•5mg TID and placebo adjunctive to lithium or valproate as maintenance treatment after remission from an acute depressive

episode. This finding is in line with previous studies. For instance, no difference in time for intervention emerged between the nutraceutical NAC and placebo in a double-blind randomized maintenance trial.[34] In a randomized controlled trial lacking placebo control examining the effects of adjunctive venlafaxine, bupropion, or sertraline treatment for up to 1 year after favorable short-term responses in bipolar depression, only 23•3% of the individuals had a sustained antidepressant response.[35] Moreover, a meta-analysis of randomized controlled trials involving efficacy studies with more than 6 months of treatment in bipolar depression reported that adjunctive antidepressants presented little protection from depression and tended to increase manic episodes when compared with mood stabilizer treatment alone.[36] Of note, the use of tianeptine as adjunctive treatment did not increase the risk of switch to mania in our study. Together, existing evidence does not support long-term use of adjunctive antidepressants as a maintenance treatment for bipolar disorder. Future studies should investigate if there is a specific subtype of bipolar subjects that may benefit from long-term use of adjunctive antidepressants.

In the 8-week open-label phase, we found a significant improvement in depressive symptoms, psychosocial functioning, self-reported biological rhythms and quality of life with tianeptine 12•5mg TID adjunctive to lithium or valproate. This result is consistent with two independent meta-analyses that found superiority of antidepressants over placebo in acute trials for bipolar depression [9,37] and a strong trend (p=0•06) towards superiority with antidepressants in another meta-analysis.5 Also consistent with all 3 meta-analyses of randomized clinical trials using antidepressants for acute bipolar depression suggesting that the more modern antidepressants displayed similar rates of manic switch when compared to adjunctive placebo,[5,9,37] we found that adjunctive tianeptine did not increase the risk for manic switch in the open-label or the double-blind maintenance phase.

We found no changes in serum BDNF levels with acute, open-label, or long-term, maintenance treatment with tianeptine. This finding is consistent with two large meta-analyses showing no changes in serum or plasma BDNF levels with the treatment of acute bipolar depression [38,39] and a recent prospective within-subject analysis that found no association between peripheral BDNF levels and various mood states.[40]

Our study has some limitations. Firstly, the lack of a placebo group during the open-label phase limited our findings regarding the efficacy of tianeptine in acute bipolar depression. Secondly, the inclusion of bipolar I-, II- and NOS - disorder participants might have interfered with our findings. However, this approach enhanced the generalizability of our results. Thirdly, the sample size, while similar than most randomized controlled trials of antidepressants for bipolar depression published to date limits the power to conduct secondary/exploratory analyses.[37]

In summary, this randomized placebo-controlled maintenance trial did not support long-term use of tianeptine adjunctive to mood stabilizers in bipolar disorder. Tianeptine was well tolerated and was associated with low risk for manic switch during both the acute open-label and the long-term maintenance phases.

Panel: Research in context

Evidence before this study

We searched Pubmed and Embase by using the following terms: ("tianeptine") AND ("bipolar disorder"). Mesh terms were used in Pubmed and Emtree terms were used in Embase. Articles published between 1960 and July 30th, 2016 were included. The inclusion criteria were clinical trials that assessed the use of tianeptine in patients with bipolar disorder while reviews and preclinical trials were excluded. We did not limit our search to English language publications.

Added value of this study

The present study is the first long-term randomized, double-blind maintenance trial of tianeptine in bipolar disorder. We found four clinical trials that assessed the acute efficacy of tianeptine in depressive episodes by searching Pubmed and Embase. Two studies compared tianeptine with placebo and reported the efficacy of tianeptine in the treatment of depressive episodes. One study compared tianeptine with fluoxetine while another study compared tianeptine with sertraline. Both studies showed no significant difference between groups. It is worth mentioning that all these

studies included both patients with bipolar disorder and patients with major depressive disorder.

Implications of all the available evidence

Our study combined with existing evidence showed that tianeptine is a safe medication and may be effective in the treatment of acute bipolar depression. However, tianeptine did not show beneficial effects in the maintenance randomized phase. Of note, this is also the first long-term randomized, double-blind maintenance trial of antidepressant augmentation in bipolar disorder.

