Universidade Federal do Rio Grande do Sul

Faculdade de Medicina

Programa de Pós-Graduação em Medicina: Ciências Médicas

MARCADORES BIOLÓGICOS E NÍVEL DE FUNCIONALIDADE EM PACIENTES BIPOLARES

Aluna: Adriane Ribeiro Rosa

Orientador: Dr. Flávio Kapczinski

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Catalogação-na-Publicação

R788 Rosa, Adriane Ribeiro
Marcadores biológicos e nível de funcionalidade em pacientes bipolares / Adriane Ribeiro Rosa. — 2007.
319 f.

Tese (doutorado) - Programa de Pós-Graduação em Medicina: Ciências Médicas, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, 2007.

Orientador: Prof. Dr. Flávio Kapczinski.

1. Transtorno bipolar 2. Sistema nervoso central 3. Fatores de crescimento neural 4. Neuroglia I. Kapczinski, Flávio II. Título

NLM WM 207

(Bibliotecária responsável: Lenise Di Domenico Colpo – CRB-10/1757)

Agradecimentos e Dedicatória

Ao meu mestre e orientador, *Dr. Flávio Kapczinski*, que acreditou em mim, se fez presente durante esta caminhada, e principalmente, por proporcionar-me à realização de um *"projeto-sonho"*.

A meus queridos colegas do Laboratório de Psiquiatria Molecular, PROTAHBI-HCPA, pelo estímulo e por fazerem possível a realização deste projeto. Agradeço, em especial, à super Tina, por seu, companheirismo e dedicação, à grande Keila, pela motivação e compreensão, à Márcia por fazer-me acreditar que é possível, ao Benício, pela ilustre colaboração científica. Também aos amigos (as) Alice, Jú Tramontina e Fernando, a super equipe de revisão.

Estimado Dr. *Eduard Vieta*, mi sincero reconocimiento y admiración por su trabajo. Gracias por sus enseñanzas y sobretodo por la oportunidad de participar de un equipo de alto nivel científico.

A mis queridos colegas del Programa de Trastorno Bipolar-Barcelona, muchas gracias por compartir conmigo vuestros conocimientos y motivarme a cada día a continuar en el fascinante campo de la investigación. En especial ha Anabel y Jose por la ayuda en el desarrollo de la *FAST*. A Maria, Mercè y Carla por los buenos momentos compartidos y sobretodo por su amistad.

A prof. *Sandra Fuchs* e a UFRGS, pelo empenho prestado, proporcionando a realização deste doutorado sanduíche.

Ao prof *Carlos Alberto Gonçalves* e equipe do Laboratório S-100 (Bioquímica) por sua dedicação na execução deste projeto.

Ao meu irmão e colega, André, por confiar em mim, proporcionando a realização deste trabalho, meu sincero agradecimento.

E por fim, dedico este doutorado a meus pais, *Fátima e Jairo*, que em todos os momentos me apoiaram e, principalmente, acreditaram em minhas decisões.

A vocês, que me ensinaram, pelo próprio exemplo, que devemos lutar por aquilo que acreditamos, meu "*Muito Obrigada*".

SUMÁRIO:

1. ABREVIATURAS:

ácido valpróico: Ácido valpróico

Bcl-2: fator apoptótico Bcl-2

Bcl-x: fator apoptótico Bcl-x

BDNF: Fator Neurotrófico derivado do Cérebro

c-fos: Indução dos fatores de transcrição pertencentes a família Fos

c-ret: proteínas pro-oncogênicas c-ret

CPF: Córtex pré-frontal

CREB: Fator de transcrição gênica

ECT: Eletroconvulsoterapia

GAF: Avaliação Global da Funcionalidade

GDNF: Fator de Crescimento Neurotrófico derivado de Células da Glia

GFLs: Família de ligantes das células de linhagem glial

GFR2: Receptor para neurturina

GFRα: Receptor para família GDNF

GPI: Glicosilfosfatidilinositol

GRs: receptotes para glicocorticóides

GSH-Px: Glutation cinase

HC: Hipocampo

HRQoL: Health Related Quality of Life

IP-3: Inositol trifosfato

LAQ: Questionário de Atitudes em relação ao Lítio

LFQ: Life Functioning Qualify

LKT: Teste de Conhecimento do Lítio

MAPK: Proteína quinase mitogênica ativada

NAA: N-acetil-aspartato

NE: Norepinefrina

NGF: Fator de Crescimento Neural

NT-3: Neurotrofina-3

NT-4: Neurotrofina-4

PLC-y: Fosfolipase Cy

SF-36: Short Form -36

SOD: Superóxido dismutase

SNC: Sistema Nervoso Central

TBARS: Substâncias reativas ao ácido tiobarbitúrico

TGF-β: Superfamília de fatores de crescimento de transformação

THB: Transtorno do Humor Bipolar

Trk-A: Receptor tirosina quinase A

Trk-B: Tirosina quinase B

Trk-C: Tirosina quinase C

WHO-DAS: Who Health Organization-Disability Assessment Schedule

WSAS: Work and Social Adjustment Scale

2. ABSTRACT:

Alterations in specific structures of CNS, in particular, fronto-lymbic system, and a reduction of neurons and glial cells appear to be involved in the pathophysiology of bipolar disorder. Glial cells have an important role in the CNS, for example, the production of neurotrophins, especially, Glial Cell Line-derived Neurotrophic Factor (GDNF). In this study, we showed a marked increased in the serum levels of GDNF in depressive ($F= 42.31$; $p=0.004$; one-way ANOVA) and manic bipolar patients ($F= 42.31$; $p=0.001$; one-way ANOVA), which suggested that GDNF could be involved in the physiopathology of bipolar disorder. On the other hand, alterations in the neurotrophic factors hinder synaptic plasticity mechanisms, may result in cognitive impairment in bipolar patients. In particular, memory difficulties have been reported here, and these difficulties influence occupational and social functioning in these subjects. High rates of functional impairment showed by bipolar patients and a lack of standardization of the instruments available to assess functioning in the studies motivated us to development the scale. The Functioning Assessment Short test (FAST) is a rapid instrument and easy to apply developed to use in psychiatry, especially, bipolar patients. It assesses six specific domains of functioning, such as autonomy, occupational functioning, cognitive functioning, financial issues and leisure time. The validation of FAST was performed by psychometric tests such as internal consistency (Cronbach's alpha: 0.909), concurrent validity compared to the GAF ($r=-0.903$; $p<0.001$), validity as a discriminative measure to detect the difference between euthymic (18.55; $F=23.59$; $p<0.001$) and acute patients (manic: 38.50; depressive: 42.38; mixed: 43.21), factorial analysis and test-retest reliability (0.953; $p<0.01$). The FAST scale showed strong psychometric properties and it is now available for use in both clinical practice and investigation settings.

Key words: bipolar disorder, GDNF, glia, neurotophins, functioning, impairment functional, functioning scale.

3. RESUMO:

Alterações em estruturas específicas do SNC, em particular, no sistema fronto-límbico, assim como a diminuição das células neuronais e gliais parece estar envolvida com a fisiopatologia do Transtorno do Humor Bipolar (THB). A glia exerce um importante papel no SNC, entre os quais, a produção de neurotrofinas, em especial, o Fator de Crescimento Neurotrófico derivado de Células da Glia (GDNF). Um marcado aumento dos níveis séricos de GDNF em pacientes deprimidos ($F= 42.31$; $p=0.004$; one-way ANOVA) e maníacos ($F= 42.31$; $p=0.001$; one-way ANOVA) foi demonstrado neste estudo, sugerindo um possível envolvimento desta neurotrofina com o THB. Por outro lado, alterações nos fatores neurotróficos afetam os mecanismos de plasticidade sináptica, podendo contribuir para as deficiências cognitivas apresentadas pelos pacientes. Deficiências cognitivas, em especial, as falhas de memória são descritas, as quais influenciam a funcionalidade destes indivíduos, principalmente a nível ocupacional e social. As altas taxas de disfuncionalidade apresentadas pelos pacientes e a falta de padronização dos instrumentos usados nos estudos para avaliar funcionalidade, nos levaram ao desenvolvimento de uma escala. A Escala Breve de Funcionalidade (FAST) é um instrumento de rápida e fácil aplicação desenvolvida para usar em psiquiatria, em especial, paciente com THB. A FAST avalia objetivamente seis áreas específicas da funcionalidade, tais como autonomia, trabalho, cognição, relacionamentos interpessoais, finanças e lazer. A validação da escala foi realizada através de testes psicométricos, tais como: consistência interna (alfa de Cronbach's igual a 0.909), validade concorrente comparada com a GAF ($r=-0.903$; $p<0.001$), test-retest (0.98; $p<0.01$), validade em detectar diferenças entre episódios agudos (maníacos: 40.44 ± 9.15 e deprimidos 43.21 ± 13.34) e períodos de remissão (18.55 ± 13.19; $F=35.43$; $p<0.001$) e análise fatorial. Os resultados obtidos foram muito positivos, tornando o instrumento válido e prontamente disponível para o uso na prática clínica e investigação.

Palavras-chave: transtorno do humor bipolar, GDNF, glia, neurotrofinas, funcionalidade, disfuncionalidade, escalas de funcionalidade.

4. INTRODUÇÃO:

4.1. TRANSTORNO DO HUMOR BIPOLAR

O Transtorno do Humor Bipolar (THB) é uma doença grave, crônica, com progressivo aumento da gravidade dos episódios (Goodwin & Jamison 1990; Vieta & Gastó 1997; Dean e col. 2004). Afeta igualmente homens e mulheres, iniciando sua sintomatologia entre 15-30 anos de idade (Goodwin & Jamison 1990). É caracterizado por flutuações do humor, incluindo algumas manifestações clínicas como: episódios regulares de depressão e mania (THB tipo I), recorrente depressão com mínima elevação do humor (THB tipo II), ciclagem rápida e estados mistos resistentes ao tratamento (Calabrese e col. 2004).

Atualmente, acredita-se que muitos pacientes com THB apresentam um predomínio da polaridade maníaca ou depressiva durante o curso da sua doença, o que têm importantes implicações clínicas e terapêuticas. Pacientes com predominância de episódios depressivos apresentam maior número de anos sem diagnóstico, uma maior duração da doença e mais riscos de suicídio, enquanto que aqueles com predominância maníaca apresentam mais sintomas psicóticos, história de abuso de drogas e pior funcionalidade cognitiva. (Veja em anexo I: Rosa e col. 2006 “Clinical differences between manic and depressive predominance of polarity in bipolar disorder patients” submetido; Colom e col. 2006; Daban e col. 2006 a).

A prevalência média de THB na população varia de 0.5-1.5%. No entanto, estudos genéticos mostram que pessoas com história familiar de THB em primeiro grau, as chances de desenvolver a doença aumentam em 5-10% (Yatham 2005). Suicídio é muito comum entre estes pacientes sendo que o risco de suicídio é 60 vezes maior do que na população em geral (Baldessarini e col. 2006). Além do suicídio, o THB está associado com outras comorbidades psiquiátricas, como: abuso de substâncias, transtornos de ansiedade, transtornos alimentares e também comorbidades médicas, como diabetes e dislipidemias (Baldassano 2006; Kupfer 2005; Kogan e col. 2004; Tohen e col. 1998).

A base fundamental do THB é seu caráter cíclico, pois normalmente um episódio maníaco ou hipomaníaco promove um novo episódio no futuro (Vieta & Gastó 1997; Martinez-Aran 2004 c). Além das altas taxas de recorrência (50-90%), a persistência dos sintomas é outra característica desta patologia, pois apesar do tratamento farmacológico, os pacientes podem apresentar sintomas durante metade das suas vidas (Judd e col. 2002; Martinez-Aran 2004 c).

O tratamento farmacológico é fundamental e visa diminuir a freqüência dos episódios, a gravidade da doença e melhorar as conseqüências psicossociais (Guscott & Taylor, 1994; Sproule 2002). O lítio é o medicamento de escolha, capaz de controlar a fase maníaca e os sintomas depressivos da doença, possuindo efeito profilático e ação anti-suicida (Schou 1997; Sproule 2002; Keck 2003). O valproato e a carbamazepina são considerados como segunda linha de tratamento, pois são menos eficazes que o lítio. As benzodiazepinas e os antipsicóticos são usados para o rápido controle da agitação nos quadros de mania. Os antidepressivos, embora melhorem os quadros depressivos, apresentam risco de virada maníaca. A eletroconvulsoterapia (ECT) está indicada para os episódios refratários ao tratamento farmacológico (Fountoulakis e col. 2005).

Para o tratamento da mania recomenda-se o lítio ou o ácido valpróico associado aos antipsicóticos. Os antipsicóticos atípicos devem ser preferencialmente usados, devido ao seu maior perfil de tolerabilidade em relação aos antipsicóticos convencionais, no que diz respeito a menores efeitos extrapiramidais e menor risco de discinesia tardia. O maior número de evidências aponta para uso da risperidona ou olanzapina. Em pacientes menos graves, a monoterapia com lítio, ácido valpróico ou olanzapina é recomendável enquanto que nos episódios mistos, o valproato parece ser mais efetivo. Para os quadros depressivos, a primeira linha de tratamento indica lítio seguido de lamotrigina. Alternativamente, como terceira opção se poderia usar lítio associado aos antidepressivos (Goodwin & Vieta 2005; Fountoulakis e col. 2005).

Para o tratamento de manutenção, o lítio, ácido valpróico e a carbamazepina são os fármacos indicados na maioria dos estudos, enquanto que a lamotrigina pode ser considerada para o tratamento profilático, pois previne os episódios depressivos. O uso dos antipsicóticos atípicos tem aumentado, sendo que a olanzapina oferece resultados positivos para o tratamento profilático do THB, pois previne os episódios de mania e depressão. A quetiapina diminui as recaídas maníacas e também parece ser eficaz para o tratamento de manutenção de pacientes com ciclagem rápida enquanto que a risperidona, em um estudo aberto, mostrou ser eficaz para o tratamento de manutenção, diminuindo os episódios de mania e depressão. O aripiprazol também poderia ser usado para a profilaxia, pois diminui os episódios de mania conforme demonstrado em um único estudo randomizado duplo cego. Por fim, a clozapina tem um importante papel para pacientes refratários ao tratamento, mas apresenta alguns efeitos adversos importantes como aumento de peso, problemas metabólicos e risco de agranulocitose (Veja anexo II: Vieta & Rosa 2006 “Envolving trends in the long-term treatment of bipolar disorder”).

Apesar do tratamento farmacológico intensivo, estima-se que 60 bilhões de dólares são gastos anualmente nos EUA em pacientes portadores de THB, sendo que 29.8 bilhões são gastos com custos diretos como medicamentos e hospitalizações, enquanto que o restante representa custos indiretos como perda da produtividade (Altshuler e col. 2006; Dean e col. 2004). De acordo com o Global Burden of Disease Study, o THB é considerado uma das principais patologias incapacitantes no mundo (Murray & Lopes 1997; Dean e col. 2004). Neste sentido, apesar dos estudos mais antigos descreverem total recuperação entre os episódios de humor, atualmente, se reconhece que a recuperação interepisódica é incompleta em muitos pacientes, resultando em um progressivo declínio de sua capacidade total de funcionalidade (Fagilioni e col. 2005; Macqueen e col. 2000; Coryell e col. 1998; Goldberg e col. 1995).

4.2. FISIOPATOLOGIA DO THB:

4.2.1. ALTERAÇÕES EM ESTRUTURAS CEREBRAIS

Acredita-se que a fisiopatologia do THB envolva quatro domínios: molecular, celular, sistêmico e comportamental. A influência dos mecanismos celulares e moleculares sobre o circuito neuronal e conseqüentemente sobre a manifestação comportamental e clínica do THB envolve múltiplos mecanismos de sinalização na região límbica e regiões associadas do cérebro, as quais são responsáveis pela recorrente sintomatologia afetiva do THB (Manji & Lenox 2000).

Além das alterações neuroquímicas conhecidas, as técnicas de neuroimagem, anatômica e funcional permitiram o desenvolvimento de muitos estudos, os quais descrevem alterações estruturais significativas, como a diminuição do volume em algumas regiões do Sistema Nervoso Central (SNC) e a redução do número de células neuronais e gliais (Altshuler e col. 1990; Manji & Lenox 2000).

Concretamente, as principais alterações descritas são aumento do ventrículo lateral e do terceiro ventrículo, assim como redução no volume dos gânglios basais, núcleo *accumbens*, córtex frontal (Rajkowska 2002; Manji e col. 2000) córtex temporal e amígdala (Sheline 2003; Rajkowska e col. 2001). Também há uma redução generalizada da consistência cortical em diversas regiões (Lyoo e col. 2006) juntamente com uma diminuição significativa no volume da substância cinzenta (40%) nas áreas temporal, frontal, córtex cingular posterior e no giro temporal superior em pacientes bipolares (Nugent e col. 2006; Drevets 2000; Manji e col. 2000). Por fim, uma diminuição do tamanho para-hipocampal em pacientes suicidas *pós-mortem* (Altshuler e col. 1990) e em crianças com THB (Frazier e col. 2005) também foi demonstrado.

Alguns estudos têm reportado que alterações estruturais estão correlacionadas com disfunções cognitivas. Piores resultados nas medidas de atenção foram descritos em pacientes maníacos quando comparados aos controles, as quais estavam correlacionadas com o volume pré-frontal e hipocampo (HC), mas não com o caudado

e tálamo, sugerindo anormalidades no sistema fronto-subcortical (Sax e col. 1999; Martinez-Aran 2004 c). Também alterações temporolímbicas estão relacionadas com déficit de memória verbal e atenção (Ali e col. 2000; Martinez-Aran 2004 c). Em suma, as alterações estruturais no córtex pré-frontal (CPF) e estruturas temporolímbicas, especialmente, a área ventromedial, a amígdala e HC poderiam explicar em parte, as disfunções cognitivas apresentadas por pacientes bipolares, em especial, as falhas na memória verbal e na função executiva (Martinez–Aran e col. 2004 a b).

4.2.2. ALTERAÇÕES NAS CÉLULAS GLIAIS

Além das alterações estruturais descritas acima, modificações atróficas dos neurônios e células da glia são descritas, particularmente no HC e CPF de pacientes com transtornos afetivos (Rantamaki e col. 2006; Sheline 2003). Ongur e col. (1998) mostrou uma redução significativa do número de células gliais (41%) na região subgenual do CPF em pacientes bipolares com história familiar. Um estudo mais recente mostrou uma redução de 19% na densidade média glial da camada III na região dorsolateral do CPF e uma tendência em reduzir a camada V do cérebro de pacientes com THB (Rajkowska e col.,2001). A patologia glial parece expandir-se às regiões límbicas subcorticais, uma vez que, redução no número de células gliais foi descrita em amígdala de pacientes com depressão maior e em pacientes bipolares não medicados (Rajkowska 2002). Alterações no marcador astroglial, proteína ácida fibrilar glial, também foram observadas em pacientes com transtornos afetivos (Johnston-Wilson e col., 2000).

As células gliais são células de suporte para os neurônios, e a redução da densidade glial pode resultar em perda neuronal. Além disso, as células da glia são responsáveis pelo metabolismo, recaptura e fosforilação de glicose e pela recaptura de glutamato, que é feita pelos astrócitos (Rajkowska 2002). Os astrócitos também são responsáveis pela produção de fatores neurotróficos, entre os quais, destaca-se o fator de Crescimento Neurotrófico derivado de Células da Glia (GDNF) (Saavedra e

col. 2005). Alterações no marcador astrocítico, a proteína S-100β, com aumento dos níveis séricos foram observados em pacientes maníacos e deprimidos (Andreazza e col. 2006; Machado-Vieira e col. 2002).

As alterações gliais descritas no THB não se caracterizam por gliose e proliferação glial como ocorre nas doenças neurodegenerativas, e sim, tais alterações parecem estar associadas com falhas nos mecanismos de plasticidade sináptica e resistência celular. Também está relacionada com a disfunção do sistema serotoninérgico, noradrenérgico e dopaminérgico, e pode ser um proeminente fator de patologia cortical, resultando em diminuição do número de sinapses funcionais em pacientes com THB (Rajkowska 2002).

4.2.3. ALTERAÇÕES NOS NEURÔNIOS

Estudos pós-*mortem* de pacientes com THB têm demonstrado uma redução na densidade dos neurônios não-piramidais no córtex cingular anterior (Benes e col. 2001) e na região CA2 do HC (Benes e col. 1998). Além disso, análises morfométricas mostraram redução significativa da densidade neuronal na região dorsolateral (16-22%), orbital frontal do CPF (Cotter e col. 2005; Rajkowska 1997; Manji e col. 2000) e uma tendência para a redução de tamanho das células neuronais nas camadas II, III e V. Isto resulta em diminuição das projeções excitatórias glutamatérgicas e inibitórias GABAérgicas para regiões corticais e subcorticais (Rajkowska e col. 2005; Rajkowska 2002). A degeneração dos neurônios piramidais está relacionada com a hiperintensidade de substância branca na região frontal e gânglio basal de pacientes com depressão senil (Rajkowska e col. 2005) e em estruturas subcorticais de pacientes bipolares (Strakowski e col. 1993). Esta hiperintensidade poderia refletir um processo de astrogliose, desmineralização e perda dos axônios (Junque e col. 1990).

Estudos de neuroimagem funcional em pacientes bipolares não medicados mostraram uma diminuição bilateral dos níveis de N-acetil-aspartato (NAA), um

marcador da disponibilidade neuronal, no HC e na região dorsolateral do CPF, quando comparados aos controles (Moore e col. 2000; Nestler e col. 2002).

Por outro lado, a patologia neuronal não é marcada exclusivamente pela diminuição de células. Um aumento do número de neurônios pigmentados no locus ceruleus, importantes para a transmissão de norepinefrina (NE), (Young e col.1994) assim como a ativação do eixo hipotálamo-hipófise e aumento dos níveis de cortisol têm sido descritas. A neurotoxicidade exercida pelo cortisol leva a alterações do volume do HC (que apresenta altas concentrações de receptores para glicocorticóides, GRs), amígdala e CPF e, conseqüentemente, desorganização das atividades por ele exercidas como falhas na memória, aprendizado e cognição (Duman & Monteggia 2006).

Em suma, as anormalidades estruturais, assim como a diminuição no número de células neuronais e gliais observadas nos transtornos de humor poderia indicar uma alteração do balanço entre neurogênese e morte neuronal no cérebro adulto. Tais alterações podem estar relacionadas com a diminuição da neuroproteção e dos fatores neurotróficos em pacientes com transtornos afetivos (Angelucci e col. 2005; Lim e col. 2003; Rajkowska 2002). A falta de um suporte neurotrófico adequado parece levar a uma desorganização estrutural de produção dos neurônios, com conseqüente diminuição da capacidade adaptativa cerebral e maior vulnerabilidade à neurotoxicidade, durante o desenvolvimento cerebral e cérebro adulto (Angelucci e col. 2005).

4.3. NEUROTROFINAS:

O papel funcional das neurotrofinas originalmente descrito foi de suporte para a sobrevivência e diferenciação neuronal. No entanto, hoje se sabe que elas estão envolvidas no processo de formação das sinapses e plasticidade neuronal (Lim e col. 2003), além de estarem envolvidas com os processos cognitivos (Rybakowski e col. 2006 a b).

As neurotrofinas são primeiramente sintetizadas como pré-pró neurotrofinas no retículo endoplasmático rugoso e clivadas no complexo de Golgi pela furina ou nos grânulos secretores pelas pró-proteínas convertases, adquirindo então sua forma madura de neurotrofinas. Em geral, elas são armazenadas no Golgi e então transportadas para o terminal axônico pré-sináptico ou dendritos pós-sinápticos para secreção local. A secreção celular de neurotrofinas pode ocorrer espontaneamente (permissiva, constitutiva) ou em resposta a um estímulo (instrutiva, regulada) (Lim e col. 2003; Seidah e col. 1996).

As neurotrofinas podem ser liberadas de sítios extra-sinápticos ou sinápticos, exercendo diferentes funções, dependendo de seu local de secreção. As pró-neurotrofinas, como por exemplo, pró-NGF se liga ao receptor $p75^{NTR}$ e é a forma predominante na doença de Alzheimer, indicando que existe um balanço entre a forma pró e a madura e que a descompensação deste equilíbrio pode levar a eliminação das sinapses, degeneração dos neurônios e conseqüentemente a um estado patológico (Lim e col. 2003; Lee e col. 2001).

A pró e a neurotrofina madura parecem interagir com diferentes receptores e exercer efeitos biológicos opostos. Diversas propriedades têm demonstrado que as neurotrofinas participam da plasticidade sináptica: liberação pós-sináptica das neurotrofinas e pré-sináptica de seus receptores; liberação de neurotrofinas durante o processo de despolarização; ação preferencial nos neurônios ativos; indução da sinapse junto com a síntese e liberação de neurotransmissores; ausência de neurotrofinas em sinapse deficiente (Lim e col., 2003).

A família de fatores de crescimento neural consiste do fator de crescimento neural (NGF), fator neurotrófico derivado do cérebro (BDNF), neurotrofina-3 (NT-3) e neurotrofina-4 (NT-4). Elas são agrupadas em uma mesma família, todas elas se ligam ao receptor $p75^{NTR}$ e cada uma delas se liga com alta afinidade a um receptor específico. O NGF liga-se em alta afinidade ao receptor tirosina quinase A (Trk-A), o

BDNF e o NT-4 ligam-se à tirosina quinase (Trk-B) e o NT-3 liga-se à tirosina quinase (Trk-C) (Schechter e col., 2005; Lim e col., 2003).

4.3.1. FATOR DE CRESCIMENTO NEUROTRÓFICO DERIVADO DE CÉLULAS DA GLIA (GDNF)

O GDNF, a neurturina, a artemina e a persepina são as principais proteínas da família de ligantes das células de linhagem glial (GFLs), pertencentes a superfamília de fatores de crescimento de transformação (TGF-β), também conhecidas como fator de crescente transformação. Todas estas proteínas apresentam sete resíduos de cisteína, uma homologia na seqüência de aminoácidos em torno de 40-50%, e uma pronunciada similaridade conformacional. A família GFLs é sintetizada por uma variedade de tecidos, podendo-se ligar a receptores específicos, influenciando o desenvolvimento ou suportando a sobrevivência de diferentes fenótipos em animais adultos (Airaksinen e col. 2006; Airaksinen & Saarma 2002; Saarma 2000).

O GDNF foi originalmente purificado (1993) do sobrenadante de uma linhagem-celular de gliomas de ratos, como um fator trófico dos neurônios dopaminérgicos do mesencefalo embriônico, os neurônios que estão degenerados na doença de Parkinson. Apesar de ser considerado um dos mais potentes fatores neurotróficos para os neurônios dopaminérgicos (Baloh e col. 2000), ele é fortemente expresso no cérebro (Pochon e col. 1997) e exerce efeitos neuroprotetores em diversas áreas do SNC e SNP (Airaksinen and Saarma 2002, Baloh e col. 2000). É um importante fator trófico para os motoneurônios espinhais, neurônios noradrenérgicos, axônios sensoriais e exerce importante papel nas adaptações bioquímicas e comportamentais após uso abusivo de cocaína e morfina. Além do SNC, participa dos processos de crescimento e diferenciação da espermatogênese e desenvolvimento renal (Airaksinen e Saarma 2002).

O GDNF, assim como os outros membros da família GFLs se ligam a receptores de membrana, os receptores GFRα, através de uma proteína conhecida

como glicosilfosfatidilinositol (GPI). Quatro diferentes tipos de receptores GFRα têm sido identificados, (GFRα 1-4). O GDNF se liga com alta afinidade ao receptor alfa GFRα1 formando o complexo GDNF/GFRα1 capaz de interagir com uma proteína cinase, proteínas pro-oncogênicas c-ret (c-ret), induzindo sua autofosforilação, homodimerização, promovendo a ativação e fosforilação da proteína quinase mitogênica ativada (MAPK), fosfolipase Cy (PLC-y), fator de transcrição gência (CREB) e indução dos fatores de transcrição pertencentes a família Fos (*c-fos*).

A expressão de GDNF parece estar alterada pela administração dos estabilizadores de humor. O lítio aumenta a expressão de GDNF no córtex frontal e occipital (Angelucci e col. 2003) enquanto que o valproato administrado aguda e cronicamente aumenta a expressão de GDNF em cultura celular (Rincón-Castro e col. 2005). Os fármacos antidepressivos amitriptilina, clomipramina, mianserina, fluoxetina e paroxetina (doses de 10 e 25mmol), assim como a serotonina, aumentam a expressão de GDNF mRNA e induzem sua recaptura em cultura celulares (C6 glioblastomas), enquanto que a amitriptilina também aumenta a expressão de GDNF mRNA em astrócitos de ratos (Hisaoka e col. 2001; Hisaoka e col. 2005; Hisaoka e col. 2004). Resultados contraditórios foram encontrados em relação aos antipsicóticos, onde haloperidol em doses baixas (1mmol/L) não aumenta a expressão de GDNF (Hisaoka e col. 2001), enquanto que em doses altas (10mmol/L) assim como quetiapina e clozapina (5mmol/L) aumentam sua expressão (Shao e col. 2006).

Alguns estudos reforçam o efeito neuroprotetor do GDNF sobre os neurônios dopaminérgicos. A administração exógena de GDNF aumentou a atividade locomotora dos ratos, supostamente pelo aumento de dopamina na zona nigro-estriada, efeito que foi bloqueado pelo tratamento com antagonistas seletivos de dopamina D_1 e D_2 (Kobayashi e col. (1998). Modelo animal tratado com fenciclidina, substância que mimetiza os sintomas da esquizofrenia, pela liberação de dopamina na área tegmental ventral e nigro-estriado, promoveu um aumento da expressão de GDNF e seu receptor c-ret, o que sugere um efeito de neuroproteção dopaminérgica (Semba e col. 2004).

Assim como na esquizofrenia, um excesso de dopamina é característico da mania, o que promove parte da sintomatologia clínica do THB, além de neurotoxicidade (Bozzi & Borrelli 2006). Recentemente se demonstrou que o valproato é capaz de proteger os neurônios dopaminérgicos em cultura de células neurônio-glia e que o provável mecanismo seja a estimulação de fatores neurotróficos, BDNF e GDNF (Chen e col. 2006).

Os neurônios dopaminérgicos são altamente vulneráveis ao estresse oxidativo porque eles espontaneamente produzem radicais livres do tipo superóxido e dopamina quinona. Espécies reativas de oxigênio, em cultura neurônio-gliais, promovem um aumento da secreção de GDNF, que por sua vez, estimula a produção de glutation cinase (GSH-Px), exercendo um efeito neuroprotetor aos neurônios dopaminérgicos (Saavedra e col. 2005; Saavedra e col. 2006). Em estriado de ratos, o GDNF também promoveu a remoção de espécies reativas de oxigênio através da estimulação do sistema de enzimas antioxidantes GSH-Px, catalase e superóxido dismutase (SOD) (Chao & Lee 1999).

Por outro lado, em um modelo animal de isquemia, usando a técnica de deprivação de sangue, se demonstrou um aumento da expressão endógena de GDNF nos neurônios e glia e também de seu marcador intracelular inositol trifosfato (IP-3), sugerindo um efeito neuroprotetor contra injúria cerebral na região CA2 do HC (Hwang e col. 2006). Uma diminuição do fluxo sanguíneo resultante das alterações em estruturas específicas do cérebro é uma característica dos episódios depressivos (Ito e col. 1996), e uma diminuição dos níveis sanguíneos de GDNF foi reportado em pacientes deprimidos (Takebayashi e col. 2006).

4.4. PROCESSOS COGNITIVOS E NEUTROTROFINAS:

As neurotrofinas são importantes mediadores dos mecanismos de plasticidade neuronal e a falha nestes mecanismos de transmissão parece estar relacionada com as disfunções cognitivas, contribuindo para a patogênese do THB (Lim e col. 2003).

Alterações nos fatores neurotróficos, em especial, BDNF estão associadas com falhas nos mecanismos de plasticidade, memória e outros processos cognitivos (Rybakowski 2006 a b; Dias e col. 2006). O polimorfismo do gen BDNF, onde ocorre a substituição da valina pela metionina no códon 66, leva a falha na atividade do HC, com diminuição do NAA e falha na memória (Lim e col. 2003).

O GDNF também parece estar envolvido com os processos cognitivos, pois mutações de GDNF em ratos mostraram uma anormalidade na transmissão sináptica hipocampal (Nanobashvili e col. 2000) e uma falha importante no processo de aprendizado espacial (Gerlai e col. 2001; Airaksinen & Saarma 2000; Henderson e col. 1994). Dificuldade nos testes de aprendizado e memória em ratos mutantes para receptor de neurturina, GFR2, também foi descrita (Voikar e col. 2004). Além disso, o GDNF exerce seus efeitos neurotróficos por ativação de cascatas bioquímicas, como MAPK, PLC-y e CREB, as quais estão implicadas nos processos cognitivos (Voikar e col. 2004).

As alterações celulares, em especial, alterações dos fatores neurotróficos poderiam explicar, em parte, as disfunções cognitivas apresentadas pelos pacientes. Dificuldades de atenção, de aprendizado, de memória, na funcionalidade psicomotora e nas funções executivas frontal são os processos cognitivos que parecem estar mais deterioradas durante as fases agudas do THB (Martinez Aran e col. 2007; Martinez Aran 2004 c). Entretanto, apesar da mania e da depressão estarem associados com pior cognição, estudos recentes sugerem que pacientes eutímicos também apresentam dificuldades cognitivas, em especial falhas da função executiva e memória verbal (Martinez Aran e col. 2007; Goswami e col. 2006; Martinez Aran e col. 2004 a b; Torrent e col. 2006; Van Gorp e col. 1999). Outros fatores como o índice pré-mórbido e coeficiente de inteligência também são dificuldades apresentadas por pacientes bipolares, embora que em menor extensão quando comparados aos esquizofrênicos (Daban e col. 2006 b).

Por outro lado, recentes estudos mostraram uma associação entre os fatores cognitivos e a disfuncionalidade (Martinez Aran e col. 2007; Hajek e col. 2005; Coffman e col. 1990). Falhas cognitivas, particularmente dificuldades de memória, podem ter implicações negativas na funcionalidade dos pacientes com THB (Torrent e col. 2006; Martinez-Aran e col. 2004 a b; Zarate e col. 2000).

Martinez-Aran e col. (2007) avaliou neuropsicologicamente 77 pacientes bipolares em remissão e demonstrou que o controle inibitório (medido pelo Teste de Stroop Emocional), a memória verbal (medido pelo Trail Making Test na forma B), memória tardia (medido pelo Teste de Aprendizado Verbal da Califórnia) e a recognição foram as principais diferenças encontradas entre pacientes e controles. Neste mesmo estudo, pacientes com menor funcionalidade, com medidas da Avaliação Global da Funcionalidade (GAF) inferior a 60, apresentaram piores resultados nos testes Stroop Emocional e Trail Making Test forma B. Pacientes com pobre funcionalidade demonstraram maiores dificuldades em codificar e reter informações, o que poderia justificar as dificuldades no domínio trabalho (Martinez Aran e col. 2007; Hajek e col. 2005; Coffman e col. 1990). Goswami e col. (2006) avaliaram 45 pacientes em remissão e os resultados encontrados também foram diminuição da função executiva (medidos pelo Trail Making Test na forma B e Reverse Digit Span) e dificuldades de aprendizado (medidas pelo Rey Auditory Verbal Learning Test). Ainda, neste estudo, 73% dos pacientes apresentaram moderado à grave disfuncionalidade avaliados pelo *Schedule for Assessment of Psychiatric Disability*, enquanto que o restante apresentava mínimo prejuízo social.