Contributors

FK, NSK, BNF, FKG, MK and MK-S'A were responsible for the study design. AF, ACL-S, AAD, JB, FKG, JCW, KMMC, KPBB, LSS, MK, MP and RR were responsible for the data collection, and KJ, PVM, ICP and AF participated in the data analysis. NSK, FK, ICP, KJ, PVM, ACL-S, AAD, JB, JCW, KMMC, KPBB, RR and MK-S'A were responsible for the interpretation of findings. KJ and ICP were responsible for the figures and tables. GDC participated of the trial organization, including randomization of the participants, medication and placebo packaging and performed biochemical assays. BP and BW-A participated of the blood collection, sample organization and storage. MP was responsible for patients' selection. PDG participated in the screening, recruitment, assessment and follow-up of the patients. FK, NSK, ICP, KJ, PVM, MK, LSS, BNF and MK-S'A did the scientific literature search. FK, NSK, ICP, KJ, PVM, MK, BNF and MK-S'A participated in the writing of the report, and all authors approved the final version of the manuscript.

Declaration of interest

Flávio Kapczinski has received grants or research support from AstraZeneca, Eli Lilly, Janssen-Cilag, Servier, NARSAD, and the Stanley Medical Research Institute;

has been a member of speakers' boards for AstraZeneca, Eli Lilly, Janssen, and Servier; and has served as a consultant for Servier. Keila Ceresér has received grants from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). Maurício Kunz has received consulting fees from Daiichi Sankyo. Benicio Frey has received grant/research support from Alternative Funding Plan Innovations Award, Brain and Behavior Research Foundation, Canadian Institutes of Health Research, Hamilton Health Sciences Foundation, J.P. Bickell Foundation, Ontario Brain Institute, Ontario Mental Health Foundation, Society for Women's Health Research, Stanley Medical Research Institute, Teresa Cascioli Charitable Foundation, Eli Lilly and Pfizer, and has received consultant and/or speaker fees from AstraZeneca, Bristol-Myers Squibb, Canadian Psychiatric Association, CANMAT, Daiichi Sankyo, Lundbeck, Pfizer, Servier and Sunovion. Márcia Kauer-Sant'Anna is on speaker or advisory boards for, or has received research grants from NARSAD, Stanley Medical Research Institute, and Eli-Lilly. All other authors report no competing interests.

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References

1 Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 2007; 64: 543–52.

2 Judd LL, Akiskal HS, Schettler PJ, et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. Arch Gen Psychiatry 2005; 62: 1322–30.

3 De Fruyt J, Deschepper E, Audenaert K, et al. Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis. J Psychopharmacol 2012; 26: 603–17.

4 Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. Br J Psychiatry 2009; 194: 4–9.

5 Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. J Clin Psychiatry 2011; 72: 156–67.

6 Taylor DM, Cornelius V, Smith L, Young AH. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. Acta Psychiatr Scand 2014; 130: 452–69.

7 Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 2007; 356: 1711–22.

8 Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry 2013; 170: 1249–62.

9 Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. Am J Psychiatry 2004; 161: 1537–47.

10 Kapczinski F, Vieta E, Andreazza AC, et al. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. Neurosci Biobehav Rev 2008; 32: 675–92.

11 Passos IC, Mwangi B, Vieta E, Berk M, Kapczinski F. Areas of controversy in neuroprogression in bipolar disorder. Acta Psychiatr Scand 2016; published online April 21. DOI:10.1111/acps.12581.

12 Cao B, Passos IC, Mwangi B, et al. Hippocampal volume and verbal memory performance in late-stage bipolar disorder. J Psychiatr Res 2016; 73: 102–7.

13 Mwangi B, Wu M-J, Cao B, et al. Individualized Prediction and Clinical Staging of Bipolar Disorders using Neuroanatomical Biomarkers. Biol psychiatry Cogn Neurosci neuroimaging 2016; 1: 186–94.