As disfunções executivas frontais, em especial, a falha na memória verbal, parecem ser fortes preditores de disfuncionalidade. Dificuldades em guardar informações podem representar um sério problema sócio-ocupacional, pois em geral, os pacientes têm dificuldades em recordar nomes e conversações a curto e longo prazo (Martinez–Aran e col. 2007).

4.5. FUNCIONALIDADE:

Kraepelin (1921) descreveu que pacientes com THB recuperavam sua funcionalidade durante os períodos assintomáticos. Entretanto, a maioria dos estudos modernos de longa e curta duração, mostra que grande parte dos pacientes apresenta importante prejuízo em alguma das áreas da funcionalidade, ao contrário dos resultados favoráveis inicialmente descritos (Zarate e col. 2000; Fagiolini e col. 2005; Macqueen e col. 2000; Coryell e col. 1998).

Recuperação funcional é definida como a habilidade do paciente para recuperar o mesmo grau de funcionalidade que apresentava antes do episódio de humor recente (Tohen e col.. 2000; Zarate e col.. 2000). Nas últimas duas décadas, diferentes pesquisadores demonstraram que as taxas de recuperação funcional dos pacientes variam de 27% a 40%, apesar de eles apresentarem recuperação sintomática (Zarate e col. 2000; Dion e col. 1988; Harrow e col. 1990; O'Connell e col 1991; Gitlin e col. 1995). Recentes estudos confirmaram as baixas taxas de recuperação funcional previamente descritas. Tohen e col. (2000) avaliaram longitudinalmente (2 anos) pacientes com primeiro episódio de humor onde apenas 37% deles apresentaram recuperação funcional, embora praticamente todos (97%) apresentavam completa recuperação sintomática. Strakowski e col. (2000), em um estudo de oito meses de duração, demonstraram que metade dos pacientes recuperou sua funcionalidade em três das quatro áreas avaliadas, embora apenas 5% deles recuperaram a funcionalidade em todas as quatro áreas.

As deficiências na funcionalidade dos pacientes com THB são mais evidentes que em outras patologias crônicas ou mesmo que na depressão unipolar (Coryell e col. 1998). Falhas cognitivas, incapacidade para trabalhar, incapacidade para executar as atividades diárias, dificuldades nos relacionamentos inter-pessoais, dificuldades em divertir-se e dificuldades na atividade sexual são os principais problemas apresentados por estes pacientes (Vieta e col. 2007; Martinez-Aran e col. 2007; Strakowski e col. 2000; Tohen et a. 2000; Coryell e col. 1993).

O conceito de funcionalidade é complexo e envolve diferentes domínios como a capacidade para trabalhar, a capacidade para viver independentemente, a capacidade para divertir-se, a capacidade para ter uma vida social, a capacidade para estudar, etc (Zarate e col. 2000). Além disso, existe uma falta de padronização entre os instrumentos usados para medir funcionalidade (Vieta e col. 2007; Zarate e col. 2000). Normalmente, pesquisadores têm medido um ou dois domínios da funcionalidade, mas falham em medir todos os domínios necessários para uma correta avaliação da capacidade funcional do indivíduo (Zarate e col. 2000). Em parte, isso se deve a falta de instrumentos disponíveis para avaliação das deficiências funcionais em psiquiatria, em especial, THB, o que geram resultados parciais sobre as reais dificuldades apresentadas por estes pacientes (Vieta e col. 2007; Martinez-Aran e col. 2007). A seguir descrevemos alguns instrumentos recentemente utilizados para medir disfuncionalidade em THB.

A GAF foi desenvolvida pela Associação Americana de Psiquiatria (1994) com o objetivo de avaliar a capacidade global da funcionalidade e sintomas clínicos. A GAF é um dos instrumentos mais usados em psiquiatria, quantificando a funcionalidade do indivíduo em uma faixa que varia de 0-100, mas seus resultados não fornecem dados específicos sobre quais as áreas da funcionalidade estão deficientes (Martinez Aran e col. 2007; Altshuler e col. 2002a). A Who Health Organization-Disability Assessment Schedule (WHO-DAS) é um instrumento desenvolvido pela Organização Mundial da Saúde para avaliar saúde física, saúde mental e os domínios sociais, ocupacionais e emocionais. No entanto, a WHO-DAS é um extensivo questionário, constituído de 36 itens, com uma detalhada avaliação da saúde física, o que parece menos relevante do que a saúde mental para um paciente psiquiátrico, em especial, portador de THB (World Health Organization 2004).

Outras medidas de funcionalidade recentemente descritas são: a Health Related Quality of Life (*HRQoL)* que é uma escala baseada na percepção subjetiva do paciente que mede múltiplos domínios de funcionalidade e bem estar (Dean 2004;

Leidy e col. 1999). A Work and Social Adjustment Scale (WSAS) é um instrumento auto-aplicado que consiste de cinco questões, as quais avaliam incapacidade para trabalhar, incapacidade para as atividades diárias, para leitura, para atividades sociais, para os relacionamentos e para atividades de lazer (Mundt e col. 2002; Fagiolini e col. 2005). O Life Functioning Questionnaire (LFQ) é um instrumento constituído de 14 itens que mede funcionalidade através dos domínios trabalho, relacionamentos e atividades diárias (Altshuler e col. 2002b). A Short Form (SF-36) é uma escala de qualidade de vida, de auto-aplicação que consiste de 36 itens avaliando qualidade nos domínios físico, social e emocional (Depp e col. 2006).

Entretanto, todas estas escalas são baseadas no auto-julgamento do paciente, e o caráter psicopatológico do THB como a presença dos sintomas, parece interferir na avaliação, uma vez que o julgamento de um paciente durante a mania será diferente de seu julgamento durante a depressão (Dean e col. 2004; Mundt e col. 2002; Fagiolini e col. 2005; Altshuler e col. 2006; Altshuler e col. 2002a). Outros fatores como mudanças nas medicações, eventos recentes na vida e pobre *insight* também parecem interferir, o que reflete mais precaução ao interpretar resultados medidos por escalas de auto-avaliação (Atkinson e col. 1997; Revicki e col. 2005; Gazalle e col.. 2007 in press).

Além disso, as escalas disponíveis compreendem extensas entrevistas que requerem muito tempo para sua implementação, o que muitas vezes não é factível na prática clínica. Por outro lado, outros instrumentos existentes não avaliam as reais dificuldades experimentadas pelos pacientes, uma vez que não foram desenvolvidos exclusivamente para psiquiatria, em especial, para o THB. Uma compreensiva avaliação das dificuldades que envolvem a funcionalidade (Vieta e col. 2007; Dean e col. 2004) assim como a elaboração de um instrumento que seja capaz de avaliar os múltiplos domínios ao mesmo tempo, parece ser particularmente útil (Vieta e col. 2007; Martinez-Aran e col. 2007).

Baseado nisto, o desenvolvimento de uma escala capaz de avaliar as reais dificuldades na funcionalidade apresentadas por pacientes psiquiátricos, em especial, pacientes bipolares parece ser de extrema relevância. Além disso, a escala deverá ser objetiva, de fácil aplicação, rápida e, portanto, factível para a prática clínica e pesquisa.

5.0. OBJETIVOS:

5.1. OBJETIVOS GERAIS:

1. Avaliar o possível envolvimento do Fator de Crescimento Neurotrófico derivado das células da Glia (GDNF) no THB e o nível de funcionalidade dos pacientes bipolares.

5.2. OBJETIVOS ESPECÍFICOS:

1. Determinar as concentrações séricas de GDNF em pacientes com THB durante a eutimia, mania, depressão e no grupo controle.

2. Desenvolver uma escala de funcionalidade em psiquiatria, em especial, para o THB.

3. Validar a versão espanhola da escala de funcionalidade através de testes psicométricos, tais como, consistência interna, validade concorrente, teste e reteste, validade para detectar as diferenças entre pacientes eutímicos e agudos e análise fatorial.

4. Determinar as dificuldades na funcionalidade de pacientes durante o período de remissão em comparação com o grupo controle.

5. Avaliar a associação entre história prévia de suicídio e disfuncionalidade entre pacientes bipolares eutímicos.

6.0. METODOLOGIA:

6.1. ARTIGO 1:

Increased Serum Glial Cell Line-derived Neurotrophic Factor Immunocontent During Manic and Depressive Episodes in Individuals with Bipolar Disorder

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"Neurosci Lett. 2006 Oct 23;407(2):146-50. Epub 2006 Sep 7"

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Abstract:

***Background*:** Glial cell line-derived neurotrophic factor (GDNF) is a neurotrophic factor from the transforming growth factor β family, which promotes the survival and differentiation of motor and peripheral neurons. Preclinical studies suggest that the changes in neurotrophic growth factor systems might be involved in the pathophysiology of mood disorders including bipolar disorder. This is the first study to analyse GDNF immunocontent across different, mood states, including mania, depression, and remission.

Methods: The sample consisted of 44 bipolar patients, and 14 healthy controls, diagnosed according to the Structural Clinical Interview for DSM-IV. Serum immunocontent of GDNF was measured using imunoblotting applying 50 μg per lane. Values of the GDNF were expressed in percentages assuming control sample as being 100%.

Results: Serum immunocontent of GDNF was increased in manic (140,97% ± 7,78; one-way ANOVA test F= 42.31; p=0.001) and depressive (126.27% ± 4.70; one-way ANOVA test F= 42.31; p=0.004) bipolar patients, as compared with euthymic patients (104.77% ± 7.78) and controls (100%).

Conclusion: Our results indicate that changes in GDNF immunocontent occur during acute major affective episodes. These results further support the notion that neurotrophic growth factor pathways may be involved in the pathophysiology of bipolar disorder. Whether the observed increase in GDNF immunocontent correspond to a pathological or an adaptive response remains to be established.

Key words: GDNF, bipolar disorder, neurotrophins, whole blood, imunoblotting.

Bipolar disorder is a common, chronic and life-threatening illness characterized by alternating episodes of mania and depression [39]. Postmortem studies showed abnormal density and size of neuronal and glial cells in gravel subregions of the prefrontal cortex, such as subgenual, orbitofrontal and dorsolateral prefrontal cortex [9, 30, 25]. Such morphological changes suggest impairment in cellular plasticity and resilience rather than a neurodegenerative pattern [29]. There is increasing evidence suggesting that neurotrophic signaling systems, which regulate cellular plasticity and survival, may be altered in bipolar disorder [11, 16, 36].

We have recently demonstrated that serum brain-derived neurotrophic factor (BDNF) is decreased in bipolar patients during acute manic and depressive episodes [10]. A recent study showed that glial cell line-derived neurotrophic factor (GDNF) is decreased in the whole blood of bipolar and unipolar subjects during “partial or full remission state” [36. In addition, it has been demonstrated that the first-line mood stabilizers lithium and valproate increase BDNF and GDNF levels [4, 7, 13].

GDNF is a neurotrophic factor belonging to the transforming growth factor β family, and was initially isolated based on its ability to induce dopamine uptake and cell survival in embryonic ventral midbrain cultures [22]. Although considered one of the most potent neurotrophic factor for dopaminergic neurons [6], GDNF is widely expressed throughout the brain [28], and exerts neuroprotective effects in gravel central and peripheral neuronal populations [1, 6]. Moreover, GDNF+/- mutant mice demonstrate abnormal hippocampal synaptic transmission [24] and poorer spatial learning performance [14].

This is the first study to analyse GDNF immunocontent across different, mood states, including mania, depression, and remission in bipolar patients as compared with matched healthy controls.

The sample consisted of 44 bipolar disorder type I patients (14 depressed, 15 manic, and 15 euthymic) and 14 age- and gender-matched healthy volunteers. All

patients were recruited from the Bipolar Disorders Program - Federal University of Rio Grande do Sul, Porto Alegre, Brazil, and the Inpatient Psychiatric Unit – Hospital University of Santa Maria, Santa Maria, Brazil. Patients were 18 years or older, non-smokers, did not present active medical conditions and were not on any other medication, other from those prescribed for their psychiatric illness. However, all efforts were made to ensure that GDNF measurement was made before changing baseline medication. Bipolar Disorder diagnosis was carried out using the Structured Clinical Interview for DSM-IV – Axis I (SCID-I) [12], and manic and depressive symptoms were assessed using the Young Mania Rating Scale (YMRS) [40] and the Hamilton Depression Rating Scale (HDRS) [15], respectively. The control group consisted of healthy individuals who manifested interest in participating in the study. Controls did not have history of major psychiatric disorders, as assessed by the SCID-I non-patient version, or history of dementia, mental retardation, cancer or tumor in their first-degree relatives. Control subjects were no smokers and were not on medication. This study was approved by the local ethics committee (Hospital of Clinic of Porto Alegre, Porto Alegre, Brazil), and all subjects signed the informed consent before entering in the study. The trial was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki and its subsequent revisions.

Collection and processing of blood samples: Each subject had 5 ml blood sample collected by venipuncture without anticoagulants, and serum was obtained by centrifugation at 3,000 g for 5 minutes and kept frozen at -80°C until the biochemical assay. Glial cell line-derived neurotrophic factor (GDNF): Western blot analysis was performed according to the following protocol: Samples were diluted (1:4) with phosphate-buffered saline and then were dissolved (about 90 μg of protein) is stopping solution containing at final (100 mM Tris-HCl, pH 8.8, 0.5 mM EDTA, 4% SDS and 4% glycerol). Protein samples were separated on 10% SDS-PAGE and then electro-transferred at 15 V a PVDF membrane. Membranes were blocked with 5% albumin

overnight at room temperature and then incubated for 1 h at room temperature with anti-human GDNF polyclonal (1:1000, Promega, Madison, USA). Blots were washed three times with tris-buffered saline (containing 0.5% Tween) and incubated with biotin-conjugated anti-chicken IgG (1:1000, Promega, Madison, USA) for 1 h at room temperature. Then blots were washed with Tween-TBS and incubated with streptavidin (1:1000, Dako, Corporation A/S, Denmark) for 1 h at room temperature. The signal was detected by an enhanced chemiluminescence method (ECL kit, Amersham) and registered in a Kodak X-OMAT film. The intensity of the selected bands was analyzed using Optiquant program. Because peripheral GDNF levels are known to be altered in subjects with renal insufficiency [26, 33] we assessed urea and creatinine levels in all subjects. Urea levels: serum urea levels were assayed by urease-Berthelot reaction (Biodiagnostica, Paraná, Brazil) and measured at 600 nm. Creatinine levels: serum creatinine levels were assayed by Jaffe reaction-picrate alkaline (Biodiagnostica, Paraná, Brazil) and measured at 490 nm.

Statistical analysis was performed in SPSS for Windows - Version 12.0 (SPSS Inc., Chicago, USA). GDNF immunocontent of four groups (manic, depressive, euthymic, and controls) were compared using one-way ANOVA, and the individual differences were tested using Tukey HSD test if ANOVA was significant. Data are presented as percentage of control group. Demographic characteristics between groups were compared using Chi-square and one-way ANOVA. Statistical significance was set at $p < 0.05$.

Demographic and clinical characteristics of bipolar patients and controls are displayed in table 1. Patients and controls did not differ in terms of age, gender, or education (all $p > 0.05$). Age of first episode and years of illness were not significantly different between depressed, manic, and euthymic bipolar patients. Serum GDNF immunocontent was higher in manic ($F_{X,X} = 42.31$; $p=0.001$) and depressive ($F_{X,X} = 42.31$; $p=0.004$) bipolar patients, as compared with euthymic patients and controls (see

figure 1). All subjects had urea and creatinine levels within normal limits, and no differences in urea or creatinine levels were observed between groups (all $p > 0.05$, see table 1), suggesting that GDNF immunocontent was not altered by renal insufficiency.

We found that serum GDNF immunocontent was increased in bipolar patients during manic and depressive episodes and there was no difference between euthymic bipolar patients and healthy controls. This finding suggests that peripheral GDNF synthesis or release is increased during acute episodes in bipolar disorder. Whether it represents a pathological or a compensatory mechanism remains to be determined. This result is in contrast to a recent report of lower whole blood GDNF levels assessed with ELISA in remitted bipolar and unipolar subjects [36]. Differences in sampling and immunoassay may account for this discrepancy. In addition, Takebayashi e col. (2005) studied older subjects and did not control for possible effects of renal impairment, which is more common with increased age.

It has been demonstrated that bipolar patients have significant enlargement in the size of glial cells in specific cortical layers [30, 38]. Moreover, it has been reported that manic patients have increased serum S100β, an astrocytic neuroprotective protein [23]. It is known that neuronal injury may stimulate glial activity, and separation of astroglial cells from cortical neurons was show to promote neuronal death [31]. GDNF supports the survival of dopaminergic [21] and noradrenergic [5] brain cells in vivo, as well as peripheral motor [17] and sensory neurons [37]. In peripheral blood, studies showed that bipolar patients have increased malondialdehyde (a marker of lipid peroxidation) [20, 27], and decreased catalase [27, 32], indicating an increased oxidative stress status. In this context, we have recently found increased DNA fragmentation in peripheral blood in bipolar disorder [3]. Chao and Lee (1999) demonstrated that subchronic infusion of recombinant human GDNF increased superoxide dismutase, catalase, and glutathione peroxidase activity in rat striatum,

suggesting that GDNF may exert antioxidant properties. Interestingly, Sawada e col. (2000) demonstrated that preincubation with GDNF blocked the DNA cleavage induced by bleomycin sulphate and L-buthionine-[S,R]-sulfoximine exposure in cultured mesencephalic neurons. Although speculative, it is possible that the increment in GDNF immunocontent during acute manic and depressive episodes might be an adaptative response against oxidative stress.

Some limitations must be taken in consideration. In the present study, all bipolar patients were on medication, thus we cannot exclude that the GDNF immunocontent may be influenced by the treatment. Although a previous study found no differences in GDNF levels between bipolar patients with or without lithium/antidepressant therapy [36], preclinical studies demonstrated that GDNF levels may be altered by antidepressants [18], antipsychotics [35], and mood stabilizers [4, 7]. However, all efforts were made to ensure that GDNF measurement was made before changing baseline medication. Studies conducted in medication-free subjects are warranted to further clarify this issue. Second, we measured GDNF immunocontent in the serum but we are not sure whether these peripheral changes reflect actual changes in central nervous system. Data indicate that GDNF penetrates very poorly across the brain blood barrier [2, 19].

In conclusion, serum GDNF immunocontent is increased in bipolar patients during acute manic and depressive episodes. Whether it represents a pathological or a compensatory response remains to be determined. This finding further support that bipolar disorder is associated with multiple changes in neurotrophic signalling systems.

Acknowledgements:

** This study was supported in part by CAPES (Brazil), CNPQ (Brazil) and FIPE-HCPA.

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Table1. Clinical and Demographics Caractheristics

	Control group n=14	Euthymic n=15	Manic n=15	Depressive n=14	p value
Gender					
Male	31.2%	37.5%	56.3%	28.6%	0.12
Female	68.8%	62.5%	43.8%	71.4%	
Age (years)	41.1 (11.1)	40.4 (10.3)	40.1 (9.3)	42.1 (8.2)	0.7
Schooling (years)	7.9 (2.9)	9.6 (4.8)	8.3 (3.6)	8.5 (1.7)	0.10
Number of medication		2.2 (0.1)	3.2 (1.3)	2.9 (1.2)	0.024
Age of first mood episode		21.3 (11.2)	27.1 (9.9)	22.0 (11.3)	0.41
Years of illness		16.4 (12.0)	13.1 (8.3)	18.0 (14.1)	0.21
HDRS		4.1 (2.1)	5.6 (2.9)	21.9 (2.36)	0.001
YMRS		3.3 (3.4)	33.1 (4.1)	5.6 (3.1)	0.001
Creatinine mg/dl					
Male	0.90 (0.21)	1.10 (0.32)	1.13 (0.21)	1.24 (0.19)	0.23
Female	0.78 (0.31)	0.81 (0.37)	1.19 (0.23)	0.99 (0.24)	0.46
Urea mg/dl	16.45 (1.24)	18.33 (2.55)	20.1 (1.44)	19.5 (1.44)	0.56

*Chi Square test, ** One- Way ANOVA test, **HDRS = Hamilton Depression Rating Scale;

[a] Serum reference levels → Male: 0.6 – 1.5 mg/dL Female: 0.5 – 1.3 mg/dL

[b] Serum reference levels → 10-52 mg/dL

YMRS = Young Mania Rating Scale; BDNF = brain-derived neurotrophic factor

Figure 1. Serum GDNF content in BD patients and control.

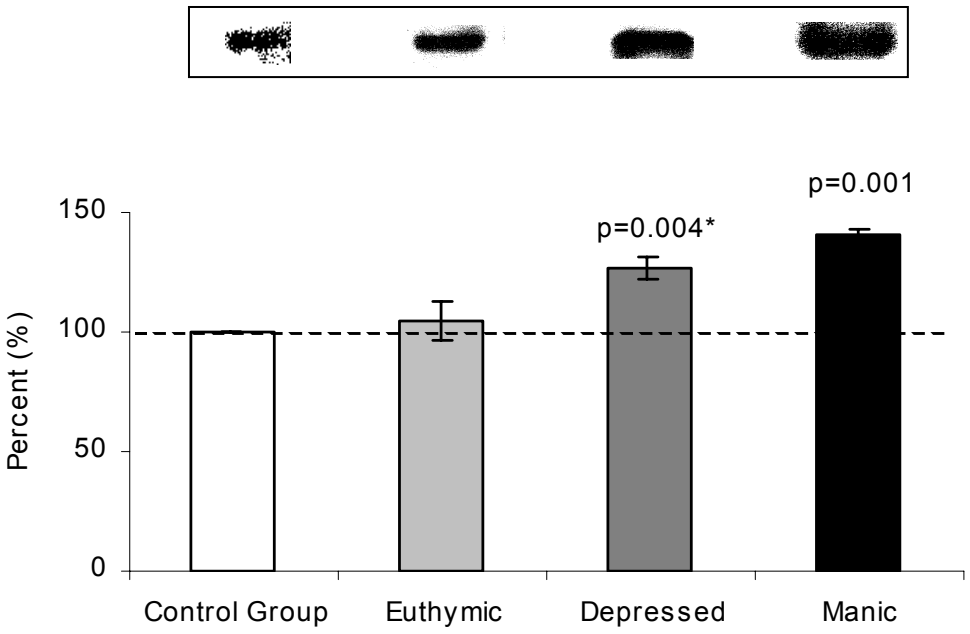

Figure 1. Serum GDNF content in BD patients and control. Serum content of GDNF was measured by immunoblotting applying 50 μg per lane. Values of the GDNF were expressed in percentages assuming control sample as being 100%. Each value is a mean of patients ± SEM. Inset is a representative immunoblot from BD patients and control.

6.1.1. ARTIGO 1 TRADUZIDO:

Aumento do Fator de Crescimento Neurotrófico Derivado de Células da Glia (GDNF) durante os episódios de mania e depressão em indivíduos com Transtorno do Humor Bipolar

"Neurosci Lett. 2006 Oct 23;407(2):146-50. Epub 2006 Sep 7"

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Resumo:

Introdução: Fator de Crescimento Neurotrófico derivado de Células da Glia (GDNF) é uma neurotrofina pertencente à família do fator β de crescimento, que tem importante papel no desenvolvimento e função das células hipocampais. Estudos pré-clínicos sugerem que alterações nos fatores neurotróficos devem estar envolvidas com a fisiopatologia dos transtornos de humor, incluindo o transtorno de humor bipolar (THB). Este é o primeiro estudo que analisou as concentrações do imunoconteúdo de GDNF em pacientes bipolares durante os diferentes estados de humor, mania, depressão e remissão (eutimia).

Métodos: Quarenta e quatro pacientes bipolares (14 deprimidos, 15 maníacos, 15 eutímicos) e 14 controles diagnosticados segundo o DSM-IV foram estudados. As concentrações séricas de GDNF foram medidas pela técnica de Western Blotting.

Resultados: O imunoconteúdo sérico de GDNF estava aumentado nos pacientes maníacos e deprimidos, enquanto que os eutímicos mostraram resultados similares aos controles.

Conclusão: Nossos resultados demonstraram alterações séricas de GDNF durante os episódios agudos, mania e depressão, o que sugere que as neurotrofinas estão envolvidas com a fisiopatologia do THB. Se o aumento do imunoconteúdo de GDNF sérico representa uma resposta adaptativa ou patológica; isto ainda precisa ser elucidado.

Palavras-chave: GDNF, trasntorno bipolar, neurotrofinas, sangue total, imunoblotting.

O Transtorno do Humor Bipolar (THB) é uma doença prevalente, crônica e que requer tratamento durante toda a vida. É caracterizada por alternância de episódios de mania e depressão (41). Estudos *pós-mortem* mostraram anormalidades na densidade e tamanho das células neuronais e gliais em diversas regiões do córtex pré-frontal, tais como, córtex subgenual, orbitofrontal e dorsolateral em THB (10, 26, 33). Tem sido descrito que tais mudanças morfológicas sugerem falhas na plasticidade e resistência

celular, mais que um padrão neurodegenerativo (32). Além disso, há um crescimento de evidências sugerindo que os sistemas neurotróficos de sinalização, que regulam a plasticidade e sobrevivência celular, devem estar alterados no THB (16, 25, 36).

Nós recentemente demonstramos que os níveis séricos de BDNF estavam diminuídos em pacientes bipolares durante os episódios agudos de mania e depressão (11). Um recente estudo mostrou que o Fator de Crescimento Neurotrófico derivado de Células da Glia (GDNF) medido no sangue total está diminuído nos pacientes bipolares e unipolares durante os estados de remissão parcial ou total (38). Além disso, estudos pré-clínicos demonstraram que a primeira linha de estabilizadores de humor, lítio e valproato aumentam as concentrações de BDNF e GDNF in vivo e in vitro (4, 7, 13).

O GDNF é um membro da superfamília do fator de crescimento β e foi inicialmente isolado, baseado na sua habilidade em induzir a recaptação de dopamina e sobrevivência celular em culturas cerebrais embriônicas (22). Embora seja considerado um dos mais potentes fatores tróficos dos neurônios dopaminérgicos (6), ele é expressamente difundido através do cérebro (29), exercendo efeitos neuroprotetores centrais e periféricos (1,6). Ao mesmo tempo, foi demonstrado que o GDNF regula a sinalização noradrenérgica no *locus cereleus* hipocampal (30) e protege o hipocampo de ratos do estresse oxidativo produzidos pelo kainato (9). Entretanto, ratos mutantes de GDNF apresentam falha na transmissão sináptica hipocampal e pobre *performance* nos processos de aprendizado espacial (14).

Considerando estudos recentes que relataram a importância do GDNF na fisiopatologia do THB e os efeitos dos estabilizadores de humor sobre ele, nós investigamos pela primeira vez o imunoconteúdo sérico de GDNF em todos os estados de humor do THB, incluindo mania, depressão e remissão (eutimia) em pacientes comparados a controles.

A amostra consistiu de 44 pacientes bipolares tipo I (14 deprimidos, 15 maníacos, 15 eutímicos) e 14 controles, pareados por sexo e idade. Todos os

pacientes foram selecionados do Programa de Transtorno do Humor Bipolar – Universidade Federal do Rio Grande do Sul, Porto Alegre, Brasil e da Unidade de Psiquiatria Intensiva do Hospital Universitário de Santa Maria, Santa Maria, Brasil. Os pacientes eram maiores de 18 anos (30-51 anos), eram não fumantes, não apresentavam outras complicações médicas ativas e não usavam outras medicações, além do tratamento psiquiátrico prescrito para o THB. O diagnóstico de THB foi avaliado pela Entrevista Clínica Estruturada segundo o DSM-IV (SCID) (12) e os sintomas depressivos e maníacos foram avaliados pela Escala de Sintomas para Depressão (HAM-D) (15) e Escala de Sintomas para Mania (YMRS), (42) respectivamente. Os pacientes foram considerados deprimidos, maníacos e eutímicos se eles preenchiam critérios para episódio maníaco atual, episódio depressivo maior atual ou remissão atual, segundo o SCID. O grupo controle consistia de sujeitos sadios que estavam dispostos a participar do estudo. Controles eram maiores de 18 anos (18-52 anos), não tinham história de transtorno psiquiátrico avaliado pelo SCID-I, nem história de demência, retardo mental, câncer ou tumor, assim como nenhuma história familiar em primeiro grau destas patologias. Controles eram não fumantes e não tomavam medicação. Cinco controles, seis maníacos e três deprimidos haviam sido usados em nosso estudo prévio (11). O estudo foi aprovado pelo Comitê de Ética Local (Hospital de Clínicas de Porto Alegre) e todos os participantes assinaram o consentimento informado antes de entrar no estudo. O estudo foi realizado de acordo com os princípios das boas práticas clínicas e de acordo com as normas da declaração de Helsinki e suas subseqüentes revisões.

5 mL de sangue foram coletados por *Vacutainer*, sem anticoagulante, o soro foi centrifugado a 3000 r.p.m por 5 minutos e congelados a -80C até a realização das análises bioquímicas. A técnica de *Western Blotting* foi realizada de acordo com o seguinte protocolo: as amostras foram diluídas (1:4) com tampão de fosfato e então foram dissolvidas (90mcg de proteína) na solução *Stopping* (100mM Tris-HCl, pH 8.8, 0.5mM EDTA, 4% SDS, 4% glicerina e 2% de mercaptoetanol). As amostras de

proteínas foram separadas em solução de *SDS-page* a 120V e foram eletrotransferidas a 15V para membrana de polivinilpivolidona. As membranas foram bloqueadas com 5% de albumina durante toda a noite e incubadas por 1h à temperatura ambiente com anti-policlonal GDNF (1:1000, Promega, Madison, USA). Os *blots* foram lavados por três vezes com solução salina (contendo 0.5% Tween) e incubadas com *anti-chicken* IgG (1:1000, Promega, Madison, USA) por 1 h à temperatura ambiente. Os *blots* foram novamente lavados por três vezes e incubados com estreptavidina (1:1000, Promega, Madison, USA) por 1h à temperatura ambiente. O sinal foi detectado por imunofluorescência (ECL Kit, Amersham) e revelados em filme Kodak X-OMAT. A intensidade das bandas foi analisada usando programa Optiquant. A concentração de proteínas total foi quantificada pela técnica de Lowry, usando albumina bovina sérica como padrão.

Conforme descrito na literatura, os níveis de GDNF podem ser alterados em pacientes com insuficiência renal (27, 35). Em função disto, nós avaliamos as concentrações séricas de uréia e creatinina em todos os pacientes. As concentrações séricas de uréia foram medidas pelo método da *Urease-Berthelot* (Biodiagnóstica, Paraná, Brasil) usando uma absorbância de 600nm. As concentrações séricas de creatinina foram medidas pelo método de Jaffé-Picrato alcalino usando uma absorbância de 490nm (Biodiagnóstica, Paraná, Brasil).

Análise estatística foi realizada usando o SPSS para Windows, versão 12.0 (SPSS Inc., Chicago, USA). O imunoconteúdo de GDNF para os quatro grupos: maníacos, deprimidos, eutímicos e controles foram comparados usando ANOVA e aqueles que apresentaram diferença estatisticamente significativa foram testados pelo método de Tukey HSD. As características demográficas entre os grupos foram comparadas usando o método do Qui-Quadrado e ANOVA e consideramos significantemente estatísticos $p<0.05$. Os dados são apresentados em porcentagem para cada grupo.

Pacientes e controles não diferiram em relação à idade, sexo ou nível de escolaridade (todos p>0.05), conforme mostrados na tabela 1. A idade do primeiro episódio e o tempo de evolução da doença não foi estatisticamente diferente entre os deprimidos, maníacos e eutímicos. O imunoconteúdo sérico de GDNF mostrou-se maior no grupo dos maníacos (F= 42.31; p= 0.001) e no grupo dos deprimidos (F= 42.31; p= 0.004). Os pacientes eutímicos mostraram valores de GDNF comparáveis ao grupo controle (veja figura 1). Todos os sujeitos mostraram concentrações séricas de uréia e creatinina dentro da faixa terapêutica, e não observamos diferença entre os grupos (todos >0.05), indicando que as alterações do imunoconteúdo sérico de GDNF não poderia ser atribuído à presença de insuficiência renal.

O imunoconteúdo sérico de GDNF mostrou-se aumentado nos pacientes durante os episódios de mania e depressão e não havia diferença entre os eutímicos e o grupo controle. Estes resultados sugerem que a síntese ou recaptura de GDNF está aumentada durante os episódios agudos da doença. Se este resultado representa um mecanismo patológico ou de compensação permanece a ser determinado. Recente estudo determinou as concentrações sanguíneas de GDNF pelo método de ELISA e mostrou que os níveis de GDNF estavam diminuídos em pacientes bipolares e unipolares durante os períodos de remissão (38). Diferenças na amostra e na técnica utilizada para a determinação de GDNF podem levar a estas discrepâncias. Além disso, no estudo de Takabayashi e col. (38) os pacientes eram mais velhos que os nossos e não foi controlado o efeito da insuficiência renal, que é mais comum em pacientes idosos.

Tem sido demonstrado que pacientes bipolares apresentam um alargamento do tamanho das células da glia em lâminas específicas do córtex (33, 40). Entretanto, tem sido descrito um aumento sérico de uma proteína neuroprotetora dos astrócitos, a proteína S-100β (23). Sabe-se que a injúria neuronal pode estimular a atividade glial, e que a separação das células astrogliais dos neurônios corticais promove a morte neuronal (31). O GDNF dá suporte para a sobrevivência dos neurônios

dopaminérgicos, noradrenérgicos, *in vivo*, assim como os neurônios motores e sensoriais. Pacientes bipolares tem aumento sérico de malonildialdeído (um marcador da peroxidação lipídica) (20, 28) e diminuição da catalase (28, 34), indicando um aumento de estresse oxidativo. Usando a técnica de eletroforese em gel, nós recentemente encontramos uma fragmentação do DNA no sangue periférico de pacientes com THB, possivelmente devido a um aumento de estresse oxidativo (3). Chao & Lee (8) demonstraram que a infusão crônica de GDNF humano recombinante aumentou a superóxido dismutase, a catalase e a glutation-peroxidase em estriado de ratos, sugerindo que o GDNF deve exercer propriedades antioxidantes. Interessantemente, Sawada e col. (36) mostraram que a pré-incubação com GDNF bloqueou a clivagem ao DNA induzida por sulfato de bleomicina e de butionina-sulfoximina em cultura de neurônios mesencéfálicos. Embora especulativo, é possível que o aumento de GDNF durante as fases agudas, mania e depressão, possa representar uma resposta adaptativa contra o estresse oxidativo.

Algumas limitações devem ser consideradas. No presente estudo, todos os pacientes estavam medicados; na verdade, nós não podemos excluir o fato que o aumento do imunoconteúdo de GDNF esteja influenciado pelos medicamentos. Embora um estudo clínico prévio não tenha encontrado diferença entre as concentrações sanguíneas de GDNF em pacientes com e sem uso lítio ou com e sem uso de antidepressivos (38), estudos pré-clínicos mostram que os níveis de GDNF podem ser alterados pelos antidepressivos (18), antipsicóticos (37) e ou estabilizadores de humor (4,7). Estudos em pacientes não medicados são necessários para esclarecer esta questão. Uma outra limitação é que nós medimos o GDNF no soro e nós não podemos assegurar que as concentrações periféricas de GNDF aqui encontradas reflitam mudanças ao nível do SNC. Estudos prévios indicam que o GDNF atravessa fracamente a barreira hematoencefálica (2, 19).

Concluindo, o imunoconteúdo de GDNF está aumentado em pacientes bipolares durante os episódios agudos de mania e depressão. Se isto representa uma

resposta patológica ou compensatória, precisa ser elucidado. Múltiplas mudanças nas cascatas de sinalização das neurotrofinas estão envolvidas no THB.

Agradecimentos:

** Este estudo foi financiado em parte pela CAPES (Brasil), CNPQ (Brasil) e FIPE-HCPA.

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Tabela 1. Características Clínicas e Demográficas

	Controles n=14	Eutímicos n=15	Maníacos n=15	Deprimidos n=14	p
Sexo					
Femenino	31.2%	37.5%	56.3%	28.6%	0.12
Masculino	68.8%	62.5%	43.8%	71.4%	
Idade (anos)	41.1 (11.1)	40.4 (10.3)	40.1 (9.3)	42.1 (8.2)	0.7
Escolaridade (anos)	7.9 (2.9)	9.6 (4.8)	8.3 (3.6)	8.5 (1.7)	0.10
Número de fármacos		2.2 (0.1)	3.2 (1.3)	2.9 (1.2)	0.024
Idade do primeiro episódio		21.3 (11.2)	27.1 (9.9)	22.0 (11.3)	0.41
Duraçao da doença		16.4 (12.0)	13.1 (8.3)	18.0 (14.1)	0.21
HDRS		4.1 (2.1)	5.6 (2.9)	21.9 (2.36)	0.001
YMRS		3.3 (3.4)	33.1 (4.1)	5.6 (3.1)	0.001
Creatinina mg/dl					
Masculino	0.90 (0.21)	1.10 (0.32)	1.13 (0.21)	1.24 (0.19)	0.23
Feminino	0.78 (0.31)	0.81 (0.37)	1.19 (0.23)	0.99 (0.24)	0.46
Uréia mg/dl	16.45 (1.24)	18.33 (2.55)	20.1 (1.44)	19.5 (1.44)	0.56

*Chi Square test, ** One- Way ANOVA test, **HDRS = Hamilton Depression Rating Scale;

[a] Níveis séricos de referência → Homem: 0.6 – 1.5 mg/dL Mulher: 0.5 – 1.3 mg/dL

[b] Níveis séricos de referência → 10-52 mg/dL

YMRS = Young Mania Rating Scale; BDNF = brain-derived neurotrophic factor

Figura 1. Conteúdo sérico de GDNF em pacientes com THB e controles.

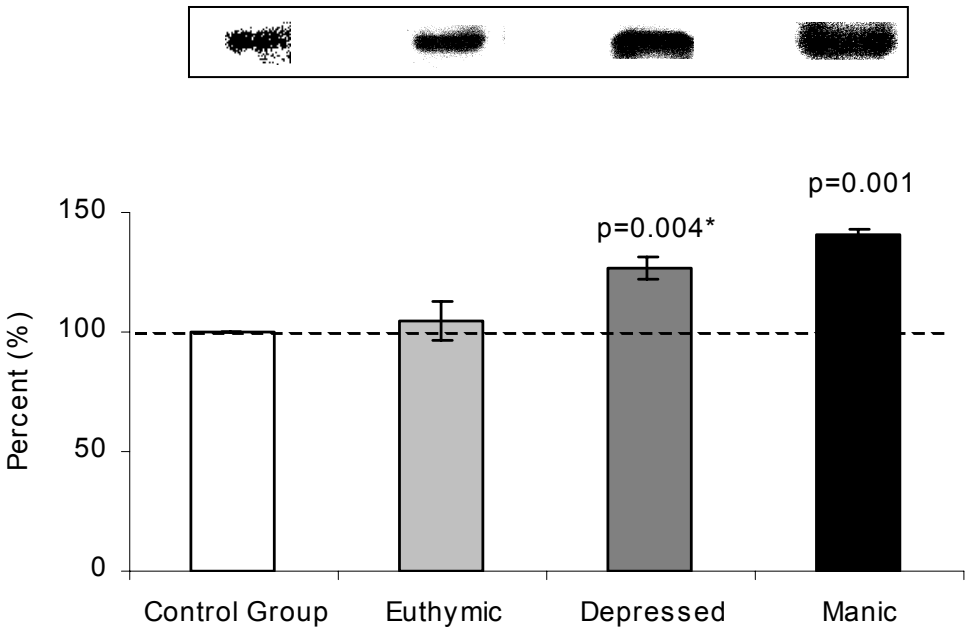

Figura 1. Conteúdo sérico de GDNF em pacientes com THB e controles. Conteúdo sérico de GDNF foi medido pela técnica de *imunoblotting* aplicando 50 μg por coluna. Valores de GDNF foram expressos em porcentagens assumindo 100% para controles. Os valores representam a media dos pacientes ± SEM. Cada figura representa o *imunoblotting* de um paciente e controle.

6.2. ARTIGO 2:

Reliability and Validity of the Functioning Assessment Short Test (FAST) in bipolar disorder

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Submitted to Clin Pract Epidemol Ment Health

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Competing Interests:

“The author(s) declare that they have no competing interests related to this report”.

Acknowledgements:

The authors thank Nicol Ferrier and Lucy Robinson, from the University of Newcastle-upon-Tyne, U.K., for their helpful comments to the manuscript and scale.

Abstract:

Background: High rates of functional impairment among bipolar patients, even during remission, have been documented in numerous studies. However, the majority of instruments available to date have been focused on global or limited measures of functional recovery, rather than specific domains of psychosocial activity. In this context, the Functioning Assessment Short Test (FAST) was designed as a brief instrument assessing the main functioning problems experienced by psychiatric patients, and particularly bipolar patients. It comprises 24 items that assess impairment or disability in six specific areas of functioning such as autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time.

Methods: 101 patients with DSM-IV TR bipolar disorder and 61 healthy controls were assessed by the Bipolar Disorder Program, at the Hospital Clinic of Barcelona. The feasibility, internal consistency, concurrent validity, discriminant validity between euthymic and acute patients, factorial analyses, and test-retest reliability were analysed.

Results: The internal consistency obtained was high, Cronbach's alpha being 0.909. Concurrent validity showed highly significant negative correlation with GAF ($r=-0.903$; $p<0.001$). The test-retest reliability analysis showed a strong correlation between the two measures (ICC=0.98; $p<0.001$). The total mean FAST scores were lower in euthymic (18.55 ± 13.19; $F=35.43$; $p<0.001$) patients, as compared with manic (40.44 ± 9.15) and depressive patients (43.21 ± 13.34).

Conclusions: The FAST showed strong psychometrics properties and was able to detect differences between euthymic and acute patients. In addition, it is a short (6 minutes) simple interview-administered instrument, which is easy to apply, only requires short period of time for implementation, and it is now available for use in both clinical practice and research settings.

Key words: functioning - disability - brief scale - bipolar disorder.

Introduction:

Kraepelin in 1921[1] noted that manic or depressive episodes were periodic in nature, and typically were followed by a return to what was then considered normal functioning. In contrast to early studies, recent studies do not describe such a favourable outcome in patients with bipolar disorder [2-5]. T*ohen et al.* (2000)[6] showed that although 97.5% of bipolar patients achieved syndromal recovery by 24 months after admission, only 37.6% achieved functional recovery. *Strakowski et al*. (2000)[7], in a 8-month follow-up study, reported that nearly all of the remitted patients exhibited persistent impairment in at least one area of functioning and less than half achieved good functional outcome in three of the four areas of functioning studied.

Functioning is complex and involves many different domains including the capacity to work, capacity to live independently, capacity for recreation, capacity for romantic life, capacity to study, etc. [4;6;8]. Researchers traditionally measure one or two elements of functioning and typically fail to take into account all the other elements necessary for optimal functioning. The measures used to assess functional impairment in BD varied greatly across studies, only a few instruments were used by more than two researchers [3;9-11]. Among multidimensional scales assessing outcome, the Global Assessment of Functioning scale (GAF) is the most commonly used instrument for assessing functional outcome, but the original GAF instructions call for rating symptoms or functioning [12-14]. Beyond these scales, the Social Adjustment Scale (SAS), the Life Functioning Questionnaire (LIFE), the Short Form-36 (SF-36) and the WHO-DAS are also used, but none were specific instruments developed to assess specific areas of functional impairment in bipolar disorder and both required longer duration of administration.

Future studies should be sensitive to the need for measures to evaluate the impact of illness factors on each domain of functioning [3] and the development of instruments that capture the specific issues related to severe mental illness and particularly BD are required [11]. The FAST (Functioning Assessment Short Test) was

developed for the clinical evaluation of functional impairment presented by patients suffering from mental disorders including bipolar disorder. It is a simple instrument, easy to apply and that requires a very short time to be administered. The 24 items of the scale are divided among 6 specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time; by considering previous scales and literature, it was identified that these were the main problems experienced by the mentally ill, including bipolar patients [7;15-17].

The purpose of the present study was to validate the Spanish version of the FAST for use as an instrument to assess functional impairment in subjects with bipolar disorder. The FAST is now being validated as well in English and Portuguese.

Methods:

1. Subjects

The study was conducted in inpatient and outpatient services specialized in the Bipolar Disorder Program, Hospital Clinic of Barcelona, Spain. One hundred and one bipolar patients were selected in according to the Structured Clinical Interview for the DSM-IV TR criteria [12].

The study was approved by the Hospital Clinic of Barcelona Ethics Committee and was carried out in compliance with the Helsinki Declaration of 1975 (the Evaluation, Support and Prevention Unit).

2. Variables

After informing the patients and obtaining their consent, the investigator recorded their socio-demographic and clinical variables and administered the Spanish version of the Young Mania Rating Scale (YMRS) [18], Spanish version of the 17-item Hamilton Depression Rating Scale (HDRS-17) [19] and the Global Assessment Functioning (GAF) [20] to confirm the stability of the patient's condition and overall functioning. They also recorded all the medication prescribed to the patients for this visit. Finally, the investigator administered the FAST. Interviewers administering the FAST and the GAF were blinded to each other.

Sixty one control subjects were screened through the SCID (DSM-IV TR) to exclude subjects with prior psychiatry history. Controls had no first-degree relatives with bipolar disorder or other psychiatric disorders when asked in previous interview for selection or controls. The healthy comparison group was recruited from the general population with the catchment area around the Hospital Clinic, in Barcelona, and gave written informed consent to participate in this study.

3. FAST

3.1. Development

The FAST was developed by the Bipolar Disorder Program, Barcelona, Spain, to assess functional impairment focusing on the main problems experienced by the mentally ill, including bipolar patients. The initial version of the FAST included 56 items divided into 10 specific areas, such as autonomy, work functioning, cognitive functioning, finances, insight, social/marital life, acceptance/knowledge disorder, strategies to cope with symptoms, use of medication, and self-fulfilment and was performed as a pilot study with ten bipolar patients and ten healthy controls. After preliminary analysis, the scale was discussed in a meeting with experts from Spain, Brazil and England and gravel changes were made and some items were rejected. Then, the final version of the FAST was concluded. The scale is available so far in two languages: Spanish, English (see annex) and other language versions are in process.

3.2. Description

The FAST is interviewer-administered by a trained clinician and the studied time frame refers to the last 15 days before assessment. It is a quite simple instrument, easy to apply and which only requires a short time to apply. It comprises 24 items, which are divided among 6 specific areas of functioning:

1) Autonomy refers to the capacity of the patient of doing things alone and takes his/her own decisions.

2) Occupational functioning refers to the capacity to maintain a paid job, efficiency of performing tasks at work, working in the field in which the patient was educated and earning according to the level of the employment position.

3) Cognitive functioning is related to the ability to concentrate, perform simple mental calculations, solve problems, learn new information and remember learned information.

4) Financial issues involve the capacity of managing the finances and spending in a balanced way.

5) Interpersonal relationships refer to relations with friends, family, involvement in social activities, sexual relations and the ability to defend ideas and opinions.
6) Leisure Time refers to the capability of performing physical activities (sport, exercise) and the enjoyment of hobbies.

All of items are rated using a 4-point scale, 0=no difficulty, 1=mild difficulty, 2=moderate difficulty and 3=severe difficulty. The global score is obtained when the scores of each item are added up. The higher the score, the more serious the difficulties are, so it is actually measuring disability.

4. Psychometrics

We analysed the feasibility, internal consistency, concurrent validity, validity as a discriminative of measure to detect difference between euthymic and acute patients, factorial analyses and test-retest reliability of the FAST. Except for test-retest reliability, the psychometric characteristics of the FAST are derived from the first administration of the questionnaire, including all the subjects who completed it in the analysis, thus simulating its normal clinical use.

4.1. Feasibility is described as the percentage of patients who did not respond to the questionnaire in its entirety. It also includes the time spent in completing the instrument as a measure of how practical it may be for busy clinicians and for its inclusion in clinical trials and other studies.

4.2. Internal consistency reliability assesses the degree to which questions on an instrument measure the same underlying concept. The alpha internal consistency coefficient of reliability (Cronbach's Alpha) was used to examine the internal consistency of the FAST items in each domain and total scale. The correlation between each domain and the total scores was calculated.

4.3. Concurrent validity was studied considering GAF instrument and the score obtained on the FAST applying the Pearson correlation coefficient [21]. The GAF was chosen as the scale to assess concurrent validity of the FAST because it is probably the main instrument for assessing functional outcome in mental disorders.

4.4. The optimal point for the FAST was determined by means of ROC curves.

4.5. Test-retest reliability: Intra-class correlation coefficient was performed to assess test-retest reliability, 15 subjects were identified who had remained stable for at least one week, according to YMRS, HDRS-17 and GAF. These 15 subjects then participated in a Test-Retest reliability assessment one week later.

4.6. Validity as a discriminative measure to detect difference between euthymic and acute patients: the participants were stratified by severity of symptoms in euthymic, manic, and depressed, as determined by a clinical assessment based on DSM-IV TR and ANOVA analysis to evaluate whether the FAST total scores are sensitive to the level of severity of symptoms.

4.7. An orthogonal factorial analysis by matrix rotation was performed to describe the internal structure of each domain of the FAST.

5. Statistical analysis:

Statistical analysis was performed using SPSS for Windows - Version 12.0 (SPSS Inc., Chicago, IL, USa). Pearson's correlation coefficient was performed to examine the correlation between FAST and GAF scores and to examine the test-retest reliability. Internal consistency was analyzed using the Cronbach's alpha. Total scores of FAST of four groups (euthymic, manic or depressed) were compared using one-way ANOVA.

When ANOVA comparing more than two groups showed significant differences, the individual Tukey HSD test was performed. Intra-class correlation coefficient was performed to assess the reliability between test and retest. The rotation was performed by Varimax method.

Results:

Seventy three euthymic, fourteen depressive and sixteen manic patients were enrolled to participate in the study. The mean age of the patients was 45 years (standard deviation [SD: 13.66, median 45.45, ranging from 22 to 82) and mean age of the controls was 49 years (standard deviation [SD:17.66, median 49.16, ranging from 22 to 81). Table 1 describes the principal socio-demographic and clinical characteristics of the study sample, consisting 51.5% women in the group of patients and 42.6% in the control group.

Among the 103 bipolar patients, mood stabilizing agents were the most commonly prescribed agents (81.6%), including lithium (59.2%), valproate (13.6%) and carbamazepine (9.7%); 12.6 % received lamotrigine; 63.1% antipsychotics, 30.1% antidepressants and 48.5% anxiolytic-sedatives.

All the FAST items were answered by 99% the patients (n=100) completing the study, for every test session. The mean time spent in completing the instrument was 6.00 minutes (ranging from 2 to 12; SD: 2.79) for the total sample, 5.69 (SD: 2.67) for euthymic, 5.29 (SD: 1.64) for depressive and 7.25 (SD: 3.26) for manic patients. There was not difference between the groups ($F=2.65$; $p=0.075$). Because of this, this scale showed high feasibility.

The internal consistency coefficient obtained was high, Cronbach's alpha of 0.909, for the total scale, indicating that the items are sufficiently homogeneous. The FAST also had high internal consistency on each of the twenty-four items.

Concurrent validity based on functioning impairment according to GAF scale showed highly significant negative correlation ($r=-0.903$; $p<0.001$). This result indicates that patients with good functioning assessed by the FAST obtained higher scores on the

GAF scale, as shown in figure 1, because the FAST scores disability and the GAF scores adjustment.

We analysed the scale's discriminant capacity between patient and controls by means of the diagnostic performance or ROC curve. The area under the curve was 0.86, 95%CI: (0.809, 0.917) which, being close to 1, indicates a good capacity. The discriminant capacity study indicates that a score above 11 obtains the best balance between sensitivity (72%) and specificity (87%). The mean total FAST score in patients and the control group were 25.43 (0-66; SD:16.31) and the 6.07(0-20; SD: 4.72) respectively.

Intra-class correlation coefficient was 0.98 ($p<0.01$), as shown in table 2. The YMRS, HDRS-17 and GAF were assessed during test and retest to verify stability on the mood states of patients. This results indicating that the stability of the FAST would not be altered by natural mood variations in the patients' condition through clinical scales (YMRS and HDRS-17).

Validity as a discriminant measure to detect difference between euthymic and acute patients. The total scores mean of FAST were lower in euthymic (18.55 ± 13.19; $F=35.43$; $p<0.001$) patients, as compared with manic (40.44 ± 9.15) and depressed patients (43.21 ± 13.34) as shown in figure 2.

The study of the internal structure of the FAST, after rotation (using Varimax method), determined a five-factor structure, as shown in table 3. In this analysis it was observed that the interpersonal relationship and leisure time domains are loading on the same factor.

Discussion:

High rates of functional impairment among bipolar patients, even amongst patients whose symptoms have remitted, have been documented in numerous studies [4;7;22-25]. Cognitive impairment, work impairment, household duty difficulties, interpersonal relationship difficulties, leisure time difficulties, and sexual problems are the main functioning problems presented by patients [6;7;11;14;17]. However, the majority of instruments available to date are very lengthy and have been focused on global or limited measures of functional recovery, rather than examining specific, discrete areas of psychosocial activity [4;7]. Therefore, the development of specific instruments to assess the functional outcome in BD is needed [11;14] and in this context, the FAST could become particularly useful.

The FAST comprises twenty-four items that assess six specific areas of functioning such as autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. The FAST presents advantages due to the simplicity of the instrument, the ease of its application and the time frame required for its implementation. In addition, the FAST shows high feasibility, a quality that makes it applicable in both clinical practice and in research settings. The instrument is also available in three languages, a Spanish version, a Portuguese and an English version.

The psychometric properties of the FAST showed high internal consistency, where the total items had alpha Cronbach's results above of 0.9. In addition, we found a strong concurrent validity, a strong discriminant validity to detect differences between euthymic and acute patients, and a strong factorial analysis. The test-retest reliability, which only featured patients with stable mood states, showed very similar results. The mean FAST score for the first subgroup was 37.73 (SD: 16.79, ranging from 13 to 66) and was 34.87 (SD: 16.14, ranging from 12 to 64) for the second subgroup. The FAST was a sensitive instrument for the detection of different mood states, and this was supported when the euthymic patients showed functioning results that were twice

better than depressed and manic patients. Previous studies showed moderate to marked impairment in specific areas of functioning and the persistence of depressive symptoms was also significantly associated with the degree of impairment [3;5;13;17;24]. Strakowski et al. (2000)[7] reported that functional recovery, and in particular, interpersonal relationships recovery was associated with manic symptoms recovery. Nonetheless, we also found that severity of symptoms was associated with higher scores of FAST and poorer functioning.

In this study, we found a putative cut-off point higher than 11, because this value improved the test's discriminant properties, obtaining a sensitivity of 72% and a specificity of 87%. In this cut-off, the total FAST score was 25.43 for patients (0-66; SD: 16.31) and 6.07 for healthy controls (0-20; SD: 4.72); only five healthy controls showed a score superior of 11. These results are consistent with previous studies, suggesting that functional impairment is not restricted to acute episodes, remitted patients showing functional impairment despite symptomatic recovery [5-7;24].

As regard to concurrent validity, the FAST showed a strong negative correlation with the GAF scale, which is the main instrument for assessing the current level of functioning [11;14]. The GAF gives ratings from 0 to 100, which specifies anchors for quantification of overall psychosocial functioning adjustment, where the higher scores of GAF represents better psychosocial functioning [13;14;26]. In opposition to the GAF, the FAST assesses specific domains of functioning and also identifies the level of impairment in each area; higher scores represent higher disability and this is why a negative correlation was actually expected.

There are also other instruments to assess functioning such as the WHO-DAS-II, SF-36, SAS and LIFE scale. WHO-DAS is an instrument developed by The World Health Organization, which can predict objectively measures of disability related outcomes. However, the instrument is an extensive interview, which limits its use in clinical practice and it also assesses numerous physical domains which are less relevant than mental domains to psychiatric patients in general and bipolar patients in

particular [27]. On the other hand, the SF-36 is a self-reported instrument, consisting of 36 items and 8 subscales (ranging 0-100) measuring the domains of physical and social functioning, as well as general and emotional health [23;28]. The Social Adjustment Scale (SAS) is a comprehensive instrument to assess multiple domains of social functioning and its length is a barrier to use in screening or routine assessment. In addition, it is most commonly used in the area of depression treatment. The Life Functioning Questionnaire (LFQ) is a brief questionnaire which assess duties at home, leisure activities (family/friends) beyond to evaluate carefully duties at work [27]. However, all the scales above did not assess important areas of functioning such as cognitive functioning and finances. Furthermore, the self-reported scales to assess functional impairment in psychiatric illness, particularly bipolar patients, are not reliable because the extensive psychopathology of these patients may make them more prone to over-estimate or under-estimate their own disability [5;29;30]. However, at this moment, the instruments available were not developed to measure the health problems particularly associated with BD. This results in a lack of standardisation of these instruments which gives difficulties in understanding the results. In addition, the validation of the scales in other languages, in particular, Spanish version is very important because Spanish is spoken by over 352 million people worldwide [11;18;31-33]. In this context, the FAST, in opposition to the above instruments, was designed considering the main difficulties experienced by psychiatric patients reported in the literature and previous scales including those expressed by bipolar patients and it is promoting a new option to assess functional impairment in specific domains that may be affected in bipolar patients.

Conclusion:

In conclusion, the FAST showed strong psychometric properties and it was sensitive to different mood states. In addition, it is a simple interviewer-administered instrument, which is easy to apply, only requires a short period of time for

implementation, and it is now available for use in both clinical practice and in investigation settings. The FAST promotes the assessment of specific domains of functioning impairment in bipolar disorder patients and it could help the creation of supplemental interventions targeting rehabilitation/functional enhancement of these patients and may be able to assess the effect of pharmacologic and psychosocial interventions on the functioning of psychiatric patients, being valid, reliable and friendly in the field of bipolar disorder.

Acknowledgements:

** This study was supported in part by CAPES (Brazil) and The Stanley Medical Research Institute, The Institute Carlos III. FIS (PI05206)

Table 1: Demographic and clinical variables

Demographic and clinical variables	Bipolar patients		Control group	
	Mean	SD	Mean	SD
Age	45.45	13.66	49.16	17.66
Age of onset	27.82	11.84		
Chronicity	17.92	11.51		
Total episodes	12.35	15.06		
Manic episodes	3.43	4.61		
Hypomanic episodes	3.00	9.43		
Depressed episodes	5.60	6.67		
Hospitalization	1.93	1.96		
Suicide attempts	1.44	0.49		
HDRS	5.41	7.17		
YMRS	4.08	6.67		
GAF	63.90	19.05		
	n	%	n	%
Sex				
Female	49	48.5	35	57.4
Male	51	51.5	26	42.6
Bipolar type I	89	88.3		
Bipolar type II	11	10.7		
Bipolar NOS	1	1		

Table 2: Test-Rest reliability of the FAST

N=15	mean	SD	mean	SD	Intraclass correlation	F	gl	p	t test	F	gl	p
FAST	37.73	16.79	34.87	16.14	0.98	40.98	14	0.0001	0.48	0.006	28	0.94
GAF	49.40	17.80	52.53	16.74	0.95	18.63	14	0.0001	-0.50	0.29	28	0.60
HDRS	10.53	10.21	9.87	9.99	0.87	7.59	14	0.0001	0.18	0.047	28	0.83
YMRS	9.80	10.10	9.00	8.44	0.93	14.23	14	0.0001	0.24	1.47	28	0.24

Legend table 2: We found a significant intra-class correlation between Test and Retest assessments ($r=0.98$; $F=40.98$; $p<0.0001$). The mean scores of YMRS, HDRS-17 and GAF of patients remained stable during Test-Retest.

Table 3: Factorial loading on the FAST

FAST	1	2	3	4	5
EF 5	0.938				
EF 9	0.908				
EF 7	0.902				
EF 6	0.882				
EF 8	0.852				
EF 17		0.741			
EF 18		0.628		0.437	
EF 21		0.596			
EF 24		0.577	0.544		
EF 23		0.552			
EF 20		0.466			
EF 19		0.403			
EF 12					
EF 13			0.746		
EF 14			0.694		
EF 11			0.668		
EF 10			0.480		
EF 4				0.741	
EF 1				0.724	
EF 3			0.407	0.693	
EF 2				0.531	
EF 22					
EF 16					0.897
EF 15					0.870

Legend table 3: Coefficient less than 0.42 are omitted

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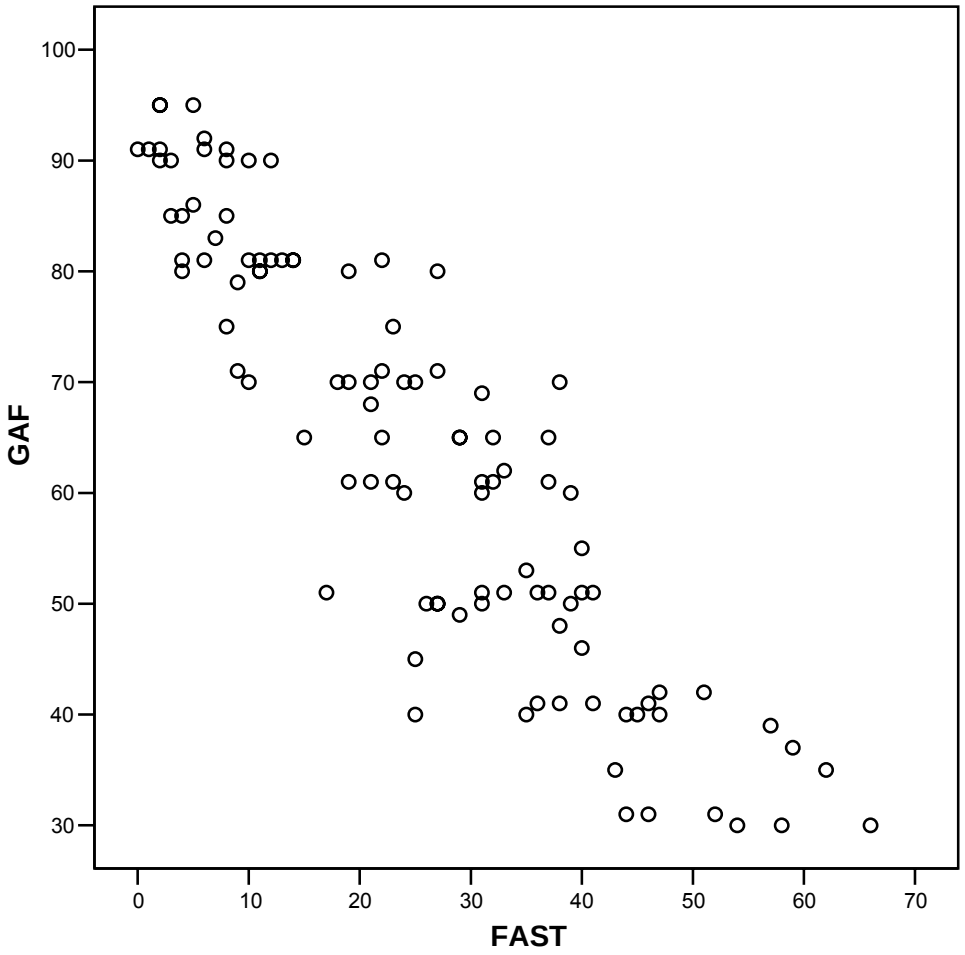
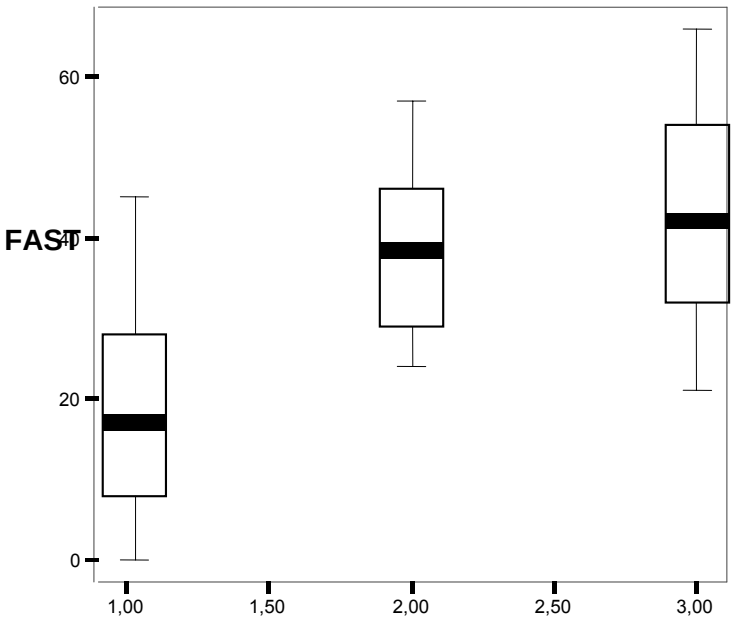
Figure 1: A Pearson correlation between scores of GAF and scores of FAST



Legend: We found a significant negative correlation between total scores of FAST and GAF ($r=-0.903$; $p<0.001$). This result indicates that patients with poor functioning assed by the FAST obtained higher scores on the GAF scale, showing that disability (FAST) and adjustment (GAF) negatively correlated.

Figure 2: FAST scores across different mood states in bipolar patients



(1) euthymic (n=71), (2) manic (n=16), (3) depressed patients (n=14)

Legend: Total mean FAST scores were as follows: (1) euthymics (18.55±13.19), (2) manic (40.44±9.15) and (3) depressed (43.21±13.34). We performed an ANOVA test followed by the Tukey test and found a significant difference between euthymic patients (18.55; F=35.43; p<0.001) and acute patients.

APPENDIX I:

PRUEBA BREVE DEL EVALUACIÓN DEL FUNCIONAMIENTO (FAST)

¿Cuál es el grado de dificultad del paciente en relación con los siguientes aspectos?
Interrogue al paciente respecto a las áreas de funcionamiento que se especifican a continuación, utilizando la siguiente escala: (0): Ninguna, (1): Poca, (2): Bastante o (3): Mucha.

AUTONOMIA				
1. Encargarse de las tareas de casa	0	1	2	3
2. Vivir solo	0	1	2	3
3. Hacer la compra	0	1	2	3
4. Cuidar de sí mismo (aspecto físico, higiene)	0	1	2	3
FUNCIONAMIENTO LABORAL				
5. Realizar un trabajo remunerado	0	1	2	3
6. Acabar las tareas tan rápido como era necesário	0	1	2	3
7. Trabajar en lo que estúdio	0	1	2	3
8. Cobrar de acuerdo con el puesto que ocupa	0	1	2	3
9. Alcanzar el rendimiento previsto por la empresa	0	1	2	3
FUNCIONAMIENTO COGNITIVO				
10. Concentrarse en la lectura, película	0	1	2	3
11. Hacer cálculos mentales	0	1	2	3
12. Resolver adecuadamente un problema	0	1	2	3
13. Recordar el nombre de gente nueva	0	1	2	3
14. Aprender una nueva información	0	1	2	3
FINANZAS				
15. Manejar el propio dinero	0	1	2	3
16. Hacer compras equilibradas	0	1	2	3
RELACIONES INTERPERSONALES				
17. Mantener uma amistad	0	1	2	3
18. Participar en actividades sociales	0	1	2	3
19. Llevarse bien con personas cercanas	0	1	2	3
20. Convivencia familiar	0	1	2	3
21. Relaciones sexuales satisfactorias	0	1	2	3
22. Capaz de defender los propios intereses	0	1	2	3
OCIO				
23. Praticar deporte o ejercicio	0	1	2	3
24. Tener una afición	0	1	2	3

APPENDIX II:

FUNCTIONING ASSESSMENT SHORT TEST (FAST)

To what extent is the patient experiencing difficulties in the following aspects?
Ask the patient about the areas of difficulty in functioning and score according to the following scale: (0): no difficulty, (1): mild difficulty, (2): moderate difficulty, (3): severe difficulty.

AUTONOMY				
1. Taking responsibility for a household	0	1	2	3
2. Living on your own	0	1	2	3
3. Doing the shopping	0	1	2	3
4. Taking care of yourself (physical aspects, hygiene)	0	1	2	3
OCCUPATIONAL FUNCTIONING				
5. Holding down a paid job	0	1	2	3
6. Accomplishing tasks as quickly as necessary	0	1	2	3
7. Working in the field in which you were educated	0	1	2	3
8. Occupational earnings	0	1	2	3
9. Managing the expected work load	0	1	2	3
COGNITIVE FUNCTIONING				
10. Ability to concentrate on a book, film	0	1	2	3
11. Ability to make mental calculations	0	1	2	3
12. Ability to solve a problem adequately	0	1	2	3
13. Ability to remember newly-learned names	0	1	2	3
14. Ability to learn new information	0	1	2	3
FINANCIAL ISSUES				
15. Managing your own money	0	1	2	3
16. Spending money in a balanced way	0	1	2	3
INTERPERSONAL RELATIONSHIPS				
17. Maintaining a friend or friendships	0	1	2	3
18. Participing in social activities	0	1	2	3
19. Having good relationships with people close you	0	1	2	3
20. Living togheter with your family	0	1	2	3
21. Having satisfactory sexual relationships	0	1	2	3
22. Being able to defend your interests	0	1	2	3
LEISURE TIME				
23. Doing exercise or participing in sport	0	1	2	3
24. Having hobbies or personal interests	0	1	2	3

6.2.1. ARTIGO 2 TRADUZIDO:

Validade e Confiabilidade da Escala Breve de Funcionalidade (FAST) para o Transtorno do Humor Bipolar

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Conflitos de Interesse:

"Os autores declaram não ter conflitos de interesse relacionado a este artigo".

Agradecimentos:

Os autores agradecem a Nicol Ferrier e Lucy Robinson, da Universidade de Newcastle-upon-Tyne, U.K. pelos comentários para a elaboração da escala e deste artigo.