14 Cunha ABM, Frey BN, Andreazza AC, et al. Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. Neurosci Lett 2006; 398: 215–9.

15 Yurgelun-Todd DA, Gruber SA, Kanayama G, Killgore WD, Baird AA, Young AD. fMRI during affect discrimination in bipolar affective disorder. Bipolar Disord 2000; 2: 237–48.

16 Machado-Vieira R, Lara DR, Souza DO, Kapczinski F. Purinergic dysfunction in mania: an integrative model. Med Hypotheses 2002; 58: 297–304.

17 Czéh B, Michaelis T, Watanabe T, et al. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci U S A 2001; 98: 12796–801.

18 Kole MHP, Swan L, Fuchs E. The antidepressant tianeptine persistently modulates glutamate receptor currents of the hippocampal CA3 commissural associational synapse in chronically stressed rats. Eur J Neurosci 2002; 16: 807–16.

19 Fuchs E, Czéh B, Michaelis T, de Biurrun G, Watanabe T, Frahm J. Synaptic plasticity and tianeptine: structural regulation. Eur Psychiatry 2002; 17 Suppl 3: 311–7.

20 McEwen BS, Magarinos AM, Reagan LP. Structural plasticity and tianeptine: cellular and molecular targets. Eur Psychiatry 2002; 17 Suppl 3: 318–30.

21 Campbell AM, Park CR, Zoladz PR, Muñoz C, Fleshner M, Diamond DM. Pre-training administration of tianeptine, but not propranolol, protects hippocampus-dependent memory from being impaired by predator stress. Eur Neuropsychopharmacol 2008; 18: 87–98.

22 Reagan LP, Hendry RM, Reznikov LR, et al. Tianeptine increases brain-derived neurotrophic factor expression in the rat amygdala. Eur J Pharmacol 2007; 565: 68–75.

23 Reznikov LR, Grillo CA, Piroli GG, Pasumarthi RK, Reagan LP, Fadel J. Acute stress-mediated increases in extracellular glutamate levels in the rat amygdala: differential effects of antidepressant treatment. Eur J Neurosci 2007; 25: 3109–14.

24 Uzbay TI, Kayir H, Ceyhan M. Effects of tianeptine on onset time of pentylenetetrazole-induced seizures in mice: possible role of adenosine A1 receptors. Neuropsychopharmacology 2007; 32: 412–6.

25 McEwen BS, Chattarji S, Diamond DM, et al. The neurobiological properties of tianeptine (Stablon): from monoamine hypothesis to glutamatergic modulation. Mol Psychiatry 2010; 15: 237–49.

26 Novotny V, Faltus F. Tianeptine and fluoxetine in major depression: a 6-week randomised double-blind study. Hum Psychopharmacol 2002; 17: 299–303.

27 Lôo H, Saiz-Ruiz J, Costa E Silva JA, et al. Efficacy and safety of tianeptine in the treatment of depressive disorders in comparison with fluoxetine*. Hum Psychopharmacol 2001; 16: S31–8.

28 Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978; 133: 429–35.

29 Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997; 73: 159–71.

30 Aas IHM. Guidelines for rating Global Assessment of Functioning (GAF). Ann Gen Psychiatry 2011; 10: 2.

31 Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol Med 1998; 28: 551–8.

32 Giglio LMF, Magalhães PV da S, Andreazza AC, et al. Development and use of a biological rhythm interview. J Affect Disord 2009; 118: 161–5.

33 Rosa AR, Sánchez-Moreno J, Martínez-Aran A, et al. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin Pract Epidemiol Ment Health 2007; 3: 5.

34 Berk M, Dean OM, Cotton SM, et al. Maintenance N-acetyl cysteine treatment for bipolar disorder: a double-blind randomized placebo controlled trial. BMC Med 2012; 10: 91.

35 Leverich GS, Altshuler LL, Frye MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry 2006; 163: 232–9.

36 Ghaemi SN, Wingo AP, Filkowski MA, Baldessarini RJ. Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. Acta Psychiatr Scand 2008; 118: 347–56.