Este estudo foi financiado, em parte, pela CAPES (Brasil) e pela Stanley Medical Research Institute, The Institute Carlos III. FIS (PI05206)

Resumo:

Introdução:

Altas taxas de disfuncionalidade entre pacientes bipolares, inclusive entre aqueles que estão em remissão, têm sido documentadas em numerosos estudos. No entanto, a maioria dos instrumentos disponíveis até o momento tem focado em medidas globais ou limitadas da funcionalidade, não avaliando domínios específicos da atividade psicossocial. Neste contexto, a Escala Breve de Funcionalidade (FAST) foi desenvolvida como um instrumento prático para avaliar os principais problemas apresentados pelos pacientes psiquiátricos, em especial, pacientes bipolares. A escala consiste de 24 itens que avaliam dificuldades na funcionalidade em seis áreas específicas, tais como autonomia, trabalho, cognição, finanças, relações inter-pessoais e lazer.

Métodos: 101 pacientes com Transtorno do Humor Bipolar (THB) e 61 controles sadios diagnosticados segundo o DSM-IV TR foram avaliados pelo Programa de Transtorno Bipolar do Hospital de Clínicas de Barcelona. O tempo de aplicação, a consistência interna, a validade concorrente, a validade discriminante entre pacientes eutímicos e pacientes agudos, a análise fatorial e a confiabilidade Teste-Reteste foram analisadas.

Resultados: A consistência interna obtida foi alta, com alfa de Cronbach's igual a 0.909. A validade concorrente mostrou uma forte correlação com a GAF ($r=-0.903$; $p<0.001$). A confiabilidade Teste-Reteste também mostrou uma forte correlação entre as duas medidas (ICC=0.98; p=0.00). O escore médio total da FAST foi menor nos eutímicos (18.55±3.19; $F=35.43$; $p<0.001$) quando comparado aos pacientes maníacos (40.44 ± 9.15) e pacientes deprimidos (43.21 ± 13.34).

Conclusão: As características psicométricas da FAST mostraram resultados muito positivos e a escala foi capaz de detectar diferenças entre pacientes eutímicos e agudos. Além disso, é um instrumento simples, de fácil aplicação, que requer pouco

tempo para sua administração (6 min.) e já está disponível para o uso na prática clínica e investigação.

Key words: funcionalidade - disfuncionalidade – escalas curtas – transtorno bipolar

Introdução:

Kraepelin em 1921 notou que os episódios de mania e depressão eram periódicos *in natura*, e tipicamente retornavam ao que se considerava funcionalidade normal. Ao contrário dos estudos mais antigos, estudos recentes não descrevem resultados tão favoráveis em pacientes com THB. Tohen e col.(2000)[6] mostraram que apesar de 97.5% dos pacientes bipolares apresentarem recuperação sintomática, somente 37.6% apresentaram recuperação funcional em 24 meses após a hospitalização. *Strakowski e col.* (2000) em um estudo de oito meses de seguimento relataram que quase a metade dos pacientes em remissão exibiram persistente disfuncionalidade em pelo menos uma das áreas da funcionalidade analisadas, e menos da metade apresentava adequada funcionalidade em três das quatro áreas estudadas.

A funcionalidade é complexa e envolve diferentes domínios, incluindo a capacidade para trabalhar, a capacidade para viver independentemente, capacidade para recreação, capacidade para vida social, capacidade para estudar, etc. Pesquisadores tradicionalmente medem um ou dois elementos da funcionalidade e tipicamente falham em considerar todos os elementos necessários para uma medida mais completa do mesmo. As medidas usadas para avaliar difuncionalidade em THB variam muito entre os estudos e somente poucos instrumentos foram usados por mais de dois pesquisadores. Entre as escalas multidimensionais que avaliam resultados, a escala de Avaliação Global da Funcionalidade (GAF) é o instrumento mais comumente usado para medir funcionalidade, embora as instruções originais da mesma indiquem que ela mede sintomas e/ou funcionalidade. Além da GAF, a Escala de Ajustamento Social (SAS), o Questionário de Funcionalidade de Vida (LIFE), a Short Form-36 (SF-36) e a WHO-DAS também são usadas, mas nenhuma delas foi desenvolvida especificamente para avaliar áreas da funcionalidade de pacientes bipolares e ambas requerem longo tempo para sua administração.

Estudos futuros deveriam ser sensíveis à necessidade de medidas que avaliem o impacto da doença (THB) em cada domínio da funcionalidade e o desenvolvimento de instrumentos capazes de avaliar questões específicas relacionadas à doença mental e, particularmente, em relação ao THB são necessários. A FAST foi desenvolvida para a avaliação clínica da funcionalidade apresentada por pacientes que sofrem de transtorno mentais, em especial, pacientes bipolares. É um instrumento simples, fácil de aplicar e que requer um pouco tempo para sua aplicação. Os 24 itens da escala estão divididos em seis áreas específicas da funcionalidade: autonomia, trabalho, cognição, finanças, relações inter-pessoais e lazer; revisados na literatura e em escalas mais antigas, estes foram identificados como os principais problemas vivenciados por pacientes com transtornos mentais, em especial, bipolaridade.

O objetivo do presente estudo foi validar a versão Espanhola da FAST para ser usada como um instrumento capaz de avaliar funcionalidade em pacientes com THB. A FAST está disponível em duas versões, Inglês e Português.

Métodos:

1. Sujeitos

O estudo foi realizado com pacientes ambulatoriais e hospitalizado do Programa de Transtorno do Humor Bipolar, do Hospital de Clínicas de Barcelona, Barcelona. Foram incluídos101 pacientes bipolares de acordo com os critérios da Entrevista Clínica Semi-Estruturada (DSM-IV TR)

O estudo foi aprovado pelo Comitê de Ética do Hospital de Clínicas de Barcelona e realizado em conformidade com a Declaração de Helsinki de 1975 (the Evaluation, Support and Prevention Unit).

2. Variáveis

Após explicar aos pacientes sobre o estudo e obter Consentimento Informado, o investigador avaliou as variáveis clínicas e sócio-demográficas de cada paciente e administrou a versão espanhola da Young Mania Rating Scale (YMRS), a versão espanhola de Hamilton Depression Rating Scale (HDRS-17) e a Avaliação Global da Funcionalidade (GAF) para avaliar a estabilidade dos pacientes e a funcionalidade global. Toda a medicação prescrita aos pacientes também foi registrada nesta visita. Por fim, o investigador aplicou a FAST. Os entrevistadores eram cegos quanto à administração da FAST e da GAF.

Sessenta e um controles sadios foram selecionados através da Entrevista Clínica Semi-Estruturada (DSM-IV TR), para excluir sujeitos com história psiquiátrica prévia. Controles não apresentavam parente em primeiro grau com doenças psiquiátricas no momento em que a entrevista foi feita. O grupo controle foi recrutado de um grupo de voluntários sadios do Hospital de Clínicas de Barcelona. As variáveis sócio-demográficas e a FAST foram registradas após a obtenção do Consentimento Informado.

3. FAST

3.1. Desenvolvimento

A FAST foi desenvolvida no Programa de Transtorno do Humor Bipolar de Barcelona, Espanha, com o objetivo de avaliar as dificuldades na funcionalidade, levando em conta os principais problemas apresentados pelos pacientes com transtornos mentais, especialmente, pacientes bipolares. A versão inicial incluiu 56 itens, divididos em 10 áreas específicas, como, autonomia, trabalho, cognição, finanças, insight, relação marital, conhecimento e aceitação pela doença, estratégias para lidar com altos e baixos, uso da medicação e auto-julgamento. Essa primeira versão foi testada em um estudo piloto com 10 pacientes bipolares e 10 controles. Após análises preliminares, a escala foi discutida em um encontro com “experts” da Espanha, Brasil e Inglaterra, onde várias modificações foram feitas e alguns itens foram rejeitados. Então, a versão final da FAST foi concluída. A escala está disponível em dois idiomas: espanhol e inglês (ver em anexo) e outras versões estão em andamento.

3.2. Descrição

A FAST é uma escala hetero-administrada, devendo ser aplicada por um clínico treinado e se refere à avaliação da funcionalidade dos pacientes durante os últimos 15 dias. É um instrumento fácil de aplicar e que requer pouco tempo para sua aplicação. Consiste em 24 itens, que estão divididos em seis áreas específicas da funcionalidade:

1) Autonomia se refere à capacidade do paciente em fazer coisas independentemente e tomar suas próprias decisões;

2) Trabalho se refere à capacidade para manter um emprego remunerado, eficácia em executar as tarefas do trabalho, trabalhar de acordo com seu nível de escolaridade e ser remunerado de acordo com o cargo ocupado;

3) Cognição está relacionada com a habilidade para se concentrar, fazer cálculos mentais, resolver problemas, aprender e recordar novas informações;

4) Finanças envolve a capacidade para administrar de forma equilibrada o dinheiro;

5) Relações Inter-pessoais se refere às relações com amigos, família, atividades socias, relações sexuais e habilidade para defender suas idéias e opiniões;
6) Lazer se refere à capacidade para realizar atividades físicas (esporte, exercício) e *hobbys*.

Todos os itens são classificados em uma escala de 4 pontos, onde 0 representa nenhuma dificuldade, 1 pouca dificuldade, 2 moderada dificuldade e 3 grave dificuldade. O escore global é obtido com a soma dos escores de cada item. Quanto mais altos os escores, mais séria são as dificuldades, o que faz a escala, na realidade, ser uma medida de disfuncionalidade.

4. Características Psicométricas:
Nós analisamos o tempo de aplicação, consistência interna, validade concorrente, validade discriminante para detectar diferenças entre pacientes eutímicos e agudos, análise fatorial e confiabilidade Teste-Reteste. Exceto para a confiabilidade Teste-Reteste, as características da FAST baseiam-se na primeira administração do questionário, incluindo todos os sujeitos que entraram na análise, na verdade, simulando o uso clínico normal.

4.1. Nós avaliamos a percentagem de pacientes que respondeu à escala por completo. Também medimos o tempo gasto para responder o instrumento como uma medida de rapidez da escala, facilitando seu uso por clínicos atarefados, para os ensaios clínicos e outros estudos.

4.2. Consistência Interna determina se cada uma das questões mede o mesmo conceito. A consistência interna foi avaliada pelo alfa de Cronbach's para o escore total e para o escore individual de cada questão da FAST. A correlação entre cada domínio e os escore total foi calculada.

4.3. Validade concorrente foi avaliada através da comparação entre os escore total da FAST e os escore total da GAF através do coeficiente de correlação bisserial[21].A GAF foi escolhida porque é provavelmente o principal instrumento para avaliar funcionalidade em transtornos mentais.

4.4. O ponto ótimo da FAST foi determinado atravé da curva ROC.

4.5. Confiabilidade do Teste-reteste: para avaliar a confiabilidade do teste-reteste, 15 sujeitos que permaneceram com estado de humor estável, avaliados pela YMRS, HDRS-17 e GAF, por pelo menos uma semana, foram identificados. Estes 15 sujeitos então participaram do Reteste, respeitando o intervalo de uma semana.

4.6. Validade discriminante para detectar diferenças entre pacientes eutímicos e agudos: os participantes foram estratificados em eutímicos, maníacos, deprimidos e mistos de acordo com os critérios do DSM-IV TR. ANOVA foi realizada para avaliar se o escore total da FAST é sensível para medir a gravidade dos sintomas.

4.7. A análise fatorial ortogonal através da rotação matrix foi utilizada para descrever a estrutura interna de cada domínio da FAST.

5. Análise Estatística:

A análise estatística foi realizada usando SPSS para Windows - Versão 12.0 (SPSS Inc., Chicago, IL, USa). O Coeficiente de Pearson foi usado para avaliar a correlação entre os escores da FAST e os escores da GAF e para examinar a confiabilidade Test-Retest. A Consistência interna foi analisada usando o alfa de Cronbach's. Os escores totais da FAST dos quatro grupos (eutímicos, maníacos, deprimidos ou mistos) foram comparados usando a one-way ANOVA e aqueles que apresentaram diferença

estatisticamente significativa foram testados pelo método de Tukey HSD. Coeficiente de correlação intra-classe foi conduzido para avaliar a confiabilidade entre o teste e reteste. A rotação foi realizada pelo método de Varimax.

Resultados:

Setenta e três pacientes eutímicos, 14 deprimidos e 16 maníacos foram selecionados para participar do estudo. A idade média dos pacientes foi de 45 anos (desvio padrão [DP: 13.66, media: 45.45, faixa etária: 22 to 82) e a idade média dos controles foi de 49 anos (desvio padrão [DP:17.66, média 49.16, faixa etária: 22 to 81). A Tabela 1 descreve as principais características clínicas e sócio-demográficas da amostra estudada, que consistiu de 51.5% de mulheres no grupo de pacientes e de 42.6% de mulheres no grupo controle.

Entre os 101 pacientes bipolares, os estabilizadores de humor foram os fármacos mais comumente prescritos (81.6%), incluindo lítio (59.2%), valproato (13.6%) e carbamazepina (9.7%); 12.6% deles tomavam lamotrigina; 63.1% antipsicóticos, 30.1% antidepressivos e 48.5% ansiolíticos.

Todos os itens da FAST foram respondidos por 99% (n=100) dos pacientes que participaram do estudo. Nenhum paciente se negou a completar o questionário. O tempo médio gasto para completar o questionário foi de 6.00 minutos (variando de 2 à 12; DP: 2.79) para a amostra total, 5.69 (DP:2.67) para os eutímicos, 5.29 (DP: 1.24) para os deprimidos e 7.25 (DP:3.26) para os maníacos. Não detectamos diferença entre os grupos (F=2.65; p=0.075). Em função disto, a escala mostrou-se um instrumento de rápida aplicação e aceitação.

O coeficiente de consistência interna para a escala total foi muito satisfatório, com alfa de Cronbach's igual a 0.909, indicando que todos os itens são suficientemente homogêneos. A FAST também mostrou uma alta consistência interna. Os resultados estão descritos na tabela 2.

A validade concorrente foi analisada através da comparação com a GAF, a qual mostrou forte correlação ($r=-0.903$; $p<0.001$). Estes resultados indicam que pacientes com boa funcionalidade avaliados pela FAST (baixos escores) obtiveram altos escores na GAF, assim como demonstrado na figura 1, uma vez que, os escores da FAST medem disfuncionalidade e os escores da GAF medem funcionalidade.

Nós analisamos a capacidade discriminativa entre pacientes e controles através da curva ROC. A área sob a curva foi 0.86, 95%CI: (0.809, 0.917), próximo de 1, indicando uma boa capacidade. O ponto de corte foi estabelecido em valores igual ou superior a 11, onde se obteve uma sensibilidade de 72% e uma especificidade 87%. Escores menores que 11 indicam boa funcionalidade e escores de 11 ou mais indicam pior funcionalidade. O escore total médio da FAST em pacientes foi 25.44 (0-66; SD:16.48) e em controles foi 6.07(0-20; SD: 4.72).

Coeficiente de correlação intra-classe foi 0.98 ($p<0.01$), assim como mostrado na tabela 2. A YMRS, HDRS-17 e GAF foram avaliadas durante o teste e o reteste para garantir a estabilidade do estado de humor dos pacientes. Estes resultados indicam que a FAST foi estável e não sofreu modificações em função da variação natural do estado de humor dos pacientes avaliadas pelas escalas clínicas de HDRS e YMRS.

O escore total da FAST foi menor em eutímiocos quando comparados com os pacientes maníacos e deprimidos, conforme mostrado na figura 2.

A validade discriminante foi usada para detectar diferenças entre os pacientes eutímicos (18.55 ± 13.19; $F=35.43$; $p<0.001$) quando compardos aos maníacos (40.44 ± 9.15) ou deprimidos (43.21 ± 13.34) como mostrados na tabela 2.

Após a análise fatorial ortogonal (usando método de Varimax), a escala se dividiu em 5 estruturas, conforme mostrado na tabela 4. Nesta análise foi observado que os relacionamentos inter-pessoais e as atividades de lazer foram considerados no mesmo domínio.

Discussão:

Altas taxas de disfuncionalidade entre os pacientes bipolares, inclusive entre aqueles cujos sintomas têm remitido, têm sido documentado em muitos estudos. Falhas cognitivas, falhas no trabalho, dificuldades nas tarefas de casa, dificuldades nos relacionamentos inter-pessoais, dificuldades nas atividades de lazer e nas atividades sexuais são os principais problemas apresentados pelos pacientes. No entanto, a maioria dos instrumentos disponíveis até o momento tem focado em medidas globais ou limitadas da funcionalidade, mais que examinar áreas específicas da atividade psicossocial, além de serem muito extensos. Conseqüentemente, o desenvolvimento de instrumentos específicos para avaliar funcionalidade em THB é necessário e, neste contexto, a FAST torna-se particularmente útil.

A FAST consiste em vinte e quatro itens que avaliam seis áreas específicas da funcionalidade, como, autonomia, trabalho, cognição, finanças, relações inter-pessoais e lazer. A vantagem da FAST é o fato de que é um instrumento simples, de fácil aplicação e que requer pouco tempo para sua administração. Além disso, a FAST é extremamente prática, facilitando seu uso na clínica e no âmbito da pesquisa. O instrumento também está disponível em dois idiomas, Espanhol e Inglês.

As características psicométricas da FAST mostraram alta consistência interna em todos os itens, com alfa de Cronbach's total igual a 0.9. Além disso, nós encontramos bons resultados no que diz respeito à validade concorrente, à validade discriminante para detectar diferenças entre pacientes eutímicos e agudos, e à análise fatorial. A confiabilidade do Teste-reteste, que foi avaliada somente em pacientes que permaneceram estáveis, mostrou resultados similares. O escore médio para o grupo Teste foi 37.73 (DP: 16.79, variando de 13 to 66) enquanto que para o grupo Reteste foi 34.87 (DP: 16.14, variando de 12 to 64). A FAST mostrou ser sensível para detectar diferenças entre os estados de humor, uma vez que, pacientes eutímicos mostraram resultados de funcionalidade duas vezes melhor que os pacientes deprimidos, maníacos ou mistos. Estudos prévios mostraram moderada disfuncionalidade em

áreas específicas e que a persistência dos sintomas depressivos estavam associadas com uma pior funcionalidade. Strakowski e col. (2000) relataram que a recuperação funcional e, em particular as relações inter-pessoais, estavam associadas com a recuperação dos sintomas maníacos/mistos. Não obstante, nós também encontramos que a gravidade dos sintomas estava associada com altos escores da FAST e, consequentemente, uma pior funcionalidade.

Neste estudo, determinamos um ponto de corte igual ou superior a 11, porque neste valor obtivemos excelentes características discriminantes, com sensibilidade igual a 72% e especificidade igual a 87%. O escore médio da FAST foi 25.44 para pacientes (0-66; DP: 16.48) e 6.07 para voluntários sadios (0-20; DP: 4.72); sendo que somente cinco controles apresentaram escores superiores a 11. Estes resultados são consistentes com estudos mais antigos, sugerindo que as dificuldades na funcionalidade não são restritas a pacientes agudos e também ocorrem durantes os períodos inter-episódios.

Considerando a validade concorrente, a FAST mostrou uma forte correlação negativa com a GAF, que é o principal instrumento para avaliar o nível de funcionalidade. Os escores da GAF variam de 0 a 100, e o resultado obtido pela GAF é uma avaliação global da funcionalidade, onde altos escores representam melhor funcionalidade. Ao contrário da GAF, a FAST avalia domínios específicos da funcionalidade e também identifica o nível de disfuncionalidade em cada área, ou seja, altos escores representam alta disfuncionalidade e por isto existe uma correlação negativa entre a FAST e a GAF, conforme esperado.

Existem outros instrumentos para avaliar funcionalidade, tais como a WHO-DAS-II, a Short-Term -36 (SF-36), a SAS e a LIFE. WHO-DAS é um instrumento desenvolvido pela Organização Mundial Da Saúde, capaz de medir objetivamente funcionalidade. No entanto, este instrumento compreende uma extensiva entrevista, o que limita seu uso na prática clínica, além de avaliar muitos domínios físicos que são menos importantes que os mentais, para pacientes psiquiátricos, em particular,

pacientes bipolares [27]. Por outro lado, a SF-36 é um instrumento de auto-julgamento, consistindo de 36 itens e oito sub escalas (variando 0-100) medindo os domínios da funcionalidade física e social, assim como saúde geral e emocional [23;28]. A escala de Ajustamento Social (SAS) é um instrumento que de larga duração que avalia detalhadamente múltiplos domínios da funcionalidade social, o que limita seu uso na prática clínica e pesquisa. Além disso, é mais comumente usado para avaliação da depressão. O Questionário de Funcionalidade da Vida (LIFQ) é um rápido instrumento que avalia as atividades em casa, as atividades de lazer (família e amigos), além de avaliar minunciosamente o domínio trabalho [27]. No entanto, estas escalas não avaliam importantes áreas da funcionalidade, tais como, a cognição e a parte financeira. Apesar disto, as escalas de auto-julgamento que disfuncionalidade em pacientes psiquiátricos, e em particular, pacientes bipolares, não são confiáveis devido a extensa psicopatologia apresentada por estes pacientes, o que faz com que eles super ou subestimem a própria incapacidade [5;29;30]. No entanto, até o presente momento, os instrumentos disponíveis não foram desenvolvidos para medir problemas de saúde particularmente associados ao THB. Isto reflete em uma falta de padronização dos instrumentos usados entre os estudos, o que resulta em dificuldades na hora de interpretar os resultados obtidos. Além disso, a validação de instrumentos em outros idiomas, em especial, o espanhol é extremamente importante porque o Espanhol é um idioma falado por mias de 352 milhões de pessoas no mundo [11;18;3132;33]. Neste contexto, a FAST, ao contrário dos instrumentos acima descritos, foi desenvolvida levando em conta, as principais dificuldades apresentadas pelos pacientes psiquiátricos, em especial, pacientes bipolares, descritas na literatura e escalas mais antigas, sendo uma nova opção para avaliação de disfuncionalidade em áreas onde especificamente os pacientes apresentam as maiores dificuldades.

Conclusão:

Concluindo, a FAST mostrou fortes características psicométricas e foi sensível em detectar diferenças entre pacientes eutímicos e agudos. Além disso, é um instrumento hetero-administrado, simples, de fácil aplicação, que requer pouco tempo para sua completa implementação, e está desde já disponível para o uso na prática clínica e no âmbito da pesquisa. A FAST oferece a avaliação dos domínios específicos da funcionalidade de pacientes bipolares, e poderia ajudar na elaboração de estratégias de reabilitação funcional para estes pacientes, sendo capaz também de avaliar o efeito das intervenções farmacológicas e psicosocias sobre a funcionalidade de pacientes psiquiátricos, tornando-se válida, confiável e útil para o uso no THB.

Agradecimentos:

** Este estudo foi financiado em parte pela CAPES (Brasil) e Stanley Medical Research Institute, The Institute Carlos III. FIS (PI05206).

Tabela 1: Variáveis Clínicas e Demográficas

Variáveis Clínicas E Demográficas	Pacientes Bipolares		Grupo Controle	
	Média	DP	Média	DP
Idade	45.45	13.66	49.16	17.66
Idade de início	27.82	11.84		
Cronicidade	17.92	11.51		
Episódios totais	12.35	15.06		
Episódios maníacos	3.43	4.61		
Episódios hipomaníacos	3.00	9.43		
Episódios depressivos	5.60	6.67		
Episódios mistos	0.51	1.00		
Hospitalização	1.93	1.96		
Tentativas de suicídio	1.44	0.49		
HDRS	5.41	7.17		
YMRS	4.08	6.67		
GAF	63.90	19.05		
	N	%	n	%
Sexo				
Mulheres	49	48.5	35	57.4
Homens	51	51.5	26	42.6
Bipolar tipo I	89	88.3		
Bipolar tipo II	11	10.7		
Bipolar NOS	1	1		

Tabela 2: Confiabilidade Teste-Reste

N=15	média	DP	méida	DP	Intraclass correlação	F	gl	p	t teste	F	gl	p
FAST	37.73	16.79	34.87	16.14	0.98	40.98	14	0.0001	0.48	0.006	28	0.94
GAF	49.40	17.80	52.53	16.74	0.95	18.63	14	0.0001	-0.50	0.29	28	0.60
HDRS	10.53	10.21	9.87	9.99	0.87	7.59	14	0.0001	0.18	0.047	28	0.83
YMRS	9.80	10.10	9.00	8.44	0.93	14.23	14	0.0001	0.24	1.47	28	0.24

Legend: Nós encontramos uma significativa correlação intra-classe entre o Teste e o Reteste (ICC=0.98; F=40.98; p<0.0001). A média dos escores da YMRS, HDRS-17 e GAF dos pacientes permaneceram estáveis durante a avaliação do Teste e Reteste.

Tabela 3: Análise Fatorial

FAST	1	2	3	4	5
EF 5	0.938				
EF 9	0.908				
EF 7	0.902				
EF 6	0.882				
EF 8	0.852				
EF 17		0.741			
EF 18		0.628		0.437	
EF 21		0.596			
EF 24		0.577	0.544		
EF 23		0.552			
EF 20		0.466			
EF 19		0.403			
EF 12					
EF 13			0.746		
EF 14			0.694		
EF 11			0.668		
EF 10			0.480		
EF 4				0.741	
EF 1				0.724	
EF 3			0.407	0.693	
EF 2				0.531	
EF 22					
EF 16					0.897
EF 15					0.870

Legenda: Coeficientes menores que 0.42 estão omitidos

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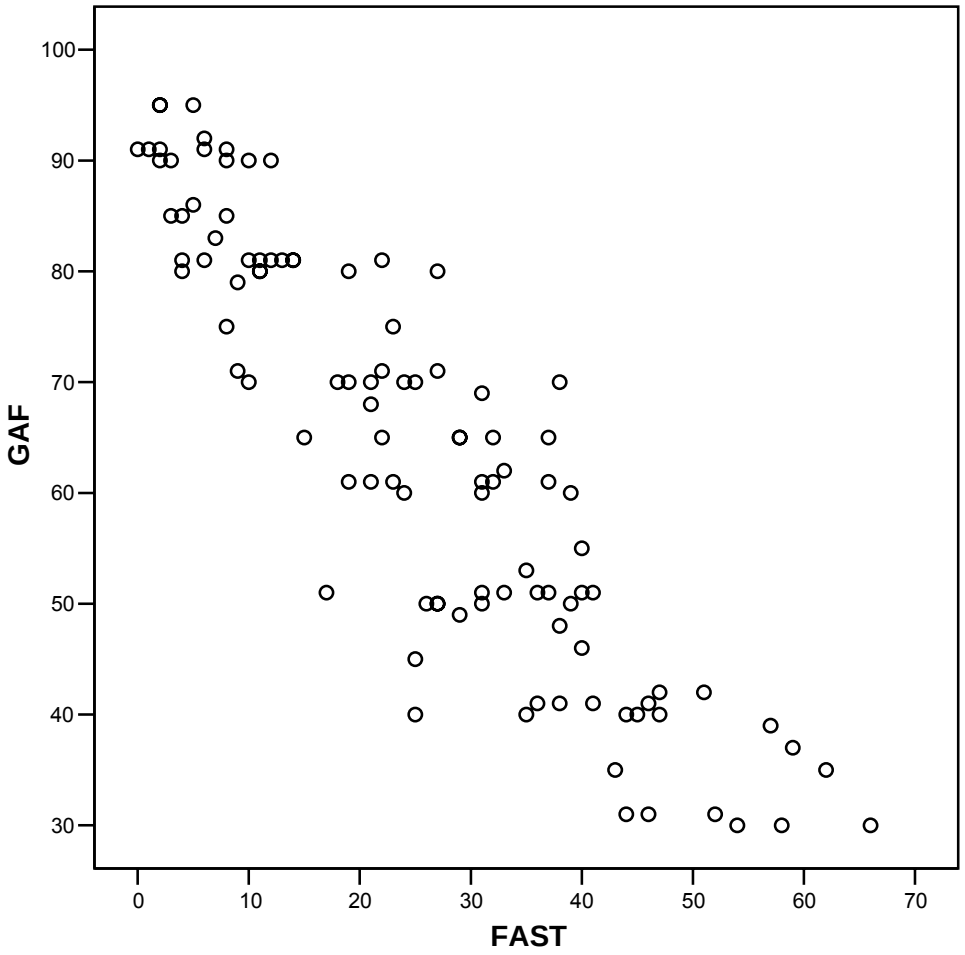
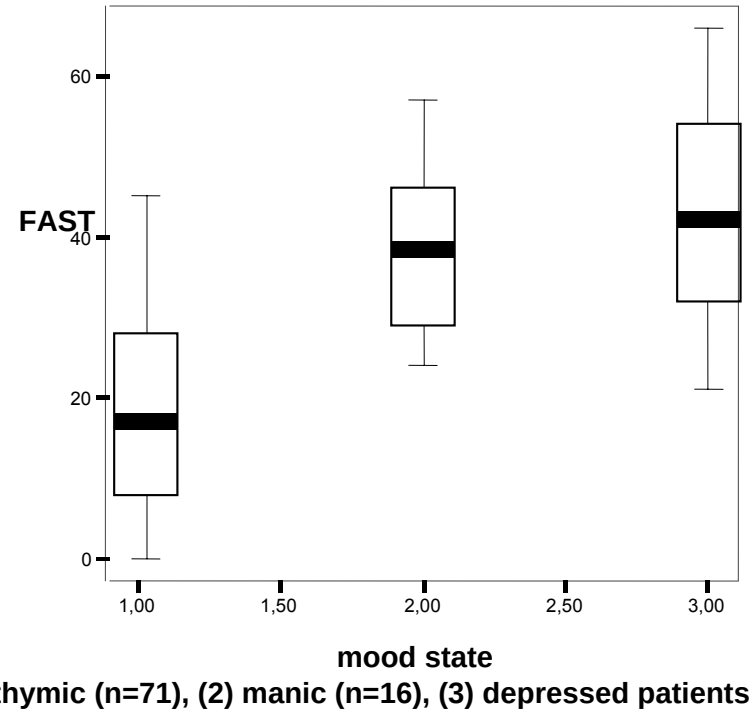
Figura 1: Correlação de Pearson entre os escores da GAF e os escores da FAST



Legenda: Nós encontramos significativa correlação negativa entre os escore total da FAST e da GAF (r=-0.903; p<0.001). Estes resultados indicam que pacientes com baixos escores na FAST, ou seja, alta funcionalidade, obtiveram altos escores na GAF, mostrando que a FAST avalia disfuncionalidade e a GAF avalia funcionalidade e por isto, estão negativamente correlacionadas.

Figura 2: Escores da FAST em diferentes estados de humor



Legenda: A media dos escores da FAST foi 18.55±13.19 para os eutímicos (1), 40.44±9.15 para os maníacos e 43.21±13.34 para os deprimidos. Nós realizamos uma ANOVA seguida do teste de Tukey test e encontramos uma diferença significativa entre eutímicos (18.55; $F=35.43$; $p<0.001$) e pacientes agudos.

APPENDIX I:

PRUEBA BREVE DEL EVALUACIÓN DEL FUNCIONAMIENTO (FAST)

¿Cuál es el grado de dificultad del paciente en relación con los siguientes aspectos? Interrogue al paciente respecto a las áreas de funcionamiento que se especifican a continuación, utilizando la siguiente escala: (0): Ninguna, (1): Poca, (2): Bastante o (3): Mucha

AUTONOMIA				
1. Encargarse de las tareas de casa	0	1	2	3
2. Vivir solo	0	1	2	3
3. Hacer la compra	0	1	2	3
4. Cuidar de sí mismo (aspecto físico, higiene)	0	1	2	3
FUNCIONAMIENTO LABORAL				
5. Realizar un trabajo remunerado	0	1	2	3
6. Acabar las tareas tan rápido como era necesário	0	1	2	3
7. Trabajar en lo que estúdio	0	1	2	3
8. Cobrar de acuerdo con el puesto que ocupa	0	1	2	3
9. Alcanzar el rendimiento previsto por la empresa	0	1	2	3
FUNCIONAMIENTO COGNITIVO				
10. Concentrarse en la lectura, película	0	1	2	3
11. Hacer cálculos mentales	0	1	2	3
12. Resolver adecuadamente un problema	0	1	2	3
13. Recordar el nombre de gente nueva	0	1	2	3
14. Aprender una nueva información	0	1	2	3
FINANZAS				
15. Manejar el propio dinero	0	1	2	3
16. Hacer compras equilibradas	0	1	2	3
RELACIONES INTERPERSONALES				
17. Mantener una amistad	0	1	2	3
18. Participar en actividades sociales	0	1	2	3
19. Llevarse bien con personas cercanas	0	1	2	3
20. Convivencia familiar	0	1	2	3
21. Relaciones sexuales satisfactorias	0	1	2	3
22. Capaz de defender los propios intereses	0	1	2	3
OCIO				
23. Praticar deporte o ejercicio	0	1	2	3
24. Tener una afición	0	1	2	3

APPENDIX II:

FUNCTIONING ASSESSMENT SHORT TEST (FAST)

To what extent is the patient experiencing difficulties in the following aspects? Ask the patient about the areas of difficulty in functioning and score according to the following scale: (0): no difficulty, (1): mild difficulty, (2): moderate difficulty, (3): severe difficulty.

AUTONOMY				
1. Taking responsibility for a household	0	1	2	3
2. Living on your own	0	1	2	3
3. Doing the shopping	0	1	2	3
4. Taking care of yourself (physical aspects, hygiene)	0	1	2	3
OCCUPATIONAL FUNCTIONING				
5. Holding down a paid job	0	1	2	3
6. Accomplishing tasks as quickly as necessary	0	1	2	3
7. Working in the field in which you were educated	0	1	2	3
8. Occupational earnings	0	1	2	3
9. Managing the expected work load	0	1	2	3
COGNITIVE FUNCTIONING				
10. Ability to concentrate on a book, film	0	1	2	3
11. Ability to make mental calculations	0	1	2	3
12. Ability to solve a problem adequately	0	1	2	3
13. Ability to remember newly-learned names	0	1	2	3
14. Ability to learn new information	0	1	2	3
FINANCIAL ISSUES				
15. Managing your own money	0	1	2	3
16. Spending money in a balanced way	0	1	2	3
INTERPERSONAL RELATIONSHIPS				
17. Maintaining a friend or friendships	0	1	2	3
18. Participing in social activities	0	1	2	3
19. Having good relationships with people close you	0	1	2	3
20. Living togheter with your family	0	1	2	3
21. Having satisfactory sexual relationships	0	1	2	3
22. Being able to defend your interests	0	1	2	3
LEISURE TIME				
23. Doing exercise or participing in sport	0	1	2	3
24. Having hobbies or personal interests	0	1	2	3

6.3. ARTIGO 3:

Functional impairment in patients with remitted bipolar disorder

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Competing Interests:

"The authors declare that they have no competing interests related to this report."

Acknowledgements:

This work was supported by grants from the CAPES (Brazil), Spanish Ministry of Health, Instituto de Salud Carlos III, (FIS:PI050206), the Spanish Ministry of Health, Instituto de Salud Carlos III, Red de investigation en Enfermedades Mentales REM-TAP Network.

ABSTRACT

***Objectives*:** Although depressive and manic symptoms are associated with marked functional impairment, a number of studies have now shown that some individuals with bipolar disorder have significant intercritical psychosocial impairment. In this naturalistic study, our aim was to assess functional impairment in six specific domains of functioning in a sample of euthymic patients with bipolar disorder.

***Method*:** Patients and healthy controls were recruited from the Bipolar Disorder Program at the Clinic Hospital of Barcelona. A Structured Clinical Interview for DSM-IV-TR (SCID), Hamilton Depression Scale (HAM-D), and Young Mania Rating Scale (YMRS) were used for diagnostic assessment and euthymia criteria. The Functioning Assessment Short Test (FAST) was employed to assess overall and specific domains of functional impairment.

***Results*:** The mean FAST score was 18.55±13.19 for patients and 6.07± 4.72 for controls ($p<0.001$). There were differences between patients and healthy volunteers in specific areas of functioning, such as autonomy, occupational functioning, cognitive functioning, financial issues, and interpersonal relationships ($p<0.005$). A major effect size was found in occupational functioning (1.16), cognitive functioning (0.91), and autonomy (0.88).

***Conclusion*:** Euthymic bipolar disorder patients experience difficulties in gravel psychosocial domains compared to healthy controls. The most affected domains are occupational, cognitive functioning, and autonomy. There is moderate dysfunction involving interpersonal relationships, and especially difficulties with family relationships and social activities.

***Key words*:** functional impairment, functioning, bipolar disorder.

Introduction:

Bipolar Disorder (BD) represents a major public health problem, which can lead to severe disruptions in family, social, and occupational functioning, in addition to increased mortality [1], and significant caregiver burden [2;3]. The World Health Organization (WHO) identified BD as the sixth leading cause of disability-adjusted life years in the world among people ages 15 to 44 [4;5]. Subjects with BD experienced higher health care costs, job absenteeism, and short-term disability payments than subjects without BD [6].

Declines in job status and income, marital failure, and deficits in interpersonal relationships, enjoyment of recreational activities, and overall contentment are the main difficulties reported by bipolar patients [4;5;7;8]. In addition, the cognitive disability and the chronic profile of the illness have a direct impact on the psychosocial functioning of these subjects [9-16].

Recent reports showed that patients with subsyndromal depressive symptoms experienced impairments in role functioning that were 3 to 6 times greater than those who were not depressed [17-20]. Although depressive and manic symptoms were associated with marked functional impairment, a number of studies have now shown that some individuals with BD have significant intercritical psychosocial impairment[21-24]. Despite this, the extent to which individuals return to full functioning during euthymia has been relatively understudied [25;26].

Our aim was to assess functional impairment in six specific domains of functioning in a sample of euthymic bipolar patients and controls. Some a priori hypothesis, such as: We hypothesized that a patient with BD in a euthymic state would have functional impairment, especially in the autonomy, occupational and relationship/interpersonal domains. Our design is intended to ensure that we are measuring the impact of BD itself, while also minimizing any possible distortion due to acutely depressed and manic mood.

Methods:

Study Subjects

Patients:

A sample of 71 euthymic patients was recruited from the Bipolar Disorder Program at the Clinic Hospital of Barcelona. Subjects gave written informed consent to participate in this study. Subjects who met the following inclusion criteria were enrolled: age older than 18 years; meeting DSM-IV-TR criteria for bipolar affective disorder type I or II by the Structured Clinical Interview for DSM-IV-TR (SCID-P) [27]; meeting euthymia criteria defined as a score on the 17-item Hamilton Depression Rating Scale (HDRS) [28] < 9, and a Young Mania Rating Scale Score (YMRS) [29] < 7 [30].

Controls:

Sixty-one healthy controls were screened through the SCID (DSM-IV TR) to exclude a past psychiatric history. This sample reported having no first-degree relatives with bipolar disorder or other psychiatric disorders in an interview prior to screening. This group was recruited from a pool of normal volunteers who gave written informed consent to participate in this study.

Assessments:

The SCID (DSM-IV TR) was administered by trained personnel to each subject for diagnosis. Demographic variables were obtained from the structured interview with the patient and their relatives and from their medical records.

Outcome assessments: the Functioning Assessment Short Test (FAST) was used to provide an objective assessment of the level of functioning. This is a 6-minute, interviewer administered test with 24 items that measure functioning over the preceding 15 days in the following 6 specific areas: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time [31]. Items are

rated using a 4-point scale, (0)=no difficulty, (1)=mild difficulty, (2)=moderate difficulty, and (3)=severe difficulty. A score of 0 on each item indicates no difficulty, and a score ≥ 1 on any item indicates some degree of functional impairment in that domain. The FAST is not a quality scale of life style. It measures disability as assessed by the investigator, aiming at an objective evaluation of improvement in the most relevant areas of functioning [31].

The study was approved by the Hospital Clinic of Barcelona Ethics Committee.

Statistical Analyses:

Student's *t* test was used to assess the relationship between age, to compare the mean scores on the FAST (total and specific scores) between patients and controls. Effect size (ES) was used to measure the magnitude of each domain between the two groups. An ANOVA analysis was conducted to assess differences between categorical variables (work situation), gender and total FAST scores. We assume that our data did not follow a normal distribution and therefore the violation of assumptions underlying the t-test performed. There are evidence that t-test can be used with the same accuracy to analyse the data than the non-parametric test[32.] Therefore, we performed the non-parametric Mann-Whitney test and we did not find differences in the results**.** All statistical analyses were performed using the SPSS version 12.0 software package.

Results:

Table 1 describes the principal socio-demographic and clinical characteristics of the study samples. Patients and controls did not differ in sex, age, or educational level. In the control sample, 42.6% were females, 25.9% had a high level of functioning, and the mean age was 49.16 (SD: 17.66).

The total mean FAST score was 18.55 (SD: 13.19) for patients and 6.07 (SD: 4.72) for controls ($p<0.001$). There were significant differences between patients and healthy volunteers in specific domains of the FAST, such as autonomy ($t=5.17$; $p<0.001$), occupational functioning ($t=6.83$; $p<0.001$), cognitive functioning ($t=5.39$; $p<0.001$), financial issues ($t=2.09$; $p=0.04$). and interpersonal relationships ($t=3.72$; $p<0.001$). The largest difference between controls and patients was found in the occupational functioning domain (patient mean: 6.65, SD: 6.52; control mean: 1.08, SD: 1.99). In addition, employed patients showed better overall functioning than unemployed patients (employed: mean: 12.23, SD: 9.40; unemployed mean: 26.71, SD: 13.011, $p< 0.001$). We did not find a significant difference in the leisure time domain between two groups ($t=1.90$; $p=0.06$), as shown in Table 2.

We also determined the effect size for each domain of the FAST as shown in Table 2. The analysis of effect size pointed to marked differences between patients and controls in occupational functioning (Cohen's *d*: 1.16), cognitive functioning (Cohen's *d:* 0.91), and autonomy (Cohen's *d:* 0.88) while a moderate difference was observed in the interpersonal relationships domain (Cohen's *d:* 0.65), and weak difference in financial issues (Cohen's *d:* 0.35) and leisure time (Cohen's *d:* 0.33).

Table 3 shows the frequencies of FAST answers for patients and controls.

Discussion:

Although Kraepelin described a relatively good outcome for manic-depressive illness, BD has an impact on the patient's family, social, and work life, in addition to the stigma and prejudice that affect perception of the patient's quality of life. All of these factors lead to functional impairment, even in remission of mood symptoms, as confirmed in recent studies [12;23;33-36]. Patient opinion surveys may help to understand how patients live with their disorder, as well as their needs and wishes. For that reason, in this study, we examined functional impairment in euthymic bipolar patients during inter-episode intervals and demonstrated that these patients experience not only three-fold higher overall functional impairment than healthy controls, but also difficulties in six specific life domains, occupational functioning being the most affected.

Disability domains in bipolar disorder

In a detailed analysis, subjects with BD showed significantly more difficulties with autonomy, occupational functioning, cognitive functioning, financial issues and interpersonal relationships, as demonstrated by FAST scale scores in those specific domains compared with healthy controls.

1- Autonomy

Patients experienced difficulties in taking responsibility for care of their household, self-care, independence, and taking their medication. These hindrance experienced by remitted patients might result in an increase in the level of caregiver burden[37]. Our sample showed more difficulties in living alone, while they did better with basic self care, such as hygiene and habits. This fact is probably explained by the fact that living alone involves more responsibilities, financial autonomy, and an appropriate level of cognitive functioning.

2- Occupational functioning

Euthymic bipolar patients have the strongest impairment in this domain and a good number of them have permanent disability (18.3%). Of the employed patients (57.7%), some reported having problems with their jobs. The main problem was finishing their tasks as quickly as necessary. A quarter of them showed difficulties in achieving the expected performance and a quarter also had lower qualifications jobs. In addition, around 20% of the patients had lower earnings for the same job than non-bipolar subjects. Current employment status has been reported to be significantly associated with cognitive functioning [38]. Euthymic bipolar patients experience some cognitive impairment, so this may explain the functional problems reported in previous studies.. The presence of these job handicaps creates barriers to job retention and finding stable employment. Taking into account that the mean age of our sample was 45 years, these data indicate the magnitude of the negative financial impact and the interference of illness with the patient's life. In our study, we did not measure the economic impact of BD, but there are plenty of data on this issue. On average, employees in the United States with BD missed 18.9 workdays annually, while employees without BD missed 7.4 days per year [6]. The total health benefit costs of subjects with BD are higher than those of subjects without BD. Prescription drugs, sick leave, short-term disability and long-term disability have an estimated total cost of $60 billion [7;39].

3-Cognitive functioning

Recent studies point out a significant degree of cognitive impairment in euthymic bipolar patients and the persistence of this impairment over time. However, the subjective experience of being cognitively impaired and objectively measured neuropsychological disturbances do not necessarily coincide[40]. There is a significantly positive correlation between both[41]. Euthymic bipolar patients reported more difficulties in concentration, memory, and arithmetic abilities and, to a lesser degree, difficulties in problem solving and learning. Verbal recovery of information is the variable that best

predicts psychosocial outcome and difficulties in remembering long-term information are associated with occupational functioning in euthymic patients [16;42-44]. Impaired executive functions may partly lead to difficulties in retaining and recovering information, independent of mood state and phase of illness. There is a strong relationship between cognitive dysfunction and structural changes in prefrontal and temporolimbic structures and also hormonal and neurotrophic alterations that might explain the permanent impairment that patients report during the euthymic period[45-48].

4- Financial issues

Patients with mood disorders, especially during hypomanic episodes. may show behavioural problems including excessive spending and excessive shopping [49]. In our sample, we found that 15-20% of the patients experienced some degree of difficulty in handling money.

5- Interpersonal relationships

Despite symptomatic recovery, BD has a negative impact on patients' lives, interfering with quality of life and lifestyle [50]. Although interpersonal relationships may improve during the euthymic phase, almost a third of our sample reported some degree of difficulty in family and social activities. Some authors have also suggested that these are areas where patients report more barriers [51-54]. Stigmatization, feelings of rejection, and fear of ridicule may also explain these results [55]. Moreover, partner's stress, burden, marital and sexual satisfaction are important areas that patients identify as problematic. The side effects of medication might also possibly explain sexual difficulties. On the other hand, behavioural changes, specifically, irritability and inappropriate or volatile behaviour experienced by patients during hypo/manic episodes, could have an influence on interpersonal relationships [50]. A possible third factor could be changes in socioeconomic status. Restrictions in social activities and decreased income may change the dynamic of the marital relation [37;56]. In addition, high levels of expressed emotion and caregiver burden may adversely affect marital intimate relations, eventually resulting in separation and divorce [37;57].

6. Leisure Time

Although a number of studies have provided evidence of the negative impact of BD on life enjoyment [58], differences between patients and controls were only marginally significant with respect to leisure time. Moreover, another study reported that bipolar patients experienced higher scores in the leisure time satisfaction domain (24.02, SD: 5.87) than healthy controls (20.40, SD: 4.97) and than patients with schizophrenia (17.55, SD: 5.17) as determined by Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) [52]. This area of functioning may be one of the most strongly influenced by mood state at the time of the assessment.

It is important to highlight some methodological limitations. Firstly, this is a naturalistic study and we assessed functional impairment on only one occasion. A longitudinal study is underway. Secondly, the patients were enrolled in the Bipolar Disorders Program at the Hospital Clinic and University of Barcelona and it is possible that our sample represents a more severe illness profile. Finally, due to transversal design, we can not exclude any carry–over effects from previous manic/hypomanic or depressive episodes.

In conclusion, the most affected area of functioning in euthymic bipolar patients, showing the largest effect size, is occupational functioning. Unemployment was a strong predictor of poor overall functioning, and occupational dysfunction has been reported to be predictive of a short time to relapse [23].

During the past decade, a change of paradigm in the treatment of bipolar disorders started to develop when crucial findings regarding the impact of bipolar disorders on quality of life and social, cognitive, and occupational functioning suggested that therapy targets should be changed from symptomatic recovery to functional recovery [59]. In the very near future, further efforts are needed to improve functional outcome in individuals suffering from bipolar disorder. Medication and psychoeducation are useful interventions, but are not sufficient [60;61]. From the results of this study, it becomes clear that social interventions upon employment, such as promotion of protected jobs, affirmative action, and occupational counselling for bipolar patients might be the best way to address some of the major sources of functional disability in this population. Moreover, cognitive rehabilitation programmes might also become a useful approach, with a potential impact on the cognitive and occupational domains of disability.

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Table I: Demographic and clinical characteristics

	Patients (n=71)	
	Mean	SD
Age	44.99	13.51
Age at onset	27.51	11.18
Total episodes	11.89	15.20
Manic episodes	2.73	3.88
Depressive episodes	5.23	6.42
Number of hospitalisations	1.37	1.53
HAM-D	2.08	3.31
YMRS	1.07	2.07
	n=71	%
Gender (female)	34	47.9
Bipolar type I	59.85	84.3
Education		
High level	23	32.4
Low level	36.99	52.1
Student	9.02	12.7
Work situation		
Employed	40.97	57.7
Unemployed	12.99	18.3
Medical benefits	2.98	4.2
Disability	12.99	18.3
Marital status, married	24.99	35.2
Living alone	11.00	15.5
Rapid cycling	8.24	11.6
Alcohol abuse	11.64	16.4
Other substance abuse	3.90	5.5

Table 2: FAST total and specific domains in patients and controls

	Patients		Controls				
	Mean	**SD**	**Mean**	**SD**	**t**	**p**	**Cohen's d**
Total FAST	18.55	13.19	6.07	4.72	7.44	<0.001	1.26
Autonomy	2.32	2.95	0.39	1.00	5.17	<0.001	0.88
Occupational Functioning	6.65	6.52	1.08	1.99	6.83	<0.001	1.16
Cognitive Functioning	3.39	3.28	1.11	1.31	5.39	<0.001	0.91
Financial Issues	0.58	1.42	0.20	0.54	2.09	0.040	0.35
Interpersonal Relationships	3.79	3.11	1.90	2.65	3.72	<0.001	0.65
Leisure Time	1.89	1.80	1.38	1.28	1.90	0.06	0.33

Student's t test

Cohen's d

Table 3: Frequency of FAST answers in patient and control groups

	Pat	Cont	Pat	Cont	Pat	Cont	Pat	Cont
AUTONOMY	0	0	1	1	2	2	3	3
1. Taking responsibility for a household	64.8	88.5	14.1	8.2	15.5	3.3	5.6	0.0
2. Living on your own	60.6	90.2	7.0	4.9	8.5	1.6	23.9	3.3
3. Doing the shopping	70.4	95.1	11.3	3.3	11.3	1.6	7.0	0.0
4. Taking care of yourself	87.3	100	8.5	0.0	1.4	0.0	2.8	0.0
OCCUPATIONAL FUNCTIONING								
5. Holding down a paid job	57.7	91.8	1.4	0.0	1.4	3.3	39.4	4.9
6. Accomplishing tasks as quickly as necessary	65.9	86.9	26.8	13.1	4.9	0.0	2.4	0.0
7. Working in the field in which you were educated	75.6	86.9	12.2	0.0	7.3	1.6	4.9	11.5
8. Occupational earnings	80.5	80.3	12.2	18.0	7.3	0.0	0.0	1.6
9. Managing the expected work load	75.6	90.2	12.2	4.9	9.8	3.3	2.4	1.6
COGNITIVE FUNCTIONING								
10. Ability to concentrate on a book, film	52.1	90.2	22.5	6.6	19.7	3.3	5.6	0.0
11. Ability to make mental calculations	66.2	80.3	9.9	16.4	8.5	3.3	15.5	0.0
12. Ability to solve a problem adequately	70.4	82.0	21.1	14.8	4.2	3.3	4.2	0.0
13. Ability to remember newly-learned names	54.9	67.2	15.5	27.9	19.7	4.9	9.9	0.0
14. Ability to learn new information	64.8	83.6	16.9	16.4	11.3	0.0	7.0	0.0
FINANCIAL ISSUES								
15. Managing your own money	81.7	91.8	9.9	8.2	2.8	0.0	5.6	0.0
16. Spending money in a balanced way	87.3	88.5	4.2	11.5	4.2	0.0	4.2	0.0
INTERPERSONAL RELATIONSHIPS								
17. Maintaining a friend or friendships	70.4	75.4	15.5	18.0	8.5	3.3	5.6	3.3
18. Participating in social activities	63.4	65.6	16.9	16.4	8.5	6.6	11.3	11.5
19. Having good relationships with people close to you	83.1	95.1	12.7	4.9	2.8	0.0	1.4	0.0
20. Living together with your family	67.6	88.5	23.9	8.2	5.6	0.0	2.8	3.3
21. Having satisfactory sexual relationships	42.3	78.7	9.9	4.9	11.3	3.3	36.6	13.1
22. Being able to defend your interests	64.8	83.6	23.9	14.8	4.2	1.6	7.0	0.0
LEISURE TIME								
23. Doing exercise or participating in sports	43.7	39.3	11.3	26.2	7.0	14.8	38.0	19.7
24. Having hobbies or personal interests	70.4	80.3	16.9	16.4	5.6	3.3	7.0	0.0

6.3.1. ARTIGO 3 TRADUZIDO:

Disfuncionalidade em pacientes com Transtorno Bipolar em remissão

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"Submetido a J Clin Psychiatry"

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Conflito de Interesses:

"Os autores declaram não possuírem conflitos de interesse relacionados com este trabalho".

Agradecimentos:

Este trabalho foi financiado pela CAPES (Brasil), Spanish Ministry of Health, Instituto de Salud Carlos III, (FIS:PI050206), the Spanish Ministry of Health, Instituto de Salud Carlos III, Red de investigation en Enfermedades Mentales REM-TAP Network.

Resumo:

Introdução: Embora a sintomatologia depressiva e maníaca esteja relacionada com grandes dificuldades na funcionalidade, um grande número de evidências tem mostrado que indivíduos com transtorno bipolar apresentam tais dificuldades durante os períodos interepisódicos. Neste estudo naturalístico, nosso objetivo foi avaliar as dificuldades na funcionalidade em seis áreas específicas em uma amostra de pacientes bipolares eutímicos.

Métodos: Pacientes e controles sadios foram selecionados do Programa de Transtorno Bipolar do Hospital Clínic de Barcelona. Nós usamos a Entrevista Clínica Semi-Estruturada conforme o DSM-IV-TR (SCID), a escala de depressão (Hamilton Depression Rating Scale: HDRS) e de mania (Young Mania Rating Scale: YMRS) para avaliação do diagnóstico e dos critérios de eutimia. A Escala Breve de Funcionalidade (FAST) foi usada para avaliação total e em áreas específicas da funcionalidade.

Resultados: O escore médio da FAST foi 18.55±13.19 para pacientes e 6.07± 4.72 para os controles ($p<0.001$). Nós demonstramos diferença entre pacientes e controles em áreas específicas da funcionalidade, tais como: autonomia, trabalho, funcionalidade cognitiva, finanças e relacionamentos ($p<0.005$). Ainda, a análise do tamanho do efeito, demonstrou maior impacto nas áreas laboral (1.16), cognitiva (0.91) e autonômica (0.88).

Conclusão: Pacientes eutímicos apresentam disfuncionalidade quando comparados aos controles. As áreas mais afetadas foram a laboral, a cognitiva e a autonômica. Ainda, moderadas dificuldades foram demonstradas nos relacionamentos inter-pessoais, especialmente problemas com a família e nas atividades sociais.

Palavras-chaves: disfuncionalidade, funcionalidade, transtorno bipolar.

Introdução:

Transtorno do Humor Bipolar (THB) representa um sério problema de saúde pública, resultando em dificuldades nos relacionamentos familiares, sociais e no trabalho, além de ser clinicamente relevante pelas altas taxas de mortalidade (Goodwin and Jamison 1990), e maior necessidade de cuidados por terceiros (Reinares e col. 2007; Cooke e col. 1996). A Organização Mundial da Saúde apontou o THB como a nona patologia mais incapacitante entre adultos de 15 a 44 anos de idade (Vieta e col. 2007; Calabrese e col. 2003). Os custos de saúde para pacientes com THB são mais altos que os custos com pacientes sem THB, sendo principalmente representados pela ausência ao trabalho e pelos benefícios concedidos por licenças médicas de curta duração (Gardner e col. 2006).

Declínios no trabalho e salários mais baixos que a média da popualção, dificuldades na relação conjugal, nos relacionamentos inter-pessoais, e incapacidade para o lazer e para sentir-se bem, são os principais problemas apresentados por estes pacientes (Vieta e col. 2007; Sanchez-Moreno e col. 2007; Calabrese e col. 2003; Dean e col. 2004). Além disso, o deterioro cognitivo e o padrão crônico do THB promovem um impacto direto na funcionalidade destes indivíduos (Martinez Aran e col. 2007; Keck 2006; Depp e col. 2006; Hajek e col. 2005; MacQueen e col. 2001 review; Cannon e col. 1997; Goldberg e col. 1995; Rosen e col. 1983).

Estudos recentes mostraram que pacientes com sintomatologia depressiva apresentam três vezes mais disfuncionalidade que os pacientes não deprimidos (Altshuler e col. 2006; Altshuler e col. 2002; Kessler e col. 2006 prevalence; Coryell e col. 1998). Embora a sintomatologia depressiva e maníaca esteja associada com uma marcada incapacidade funcional, um grande número de estudos tem prontamente mostrado que pacientes bipolares apresentam disfuncionalidade durante o período de remissão (Fagiolini e col. 2005; Tohen e col. 2000; Strakowski e col. 2000). Apesar disto, a extensão com que pacientes eutímicos retornam à sua funcionalidade durante o período de eutimia tem sido pouco estudada (MacQueen 2000).

Nosso objetivo foi avaliar as dificuldades na funcionalidade considerando seis áreas específicas em uma amostra de pacientes com THB. Nosso delineamento permitirá avaliar o impacto da própria doença sobre a funcionalidade, minimizando o possível efeito da sintomatologia depressiva e maníaca.

Métodos:

Pacientes:

Uma amostra de 71 pacientes eutímicos foi selecionada do Programa de Transtorno Bipolar do Hospital Clínic de Barcelona. Sujeitos deram Consentimento Informado para participar do estudo. Os critérios de inclusão foram: sujeitos maiores de 18 anos; com diagnóstico de THB pelo DSM-IV-TR (tipo I ou II) avaliados pela Entrevista Clínica Estruturada (SCID) (Frist e col.); e que cumprissem critérios para eutimia definidos por escores menores que 9 na 17-Hamilton Depressive Rating Scale (HDRS) e escores menores que 7 na Young Mania Rating Scale (YMRS) (Vieta e col. 2001).

Controles:

Os controles foram selecionados de um pool de voluntários sadios do Hospital Clinic de Barcelona. Em todos eles, aplicamos o SCID (DSM-IV TR) para excluir qualquer história de doença psiquiátrica. Os controles não tinham familiares em primeiro grau com história de doença psiquiátrica e deram consentimento Informado para participar do estudo.

Avaliação Diagnóstica: Pesquisadores treinados aplicaram a Entrevista Clínica Estruturada segundo o DSM-IV-TR (SCID) para confirmar o diagnóstico de THB. Variáveis demográficas e clínicas também foram perguntadas durante a entrevista para o paciente ou para os familiares e foram revisadas na história clínica.

Avaliação dos Resultados: a Escala Breve de Funcionalidade (FAST) foi administrada com o objetivo de avaliar o grau de funcionalidade. A FAST é uma escala de avaliação clínica, de rápida aplicação (6 min.), que avalia as dificuldades na funcionalidade dos indivíduos considerando os últimos 15 dias. Consiste de 24 itens, os quais são divididos em 6 áreas específicas da funcionalidade, tais como: autonomia, trabalho, cognição, finanças, relacionamentos inter-pessoais e lazer. A

pontuação total da FAST varia de 0-72 pontos, e cada item pode apresentar pontuações que variam de 0-3 pontos, onde 3 representa grave dificuldade, 2 moderada dificuldade, 1 pouca dificuldade e 0 nenhuma dificuldade. A FAST não é uma escala de qualidade de vida. Ela mede disfuncionalidade, avaliando objetivamente as áreas mais relevantes da funcionalidade dos pacientes bipolares (Rosa e col 2007 submetido).

Este estudo foi aprovado pelo Comitê de Ética do Hospital Clinic de Barcelona.

Análise Estatística:

Teste t foi usado para avaliar a relação entre sexo e idade, para comparar as medias dos escores da FAST (total e específico) entre pacientes e controles. O cálculo do tamanho de efeito foi usado para medir a magnitude de cada domínio da FAST entre dos dois grupos. ANOVA foi conduzida para avaliar diferenças entre variáveis categóricas (trabalho ativo) e os escore total da FAST. Todas as análises foram realizadas no SPSS versão 12.0.

Resultados:

Tabela 1 descreve as principais características sócio-demográficas e clínicas do estudo. Pacientes e controles não diferiram quanto ao sexo, idade e nível de escolaridade. No grupo controle, 42.6% eram mulheres e 25.9% apresentavam alto nível de escolaridade.

A média total da FAST foi de 18.55 (DP: 13.19) para pacientes e 6.07 (DP: 4.72) para controles ($p<0.001$). Havia diferença entre pacientes e controles em 5 domínios da FAST: autonomia ($t=4.87$; $p<0.001$), trabalho ($t=6.41$; $p<0.001$), cognição ($t=5.01$; $p<0.001$), finanças ($t=1.97$; $p=0.04$) e relacionamentos inter-pessoais ($t=3.72$; $p<0.001$). Uma grande diferença entre pacientes e controles foi observada no domínio trabalho (pacientes, média: 6.65, DP: 6.52; controles, média: 1.08, DP: 1.99). Além disso, pacientes que continuavam trabalhando mostravam melhor funcionalidade que aqueles que não trabalhavam (empregados: média: 12.23, DP: 9.40; desempregados: média: 26.71, SD: 13.011, $p< 0.001$). Nós não encontramos diferenças entre pacientes e controles no domínio lazer ($t=1.85$; $p=0.06$), assim como mostrados na tabela 2.

Nós determinamos o tamanho do efeito para cada área da funcionalidade da FAST, assim como mostrado na tabela 2. Nesta análise, marcado impacto foi observado nas áreas da funcionalidade laboral (Cohen's *d*: 1.16), cognição, (Cohen's *d:* 0.91) e autonomia (Cohen's *d:* 0.88) enquanto que moderado impacto foi observado nos relacionamentos inter-pessoais (Cohen's *d:* 0.65) e fraco impacto no domínio financeiro (Cohen's *d:* 0.35) e de lazer (Cohen's *d:* 0.33).

Tabela 3 mostra as freqüências da FAST para pacientes e controles.

Discussão:

Embora Kraepelin tenha inicialmente descrito uma adequada funcionalidade durante os períodos interepisódicos, o THB oferece um importante impacto na vida social, familiar e no trabalho, além do estigma de ser um doente mental e dos prejuízos oferecidos na qualidade de vida destes pacientes. Todos estes fatores promovem disfuncionalidade, mesmo durante os períodos de remissão da doença, assim como recentemente demonstrado em diversos estudos (Fagiolini e col., 2005a;MacQueen e col., 2001a;Kusznir e col., 2000;Gitlin e col., 1995). Uma pesquisa junto aos pacientes nos ajudaria a compreender como eles convivem com sua doença, quais as suas reais necessidades e o que eles desejam. Por esta razão, neste estudo nós investigamos as dificuldades na funcionalidade em pacientes eutímicos durante os intervalos interepisódicos e demonstramos que estes pacientes apresentam três vezes mais dificuldades que os controles, sendo a área laboral, a mais afetada.

Áreas da Funcionalidade afetadas pelo THB

Em uma análise detalhada, nós demonstramos através da escala FAST, que pacientes apresentavam mais dificuldades que os controles nas áreas de autonomia, trabalho, cognição, finanças e relacionamentos inter-pessoais.

1- Autonomia

Pacientes apresentam dificuldades em assumir as responsabilidades domésticas, dificuldades em manter sua própria higiene, assim como se sentem incapazes de viver independentemente e de administrar sua própria medicação. As dificuldades autonômicas apresentadas pelos pacientes ainda quando eutímicos deve resultar em uma maior necessidade de cuidados por terceiros (Dore and Romans, 2001c). Nossos pacientes se sentiam capazes de manter os cuidados básicos de higiene e incapazes de morar sozinho. Isto provavelmente reflita o fato de que para morar sozinho eles

precisam ser independentes economicamente, assim como assumir mais responsabilidades domésticas, o que exige um bom nível de funcionalidade cognitiva.

2- Trabalho

Trabalho foi a área onde pacientes eutímicos relataram mais dififculdades e ainda 18.3% deles possuíam invalidez definitiva. Entre os pacientes que trabalhavam (57.7%), muitos deles relatavam ter problemas em seus trabalhos. O principal problema reportado foi dificuldade em executar as tarefas propostas tão rápido quanto era necessário. Um quarto deles ainda apresentava dificuldades em ter um bom rendimento em seu trabalho em relação aos demais e um quarto deles também trabalhava em um nível inferior ao seu grau de escolaridade. Além disso, 20% deles recebiam baixos salários quando comparados a pessoas sem THB. O nível de funcionalidade cognitiva do paciente parece interferir na atividade laboral (Dickerson e col., 2004). Diversos estudos têm demonstrado que pacientes eutímicos apresentam deterioro cognitivo, e isto poderia justificar os problemas na funcionalidade laboral. Particularmente, dificuldades na memória verbal e função executiva estão associadas com dificuldades no trabalho (Torrent e col., 2006;Martinez-Aran e col., 2005;Zarate, Jr. e col., 2000). As dificuldades no trabalho criam barreiras para encontrar e manter um emprego estável. Considerando que os pacientes têm em média 45 anos de idade, nossos resultados evidenciam o impacto negativo da doença na vida destes indivíduos. Neste estudo, nós não medimos o impacto econômico do THB, mas há uma série de estudos que avaliaram este tema. Em média, trabalhadores com THB faltam 18.9 dias/ano o trabalho, enquanto que trabalhadores sem THB faltam 7.4 dias/ano (Gardner e col., 2006a). Os gastos concedidos com benefícios médicos em pacientes bipolares são mais altos que para pessoas sem THB. Estima-se que 60 bilhões de dólares são gastos com medicamentos, pagamentos por licença médica de curta duração e invalidez nestes pacientes (Dean e col., 2004;Altshuler e col., 2006a).

3-Funcionalidade Cognitiva

Estudos atuais demonstram que pacientes eutímicos apresentam deterioro cognitivo e que este deterioro permanence ao longo do tempo. Embora as medidas subjetivas de avaliação de deterioro cognitivo e medidas objetivas como os testes neuropsicológicos nem sempre coincidam nos resultados (Burdock e col. 2005), há uma significativa associação entre elas (Martinez-Aran e col.,2005). Pacientes eutímicos relatam maiores dificuldades de concentração, dificuldades de memória e dificuldades para executar cálculos mentais e ainda em menor grau relatam dificuldades em resolver problemas e problemas com aprendizado. Falhas na função executiva resulta em problemas para reter e recuperar a informação aprendida independentemente do estado de humor ou da fase da doença. Recuperação verbal da informação é a melhor preditora da funcionalidade e as dificuldades em lembrar estas informações estão associadas com as dificuldades laborais dos pacientes, ainda durante os períodos de eutimia (Torrent e col. 2006; Martinez–Aran e col. 2004). A pobre funcionalidade apresentada pelos pacientes justifica porque o THB foi descrito como a sétima patologia no mundo em termos de sobrecarga não-fatal, avaliada pelo número de número de anos perdidos com marcada incapacidade (DALYs) (WHO 2001). Existe uma forte correlação entre as mudanças estruturais no sistema pré-frontal-temporal límbico e o deterioro cognitivo, assim como alterações neurotróficas e hormonais, as quais poderiam explicar as dificuldades permanentes que pacientes bipolares apresentam ainda durante a eutimia (Benabarre e col. 2002; Daban e col 2005; Ferrier e col. 2006; Rosa e col. 2006).

4- Finanças

Pacientes com THB, principalmente, quando maníacos podem apresentar mudanças no comportamento que resultam em sérias conseqüências financeiras como compras e gastos excessivos (Ramasubbu, 2004). Nós encontramos que 15-20% da amostra estudada apresentava algum grau de dificuldade em manejar suas finanças. Isto

sugere que, apesar de eutímicos, pacientes apresentam problemas com questões financeiras.

5- Relacionamentos Inter-pessoais

Apesar da recuperação sintomática, o THB tem um impacto negativo na vida destes pacientes, repercutindo em mudanças no estilo e qualidade de vida (Michalak e col. 2006). Embora, as relações inter-pessoais melhorem durante a fase de eutimia, um terço da nossa amostra reportou algum grau de dificuldade nas atividades sociais e no relacionamento familiar. Outros autores também demonstraram que pacientes encontram grandes dificuldades na área social (Reinares e col. 2006; MacQueen and Young, 2001;Chand e col., 2004b; Strakowski e col., 2000a). A estigmatização, o medo da rejeição e o medo de sentir-se ridículo poderiam explicar estes achados (Morselli e col. 2004). Entretanto, o estresse conjugal, a sobrecarga familiar, o grau de satisfação na relação conjugal e sexual também foram áreas identificadas como problemáticas por nossos pacientes. Os efeitos adversos da medicação poderiam explicar, em parte as dificuldades sexuais. Por outro lado, mudanças no comportamento, especialmente, a presença de irritabilidade, agressividade ou comportamento inapropriado durante os episódios de hipomania/mania podem influenciar nos relacionamentos inter-pessoais (Michalak e col. 2006). Ainda, mudança no padrão sócio-econômico poderia justificar esta problemática. Restrições nas atividades sociais, assim como a diminuição no orçamento familiar pode resultar em mudanças na dinâmica familiar (Lam e col., 2005;Dore and Romans, 2001b). Além disso, os altos níveis de emoção expressada e a sobrecarga familiar afetam negativamente o relacionamento conjugal, podendo resultar em separação ou divórcio (Dore and Romans, 2001a;Atkinson e col., 1997).

6. Lazer

Embora, um grande número de estudos mostrem um impacto negativo do THB nas atividades de lazer (Revicki e col., 2005), nós não encontramos aqui tais diferenças entre pacientes e controles. Entretanto, um outro estudo, demonstrou que pacientes bipolares apresentavam maiores escores no domínio lazer (média:24.02, DP:5.87), avaliados pelo *Questionário de Satisfação pela Vida* (Q-LES-Q) quando comparados aos controles sadios (média:20.40, DP:4.97) e pacientes esquizofrênicos (média:17.55, DP:5.17) (Chand e col., 2004a). Esta área da funcionalidade deve ser influenciada pelo estado de humor no momento da avaliação.