37 Vázquez GH, Tondo L, Undurraga J, Baldessarini RJ. Overview of antidepressant treatment of bipolar depression. Int J Neuropsychopharmacol 2013; 16: 1673–85.

38 Munkholm K, Vinberg M, Kessing L V. Peripheral blood brain-derived neurotrophic factor in bipolar disorder: a comprehensive systematic review and meta-analysis. Mol Psychiatry 2016; 21: 216–28.

39 Fernandes BS, Molendijk ML, Köhler CA, et al. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. BMC Med 2015; 13: 289.

40 Jacoby AS, Munkholm K, Vinberg M, Pedersen BK, Kessing LV. Cytokines, brain-derived neurotrophic factor and C-reactive protein in bipolar I disorder - Results from a prospective study. J Affect Disord 2016; 197: 167–74.

TABLES AND FIGURES:

Table 1: Sociodemographic variables and clinical features at the baseline of the open-label phase.

Characteristics	Distribution n = 161
Gender [a]	
Male	32 (19.9%)
Female	129 (80.1%)
Age (years) [b]	42.8 ±10.6
Age of onset (years) [b]	24.4 ±10.3
Education level (years) [b]	11.0 ±4.3
Bipolar disorder subtype [a]	
BD-I	105 (65.2%)
BD-II	54 (33.6%)
BD-NOS	2 (1.2%)
Number of manic episodes [c]	3 (1 - 9.5)
Number of depressive episodes [c]	8 (4 - 13.5)
Number of psychiatric hospitalizations [c]	1 (0 - 3)
MADRS score [b]	26.9 ±7.6
YMRS score [c]	0 (0 - 2)

CGI-BP score [b]	4.6 ±1.0
GAF score [b]	54.2 ±10.6
FAST score [b]	43.6 ±13.2
BRIAN score [b]	54.9 ±9.8
WHOQOL [b]	
Physical health	34.9 ±13.6
Psychological	29.2 ±15.8
Social relationships	36.9 ±18.9
Environment	44.8 ±13.7

Legend: MADRS = Montgomery Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale; CGI-BP = Clinical Global Impressions scale for bipolar disorder; GAF = Global Assessment of Functioning; FAST = Functioning Assessment Short Test; BRIAN = Biological Rhythms Assessment in Neuropsychiatry; WHOQOL = World Health Organization Quality of Life Questionnaire.

[a] Absolute and relative frequencies; [b] Mean and standard deviation; [c] Median and interquartile range.

Table 2: Descriptive statistics depicting the differences between tianeptine and placebo groups on demographic and clinical variables at Week 8 (at randomization).

Characteristics	Tianeptine (n=36)	Placebo (n=33)	Statistic	*p* value
Gender (female) [a]	86.1%	75.8%	0.625	0.429
Age (years) [b]	41.2±11.4	44.6±10.9	-1.258	0.213
Age of onset (years) [b]	21.2±10.5	24.0±9.5	-1.149	0.255

Education level (years) [b]	10.1±3.3	10.6±4.7	-0.468	0.641
Bipolar disorder subtype [a]			3.721	0.054
BD-I	52.8%	78.1%		
BD-II	47.2%	21.9%		
Number of manic episodes [c]	2.5 (1 - 10)	3 (2 - 8)	314.0	0.849
Number of depressive episodes [c]	10 (5 - 15)	5 (3 - 12)	434.5	0.216
Number of hospitalizations [c]	0 (0 - 3)	1 (0 - 1.75)	536.5	0.607
Symptoms [b]				
MADRS score	6.7±3.6	8.4±5.7	-1.442	0.154
CGI-BP score	1.8±0.9	2.1±1.1	-1.191	0.238
Other clinical features [b]				
GAF score	76.4±10.6	73.1±12.1	1.206	0.232
FAST score	29.3±14.0	26.8±13.6	0.738	0.463
BRIAN score	44.4±10.9	40.0±8.5	1.852	0.069
WHOQOL - Physical health	53.1±13.3	55.5±14.4	-0.712	0.479
WHOQOL - Psychological	50.8±14.3	52.3±17.4	-0.373	0.710
WHOQOL - Social relationships	50.0±19.2	52.5±19.4	-0.540	0.591
WHOQOL - Environment	53.9±11.5	55.3±15.1	-0.424	0.673

Legend: MADRS = Montgomery Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale; CGI-BP = Clinical Global Impressions scale for bipolar disorder; GAF = Global Assessment of Functioning; FAST = Functioning Assessment Short Test; BRIAN = Biological Rhythms Assessment in Neuropsychiatry; WHOQOL = World Health Organization Quality of Life Questionnaire.