É importante ressaltar algumas limitações metodológicas inerentes a este estudo. Primeiro, é um estudo naturalístico e nós avaliamos funcionalidade em apenas uma ocasião. Um estudo longitudinal é necessário. Segundo, os pacientes foram selecionados do programa de Transtorno de Humor Bipolar do Hospital Clinic de Barcelona, e é possível que nossa amostra represente um padrão mais grave da doença. Finalmente, devido ao delineamento transversal, nós não podemos excluir o efeito dos episódios passados de hipomania/mania nos nossos resultados.

Em conclusão, a área laboral foi a mais afetada entre pacientes eutímicos. A inatividade laboral representa um forte preditor de pior funcionalidade, além do fato que as dificuldades na funcionalidade laboral estão associadas com mais recaídas (Fagiolini e col 2005).

Durante a última década, mudanças no paradigma do tratamento do THB tem sido iniciado, uma vez que recentes evidências enfatizam o forte impacto do THB na qualidade de vida e na funcionalidade social, cognitiva e laboral destes pacientes, sugerindo que novas estratégias devem ser implementadas com o objetivo de obter não só a recuperação sintomática, e sim, a recuperação funcional (Colom e Vieta

2004). Em um futuro próximo, novos esforços são necessários para melhorar a funcionalidade psicossocial de pacientes com THB. Medicamentos e programas de psicoeducação são intervenções úteis, mas não suficientes (Colom e col, 1998). Com base nos resultados deste estudo, parece claro que intervenção social até a área laboral, tais como, a promoção de emprego para doentes mentais, como uma forma positiva de discriminação, assim como um melhor aconselhamento no âmbito laboral poderia ajudar a sociedade a enfrentar o problema da incapacidade gerado pelos pacientes com THB. Entretanto, programas de reabilitação cognitiva podem ser de extrema utilidade, fornecendo um impacto positivo sobre a cognição e no âmbito do trabalho.

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Tabela 1: Características Clínicas e Demográficas

	Pacientes n=71 Média	DP
Idade	44.99	13.51
idade de início	27.51	11.18
Episódios totais	11.89	15.20
Episódios maníacos	2.73	3.88
Episódios depressivos	5.23	6.42
Número de hospitalizações	1.37	1.53
HDRS	2.08	3.31
YMRS	1.07	2.07
	n=71	%
Sexo (Feminino)	34	47.9
THB I	59,85	84.3
Nível de escolaridade		
Alto	23.0	32.4
Baixo	36.99	52.1
Estudantes	9.02	12.07
Trabalho		
Empregado	40.97	57.7
Desempregado	12.99	18.3
Licença médica	2.98	4.20
Incapacidade absoluta	12.99	18.3
Situação conjugal, Casados	24.99	35.2
Morar sozinho	11.00	15.5
Cicladores rápido	8.24	11.6
Abuso de álcool	11.64	16.4
Abuso de outras substâncias	3.90	5.50

Tabela 2: Escores total e específico da FAST em pacientes e controles

	Pac		Cont				
	Média	**DP**	**Média**	**DP**	**t**	**p**	**Cohen's d**
FAST total	18.55	13.19	6.07	4.72	7.44	<0.001	1.26
Autonomia	2.32	2.95	0.39	1.00	5.17	<0.001	0.88
Trabalho	6.65	6.52	1.08	1.99	6.83	<0.001	1.16
Funcionalidade Cognitiva	3.39	3.28	1.11	1.31	5.39	<0.001	0.91
Finanças	0.58	1.42	0.20	0.54	2.09	0.040	0.35
Relacionamentos Interp.	3.79	3.11	1.90	2.65	3.72	<0.001	0.65
Lazer	1.89	1.80	1.38	1.28	1.90	0.06	0.33

Student's t test

Cohen's d

Table 3: Respostas da FAST entre pacientes e controles

	Pat	Cont	Pat	Cont	Pat	Cont	Pat	Cont
AUTONOMY	0	0	1	1	2	2	3	3
1. Taking responsibility for a household	64.8	88.5	14.1	8.2	15.5	3.3	5.6	0.0
2. Living on your own	60.6	90.2	7.0	4.9	8.5	1.6	23.9	3.3
3. Doing the shopping	70.4	95.1	11.3	3.3	11.3	1.6	7.0	0.0
4. Taking care of yourself	87.3	100	8.5	0.0	1.4	0.0	2.8	0.0
OCCUPATIONAL FUNCTIONING								
5. Holding down a paid job	57.7	91.8	1.4	0.0	1.4	3.3	39.4	4.9
6. Accomplishing tasks as quickly as necessary	65.9	86.9	26.8	13.1	4.9	0.0	2.4	0.0
7. Working in the field in which you were educated	75.6	86.9	12.2	0.0	7.3	1.6	4.9	11.5
8. Occupational earnings	80.5	80.3	12.2	18.0	7.3	0.0	0.0	1.6
9. Managing the expected work load	75.6	90.2	12.2	4.9	9.8	3.3	2.4	1.6
COGNITIVE FUNCTIONING								
10. Ability to concentrate on a book, film	52.1	90.2	22.5	6.6	19.7	3.3	5.6	0.0
11. Ability to make mental calculations	66.2	80.3	9.9	16.4	8.5	3.3	15.5	0.0
12. Ability to solve a problem adequately	70.4	82.0	21.1	14.8	4.2	3.3	4.2	0.0
13. Ability to remember newly-learned names	54.9	67.2	15.5	27.9	19.7	4.9	9.9	0.0
14. Ability to learn new information	64.8	83.6	16.9	16.4	11.3	0.0	7.0	0.0
FINANCIAL ISSUES								
15. Managing your own money	81.7	91.8	9.9	8.2	2.8	0.0	5.6	0.0
16. Spending money in a balanced way	87.3	88.5	4.2	11.5	4.2	0.0	4.2	0.0
INTERPERSONAL RELATIONSHIPS								
17. Maintaining a friend or friendships	70.4	75.4	15.5	18.0	8.5	3.3	5.6	3.3
18. Participing in social activities	63.4	65.6	16.9	16.4	8.5	6.6	11.3	11.5
19. Having good relationships with people close you	83.1	95.1	12.7	4.9	2.8	0.0	1.4	0.0
20. Living togheter with your family	67.6	88.5	23.9	8.2	5.6	0.0	2.8	3.3
21. Having satisfactory sexual relationships	42.3	78.7	9.9	4.9	11.3	3.3	36.6	13.1
22. Being able to defend your interests	64.8	83.6	23.9	14.8	4.2	1.6	7.0	0.0
LEISURE TIME								
23. Doing exercise or participing in sport	43.7	39.3	11.3	26.2	7.0	14.8	38.0	19.7
24. Having hobbies or personal interests	70.4	80.3	16.9	16.4	5.6	3.3	7.0	0.0

6.4. ARTIGO 4:

Functional impairment and suicide attempts in bipolar disorder

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Competing Interests:

"The author(s) declare that they have no competing interests related to this report".

Acknowledgements:

This work was supported by grants from the CAPES (Brazil), Spanish Ministry of Health, Instituto de Salud Carlos III, (FIS:PI050206), the Spanish Ministry of Health, Instituto de Salud Carlos III, Red de investigation en Enfermedades Mentales REM-TAP Network.

Abstract:

Objective: The aim of the present study was to assess the association between history of suicide attempts and functional impairment among euthymic patients with Bipolar Disorder.

Methods: Seventy-one DSM-IV bipolar euthymic patients and 61 healthy volunteers were consecutively assessed using the (FAST). Patients with (n=36, 54%) and without (n=31, 46%) a history of suicide attempts were assessed with the Structural Clinical Interview for DSM-IV and compared. The association between FAST total score and suicide attempts was analysed using a logistic regression model.

Results: A logistic regression model showed that the FAST total score was higher in patients with suicide attempts (R=0.20; β=0.088; p=0.028). Euthymic patients with history of suicide attempts showed functional impairment, particularly in occupational (F=6.59; p=0.013) and cognitive domains (F=4.01; p=0.048). In addition, family history of psychiatric illness (X^2: 6.49; gl=1;70; p=0.011), family history of affective disorders (X^2=5.57; p=0.018) psychotics symptoms (X^2=5.88; p=0.015) and axis II comorbidity were associated with suicide attempts (X^2=5.16; p=0.023).

Conclusion: Bipolar patients who suicide attempts had lower overall functioning than patients who did not present a history of suicide attempts. The impairment associates with suicidality affected basically the occupational and cognitive domains.

Key-words: bipolar disorder, suicide attempts, functioning, cognition, occupational functioning.

Introduction:

Bipolar disorder (BD) is a prevalent, often severe and disabling illness with elevated lethality, mostly but not exclusively due to suicide [1]. Suicide rates among BD patients average approximately 1% annually. Such rates are about 60 times higher than the international population rate. The high lethality of suicide acts in BD translates into a much lower ratio of attempts/suicide (approximately 3:1) than in the general population (approximately 30:1) [2]. This is particularly important if one takes into account the evidence pointing out that lithium prophylactic treatment reduces lethality of suicidal acts among BD patients [2;3].

By 2020, BD is estimated to become the sixth leading cause of time lost due to disability or death among those aged 15 to 55 years [4]. Even in samples with older age, there is evidence of rates of disability which are comparable to those of people suffering from schizophrenia [5]. Most importantly, the disability related to BD is not restricted to the symptomatic phases. According to gravel studies, occupational functioning seems to be particularly impaired in this population [6-8]

An emerging body of evidence suggest that BD patients with suicide attempts are more predisposed to be functionally impaired, as assessed using the Global Assessment of Functioning Scale (GAF); [9;10]. Specifically, cognitive functioning seems to be altered in patients with BD who attempted suicide [11;12]. The small number of studies carried out so far within this topic did not focus in this particular relationship. Rather, the association between suicide attempts and functioning has been described as a secondary finding. Also, most of the studies carried out in this area have been performed using the General Assessment of Functioning (GAF) scale [10]. Such scale is widely used, as it is part of the DSM-IV assessment. However, the assessment performed using the GAF mixes social adjustment with symptoms and it is expressed with a single number which does not convey specific information about important domains of functioning such as work and interpersonal relationships.

The present study aims to assess whether previous suicide attempts were associated with lower functioning in a sample of well defined, clinically euthymic BD patients. We have hypothesized that patients who experienced suicide attempts would have a lower psychosocial functioning. In addition, we have investigated whether variables related to the course of illness would present a differential impact in BD patients who had a previous history of suicide attempts.

Methods:

Patients:

The analysis sample is derived from the Bipolar Disorder Program at the Clinic Hospital of Barcelona (n=71). Subjects gave written informed consent to participate in this study. Subjects who met the following criteria were included: age older than 18 years; met DSM-IV-TR criteria for bipolar affective disorder type I or II by the Structured Clinical Interview for DSM-IV-TR (SCID-P) (First et al., 1995); met euthymia criteria defined by the 17-item Hamilton Depression Rating Scale (HDRS) [13] < 9 and a Young Mania Rating Scale Score (YMRS) [14] < 7 [15]

Controls:

Control subjects were screened through the SCID (DSM-IV TR) to exclude subjects with prior psychiatry history (n=61). This sample had no first-degree relatives with bipolar disorder or other psychiatric disorders when asked in previous interview for the screening. The healthy comparison group was recruited from the general population with the catchment area around the Hospital Clinic, in Barcelona, and gave written informed consent to participate in this study.

The study was approved by the Hospital Clinic of Barcelona Ethics Committee.

Diagnostic assessment: the SCID (DSM-IV TR) was administered by trained personnel to each subject for diagnosis. The history of suicide attempts was careful and deeply investigated by patient and caregiver systematic interview. Other clinical variables as age of onset, duration of illness or chronicity, number of past episodes, past depressive episodes, past manic episodes, past of mixed episodes, as well as, the number of past hospitalization, suicide attempts, psychotic symptoms, rapid cycling, current drugs abuse and family history of psychiatric and affective disorders were also assessed.

Outcome assessments: the Functioning Assessment Short Test (FAST) was employed to provide an objective assessment of the level of functioning. The FAST is a valid and reliable, short scale administered by a trained clinician. It comprises 24 items, which are divided among 6 specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. Items are rated using a 4-point scale, 0=no difficulty, 1=mild difficulty, 2=moderate difficulty, and 3=severe difficulty. A score of 0 on each item indicates no difficulty, and a score ≥ 1 on any item indicates some degree of functional impairment in that domain. The FAST scale scores from 0 to 72. A total score of 72 represents the lowest possible functioning, and 0 represents the highest possible functioning with a cut-off point at ≥11 [16]

Statistical analysis:

Suicidal and no suicidal BP patients were compared by means of Chi-square tests for dichotomous variables and an ANOVA analysis for continuous variables. In a logistic regression analysis we examined the relationship of previous suicide attempts and the total scores of FAST as the predictive variable using the HAM-D scores, YMRS, number of total episodes, number of depressive episodes, and number of hospitalizations, age and sex as the confounding factors. Data are reported as mean with standard deviations, frequencies or percentages. Two-tailed $p < 0.05$ was required for statistical significance. All statistical analyses were performed using the SPSS version 12.0 software package.

Results:

Our sample consists 34 women (47.9%) in the group of patients and 61 in the control group (42.6%). The mean age of the patients was 45 years (standard deviation (SD: 13.66, median 45.45) and mean age of the controls was 49 years (standard deviation (SD: 17.66, median 49.16). There was not difference between patients and controls regarding gender and age. Table 1 compares FAST total scores and subscores in patients with and without attempted suicide. Clinical features as a family history of psychiatric illness (x^2=6.49, p=0.011), family history of affective disorders (x^2=5.57; p=0.018), psychotic symptoms (x^2= 5.88, p=0.015) and axis II comorbidity (x^2=5.16, p=0.023) were overrepresented in suicide attempters. There was no significant difference between the two groups with regard to number of hospitalizations, number of total episodes, number of depressive episodes, depressive symptoms, number of manic episodes, number of mixed episodes and manic symptoms.

Our data shows that patients with lifetime suicide attempts (SA) had a higher FAST total score that patients without past suicide attempts (SA: mean 22.78, SD: 14.18; w/o SA: mean 14.81, SD: 10.53; p=0.012). In these patients, the specific domains that showed differences were occupational functioning (SA: mean 8.81, SD: 6.66; w/o SA: mean 4.84, SD: 5.86, p=0.013) and cognitive functioning (SA: 4.28, SD: 3.60; w/o SA: mean 2.68, SD: 2.75, p=0.048).

A logistic regression was carried out using the suicide attempts (SA) as the criterium measure and the FAST total score as the predictive variable, with HAM-D, YMRS, number of total episodes, number of depressive episodes, hospitalization, sex and age as possible confounders; within this model, the total score of FAST was the only variable that showed significant statistical association (p=0.028) and this model explained 27% of the variance (R=0.20; R^2=0.27).

Discussion:

The present study shows that patients with lifetime history of suicide attempts have lower overall functioning as assessed using the FAST as compared to non-suicide attempters. Occupational functioning and cognitive functioning were significantly more impaired among patients who attempted suicide previously. Suicidality may represent a marker of severity of illness which explains some of the variance in assessments of functioning in euthymic bipolar patients.

In previous studies using cognitive tests, we reported that suicide attempts were also related to cognitive difficulties in BD patients, especially verbal learning and memory tasks. More specifically, problems in encoding and retrieval of verbal information seem to explain the impairment in daily functioning, even during remission, that such patients experience [17]. BD II patients demonstrated worsen performance than controls and BD I patients with respect to measures of attention, working memory and motor functioning [11]. In this same vein, the cognitive domain of FAST was altered in BD patients. This is noteworthy, as both neuropsychological tests [12] and a clinical assessment (FAST) pointed to the same direction. Also, this finding adds weight to the construct validity of the clinical assessment of the cognitive domain as performed using FAST.

In a recent study we showed that impairments in verbal memory, as defined by difficulties in retaining and retrieving new verbal information, were the best predictors of occupational functioning in BD patients [18;19]. In the present study we have shown that both the cognitive and occupational domains of FAST were impaired in patients with history of suicide attempts. This further validates the findings of our previous studies [18;19] as the cognitive and occupational domains seem to vary in a co-linear fashion. Further, illness severity and cognitive impairment are not independent, so it is difficult to assess and discuss their respective influence in functional outcome [12]. Thus, the present study supported this view, as occupational functioning and cognitive domains

of FAST were also shown to be more severely impaired in patients with history of suicide attempts.

There is evidence pointing that past suicidal behaviour is perhaps the best predictor of future suicidal behaviour [20;21]. The present study, suggests that in BD populations it is important to consider clinical features such as family history of psychiatric and affective disorders whenever assessment of risk of suicide is concerned. Moreover, the findings of the present study suggest that familial loading, apart from being a marker of risk for the development of BD may also reflect the severity of illness, in the sense that it is increased in the subgroup of patients who already had attempted suicide.

Rates of suicidal behaviour appear to be similar among BD I and BD II patients [22]. Previous studies identified gravel risk factors for completed suicide in BD, namely, early age at onset, psychosis, rapid-cycling, mixed mania, antidepressants-induced mania, total number of previous depressive episodes, high rates of comorbidities and alcohol- substance abuse; [23;24]. Still, particular characteristics as age, marital status, affective disorder and psychiatric comorbidities are associated with violent method of suicide behaviour [22;25]. The present study did not fully reproduce such previous findings, which is expected as here we studied suicide attempts and not complete suicide. Sample size should also be considered here as with a sample of 71 subjects, the power was not sufficient to detect less pronounced associations. Our findings are in line with a recent study which showed that rates of psychosis were greater among patients with history of suicide among pediatric patients [26].

Here we found that the axis II comorbidity was associated with higher rates of history of suicide attempts. Psychiatric comorbidity, especially axis II comorbidity [21] is very common in BD. Beyond that, such patients tend to present a more severe disorder, which is difficult to treat. These patients also experience poor adherence to treatment, which may, in its turn, relate to higher rates of relapse [27]. The fact that Axis-II comorbidity is related to poor adherence, may offer an explanation as to why such

patients presented higher rates of history of suicide in the present study. Such assumption is based on recent evidence showing that lithium treatment reduced both suicide attempts as well as the lethality of suicide acts among BD patients [2;3]

In conclusion, here we demonstrate that functioning, particularly cognitive and occupational, were lower among patients with previous suicide attempts. Moreover, family history, Axis-II comorbidity and lifetime psychosis were associated with higher rates of suicide attempts. An inner strength of this study is the fact that we used a scale tailored for BD patients to assess functioning. The assessment of functioning, as carried out using the FAST, allowed a more complete exploration of specific domains, namely autonomy, occupational functioning, cognitive functioning, interpersonal relationships, financial issues and leisure time. Our finding should be interpreted in the light of the fact that this was a naturalistic cross-sectional study which does not allow for assumptions of causality. Prospective studies are warranted to asses whether a causal relationship between functionality and suicide attempts can be ascertained.

Table 1: Differences between patients with/without lifetime suicide attempts and clinical features

	Total	with suicide attempts	without suicide attempts	Chi square	p
	n (%)	n (%)	n(%)		
Men	37 (52.1%)	20 (54.1)	17(45.9)	0.35	0.56
Woman	34 (47.9%)	16 (47.1)	18 (52.9)		
Family history of psychiatric illness	36 (53.7%)	24 (66.7)	12 (33.3)	6.49	0.011
Family history of Affective disorders	32 (49.2)	21 (65.6)	11 (34.4)	5.57	0.018
Suicide history family	14 (20,6)	8 (57.1)	6 (42.9)	0.23	0.63
Drug abuse	58 (81.7)	31 (53.4)	27 (46.6)	0.95	0.33
Psychotics symptoms	45 (64.3)	28 (62.2)	17 (37.8)	5.88	0.015
Lifetime events	31 (46.3)	16 (51.6)	15 (48.4)	0.13	0.72
Axis I comorbidity	33 (46,5)	20 (60.6)	13 (39.4)	2.42	0.12
Axis II comorbidity	29 (40.8)	19 (34.5)	10 (65.5)	5.16	0.023
Rapid cycling	8 (11.6)	3 (4.30)	5 (7.20)	0.63	0.43

	Mean	SD	mean	SD	mean	SD	F	p
Age	44.99	13.5	43.94	9.43	46.06	16.79	0.43	0.51
age of first hospitalization	25.25	17.28	26.80	12.66	23.52	21.40	0.51	0.48
Hospitalizations	1.37	1.53	1.67	1.88	1.11	1.13	1.74	0.19
mania episodes	2.73	3.88	3.71	4.78	1.18	2.66	3.03	0.09
mixed episodes	0.35	0.91	0.48	1.16	0.24	0.60	0.82	0.37
depressive episodes	5.23	6.42	5.46	5.19	5.04	7.41	0.055	0.82
hypomanic episodes	3.82	11.36	1.61	2.41	5.77	15.3	1.67	0.20
total episodes	11.89	15.20	11.17	8.68	12.71	20.35	0.17	0.69
duration of illness	17.88	10.95	18.37	9.60	17.36	12.35	0.14	0.71
YMRS	1.07	2.07	1.14	1.82	1.00	2.33	0.08	0.78
HAM-D	2.08	3.31	2.17	3.81	2.00	2.76	0.04	0.83

ANOVA

Table 2: Funtional Impairment across different domains in bipolar patients with and without previous suicide attempts

	(A) com suicídio		(B) sem suicídio		(C) controles				Tukey post-hoc
	36 (50.7%)		35 (49.3%)						
	Mean	SD	mean	SD		SD	F	p	
FAST total	22.78	14.18	14.20	10.63	6.07	4.72	33.89	0.001	A>B>C
FAST autonomy	2.83	3.29	1.80	2.50	0.39	1.00	13.99	0.001	A=B; A>C; B>C
FAST occupational	8.81	6.66	4.43	5.65	1.08	1.99	30.39	0.001	A>B>C
FAST cognitive	4.28	3.60	2.49	2.65	1.11	1.30	18.43	0.001	A>B>C
FAST interpersonal rel.	4.28	3.4	3.29	2.73	1.90	2.65	8.02	0.01	A=B; A>C; B=C
FAST financial	0.83	1.81	0.31	0.80	0.20	0.54	3.99	0.021	A=B; A>C; B=C
FAST leisure time	1.81	1.80	1.97	1.81	1.38	1.28	1.80	0.17	A=B=C

ANOVA

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6.4.1. ARTIGO 4 TRADUZIDO:

Disfuncionalidade e tentativas de Suicídio em pacientes bipolares

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Conflitos de Interesse:

"Os autores declaram não ter conflitos de interesse relacionados a este artigo".

Agradecimentos:

Este estudo foi suportado em parte pela CAPES (Brasil) e pela Stanley Medical Research Institute, Ministério Espanhol de Saúde, The Institute Carlos III. FIS (PI05206), Rede de Pesquisa de Patologias Mentais REM-TAP Network.

Resumo:

Objetivo: O objetivo deste estudo foi avaliar a associação entre história prévia de suicídio e disfuncionalidade entre pacientes bipolares eutímicos.

Métodos: Setenta e um pacientes bipolares eutímicos diagnosticados segundo a Entrevista Clínica Estruturada, DSM-IV, e 61 controles sadios foram avaliados pela Escala Breve de Funcionalidade (FAST). Pacientes com (n=36, 54%) e sem (n=35, 46%) história prévia de suicídio foram comparados em relação às variáveis clínicas. Modelo de regressão logística foi usado para avaliar a associação entre o escore total da FAST e a história prévia de suicídio.

Resultados: Modelo de regressão logística mostrou que o escore total da FAST era maior em pacientes com história prévia de suicídio (R=0.20; β=0.088; p=0.028). Pacientes eutímicos com história prévia de suicídio mostraram maior disfuncionalidade, especialmente, nos domínios laboral (p=0.013) e cognitivo (p=0.048). Além disso, a história familiar de doença psiquiátrica (x^2: 6.49; gl=1;70; p=0.011), a história familiar de transtornos afetivos (x^2: 5.57; p=0.018), os sintomas psicóticos (x^2=5.88; p=0.015) e a comorbidade de eixo II (x^2=5.16; p=0.023) foram mais freqüentes em pacientes com história prévia de suicídio.

Conclusão: Pacientes eutímicos com história prévia de suicídio apresentaram pior funcionalidade quando comparados a pacientes sem história prévia de suicídio. As áreas da funcionalidade que estavam mais afetadas nestes pacientes foram a laboral e a cognitiva.

Palavras-chaves: transtorno bipolar, tentativa de suicídio, funcionalidade, cognição e trabalho.

Introdução:

Transtorno do Humor Bipolar (THB) é uma doença prevalente, grave e incapacitante com elevada taxa de mortalidade, principalmente, devido ao suicídio (Goodwin & Jamison, 1990). As taxas de suicídio são de aproximadamente 1% ao ano entre pacientes com THB. Essas taxas são aproximadamente 60 vezes maiores que as taxas de suicídio da população internacional. Enquanto que em pacientes bipolares, a cada três tentativas de suicídio, uma delas é letal, na população em geral, são necessárias trinta tentativas para que uma delas seja letal. (Baldessarini 2006). É importante lembrar que o tratamento profilático com lítio é capaz de diminuir as taxas de letalidade por suicídio nos pacientes bipolares (Gonzalez-Pinto et al. 2006; Baldessarini 2006).

Acredita-se que até 2020, o THB será a sexta patologia mais incapacitante considerando dias perdidos ou morte entre pessoas de 15-55 anos de idade (Murray & Lopez, 1997). Ainda em amostras com pessoas mais idosas, as taxas de incapacidade serão equivalentes aos pacientes que sofrem de esquizofrenia (Depp et al. 2006). É importante considerar que a alta incapacidade causada pelo THB não é restrita aos períodos sintomáticos da doença. Vários estudos têm demonstrado que a funcionalidade laboral parece ser a principal dificuldade apresentada por estes pacientes (Suppes et al. 2001; Tohen et al. 2001; Zarate et al. 2001).

Várias evidências sugerem que pacientes bipolares com história de suicídio são mais predispostos a apresentar disfuncionalidade, quando avaliados pela Escala Global de Funcionalidade (GAF) (Zanarini et al. 2006; Hajek et al. 2006). Especificamente, a funcionalidade cognitiva parece estar alterada em pacientes bipolares que tentaram suicídio (Martinez-Aran et al., 2004; Harkavy-Friedmann et al. 2006). Ainda, o pequeno número de estudos que relataram este fato não foi desenhado para estudar este tema sendo que a associação entre tentativas de suicídio e funcionalidade foi descrita como um resultado secundário (Hajek, Raja). Além disso, a maioria dos estudos utilizou a GAF como escala para avaliação da

funcionalidade (Hajek; Raja). A GAF apesar de ser muito utilizada e fazer parte da avaliação sugerida pelo DSM-IV, ela avalia funcionalidade e sintomas clínicos, e expressa o resultado como um único valor, não discriminando quais as áreas da funcionalidade (por exemplo, se laboral ou social) estão mais problemáticas.

O presente estudo tem como objetivo avaliar se a história prévia de tentativas de suicídio estava associada com disfuncionalidade em uma amostra bem definida de pacientes bipolares eutímicos comparado com grupo controle. Nossa hipótese é de que pacientes com história de suicídio têm maior disfuncionalidade. Além disso, nós investigamos se as variáveis clínicas relacionadas com o curso da doença poderiam estar relacionadas com a história prévia de suicídio.

Métodos:

Pacientes:

A amostra consiste de pacientes selecionados do Programa de Transtorno Bipolar do Hospital Clinic de Barcelona (n=71). Todos os sujeitos deram consentimento informado para participar deste estudo. Os pacientes selecionados eram maiores de 18 anos, com diagnóstico de THB tipo I ou II segundo a Entrevista Clínica Estruturada do DSM-IV-TR (SCID-P) (First et al., 1995); e preenchiam os critérios de eutimia definidos como pontuação menor que 9 na escala de depressão (17-item Hamilton Depression Rating Scale-HDRS (Bobes et al. 2003) e menor que 7 na escala de mania (Young Mania Rating Scale Score-YMRS) (Colom et al., 2002, Vieta et al. 2001).

Controles:

Os controles foram avaliados através do SCID (DSM-IV TR) a fim de excluir sujeitos com história de patologia psiquiátrica (n=61). Também foram excluídos sujeitos com parentes em primeiro grau de THB ou qualquer outra patologia psiquiátrica. Os controles faziam parte da população em geral e eram moradores de um bairro onde está localizado o Hospital Clinic de Barcelona. Todos eles assinaram o consentimento informado para participar do estudo.

O estudo foi aprovado pelo Comitê de Ética do Hospital Clinic de Barcelona.

Avaliação Diagnóstica: o SCID (DSM-IV TR) foi administrado a cada sujeito por pessoal treinado. A história de tentativas de suicídio foi cuidadosamente avaliada junto ao paciente e familiar através de uma entrevista sistemática. Outras variáveis clínicas, tais como, idade de início, duração da doença ou cronicidade, número de episódios passados, número de episódios depressivos prévios, número de episódios maníacos ou mistos prévios, assim como, número de hospitalizações, sintomas psicóticos, ciclagem rápida, uso atual de drogas e história familiar de doença psiquiátrica e afetiva foram também avaliadas.

Avaliação dos Resultados: a Escala Breve de Funcionalidade (FAST) foi administrada com o objetivo de avaliar o nível de funcionalidade. A FAST é uma escala válida e confiável, de avaliação clínica e de rápida aplicação. Consiste de 24 itens que avaliam seis áreas específicas da funcionalidade: autonomia, trabalho, cognição, finanças, relacionamentos inter-pessoais e lazer. Cada item pode apresentar pontuações que variam de 0-3 pontos, onde 3 representa grave dificuldade, 2 moderada dificuldade, 1 pouca dificuldade e 0 nenhuma dificuldade. A pontuação total da FAST varia de 0-72 pontos, onde 72 representa a pior e 0 a melhor funcionalidade, sendo o ponto de corte estabelecido em escores ≥11 (Rosa et al. 2007 submetido).

Análise Estatística:

Teste do Qui-Quadrado foi usado para comparar as variáveis dicotômicas entre pacientes com e sem história de suicídio e grupo controle, enquanto que a ANOVA foi usada para comparar as variáveis contínuas. Regressão logística foi usada para avaliar a relação entre tentativas de suicídio e o escore total da FAST, considerando a FAST como preditor e os escores da HAM-D, da YMRS, o número de episódios total, número de episódios depressivos, número de hospitalização, sexo e idade como variáveis de confusão. Os resultados foram reportados como média e desvio padrão, freqüências e porcentagens. Resultados com nível de significância < 0.05 foram considerados como estatisticamente significativos. Todas as análises foram realizadas usando a versão 12.0 do SPSS.

Resultados:

Nossa amostra consistiu de 34 mulheres (47.9%) no grupo de pacientes e 26 no grupo controle (42.6%). A idade média dos pacientes foi de 45 anos (desvio padrão: 13.66, média: 45.45) e de 49 anos no grupo controle (desvio padrão: 17.66, média: 49.16). Não havia diferença quanto ao sexo e idade entre pacientes e controles. Tabela 1 mostra os resultados do escore total e subescores da FAST entre pacientes com e sem história prévia de suicídio e grupo controle. Fatores clínicos como história familiar de doença psiquiátrica (x^2=6.49, p=0.011), história familiar de transtorno afetivo (x^2=5.57; p=0.018), sintomas psicóticos (x^2= 5.88, p=0.015) e comorbidade de eixo II (x^2=5.16, p=0.023) foram mais freqüentes em pacientes com história de suicídio. Não havia diferença entre os dois grupos em relação às outras variáveis clínicas estudadas, como, número de hospitalização, número de episódios total, número de episódios depressivos, sintomas depressivos, número de episódios maníacos, número de episódios mistos e sintomas maníacos.

Nossos resultados mostraram que pacientes com história prévia de suicídio (TS) apresentavam maiores escores na FAST quando comparados aos pacientes sem história de suicídio e controles sadios (com TS: média 22.78, DP: 14.18; sem TS: média 14.20, DP: 10.63; controles: média 6.07, DP: 4.72; p=0.001). Dificuldades na funcionalidade laboral (com TS: média 8.81, DP: 6.66; sem TS: média 4.43, DP: 5.65, controles: média 1.08, DP: 1.99, p=0.001) e na funcionalidade cognitiva foram as mais proninciadas nestes pacientes (com TS: média 4.28, DP: 3.60; sem TS: média 2.49, DP: 2.65, controles: média: 1.11, DP: 1.30, p=0.001).

Um modelo de regressão logística foi conduzido usando tentativas de suicídio como desfecho e escore total da FAST como preditor, sendo a HAM-D, a YMRS, o número de episódios total, o número de episódios depressivos, as hospitalizações, o sexo e a idade usados como variáveis de confusão. Este modelo explicou 27% da variação

(R=0.20; R^2=0.27; β=0.088) sendo a FAST a única variável que mostrou associação estatisticamente significativa (p=0.028) com suicídio.

Discussão:

O presente estudo mostrou que pacientes com história prévia de suicídio apresentam mais disfuncionalidade, avaliados pela escala FAST, quando comparados com aqueles sem história prévia de suicídio. A funcionalidade laboral e cognitiva foram as áreas mais afetadas. Suicidalidade pode funcionar como marcador de gravidade da doença e isto poderia explicar porque pacientes com história de suicídio apresentam pior funcionalidade. Estudos prévios, usando uma bateria de testes neuropsicológicos, demonstraram que pacientes com história de suicídio apresentavam mais deterioro cognitivo, em especial nos testes de aprendizado e memória. Mais especificamente, pacientes eutímicos têm dificuldade em guardar e recordar as informações, o que parece ter importantes implicações na vida diária deles (Martinez-Aran et al. 2007; Martinez-Aran et al. 2004). Ainda, pacientes bipolares tipo II com história prévia de suicídio apresentavam pior rendimento que os controles e, inclusive que os bipolares tipo I, em particular nos testes de atenção, memória e funcionalidade motora (Harkavy-Friedman et al. 2006). Neste mesmo sentido, a FAST demonstrou maiores disfuncionalidades cognitivas em pacientes com história de suicídio. É importante ressaltar que tanto a avaliação feita pela FAST, como a bateria de testes neuropsicológicos (Martinez-Aran et al. 2007; Martinez-Aran et al. 2004) apresentam os mesmos resultados, ou seja, dificuldades na cognição, evidenciando a validade de constructo do instrumento.

Em um estudo recente nós demonstramos que as dificuldades na memória verbal, definida como dificuldade em guardar e depois lembrar as informações recebidas foram os melhores preditores de disfuncionalidade laboral entre pacientes bipolares (Torrent et al. 2006; Martinez-Aran et al. 2007). Aqui, nós mostramos que o domínio cognitivo e o laboral, avaliados pela escala FAST, foram os domínios da funcionalidade mais afetados entre pacientes com história passada de suicídio. Estes resultados, assim como estudos prévios, apontam que a funcionalidade cognitiva e a laboral parecem atuar de forma dependente (Martinez-Aran et al. 2007; Martinez-Aran

et al. 2004). Além disso, a gravidade da doença e o deterioro cognitivo não são independentes, e é difícil de avaliar e discutir a influência deles sobre a funcionalidade (MA, 2004, AM). Na verdade, nosso estudo suporta essa idéia, uma vez que a FAST determinou que a funcionalidade cognitiva e a laboral estavam mais afetados em pacientes com história passada de suicídio.