[a] Chi-square test, descriptive statistic was reported by absolute and relative frequencies; [b] *t* test, descriptive statistic was reported by mean and standard deviation; [c] Mann-Whitney non-parametric test, descriptive statistic was reported by median and interquartile range.

Figure 1. CONSORT flowchart for open-label and randomized phases.

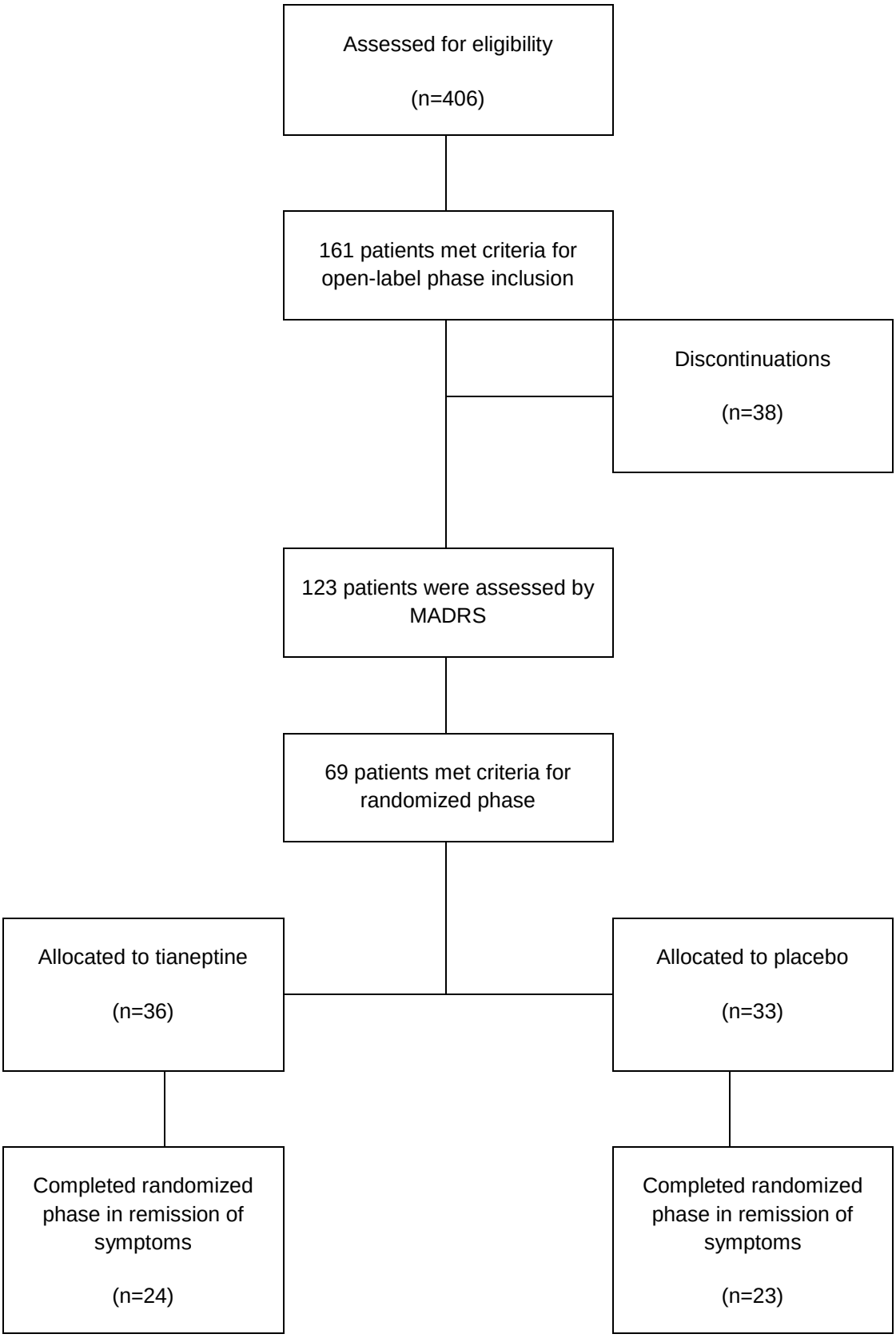
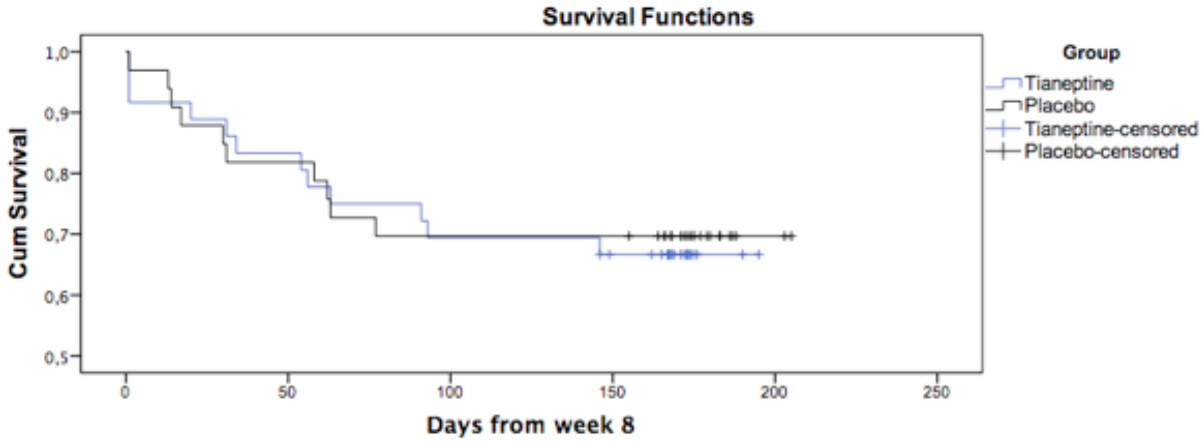


Figure 2: Survival time depicting time to intervention.



7. CONSIDERAÇÕES FINAIS

Parece que a neuroprogressão não é uma regra geral no transtorno bipolar. O número de episódios maníacos parece ser o marcador clínico mais robustamente associada com a neuroprogressão. Na verdade, a maioria das evidências em nosso estudo de revisão vieram de trabalhos com pacientes com transtorno bipolar tipo 1. Vários estudos encontraram associações significativas entre o número de episódios maníacos e alterações cerebrais [17,18], bem como com o deterioro neurocognitivo [17,27]. Trauma precoce e comorbidade psiquiátrica e clínica também parecem ser fatores de risco associados com um curso neuroprogressivo em pacientes com transtorno bipolar [28,29]. É interessante notar que duas limitações importantes dos estudos transversais incluídos na nossa revisão são a incapacidade de confirmar a causalidade e o viés de memória. Estudos retrospectivos apresentam limitações importantes para avaliar o número de episódios, história de trauma ou quando a doença começou.

Em termos de biomarcadores periféricos, o BDNF parece ser um marcador de atividade de doença no transtorno bipolar, mas não de estadiamento [30]. Por outro lado, estudos transversais apontam para um papel potencial dos marcadores inflamatórios tanto como biomarcadores da atividade da doença quanto como biomarcadores de estadiamento. Estudos longitudinais são necessários para esclarecer o papel exato da inflamação e neuroinflamação no transtorno bipolar. A hipótese de que o transtorno bipolar está associado a alterações progressivas no sistema fronto-límbico, bem como em domínios funcionais e cognitivos têm sido comprovada por estudos transversais e longitudinais [9,15,16]. Vale a pena mencionar que um estudo recente propôs um modelo de estadiamento da doença bipolar com base nas progressivas alterações de neuroimagem [31].