Existem evidências que a história passada de suicídio é um forte preditor de tentativas de suicídio no futuro (Hawton et al. 2005; Galfalvy et al. 2006). O presente estudo sugere que pacientes com história familiar de doença pisquiátrica e/ou afetiva apresentam mais risco de suicídio. Entretanto, nosso estudo sugere que a carga familiar de doença psiquiátrica além de estar associada com mais chance de desenvolver THB, também reflete um padrão de gravidade da doença, uma vez que este subgrupo de pacientes apresentaram mais tentativas de suicídio.

As taxas de suicídio parecem ser similares entre pacientes com THB tipo I ou II (Vieta et al. 1997). Estudos mais antigos identificaram alguns fatores de risco para o suicídio, tais como, idade de início, psicoses, ciclagem rápida, episódios mistos, mania induzida pelo uso de antidepressivos, episódios depressivos, presença de comorbidades e abuso de álcool ou drogas (Sanchez and lee 2001; Slama, 2004). Ainda, características particulares como idade, estado civil e comorbidades psiquiátricas ou comorbidades com outros transtornos afetivos estão relacionadas com tentativas violentas de suicídio (Vieta et al. 1997; Vieta et al. 1992). O presente estudo não reproduziu a totalidade dos dados demonstrados previamente, o que era esperado porque estudamos tentativas de suicídio e não suicídio propriamente dito. O tamanho da amostra (n=71) também deveria ser considerado, pois é possível que não tenhamos poder suficiente para encontrar associações menos pronunciadas. Entretanto, nossos resultados foram similares a um estudo recente onde as taxas de psicoses eram maiores em pacientes pediátricos com história prévia de suicídio (Caetano et al. 2006).

Aqui, nós encontramos que a comorbidade de eixo II estava associada com altas taxas de tentativas de suicídio. Comorbidade psiquiátrica, em especial, a de eixo II é muito comum no THB (Galfalvy et al. 2006). Além disso, estes pacientes tendem a ser mais graves e difíceis de tratar. Estes pacientes apresentam baixa adesão ao tratamento, o que por outro lado, resulta em mais recaídas (Colom et al. 2002). O fato de que pacientes bipolares com comorbidade de eixo II sejam menos aderentes ao tratamento oferece uma possível explicação de porque estes pacientes apresentam mais história de suicídio. Esta justificativa esta na linha de raciocínio que o tratamento profilático com lítio é capaz de reduzir tanto as tentativas de suicídio como a letalidade do suicídio (Gonzalez-Pinto, 2006; Baldessarini, 2006).

Em conclusão, nós demonstramos que pacientes com história prévia de suicídio apresentam pior funcionalidade, em especial, cognitiva e laboral. Entretanto, a história familiar de doença psiquiátrica e afetiva, assim como a comorbidade de eixo II e os sintomas psicóticos prévios estão associadas com mais tentativas de suicídio. É importante ressaltar que usamos uma escala validada em uma amostra de bipolares para avaliar a funcionalidade. A escala FAST avalia funcionalidade considerando as principais áreas da funcionalidade, tais como autonomia, trabalho, cognição, relacionamentos inter-pessoais, finanças e lazer. Nossos resultados deveriam ser interpretados com precaução, uma vez que trata-se de um estudo naturalístico transversal, não sendo possível estabelecer a razão de causa-conseqüência. Estudos prospectivos são necessários para solucionar esta questão, e confirmar que existe uma forte relação entre suicidalidade e funcionalidade.

Tabela 1: Diferenças entre pacientes com e sem tentativas de suicídio e variáveis clínicas

	Total		com tentativa de suicídio		sem tentativa de suicídio		X^2	p
	n (%)		n (%)		N (%)			
Homem	37 (52.1%)		20 (54.1)		17(45.9)		0.35	0.56
Mulher	34 (47.9%)		16 (47.1)		18 (52.9)			
História familiar de doença psiquiátrica	36 (53.7%)		24 (66.7)		12 (33.3)		6.49	0.011
História familiar de transtornos afetivos	32 (49.2)		21 (65.6)		11 (34.4)		5.57	0.018
História familiar de suicídio	14 (20,6)		8 (57.1)		6 (42.9)		0.23	0.63
Abuso de drogas	58 (81.7)		31 (53.4)		27 (46.6)		0.95	0.33
Sintomas psicóticos	45 (64.3)		28 (62.2)		17 (37.8)		5.88	0.015
Acontecimentos na vida	31 (46.3)		16 (51.6)		15 (48.4)		0.13	0.72
Comorbidade de eixo I	33 (46,5)		20 (60.6)		13 (39.4)		2.42	0.12
Comorbidade de eixo II	29 (40.8)		19 (34.5)		10 (65.5)		5.16	0.023
Ciclagem rápida	8 (11.6)		3 (4.30)		5 (7.20)		0.63	0.43
Qui-Quadrado								
	mean	SD	mean	SD	mean	SD	F	p
Idade	44.99	13.5	43.94	9.43	46.06	16.79	0.43	0.51
Idade da 1° hospitalização	25.25	17.28	26.80	12.66	23.52	21.40	0.51	0.48
Número de Hospitalizações	1.37	1.53	1.67	1.88	1.11	1.13	1.74	0.19
Episódios maníacos	2.73	3.88	3.71	4.78	1.18	2.66	3.03	0.09
Episódios mistos	0.35	0.91	0.48	1.16	0.24	0.60	0.82	0.37
Episódios depressivos	5.23	6.42	5.46	5.19	5.04	7.41	0.055	0.82
Episódios hipomaníacos	3.82	11.36	1.61	2.41	5.77	15.3	1.67	0.20
Episódios totais	11.89	15.20	11.17	8.68	12.71	20.35	0.17	0.69
Duração da doença	17.88	10.95	18.37	9.60	17.36	12.35	0.14	0.71
YMRS	1.07	2.07	1.14	1.82	1.00	2.33	0.08	0.78
HAM-D	2.08	3.31	2.17	3.81	2.00	2.76	0.04	0.83
ANOVA								

Tabela 2: Disfuncionalidade entre pacientes com e sem história prévia de suicídio

	(A) com suicídio 36 (50.7%)		(B) sem suicídio 35 (49.3%)		(C) controles				Tukey
	Mean	SD	mean	SD		SD	F	p	
FAST total	22.78	14.18	14.20	10.63	6.07	4.72	33.89	0.001	A>B>C
FAST autonomia	2.83	3.29	1.80	2.50	0.39	1.00	13.99	0.001	A=B; A>C; B>C
FAST trabalho	8.81	6.66	4.43	5.65	1.08	1.99	30.39	0.001	A>B>C
FAST cognição	4.28	3.60	2.49	2.65	1.11	1.30	18.43	0.001	A>B>C
FAST relacionamentos	4.28	3.4	3.29	2.73	1.90	2.65	8.02	0.01	A=B; A>C; B=C
FAST finanças	0.83	1.81	0.31	0.80	0.20	0.54	3.99	0.021	A=B; A>C; B=C
FAST lazer	1.81	1.80	1.97	1.81	1.38	1.28	1.80	0.17	A=B=C

ANOVA

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7.0. VALIDAÇÃO DE OUTROS INSTRUMENTOS EM THB:

A validação de instrumentos em psiquiatria parece ser relevante, porque até o momento não contamos com marcadores bioquímicos específicos para os transtornos mentais. Além disso, muitos instrumentos disponíveis foram desenvolvidos em inglês, o que dificulta a utilização em países com outros idiomas, como Brasil e Espanha. O desenvolvimento de novas escalas, assim coma validação e tradução de instrumentos já disponíveis nos parece extremamente útil (Colom e col. 2002; Sánchez-Moreno e col. 2005).

Neste sentido, apresentamos aqui a tradução e validação de outros dois instrumentos usados em psiquiatria, o "Questuinário de Atitudes em relação ao Lítio" (LAQ) (ver anexo III) e o Teste de Conhecimento do Lítio (LKT) (ver anexo IV). A LAQ é uma escala que avalia as atitudes do paciente em relação ao tratamento com lítio. É um importante instrumento, uma vez que evidências mostram que as atitudes negativas em relação ao lítio estão associadas à menor adesão ao tratamento (Rosa et al. 2007; Scott and Pope 2002; Schumann et al. 1999). A LKT é um teste que avalia o nível de conhecimento sobre o lítio, abordando aspectos farmacológicos e de toxicidade. Em um estudo prévio, nós demonstramos que pacientes que apresentavam maior nível de conhecimento sobre o lítio, também apresentavam concentrações séricas de lítio dentro da faixa terapêutica, o que é um indicativo de boa adesão ao tratamento (Rosa et al. 2007).

Estas duas escalas foram traduzidas do Inglês ao Português e validadas no Programa de Transtorno de Humor do Hospital de Clínicas de Porto Alegre. Os testes psicométricos realizados para a validação das escalas foram a consistência interna, a sensibilidade, a especificidade e a validade concorrente em relação aos níveis plasmáticos de lítio, os quais ofereceram resultados positivos, tornando-as desde já, as escalas disponíveis para a prática clínica e pesquisa.

8.0. DISCUSSÃO:

Nós observamos um aumento das concentrações séricas de GDNF durante os episódios de mania e depressão, enquanto que pacientes eutímicos mostraram resultados similares aos controles. Estes resultados sugerem que a síntese ou a recaptura de GDNF está aumentada durante os processos agudos da doença e que isto poderia representar um mecanismo patológico ou de compensação do THB.

A formação de radicais livres parece ter um importante papel na patogenesia das doenças psiquiátricas, o que se deve ao fato de que o cérebro é altamente vulnerável à formação de espécies reativas de oxigênio (Frey e col. 2006 c; Ozcan e col. 2004; Kuloglu e col. 2002). Interessantemente, um aumento de substâncias reativas ao ácido tiobarbitúrico (TBARS) durante a remissão e episódios agudos do THB, assim como um aumento de SOD e da proteína S-100β, durante a mania e depressão foi recentemente reportado por nosso grupo (Andreazza e col. 2006 a). Além disso, estes pacientes apresentaram um marcado dano ao DNA nuclear, demonstrado pela técnica do Cometa, o que pode dever-se ao aumento dos mecanismos de estresse oxidativo (Andreazza e col. 2006 b). Estes resultados sugerem que existe um desequilíbrio entre o sistema de enzimas antioxidantes, assim como um processo de apoptose durante as fases agudas do THB.

As células da glia, em especial, os astrócitos têm importante papel no SNC, pois além de proporcionar suporte físico aos neurônios e manter os processos de nutrição neuronal, oferecem proteção contra os mecanismos de estresse oxidativo através da remoção das espécies reativas de oxigênio e produção dos fatores tróficos, entre eles o GDNF (Capote 2006; Saavedra e col. 2005). O GDNF, por sua vez, parece aumentar o sistema de enzimas antioxidantes, GSH-Px, catalase e SOD, promovendo a recaptura de radicais livres (Chao & Lee 1999) além de atenuar a morte neuronal nas regiões CA2 e CA3 do HC, conforme demonstrado em um modelo de neurotoxicidade por kainato (Cheng e col. 2004). O pré-tratamento com GDNF promove a estimulação de dois fatores intracelulares anti-apoptóticos, Bcl-2 e Bcl-x,

que por sua vez, impedem a ação das caspases-1 e caspases-3, enzimas responsáveis pela formação de radicais livres, e assim impedindo a clivagem ao DNA nuclear (Sawada e col. 2000). Com base nestas evidências, embora especulativo, o marcado aumento do imunoconteúdo de GDNF aqui demonstrado, durante os episódios de mania e depressão do THB, poderia representar um mecanismo compensatório da doença.

Embora a completa compreensão sobre a fisiopatologia do THB não esteja elucidada, parece que envolve um desequilíbrio entre as espécies reativas de oxigênio e os sistemas de enzimas antioxidantes (Andreazza e col. 2006 a; Ozcan e col. 2004) e alteração dos fatores neurotróficos (Frey e col. 2006ª b; Cunha e col. 2006; Palomino e col. 2006). Isso resulta na diminuição do número de neurônios e de glia, com conseqüente dissociação neuronal-glial e perda da plasticidade sináptica (Rajkowska 2002). Após um processo de dano neuronal, a glia é ativada com o objetivo de eliminar as células mortas através da produção de fatores neuroprotetores, oferecendo suporte paras os neurônios restantes (Saavedra e col. 2005).

Os fatores neurotróficos são essenciais para a manutenção de um equilíbrio entre os processos de neurogênese e apoptose e manutenção da plasticidade neuronal (Rybakowski e col. 2006 a b; Sheline e col. 2003). As alterações neurotróficas conhecidas no THB, explicam em parte, as dificuldades cognitivas apresentadas por estes pacientes (Dias e col. 2006; Martinez-Aran 2004 c). Neste sentido, associações entre níveis plasmáticos de BDNF e testes de memória foi recentemente encontrado em pacientes bipolares (Dias e col. 2006). No mesmo sentido, estudos pré-clínicos mostraram uma associação entre GDNF e testes de memória espacial (Gerlai e col. 2001). Disfunções cognitivas, em especial, dificuldades na memória e na função executiva estão presentes em pacientes agudos e em remissão e isto parece contribuir para o prejuízo psicossocial e funcional apresentada por muitos deles (Torrent e col. 2006; Martinez-Aran e col. 2004 a b; Zarate e col. 2000).

Além das disfunções cognitivas, a persistente sintomatologia, em especial os sintomas depressivos, o número de episódios prévios, hospitalizações e tentativas de suicídio, contribuem para uma pior funcionalidade psicossocial e ocupacional destes indivíduos (Altshuler e col. 2006; Keck 2006; Depp e col. 2006; Hajek e col. 2005; Altshuler e col. 2002 a Cannon e col. 1997; Goldberg e col. 1995; Rosen e col. 1983). Segundo a *Global Burden of Disease,* o THB foi classificado como a nona patologia mais incapacitante entre pessoas de 15-44 anos (Muray & Lopez 1997; Vieta e col. 2007,) o que gera altos custos sócio-econômicos para a sociedade (kogan e col. 2004). Em função disto, o interesse pela recuperação funcional destes indivíduos vem crescendo e a identificação das principais dificuldades de funcionalidade apresentadas por eles torna-se extremamente útil (Vieta e col. 2007).

Neste contexto, a FAST foi desenvolvida, considerando os principais problemas apresentados pelos pacientes psiquiátricos, em especial pacientes bipolares, reportados previamente na literatura e em escalas mais antigas. É uma escala de avaliação clínica, objetiva, de fácil e rápida aplicação (6 min.). Consiste de 24 itens que avaliam seis áreas específicas da funcionalidade: autonomia, trabalho, cognição, relacionamentos inter-pessoais, finanças e lazer. A validação da escala foi feita mediante a realização de testes psicométricos, como consistência interna, validade concorrente comparando com a GAF, teste-reteste, validade para detectar diferenças entre episódios agudo e períodos de remissão e análise fatorial. Os resultados obtidos foram muito positivos, tornando o instrumento válido e prontamente disponível para o uso na prática clínica e investigação. Também está disponível em dois idiomas, Espanhol e Inglês, sendo que a versão em Português está em andamento.

Apesar dos sintomas depressivos e maníacos estarem associados com uma marcada disfuncionalidade, um grande número de estudos tem mostrado que pacientes apresentam sérias dificuldades na funcionalidade durante o período de remissão (Fagiolini e col. 2005; Tohen e col. 2000; Strakowski e col. 2000). Estes resultados foram demonstrados pela FAST, uma vez que, pacientes eutímicos

mostraram três vezes mais disfuncionalidade que os controles. Pacientes mostraram sérias dificuldades em cinco domínios medidos pela FAST, como autonomia, trabalho, cognição, relacionamentos inter-pessoal e financeiro. Maiores disfuncionalidades foram ainda observadas nos pacientes agudos (deprimidos, maníacos, mistos) quando comparadas aos eutímicos e controles, o que reforça a validade da escala como um instrumento capaz de detectar diferenças de funcionalidade entre pacientes em remissão e aqueles em episódios agudos.

Além disso, o número de episódios depressivos e mistos, assim como o número de hospitalizaçoes e o uso de polifarmácia terapia foram os preditores de pior funcionalidade demonstrado na nossa amostra. Estes dados sugerem que o padrao crônico do THB e a gravidade da doença poderiam justificar, em parte, as disfuncionalidades apresentadas pelos pacientes, inclusive, durante a fase de remissao.

Por fim, as baixas taxas de recuperação funcional, apesar da recuperação sintomática, sugere a necessidade de buscar novas formas de tratamento, especialmente aquelas com enfoque em intervenções psicossociais, assim como programas de educação familiar e aos pacientes. Um suporte familiar adequado, bem como um completo conhecimento do paciente sobre sua patologia, diminui as taxas de recaídas e parecem contribuir para melhorias na funcionalidade destes indivíduos (Colom e col. 2003; Reinares e col. 2006).

8.1. LIMITAÇÕES:

Algumas limitações deveriam ser consideradas ao interpretar estes resultados. Inicialmente, os níveis séricos de GDNF poderiam estar influenciados pelos fármacos, uma vez que nossos pacientes tomam em média três psicofármacos. No entanto, recente estudo em pacientes unipolares e bipolares não encontrou diferenças nas concentrações sanguíneas de GDNF comparando grupos com ou sem antidepressivos e com ou sem lítio. Outro ponto importante é determinar se há uma correlação entre os níveis séricos e cerebrais de GDNF. Até o momento, há poucos estudos sobre este tema, os quais relatam que o GDNF parece não atravessar completamente a barreira hemato-encefálica em pacientes sadios. Entretanto, sabe-se que durante os processos inflamatórios há um aumento da passagem de proteínas, e, neste sentido, seria interessante um estudo para elucidar esta questão.

8.2. CONCLUSÃO:

As neurotrofinas são importantes mediadores dos mecanismos de plasticidade sináptica, além de manter o equilíbrio entre os processos de neurogênese e apoptose. Alterações nos fatores neurotróficos, em especial um aumento das concentrações séricas de GDNF foi demonstrado neste estudo durante os episódios de mania e depressão, quando comparados a pacientes eutímicos e controles, o que sugere o envolvimento desta neurotrofina na fisiopatologia do THB. Por outro lado, alterações do GDNF parecem estar envolvidas com os processos cognitivos. Dificuldades de memória verbal e função executiva são os principais problemas cognitivos apresentadas pelos pacientes e isto parece estar associado com a pobre funcionalidade descrita. No entanto, existe uma clara dificuldade de avaliar a funcionalidade destes indivíduos pela falta de instrumentos específicos, objetivos e de fácil aplicação. Neste sentido, nós desenvolvemos a FAST, a qual avalia dificuldades na funcionalidade, abordando aspectos de autonomia, trabalho, cognição, de relacionamentos inter-pessoal, finanças e lazer. Os testes psicométricos da FAST mostraram resultados positivos, tornando a escala válida e prontamente disponível para o uso na prática clínica e pesquisa.

8.3. CONSIDERAÇÕES FINAIS:

Dada as reais disfuncionalidades apresentadas pelos pacientes bipolares (Tohen e col. 2000; Zarate e col. 2000) e aqui demonstradas, nossa intenção é continuar aprofundando o tema, já que nos parece de extrema relevância. Em curto prazo, nossa intenção é avaliar detalhadamente, as principais dificuldades apresentadas pelos pacientes com THB, através da identificação de quais as áreas da funcionalidade (autonomia, trabalho, cognição, relacionamento, finanças ou lazer) estão mais prejudicadas. Também identificar quais os principais preditores (variáveis clínicas e comorbidades) estão implicados com a pior funcionalidade.

Em um segundo momento, nos parece interessante, avaliar longitudinalmente pacientes bipolares usando a medida de funcionalidade como desfecho, pois estudos prévios já descrevem que as taxas de funcionalidade são baixas, embora outros demonstrem que a recuperação funcional aumenta em um período de 2.5 a 4.5 anos (Strakowski e col. 2000). Para isto, pensamos em seguir pacientes após um primeiro episódio de mania ou depressão e pacientes com múltiplos episódios pós-hospitalização, a fim de também avaliar as diferenças entre pacientes com primeiro episódio e pacientes crônicos. Neste contexto, parece útil a avaliação da sintomatologia clínica assim como, a persistência dos sintomas subsindrômicos, e em especial, os sintomas depressivos que parecem influir de forma negativa na funcionalidade (Altshuler e col. 2006; Altsuler e col. 2002 a).

Por outro lado, seria interessante estudar algumas deficiências cognitvas, em particular, testes de função executiva, que também estão associadas a uma pior funcionalidade (Martinez-Aran e col. 2007). Por fim, considerando que o THB é a nona patologia mais incapacitantes no mundo (Murray & Lopes 1997), nos parece fundamental a elaboração de intervenções psicosocias, com foco na reabilitação funcional, a fim de que pacientes não só remitam sua sintomatologia clínica, mas também recuperem o nível de funcionalidade que possuíam antes do episódio de humor.

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10.0 ARTIGOS ANEXADOS:

10.1. Anexo I:

Neurotrophic and Clinical Correlates of Predominant Polarity in Bipolar Disorder

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Abstract:

Background: Neurotrophins alterations, especially BDNF, have been reported in acute bipolar patients. Our aim was to replicate previous clinical findings and to investigate BDNF serum levels according to predominant polarity.

Methods: Clinical and socio-demographic characteristics were issued from a sample of 149 euthymic bipolar outpatients from the Bipolar Disorder Program of the Hospital Clinic at the Federal University, Porto Alegre, Brazil. Patients were divided into depressive or manic predominance of polarity. The clinical features, occupational functioning and BDNF serum levels were assessed in the two groups.

Results: Forty-five patients were classified as a "Depressive Polarity" and forty-seven were considered as "Manic Polarity". Depressive Polarity was associated with a higher number of years undiagnosed (F=5.022, p=0.008). There were differences between groups regarding age of onset of illness, time of illness, number of depressive symptoms, number of manic symptoms, number of suicide attempts and Hamilton Anxiety (HAM-A) scores. The BDNF serum levels was 0.16mcg/ml (SD: 0.090) among patients with "manic polarity" and 0.14mcg/ml (SD: 0.086) for patients with "depressive polarity" (p=0.491).

Conclusion: Predominant polarity is a valid and useful concept. Depressive polarity was associated with a long delay in receiving an accurate diagnosis. Patients with predominant depressive polarity had a more chronic course and more suicide attempts. The BDNF serum levels were similar in both groups, reinforcing the notion that BDNF is a biological marker for acute episodes but not a marker of course of bipolar illness.

Key words: bipolar disorder, predominant polarity, BDNF, mania, depression, suicide.

Introduction

Bipolar disorder (BD) was described with a wide spectrum of cases of mania and hypomania ranging from euphoric episodes up to predominantly dysphoric or mixed presentations with symptoms of depression (Kraepelin.E., 1976;Angst, 1978;Kukopulos et al., 1980;Winokur & Tsuang, 1996). However, modern studies have described that most bipolar disorder patients experience predominant depressive, manic or mixed episodes during the course of illness and the predominance of polarity has important therapeutic implications for the long-term treatment of these patients (Judd et al., 2003;Calabrese et al., 2004;Colom et al., 2006)

Patients with predominant manic episodes throughout their course of illness are clinically different from patients with predominant depressive episodes. The presence of substance misuse, psychotic symptoms and a higher number of hospitalizations are more frequent amongst patients with manic polarity (Judd et al., 2002;Post et al., 2003;Colom et al., 2006;Daban et al., 2006) and these patients may be more likely to have cognitive impairment (Martinez-Aran et al., 2004;Martinez-Aran et al., in press). On the other hand, predominantly depressive episodes are associated with high morbidity, mortality and overall burden (Goodwin & Jamison, 1990; Judd et al., 2002; Post et al., 2003; Calabrese et al., 2004). Bipolar disorder patients spend much of their time with some degree of depressive symptoms (Judd et al., 2002; Post et al., 2003) and may experience persistent functional impairment (Calabrese et al., 2004; Fagiolini et al., 2005; Depp et al., 2006). In addition, the patients with a longer delay in receiving a correct diagnosis present higher rates of depressive symptoms (Gazalle et al., 2005a) and show a higher number of recurrences (any recurrence) than the mixed or manic patients (Perugi et al., 2000; Daban et al., 2006; Perlis et al., 2006).

There is strong evidence suggesting that mood episodes are associated with deleterious changes in the central nervous system (Manji et al., 2000;Rajkowska, 2002; Sheline, 2003) and neurotrophins alterations, in particular brain derived neurotrophic factor (BDNF), have been reported (Cunha et al., 2006; Frey et al., 2006a; Frey et al.,

2006b; Rosa et al., 2006). We recently demonstrated that BDNF serum levels is decreased in bipolar patients during manic and depressive episodes but not during euthymia (Cunha et al., 2006). In addition, higher scores of depression (Cunha et al., 2006) and mania (Cunha et al., 2006; Machado-Vieira et al., 2006) are associated with lower levels of BDNF in serum.

The study was aimed at validating the clinical implications of the definition of predominant polarity by (Colom et al., 2006) and at investigating whether BDNF levels would be different between patients with manic and depressive predominant polarity.

Methods

Clinical and socio-demographic characteristics were issued from a sample of 149 bipolar outpatients in remission from the Bipolar Disorder Program of the Hospital Clinic at the Federal University, Porto Alegre, Brazil. Patients who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR) criteria for types I and II bipolar disorder and providing reliable information about the number and polarity of previous episodes were included. The assessment was carried out by trained psychiatrists; before starting the analysis, all patients provided informed consent for participation in this research. Confidentially was strictly preserved.

Similarly to (Colom et al., 2006) we have defined the Depressive predominant polarity (Depressive Polarity, DP) as at least two-thirds of a patient's past episodes fulfilling DSM-IV criteria for Major Depressive Episode, and Manic or hypomanic predominant polarity (Manic Polarity, MP) as at least two thirds of past episodes fulfilling DSM-IV criteria for manic or hypomanic episodes. The patients that did not meet criteria for either predominant polarity were defined with no predominant polarity. All patients were assessed at baseline with the Structured Clinical Interview for DSM-IV-TR. Episodes were prospectively assessed through DSM-IV check list for mania, hypomania, mixed episodes and depression. We considered the remission criteria as scores of eight or less on the Hamilton Rating Scale for Depression (HAM-D) and six or less on the Young Mania Rating Scale (YMRS) (Torrent et al., 2006).

Gravel clinical variables were obtained from the structured interview with the patient and their relatives and from their medical records: age of onset, years of evolution, age and number of hospitalizations, number of depressive, manic and total episodes, number of suicide attempts and number of years undiagnosed (NYU). Gravel more variables were assessed: demographic data, psychiatric history of first-degree relatives and substance abuse. Information about social and occupational functioning assessed by Global Assessment of Functioning (GAF) was also registered. A biological marker, BDNF serum levels, were determined as follows: Five millilitres of blood were

withdrawn from each subject by venipuncture into a free-anticoagulant vacuum tube. The blood was immediately centrifuged at 3000 x g for 5 min. BDNF serum levels were measured with sandwich-ELISA, using a commercial kit according to the manufacturer's instructions (Chemicon, USA). The standard curve demonstrates a direct relationship between optical density (OD) and BDNF concentration. Total protein was measured by Lowry's method using bovine serum albumin as a standard (Cunha et al., 2006)

The study was approved by the Ethical and Research Committee of the Hospital Clinic of Porto Alegre, Brazil.

Statistics

Groups (depressive and manic polarity) were compared regarding clinical and social demographic and BDNF serum levels. Statistical methods consisted of Chi-square statistic with Yates correction or Fisher's exact test for the comparison of categorical data, and Student's *t* test for dimensional variables normally distributed. All statistics were two-tailed, and significance was set at p less than 0.05.

Results

Ninety two patients fulfilled inclusion criteria, fifty seven of whom were excluded from the study because they did not present any specific predominant polarity according to our definition. Forty-five (24.2%) patients were classified as having Depressive Polarity, forty-seven (25.3%) was considered as having Manic Polarity.

Depressive Polarity was strongly associated with a high number of years undiagnosed (NYU) (F=5.022, p=0.008), as shown in figure 1.

Table 1 shows the results after comparing Manic and Depressive Polarity regarding demographic variables, work situation, clinical qualitative features and pharmacological treatment. There were no differences between groups regarding age and gender. A high proportion of the patients with manic polarity (84.1%) and the patients with depressive polarity (89.4%) were working during the assessment and there was no difference between the two groups regarding the GAF scores (MP: 63.33±13.62; DP: 61.89±15.04). Depressive polarity was more prevalent amongst bipolar II patients. Depressive onset was more prevalent in depressive polarity. We did not find difference between groups regarding rapid cycling, substance abuse and family history of psychiatric disorder.

There were differences between groups regarding clinical variables, such as age of onset, years of evolution, number of depressive symptoms, number of manic symptoms, number of suicide attempts and HAM-A scores, as shown in table 1. The age of onset of bipolar disorder was 24.22 (DP: 1.97) years for depressive polarity patients and 29.33 (DP: 11.86) years for manic polarity patients (p=0.044). Duration of illness in years was 20.07 (DP: 11.27) for depressive and 15.52 (DP: 8.96) for manic patients (p=0.038). As expected, the number of depressive episodes was higher in depressive patients (13.27; SD: 12.45) than manic patients (4.14; DP: 5.92) (p=0.001). Depressive polarity patients showed higher scores of HAM-A (DP: 13.57, SD: 8.34 x MP: 9.35, SD: 7.63; p=0.013) and a higher number of suicide attempts (2.13, DP: 2.24) than manic polarity patients (1.18, DP: 1.23) (p= 0.039).

The BDNF serum levels were 0.16mcg/ml (SD: 0.090) for manic polarity and 0.14mcg/ml (SD: 0.086) for depressive polarity, with no significant statistical difference (p=0.491).

Discussion:

The present study confirms most of the findings of (Colom et al., 2006) and gives further support to the concept of predominant polarity in the context of bipolar illness. It also shows that depressive predominant polarity is associated with a longer delay in receiving a correct diagnosis in a sample of bipolar patients. This is probably due to the fact that patients who are predominantly depressed tended to be diagnosed as suffering from major depression (Suppes et al., 2005; Solomon et al., 2006). In fact, for a large proportion of patients, the delay before an accurate diagnosis is made and appropriate treatment is initiated can be up 10 years; and we have previously showed that this delay is associated with depressive symptoms (Gazalle et al., 2005a; Gazalle et al., 2005b).

Depression was the most common first-episode polarity in predominantly depressive patients in accordance with previous studies (Perugi et al., 2000;Daban et al., 2006), which could increase the probably of an inaccurate diagnosis. This finding empathizes the importance of ascertaining whether a first depressive episode is trully unipolar or actually bipolar, because failure to detect bipolarity is associated with a risk of drug-induced mania and mixed episodes (Akiskal & Benazzi, 2005; Vieta, 2005) and the possible worsening of the long-term course of BD by the induction of treatment-resistant rapid cycling-episodes (Ghaemi et al., 1999). (Akiskal et al., 1983) identified gravel clinical features that are more frequent in bipolar depression and can be used by clinicians to improve recognition and diagnosis in BD. The clinical features reported by (Akiskal et al., 1983) were: younger age at onset, a greater number of mood episodes prior, psychosis, psychomotor retardation, hypersomnia, hyperphagia and family history of mania or hypomania. In addition, the routine use of a self-report screening tool, such as the Mood Disorder Questionnaire, could also be useful in clarifying the diagnosis (Hirschfeld et al., 2005; Suppes et al., 2005;Sanchez-Moreno et al., in press)

Researchers have reported that 31% of bipolar disorder patients had received a diagnosis of unipolar depression, whereas only 20% of patients who screened positive for BD had received the diagnosis from a physician; these patients consulted 3.3 psychiatrists before being diagnosed with BD (Ghaemi et al., 1999). One reason for misdiagnosis is the lack of insight of many bipolar patients, especially during manic episodes, which keeps them away from seeking assistance when manic or from reporting past manic symptoms when they do visit a clinician (Ghaemi & Goodwin, 2005;Gazalle et al., submitted).

BD has clearly been associated with an elevate risk of suicidal ideation and attempts, with death due to suicide estimated to occur in 10-20% of patients (Post, 2005; Simon et al., 2007), and suicide attempts were strongly associated with depressive polarity (Rihmer & Kiss, 2002;Colom et al., 2006;Daban et al., 2006). As expected, we found that the depressive polarity was associated with a high number of lifetime suicide attempts. This may be related to the fact that patients with depressive polarity had higher number of depressive episodes than patients with manic polarity.

Another difference in the two groups was that depressive patients experienced more anxiety symptoms than manic patients. This finding may also correlated with the high number of suicide attempts that we found in the depressive patients. The Systematic Treatment Enhancement Program for Bipolar Disorder has reported a strong association between lifetime anxiety diagnosis and suicidal attempts (Simon et al., 2007). Nonetheless, the more anxious patients experienced a greater risk of depressive recurrence than less anxious patients. We have recently reported that anxiety comorbidity worsen the couse of BD and is also associated with lower scores of quality of life, even when current levels of depression were controlled (Kauer-Sant'anna et al., in press). Higher rates of anxiety among patients with BD may hinder the prognosis of illness (Perlis et al., 2006).

Previous studies have reported that depressive symptoms are more severe and persistent than manic and even mixed symptoms (Perugi et al., 2001;Judd et al., 2003; Calabrese et al., 2004) and are associated with poorer psychosocial functioning (Calabrese et al., 2004; Fagiolini et al., 2005; Depp et al., 2006). However in our sample, we did not find a difference regarding the scores of GAF, between manic or depressive predominant polarity and the majority of the patients were working, as shown in the Spanish sample. The discrepancies between studies could be explained by the different instruments used to assess psychosocial functioning (Vieta et al., in press; Rosa et al., submiited).

Our sample showed a higher number of hospitalizations and a higher number of suicide attempts compared to the Spanish sample (Colom et al., 2006;Daban et al., 2006) which could be explained by a greater duration of illness, a higher total number of episodes, and, in particular, the depressive episodes experienced by the Brazilian sample. In addition, there were differences regarding the pharmacological treatment between Brazil and Spain; in particular, the frequency of use of lamotrigine, atypical antipsychotics, antidepressants and benzodiazepines that were lower in Brazil compared to Spain.

The higher number of suicide attempts, as well as the higher number of depressive episodes and the longer duration of illness in the predominantly depressed patients underscore the importance of effective prevention and treatment of depression. In this context, mood stabilizers with depression-prevention profiles or “class B” stabilizers added to the formerly existing “class A” and “C” stabilizers (Ketter & Calabrese, 2002; Vieta, 2004; Colom et al., 2006) is recommended, especially if supplemented with psychosocial interventions, such as psychoeducation and family intervention (Colom et al., 2003; Reinares et al., 2006). In addition, depressive symptoms are also associated with a more frequent need to consult a physician or

psychiatrist, a primary care provider or a psychologist/counsellor (Calabrese et al., 2004), which highlights the importance of depression treatment.

Finally, we have recently showed that serum neurotrophic factors (Cunha et al., 2006; Rosa et al., 2006) may be altered during episodes of depression and mania. However, in this study, we did not find differences in levels of BDNF regarding the predominance of polarity. This suggests that biological changes previously reported in bipolar mania and depression (Cunha et al., 2006; Rosa et al., 2006; Walz et al., submiited.), are likely to be state- rather than trait- dependent.