Futuros estudos longitudinais devem usar a abordagem de biologia de sistemas. Biologia de sistemas é a modelagem computacional e matemática de sistemas biológicos complexos. Esta abordagem poderá usar técnicas de *machine learning* e ajudar na identificação de sistemas alterados num paciente com transtorno bipolar [68].

Com relação ao ensaio clínico, a tianeptina foi bem tolerada e associada a um baixo risco de virada maníaca durante a fase aberta e a fase de manutenção do estudo. O ensaio clínico de manutenção randomizado e controlado por placebo, entretanto, não apoia o uso a longo prazo de tianeptina em associação a estabilizadores de humor no transtorno bipolar. Na fase de aberta de 8 semanas, encontramos uma melhora significativa nos sintomas depressivos, funcionamento psicossocial, ritmos biológicos auto-relatados e qualidade de vida com tianeptina adjuvante ao lítio ou valproato. O presente estudo é o primeiro ensaio clínico randomizado de manutenção de longo prazo, duplo-cego com um antidepressivo no transtorno bipolar. Esse estudo, portanto, não suporta a evidência para uso a longo prazo de antidepressivos em pacientes bipolares.

Esse estudo, entretanto, tem algumas limitações. Em primeiro lugar, a falta de um grupo placebo, durante a fase aberta limita nossos resultados em relação à eficácia da tianeptina durante o episódio depressivo (fase aberta). Em segundo lugar, a inclusão de pacientes com transtorno bipolar tipo 1, 2 e NOS pode ter interferido com os nossos achados. No entanto, esta abordagem aumentou a generalização de nossos resultados. Em terceiro lugar, o tamanho da amostra, embora semelhante aos demais estudos de manutenção de longo prazo [32], limita a nossa análise.

8. REFERÊNCIAS BIBLIOGRÁFICAS

1. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch. Gen. Psychiatry. 2007;64:543–52.
2. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. Arch. Gen. Psychiatry. 2011;68:1058–64.
3. Gitlin MJ, Swendsen J, Heller TL, Hammen C. Relapse and impairment in bipolar disorder. Am. J. Psychiatry. 1995;152:1635–40.
4. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci. Biobehav. Rev. 2011;35:804–17.
5. Passos IC, Kapczinski NS, Quevedo J, Kauer-Sant'Anna M, Kapczinski F. Staging Models and Functional Outcomes in Bipolar Disorder: Clinical Implications. Curr. Treat. Options Psychiatry. 2015;2:205–17.
6. Kapczinski F, Magalhães PVS, Balanzá-Martinez V, Dias V V, Frangou S, Gama CS, et al. Staging systems in bipolar disorder: an International Society for Bipolar Disorders Task Force Report. Acta Psychiatr. Scand. 2014;130:354–63.
7. Griesinger W. Traité des maladies mentales, pathologie et thérapeutique. Place d'éc. Paris; 1865.
8. Kapczinski F, Vieta E, Magalhães PV da S, Berk M. Neuroprogression and staging in bipolar disorder. Oxford: Oxford University Press; 2015.
9. Abé C, Ekman C-J, Sellgren C, Petrovic P, Ingvar M, Landén M. Manic episodes are related to changes in frontal cortex: a longitudinal neuroimaging study of bipolar disorder 1. Brain. 2015;awv266.
10. Kessing LV. Severity of depressive episodes according to ICD-10: prediction of risk of relapse and suicide. Br. J. Psychiatry. 2004;184:153–6.
11. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet (London, England). 2015;
12. Yatham LN, Kennedy SH, Parikh S V, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord.

2013;15:1–44.
13. Samalin L, de Chazeron I, Vieta E, Bellivier F, Llorca P-M. Residual symptoms and specific functional impairments in euthymic patients with bipolar disorder. Bipolar Disord. 2016;18:164–73.
14. Reinares M, Papachristou E, Harvey P, Mar Bonnín C, Sánchez-Moreno J, Torrent C, et al. Towards a clinical staging for bipolar disorder: defining patient subtypes based on functional outcome. J. Affect. Disord. 2013;144:65–71.
15. Rosa AR, Magalhães PVS, Czepielewski L, Sulzbach MV, Goi PD, Vieta E, et al. Clinical staging in bipolar disorder: focus on cognition and functioning. J. Clin. Psychiatry. 2014;75:e450-6.
16. Mwangi B, Wu M-J, Cao B, Passos IC, Lavagnino L, Keser Z, et al. Individualized Prediction and Clinical Staging of Bipolar Disorders using Neuroanatomical Biomarkers. Biol. psychiatry Cogn. Neurosci. neuroimaging. 2016;1:186–94.
17. Cao B, Passos IC, Mwangi B, Bauer IE, Zunta-Soares GB, Kapczinski F, et al. Hippocampal volume and verbal memory performance in late-stage bipolar disorder. J. Psychiatr. Res. 2016;73:102–7.
18. Lavagnino L, Cao B, Mwangi B, Wu M-J, Sanches M, Zunta-Soares GB, et al. Changes in the corpus callosum in women with late-stage bipolar disorder. Acta Psychiatr. Scand. 2015;
19. Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J, et al. Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. Am. J. Psychiatry. 2002;159:1841–7.
20. Passos IC, Mwangi B, Vieta E, Berk M, Kapczinski F. Areas of controversy in neuroprogression in bipolar disorder. Acta Psychiatr. Scand. 2016;
21. Uzbay TI, Kayir H, Ceyhan M. Effects of tianeptine on onset time of pentylenetetrazole-induced seizures in mice: possible role of adenosine A1 receptors. Neuropsychopharmacology. 2007;32:412–6.
22. McEwen BS, Chattarji S, Diamond DM, Jay TM, Reagan LP, Svenningsson P, et al. The neurobiological properties of tianeptine (Stablon): from monoamine hypothesis to glutamatergic modulation. Mol. Psychiatry. 2010;15:237–49.
23. Magariños AM, Deslandes A, McEwen BS. Effects of antidepressants and benzodiazepine treatments on the dendritic structure of CA3 pyramidal neurons after chronic stress. Eur. J. Pharmacol. 1999;371:113–22.

24. Czéh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, van Kampen M, et al. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc. Natl. Acad. Sci. U. S. A. 2001;98:12796–801.
25. Reagan LP, Hendry RM, Reznikov LR, Piroli GG, Wood GE, McEwen BS, et al. Tianeptine increases brain-derived neurotrophic factor expression in the rat amygdala. Eur. J. Pharmacol. 2007;565:68–75.
26. Lucassen PJ, Fuchs E, Czéh B. Antidepressant treatment with tianeptine reduces apoptosis in the hippocampal dentate gyrus and temporal cortex. Biol. Psychiatry. 2004;55:789–96.
27. Martínez-Arán A, Vieta E, Reinares M, Colom F, Torrent C, Sánchez-Moreno J, et al. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am. J. Psychiatry. 2004;161:262–70.
28. Passos IC, Jansen K, Cardoso T de A, Colpo GD, Zeni CP, Quevedo J, et al. Clinical outcomes associated with comorbid posttraumatic stress disorder among patients with bipolar disorder. J. Clin. Psychiatry. 2016;77:e555-60.
29. Leverich GS, Post RM. Course of bipolar illness after history of childhood trauma. Lancet. 2006;367:1040–2.
30. Fernandes BS, Molendijk ML, Köhler CA, Soares JC, Leite CMGS, Machado-Vieira R, et al. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. BMC Med. 2015;13:289.
31. Frank E, Nimgaonkar VL, Phillips ML, Kupfer DJ. All the world's a (clinical) stage: rethinking bipolar disorder from a longitudinal perspective. Mol. Psychiatry. 2015;20:23–31.
32. Berk M, Dean OM, Cotton SM, Gama CS, Kapczinski F, Fernandes B, et al. Maintenance N-acetyl cysteine treatment for bipolar disorder: a double-blind randomized placebo controlled trial. BMC Med. 2012;10:91.