In conclusion, the marked clinical differences between predominantly manic and depressive bipolar patients were again highlighted in the present study. Depressive predominant polarity is also associated with a longer delay to receive a correct diagnosis in BD which may result in a hinderance of long-term prognosis. The patients with depressive polarity had an earlier age of onset and a larger duration of illness, a higher number of depressive episodes, a higher number of suicide attempts and more anxiety symptoms than patients with manic polarity. In accordance to the Spanish sample, there was a clear predominant depressive or manic polarity in around half bipolar patients which resulted in important clinical and therapeutic implications. Depressive patients might be candidates for more aggressive prophylaxis against depression and such a strategy is particularly appealing in light of recent studies highlighting the morbidity and chronicity associated with bipolar depression. Predominant polarity should be accounted for in clinical trials and in clinical practice, and should likely be included as a relevant course specifier in the forecoming diagnostic classifications, such as DSM-IV and ICD-11.

Acknowledgements:

** This study was supported in part by CAPES (Brazil) and The Stanley Medical Research Institute, The Institute Carlos III. FIS (PI05206)

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Figure 1: Number of Years Undiagnosed (NYU) and predominance polarity

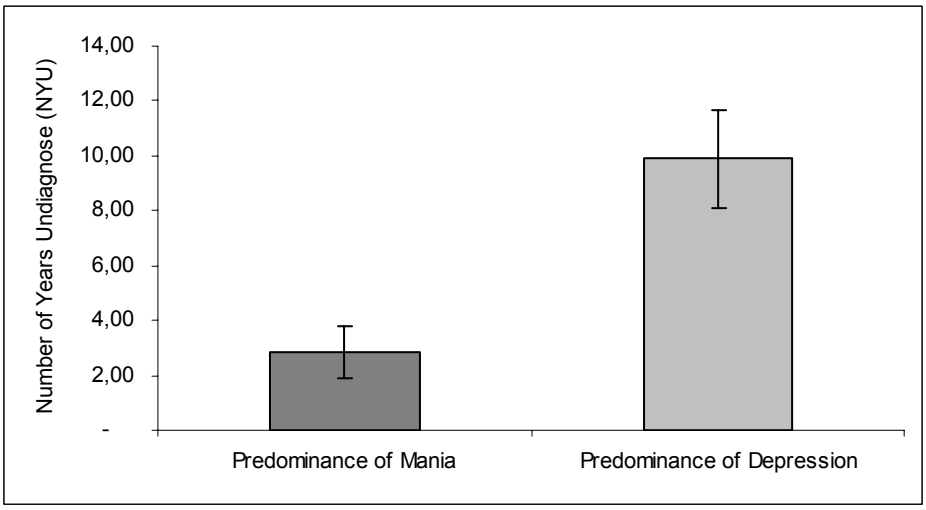

Table 1: Differential features between bipolar patients with manic (MP) and depressive (DP) predominant polarity

	MP (n=45) N(%)	DP (n=47) N(%)	T	p
Female	66.7%	85.1%	4.29	0.38
Activity Working	84.1%	89.4%	10.37	0.11
	MP (n=45) N(%)	DP (n=47) N(%)	Chi	p
BPI	43(95.55%)	36(76.60%)	6.81	0.009
BPII	2(4.4%%)	11(23.04%)		
Manic onset	21(46.66%)	10(21.74%)	12.46	0.014
Depression onset	14(31.11%)	31(67.39%)		
Mixed onset	7(15.55%)	4(8.69%)		
Hypomania onset	1(2.22%)	-		
Present substance abuse preceding first	2(4.44%)	3(6.52%)	0.189	0.664
Rapid cycling	10(22.22%)	12(27.27%)	0.305	0.581
Alcohol	11(24.44%)	9(19.15%)	0.379	0.538
Street drugs	12(26.66%)	8(17.02%)	1.257	0.262
Family history of psychiatric disorder	34(75.55%)	36(78.26%)	0.094	0.759
Family history of THB	11(24.44%)	9(19.56%)	0.316	0.574
Family history of depression	8(17.77%)	13(28.26%)	1.408	0.235
Family history of suicide	9(20%)	11(23.91%)	0.203	0.652
Treatment				
Lithium	41(91.11%)	40(85.10%)	0.787	0.375
Carbamazepine	22(48.88%)	28(59.57%)	1.058	0.304
Valproate	34(75.55%)	29(61.70%)	2.044	0.153
Lamotrigine	2(4.44%)	3(6.39%)	0.168	0.682
Antipsychotics	14(31.11%)	12(25.53%)	0.353	0.552
Antidepressants	18(40.00%)	6(12.76%)	8.843	0.003
Benzodiazapines	24(53.33%)	15(31.91%)	4.319	0.038
	Mean (SD)	Mean (SD)	T	p
Age	44.27 ± 11.66	44.70 ± 11.55	-0.18	0,858
Education level	9.78±4.59	8.89±3.71	1.01	0.32
Age of onset	29.33 ± 11.86	24.22 ± 1.97	2.048	0,044
Age of first hospitalization	34.80 ± 12.45	30.18 ± 11.53	1.647	0,104
Years of evolution	15.52 ± 8.96	20.07 ± 11.27	-2.11	0,038
Total number of episode	16.34 ± 12.82	18.07 ± 18.09	-0.473	0.638
Number of manic episodes	11.66 ± 9.77	4.49 ± 6.21	3.871	0.001
Number of hypomanic episodes	0.54 ± 2.13	0.32 ± 1.08	0.594	0.554
Number of depressive episodes	4.14 ± 5.92	13.27 ± 12.45	-3.966	0.001
Number of hospitalizations	4.11 ± 4.22	3.76 ± 5.10	0.353	0,725
Number of suicide attempts	1.18 ± 1.23	2.13 ± 2.24	-2.113	0,039
HAM-A	9.35±7.63	13.57±8.34	-2.53	0,052
HAM-D	7.84±6.53	10.63±7.06	-1.97	0.013
YMRS	5.70±7.25	3.56±3.38	1.79	0,076
GAF	63.33±13.62	61.89±15.04	0.48	0.63

10.2. Anexo II:

Evolving trends in the long-term treatment of bipolar disorder

"The World Journal of Biological Psychiatry 2007 vol.8 (1):4-11"

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Acknowledgements:

** This study was supported in part by The Stanley Medical Research Institute, The Institute Carlos III and CAPES (Brazil).

Abstract:

The episodic and chronic nature of bipolar disorder usually requires long-term treatment in all patients, yet there is an unmet need for well-tolerated and clinically effective maintenance therapy with enhanced patient adherence. Few well-tolerated treatment options are currently available that are both effective in all phases of bipolar disorder and prevent recurrence of episodes. Lithium has well-established efficacy in the prevention of further manic episodes and may also be effective in the prevention of depression, but safety is a concern due to narrow therapeutic window. For valproate and carbamazepine, data appears much less compelling. Lamotrigine has shown to be effective for long-term prevention of depressive episodes. Controlled studies suggest that atypical antipsychotics may also have mood-stabilizing properties and might become standard for long-term therapy is the new future. The role of psychoeducation in improving adherence to medication in long-term treatment and overall patient outcomes is also addressed.

Keywords: Bipolar disorder; Atypical antipsychotics; Maintenance; Relapse prevention; Prophylaxis; Psychoeducation

1. Introduction

Bipolar disorder is an episodic, chronic, and progressive illness that usually requires long-term treatment in most, if not all patients (Mendlewicz et al., 1999; Bowden et al., 2000b; Judd et al., 2002). Although treatment during episodes may resolve symptoms, impaired functioning may persist for many patients (Tohen et al., 2000; Martinez-Aran et al., 2004). Maintenance therapy is needed to maintain and build upon the initial success of treatment, and aims to prevent relapses and reduce threshold symptoms, risk of suicide, cycle frequency, and mood instability (American Psychiatric Association, 2002). Long-term or even lifelong therapy is usually required to improve functioning and maintain quality of life.

Identifying clinically effective treatments for maintenance therapy has been a significant challenge in bipolar disorder. An ideal long-term treatment or mood stabilizer would effectively treat episodes of mania and depression as well as prevent relapses. In addition, such treatment should be well tolerated, with few side effects over the long term. In the absence of an ideal mood stabilizer, lithium has been the mainstay of recommended treatment for maintenance therapy in bipolar disorder (Sachs et al., 2000; Goodwin and Geddes, 2003). Overall, some randomized, controlled studies suggest that lithium, carbamazepine, divalproex, and lamotrigine might be clinically useful as maintenance treatment in bipolar disorder (Bowden et al., 2000a,b; Keck and McElroy, 2002; Calabrese et al., 2003; Goodwin and Geddes, 2003).

Nevertheless, a substantial number of patients with bipolar disorder do not respond, suffer recurrence, or cannot tolerate the side effects of these agents. Intolerance to side effects and inadequate long-term adherence to treatment potentially translates into poor treatment outcomes. Although few adequately designed long-term maintenance studies have been conducted, data is emerging to suggest that some atypicals may be

effective maintenance therapy for patients with bipolar disorder. Recent evidence for long-term therapies in bipolar disorder is reviewed in this article.

2. Lithium and lamotrigine

Lithium has been a standard choice for long-term treatment for bipolar disorder, based on a few early clinical studies. However, these studies have been criticized due to their methodological limitations. Moreover, naturalistic studies, which more closely approximate clinical practice, have shown less activity with lithium maintenance therapy (Rybakowski et al., 2001). Most patients with bipolar disorder also have some residual illness with lithium maintenance treatment (Baldessarini and Tondo, 2000), and it is now accepted that abrupt withdrawal from lithium can induce a new manic episode.

In addition to these limitations, some subsets of patients are intolerant to lithium or are unable to achieve adequate efficacy and/or adherence at serum levels necessary for remission of symptomatology (Gelenberg et al., 1989). Results from a double-blind, prospective maintenance trial, in which patients with bipolar disorder were randomly assigned to therapy targeting either standard (0.8 to 1.0 mmol/L) or low (0.4 to 0.6 mmol/L) serum lithium levels, found that higher serum lithium levels were associated with a higher rate of side effects and lower rate of adherence (Gelenberg et al., 1989). Moreover, a post-hoc reanalysis of the data, which accounted for baseline lithium levels, showed that patients who entered the study with standard serum lithium levels and were randomized to the low range had the highest risk of recurrence (Sachs and Thase, 2000).

However, more recent trials have provided further support to the long-term efficacy of lithium. Two 18-month, randomized, double-blind trials compared lamotrigine, lithium,

and placebo as maintenance treatment in a total of 1315 recently manic or depressed patients with bipolar I disorder (Bowden et al., 2003; Calabrese et al., 2003). Individual and combined analyses of these studies showed that both lamotrigine and lithium significantly prolonged the time to intervention for any mood episode compared with placebo (figure 1); in spite of the enriched design for lamotrigine responders, lithium prevented manic episodes more effectively than lamotrigine and placebo (Goodwin et al. 2004).

3. Divalproex

Only one randomized, placebo-controlled study has assessed divalproex in comparison with placebo for maintenance therapy in patients with bipolar I disorder (Bowden et al., 2000a). Patients received divalproex, lithium, or placebo and time to relapse of any mood episode during 1 year of treatment was determined. As shown in Figure 2, there was no significant difference between treatments, although a post hoc analysis showed that patients receiving divalproex had significantly fewer relapses than those receiving placebo if patients had already started divalproex prior to randomization (Gyulai et al. 2003).

4. Carbamazepine

Earlier studies of carbamazepine for the long-term treatment of bipolar disorder have not demonstrated good efficacy (Greil et al., 1997). Lithium (n = 74) and carbamazepine (n = 70) were compared in a randomized study of 144 patients with bipolar disorder followed for 2.5 years (Greil et al., 1997). Patients treated with carbamazepine had a significantly greater number of recurrences and use of concomitant medication (P = 0.041) and/or adverse events (P = 0.007) compared with lithium.

In a smaller double-blind study, 52 patients with bipolar disorder were randomly assigned to a year of treatment with lithium or carbamazepine, then treated with the opposite drug for another year and treated with a combination of the two drugs in the final year (Denicoff et al., 1997). More patients treated with carbamazepine (37.1%) failed to complete the first full year of treatment due to lack of efficacy compared with those treated with lithium (31.0%). With the combination treatment, 24.1% of patients withdrew from the study due to lack of efficacy.

Another study randomized 94 patients in remission to double-blind treatment with lithium (*n* = 44) or carbamazepine (*n* = 50) for 2 years (Hartong et al., 2003). The frequency of mood episodes and the proportion of patients dropping out of the study were higher with carbamazepine treatment than with lithium, with a completion rate of 32% and 36%, respectively.

More recent data suggest, though, that some efficacy in prevention of relapse and recurrence of manic or mixed episodes can be demonstrated for an extended-release formulation of carbamazepine (Ketter et al., 2004). Patients (*N* = 92) who had participated in a 3-week double-blind study of carbamazepine or placebo were assigned to 6 months of further open-label treatment with carbamazepine. The estimated mean time to relapse was 141.8 ± 5.6 days and 14.3% patients relapsed during the study. Patients who had previously received carbamazepine in the 3-week treatment period maintained their improvement and those who had received placebo demonstrated significant improvements in manic symptoms. The most common adverse events with carbamazepine were headache, dizziness, and rash. These results indicate that further studies to determine the role of carbamazepine in the long-term treatment of patients with bipolar disorder are warranted.

5. Second-generation antipsychotics as maintenance therapy

Due to their superior tolerability profile compared with conventional antipsychotics with regards to extrapyramidal symptoms and tardive dyskinesia liability, atypicals are increasingly being used for the treatment of bipolar disorder. Olanzapine, quetiapine, risperidone, ziprasidone and aripiprazole have demonstrated efficacy in the treatment of bipolar mania in 3-week studies, as monotherapy (Vieta and Goikolea, 2005). When used in combination with traditional mood stabilizers, such as lithium or divalproex, olanzapine, risperidone and quetiapine also proved to be more efficacious that lithium or valproate monotherapy (Vieta and Goikolea, 2005). Evidence also suggests that some atypicals are effective in the treatment of bipolar depression (Tohen et al., 2003b; Calabrese et al., 2005). Data indicating the efficacy in long-term treatment of bipolar disorder for each of these agents are reviewed below.

5.1. Olanzapine

Gravel studies have addressed the efficacy of olanzapine as long-term therapy in bipolar disorder (Tohen et al., 2003a, 2004, 2005). Data from a study in which a 6- to 12-week phase of open-label olanzapine/lithium combination therapy was followed by 52 weeks of double-blind olanzapine or lithium monotherapy found that the prevention of depressive relapse (i.e. maintaining a 21-item Hamilton Depression Rating Scale [HAM-D21] score of 15 or less) was quite similar with both agents, but olanzapine was superior to lithium ($P < 0.001$) in reducing the incidence of manic relapse (an increase in the Young Mania Rating Scale [YMRS] score to 15 or more) (Tohen et al., 2005).

Olanzapine's efficacy in manic and depressive episodes and maintenance of remission has also been corroborated in a comparative study against divalproex (Tohen et al., 2003a). In this investigation, 251 adult patients with a bipolar I disorder, manic or mixed (DSM-IV), were randomly assigned to olanzapine (5-20 mg/day) or divalproex (500-

2500 mg/day) during a 3-week, randomized, double-blind phase followed by a double-blind continuation phase of 44 weeks (Tohen et al., 2003a).

Olanzapine was significantly superior to divalproex in mean improvement in YMRS total score from baseline to endpoint (LOCF to Week 47) (P = 0.03). A numerical but not significant difference was also observed in mean improvement of HAM-D21 score in all patients and in those with moderate-to-severe depressive symptoms (HAM-D21 $\geq$ 20 at baseline) (Tohen et al., 2003a). The median time to symptomatic remission of mania (YMRS $\leq$ 12) was significantly shorter for olanzapine (14 days) than for divalproex (62 days) (P = 0.05) (Tohen et al., 2003a), although, importantly, there was no significant difference between groups in mania remission rates and subsequent relapse into mania or depression.

Treatment with olanzapine was associated with somnolence, increased appetite, and weight gain more frequently (P < 0.05) than divalproex (Tohen et al., 2003a).

In a study conducted in patients with bipolar disorder who had previously received open-label treatment with olanzapine and were then randomized to double-blind treatment for up to 52 weeks, olanzapine was shown to be associated with lower rates of relapse and a longer time to relapse compared with placebo (P < 0.001) (Tohen et al., 2003c).

Olanzapine added to lithium or valproate has been evaluated in an 18-month study for prevention of relapse (Tohen et al., 2004). Patients achieving syndromic remission after 6 weeks of treatment with olanzapine and lithium or valproate were randomized to further treatment with olanzapine (n = 51) or placebo (n = 48) in addition to lithium or valproate. At the end of the treatment period, symptomatic (using the total score on the YMRS and the 21-item HAM-D), but not syndromic (meeting DSM-IV criteria for a

manic, mixed, or depressive episode) relapse, was significantly different in patients treated with olanzapine and lithium or valproate compared with the group treated with placebo and lithium or valproate ($P = 0.023$).

The main concerns raised by olanzapine use as long-term therapy in bipolar patients and those related to weight gain and metabolic syndrome.

5.2. Quetiapine

Quetiapine monotherapy has been shown to be superior to placebo in the improvement of mania and associated symptoms as well as maintenance of response and remission rates in two double-blind, 3-month studies of patients with bipolar disorder (Bowden et al., 2005; Vieta et al., 2005; McIntyre et al., 2005). In the first study, patients were randomized to quetiapine ($n = 107$), placebo ($n = 95$), or lithium ($n = 98$). Both quetiapine and lithium decreased YMRS scores significantly more than placebo at 3 weeks ($P < 0.001$), and this difference was maintained to Week 12 ($P < 0.001$). A similar improvement in YMRS scores was observed in quetiapine- or haloperidol-treated patients versus placebo in the second study. The response ($\geq$ 50% reduction in YMRS score) and remission (YMRS $\leq$ 12) rates in the quetiapine-treated group were significantly greater than placebo at Weeks 3 and 12. Haloperidol was more efficacious than quetiapine at week 3 but not at week 12. Similar to results from the individual studies, a combined analysis of these two studies indicated that the majority of patients who responded by Week 3 maintained their response through the end of the 3-month study period. Moreover, of the small proportion of patients who did not respond by Week 3 and who had a further assessment, 72% of quetiapine-treated versus 41% of placebo-treated patients responded by the end of the study. Similarly, remission rates in the quetiapine group were maintained to the end of treatment. Compared with placebo, a significantly greater proportion of patients in the quetiapine group met all clinical remission/euthymia criteria (YMRS $\leq$ 12 or YMRS $\leq$ 12 + MADRS $\leq$ 10 or

YMRS ≤ 12 + MADRS ≤ 8) by the primary endpoint (Day 21; *P* < 0.01) and rates of remission/euthymia continued to improve to the end of the 3-month treatment period (*P* < 0.001) (Paulsson and Jones, 2004). The results from these controlled studies suggest that a significant long-term treatment benefit is likely as the early treatment effect of quetiapine was maintained over a period of 3 months in patients with bipolar mania, but no controlled trial are available for quetiapine beyond 3 month follow-up.

Quetiapine has also been shown to have benefits as long-term therapy in two prospective, open-label studies of patients with rapid cycling (Vieta et al., 2002; Ghaemi et al., 2003). One study prospectively assessed 14 patients with rapid cycling meeting DSM-IV criteria (manic, hypomanic, mixed, depressive, or euthymic) treated with quetiapine (initiated at 50 mg/day and dosed according to tolerability and clinical response) in combination with ongoing psychotropic medication for 112 ± 33 days (Vieta et al., 2002). The Clinical Global Impressions for bipolar disorder (CGI-BP), YMRS, and HAM-D17 rating scales were included in efficacy assessments (figure 3).

Although controlled maintenance studies are needed, findings from these naturalistic, open-label investigations suggest that quetiapine may be clinically effective in the long-term treatment of rapid-cycling bipolar disorder. The main safety and tolerability concerns with the drug are related to sedation and moderate weight gain liability.

5.3. Risperidone

No controlled trials are available with risperidone beyond 12-weeks.

A 6-month, open-label study has suggested that monotherapy or combination therapy with risperidone may maintain the improvement of manic and depressive symptoms in patients with bipolar disorder over time (Vieta et al., 2001b). Forty-four bipolar II patients (DSM-IV) with a current hypomanic episode and a YMRS score > 7 showed a significant reduction from baseline in YMRS score (*P* < 0.001) by the first week of

risperidone treatment (Figure 4) (Vieta et al., 2001b). This improvement in manic symptoms was maintained throughout the 6-month study period. There was no significant difference in the rate of improvement between patients receiving combination therapy or monotherapy with risperidone (Vieta et al., 2001b). A total of 73% of patients were considered responders (those with ≥ 50% reduction in YMRS score from baseline). Risperidone treatment also significantly reduced HAM-D17 scores by Week 1 ($P < 0.001$) and until the end of the 6-month treatment period ($P < 0.001$) (Vieta et al., 2001b).

Data from this study were included in a larger analysis involving patients with different index episodes (mania, hypomania, mixed, depressive, or schizoaffective disorder, bipolar type) (Vieta et al., 2001a). In this heterogeneous sample (n = 541), highly significant reductions in mean YMRS score occurred by Week 1 and continued for 6 months ($P \leq 0.001$ vs. baseline) for all groups except in patients with depression ($P < 0.05$ vs. baseline) (Vieta et al., 2001a). Risperidone, either in combination with mood stabilizers or as monotherapy, was relatively well tolerated in bipolar II patients, with little evidence of tardive dyskinesia or EPS-related adverse events emerging over a 6-month period (Vieta et al., 2001b). Double-blind controlled studies in patients with bipolar disorder are needed to confirm the findings from these open-label studies. Safety and tolerability concerns about risperidone in bipolar disorder included some EPS liability, hyperprolactinemia, and moderate weight gain.

5.4. Clozapine

There is some evidence to suggest that clozapine is effective against mood and psychotic symptoms in patients with schizoaffective disorder, bipolar type, and bipolar I disorder. In addition, results from an open study in patients (n = 38) with treatment-resistant schizoaffective or bipolar disorder (DSM-IV) suggest that clozapine may have utility as maintenance treatment (Suppes et al., 1999). Patients in this study were

randomly assigned to clozapine add-on treatment or treatment as usual (no clozapine) and followed up to 1 year. The CGI, HAM-D24, Brief Psychiatric Rating Scale (BPRS), and Bech-Rafaelsen Mania scales were included in the monthly assessments (Suppes et al., 1999).

Significant advantages across all measures except the HAM-D24 were observed with clozapine versus treatment as usual (Suppes et al., 1999). In particular, clozapine was a strong antimanic and antimood lability agent. The decrease in the mean rate of change in BPRS score over 1 year (or until last visit) in the clozapine group revealed highly significant improvement, whereas there was worsening in the treatment-as-usual group (-3.68% vs. 2.51%, respectively; $P = 0.001$). Moreover, 65% of patients taking clozapine met the criteria for response (30% improvement in BPRS from baseline) by 3 months and 82% by 6 months.

Patients who were switched from their treatment-as-usual to clozapine also benefitted. The nine patients (seven with bipolar I disorder) in whom clozapine was substituted for treatment as usual had significant improvement in BPRS score ($P < 0.05$) over 1 year compared with their score at the termination of usual treatment (Suppes et al., 1999). Overall, the findings suggested that clozapine might have a role in patients with bipolar disorder who do not respond to standard treatments, but this needs to be confirmed in larger controlled studies. The safety profile of clozapine appeared to be worse than some other atypical antipsychotics. Side effects were noted throughout the study (Suppes et al., 1999). In particular, somatic complaints increased relative to baseline in clozapine-treated patients, and were more severe than in the treatment as usual group. No patient developed agranulocytosis during the study, but this side effect is a known concern in the use of clozapine (Ertugrul and Meltzer, 2003), besides weight gain and metabolic effects.

5.5. Aripiprazole

One randomized, double-blind study has compared aripiprazole versus placebo in the maintenance treatment of patients with bipolar disorder (Keck et al., 2006). Patients (*n* = 161) who had recently experienced a manic episode or who had just completed an aripiprazole acute mania study were assigned to aripiprazole or placebo for 26 weeks. Time to relapse of symptoms (primary endpoint) and total number of relapses (P = 0.013) were significantly decreased in patients treated with aripiprazole versus those treated with placebo. No effect was seen in prevention of depression or mixed episodes. Adverse events greater than 10% in the aripiprazole group included anxiety, insomnia, depression, and nervousness.

6. Role of psychoeducation in long-term treatment

Concomitant psychosocial intervention during bipolar maintenance treatment is increasingly being recognized as an important tool to enhance treatment adherence and other aspects of illness management (American Psychiatric Association, 2002). Supporting the benefits of psychoeducation in the maintenance setting are findings from a subanalysis of a study in bipolar I and II outpatients (all receiving a standard pharmacologic treatment), which showed that concomitant group psychoeducation produces significantly more stable lithium levels over time ($P \leq 0.05$ at 6, 16, and 24 months) than nonstructured group meetings (control) (Colom et al., 2003a). Such stable lithium levels most likely reflect enhanced long-term adherence to treatment.

Furthermore, intervention with psychoeducation translated into improved outcomes in the parent study, which consisted of a 21-week, single-blind, randomized treatment phase and 2-year follow-up (Colom et al., 2003b) (Figure 5). At the end of the follow-up period, group psychoeducation significantly reduced the number of relapsed patients ($P < 0.001$ psychoeducation vs. control) and increased the time to any recurrence ($P <$

0.001), including depressive (HAM-D17 ≥ 17), mixed (YMRS ≥ 20; HAM-D17 ≥ 12), and manic (YMRS ≥ 20) or hypomanic (YMRS ≥ 12) episodes (Colom et al., 2003b). The number and length of hospitalizations per patient were also lower in those who received psychoeducation ($P < 0.05$). Despite the benefits of psychoeducation, however, over half of the patients receiving group psychoeducation (and standard pharmacologic treatment) had relapsed by the end of the 2-year follow-up.

7. Conclusion

The treatment of patients with bipolar disorder remains a challenge for clinicians. Effective therapeutic approaches are required for the management of acute and chronic symptoms, as well as prophylaxis against future episodes. Controlled studies have shown that atypicals antipsychotics are effective in the treatment of bipolar mania and some also have efficacy in bipolar depression. Some atypicals have also shown promising results in maintenance therapy of bipolar disorder, but concerns about weight gain and metabolic syndrome are increasing. Strategies such as psychoeducation in combination with effective drug therapy may also improve maintenance therapy for bipolar disorder. In the near future, supplementary interventions such as cooperative rehabilitation may help to reduce the gap between symptomatic recovery and functional recovery.

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10.3. Anexo III:

Validation of the Portuguese version of the Lithium Attitudes Questionnaire (LAQ) in bipolar patients treated with lithium: cross-over study

"Clin Pract Epidemol Ment Health 2006 Nov 22;2:32"

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Abstract:

Background: Poor adherence to lithium is very common in bipolar patients and it is a frequent cause of recurrence during prophylactic treatment. Gravel reports suggest that attitudes of bipolar patients interfere with adherence to lithium. The Lithium Attitudes Questionnaire (LAQ) is a brief questionnaire developed as a means of identifying and grouping the problems patients commonly have with taking lithium regularly. The original version is validated in patients, but a validated version in Portuguese is not yet available.

Methods: One-hundred six patients with bipolar disorder (DSM-IV criteria) criteria under lithium treatment for at least one month were assessed using LAQ. LAQ is a brief questionnaire administered under interview conditions, which includes 19 items rating attitudes towards prophylactic lithium treatment. We analysed the internal consistency, concurrent validity, sensitivity and specificity of the Portuguese version of LAQ.

Results: The internal consistency, evaluated by Cronbach's alpha was 0.78. The mean total LAQ score was 4.1. Concurrent validity was confirmed by a negative correlation between plasma lithium concentration and total LAQ score (r=-0,198; p=0.048). We analysed the scale's discriminative capacity revealing a sensitivity of 69% and a specificity of 71% in the identification of negative attitudes of bipolar patients.

Conclusion: The psychometric assessment of the Portuguese version of LAQ showed good internal consistency, sensitivity and specificity. The results were similar to the original version in relation to attitudes of bipolar patients towards lithium therapy.

Background:

Bipolar disorder (BD) is a chronic, recurrent illness, affecting 0.3% to 1.5% of the population. BD is associated with important social and economic costs, including loss of productivity, lower quality of life, incremented healthcare costs and suicide [1;2]. Lithium remains as the mainstay in bipolar disorder treatment. It reduces manic symptoms in 73% of the treated patients, twice as many as placebo, and prevents the recurrence of mood episodes [3-6].

Non-adherence rates to long-term prophylactic pharmacotherapy range from 20 to 66% [6-9]. The median duration of lithium adherence is around 76 days [10]. Poor adherence to lithium is, unfortunately, very common and it is the most frequent cause of recurrence during prophylactic treatment [10-14]. Gravel studies reported that negatives attitudes, such as non-acceptance of lithium effectiveness, opposition to the treatment, denial of the disease and fear of side effects interfere with adherence [15-17].

The ‘Lithium Attitudes Questionnaire’ (LAQ) was developed as means of identifying and grouping the problems that patients commonly have when taking lithium regularly. The 'LAQ' evaluates the main advantages and disadvantages of lithium treatment. Its subscores are then used to describe patients who expressed opposition to continuing on lithium, and those who missed their hypomanic episodes. The original English version is validated in psychiatric population and has shown adequate reliability [18].

The purpose of the present study was to validate the Portuguese version of LAQ and to describe its psychometric properties. This validation may help the assessment of attitudes that may affect adherence in bipolar patients from Brazil and Portugal.

Methods:

2.1. Subjects:

The study was conducted in two psychiatric outpatient services specialized in mood disorders in the city of Porto Alegre, Brazil. The psychiatric outpatients selected were diagnosed with bipolar disorder according to DSM-IV criteria.

Patients were evaluated for both their symptoms and general state in weekly consultations. Patients participated in psycho-educational groups about the use of lithium and support groups to discuss topics related to the disorder. After giving the informed consent, patients were interviewed and had a lithium blood level assessment scheduled.

The study was approved by the Ethics Committee of the Hospital Materno Infantil Presidente Vargas and Hospital de Clínicas de Porto Alegre, where the research took place and was carried out in compliance with the Helsinki Declaration.

2.2. Variables:

Demographical Data

Every subject gave information about marital status, work, age, gender and level of education.

Current clinical status

Bipolar patients were diagnosed using a Structured Clinical Interview (SCID) and all patients were followed up prospectively using mood charts. The clinical status was also assessed on the day of the LAQ application and blood collection for lithium measurements.

LAQ

LAQ is a brief questionnaire comprising 19 items which rate attitudes towards prophylactic lithium treatment. Seven subscales assess the resistance to prophylaxis in general (LAQ 1), denial of therapeutic effectiveness of lithium as a prophylactic agent (LAQ 2), fear of side effects (LAQ 3), difficulties with the daily routine medication intake (LAQ 4), denial of the severity of the illness (LAQ 5), negative attitudes toward drugs in general (LAQ 6) and lack of information about lithium prophylaxis (LAQ 7) [16;18]. The correct answers are: 1-N; 2-Y; 3-N; 4-N; 5-Y; 6-N; 7-Y; 8-N; 9-Y; 10-N; 11-Y; 12-N; 13-Y; 14-N; 15-Y; 16-N; 17-Y; 18-Y; 19-N. The items are posed using a Yes/No format with low scores indicating positive attitudes and high scores indicating negative attitudes The total LAQ score is obtained by adding together the responses to the 19 points. If a patient obtains a score > 4 this indicates a negative attitude versus lithium treatment, as shown in Table 1.

The adaptation of LAQ was carried out using an instrument translated into Portuguese after translation/back translation procedures [19;20]. The items resulting in optimal word equivalence with the original text were analysed and discussed by five psychiatric investigators who agreed with the final version. After these procedures, investigators who were fluent in both English and Portuguese evaluated the degree of equivalence between the original English and the Portuguese version. Finally, the comprehension of each item was assessed with a sample of 106 bipolar patients. The Portuguese version of the LAQ used in this study was found to be appropriate and correctly understood by psychiatric patients.

The LAQ was administered on one occasion and the time spent in the application of LAQ was 6-8 minutes. On this occasion venous blood was drawn from each patient to

assess levels of lithium. The patients did not take lithium on the morning of the interview.

We analysed the internal consistency, concurrent validity in relation to plasma lithium concentration, sensitivity and specificity. The psychometric characteristics of the LAQ are derived from the administration of the questionnaire, including all the subjects who completed the analysis. Internal consistency was assessed by Cronbach's Alpha for the total scale and each individual item. Concurrent validity was studied considering plasma lithium concentration and the score obtained using LAQ. Pearson coefficient was used for verify correlation between LAQ scores and plasma lithium concentration. The cutt-off used was 4 (from the original reference).

To study the sensitivity, specificity and positive and negative predicative of the LAQ, we have used the proportion of adherent bipolar patients as compared to plasma lithium concentration. A discriminate analysis was carried out using data obtained by means of LAQ application.

Lithium plasma concentration

The subjects were instructed to be at the hospital early in the morning, without having taken their lithium dose, respecting a 12-hour interval between the last dose of lithium and the blood sampling. Venous blood was collected from each patient into Vacutainer tube containing edetic acid. The whole blood was then centrifuged 1600x g for 10 minutes and the plasma removed by aspiration. A 1/20 dilution in water was made of 99µl of plasma. Lithium concentrations were measured in plasma dilutions by the indirect method, using an Instrumentation Laboratory CELM Flame Photometer. Assays were performed in duplicate [21].

Statistical analysis:

Statistical analysis was performed using SPSS for Windows - Version 12.0 (SPSS Inc., Chicago, IL, USa). The Kolmogorov-Smirnov test was used to compare the observed cumulative distribution to a theoretical cumulative distribution function. ANOVA test was used for compare LAQ scores and plasma levels of lithium. Pearson's correlation coefficient was performed to examine the relationship between plasma lithium concentration and LAQ scores. The binomial variables (clinical state and LAQ scores) were compared using Chi-Square test.

Results:

The sample included 73 (68.9%) women, with a mean age 43.5±9.8 and 33 men with a mean age of 41.6±9.7. At the time when the present study was carried out, there were 77 (71.7%) euthymic patients, 12 (11.1%) manic and 17 (17,2%) depressed, according to the mood charts and physician is assessment. 40 (37.7%) of patients were smokers, 70 (66%) used coffee on a regular basis, and 68 (64.2%) used tea on a regular basis.

The answers to the LAQ were obtained from 106 bipolar patients and the mean score on the LAQ TOTAL was 4.1±0.5 for men and 4.1±0.4 for women. Therefore, gender did not seem to influence any of the adherence parameters evaluated using LAQ scale or lithium plasma. The demographics and clinical characteristics are shown in Table 2.

All LAQ items were answered by patients in every test session. No patient posed objections to completing the questionnaire. The internal consistency coefficient was obtained for the 19 items as shown Table 3 and the mean Cronbach's alpha of 0.78 for the total scale indicates that the items are sufficiently homogeneous.

We analysed the scale's discriminative capacity for bipolar patients by means of the performance of 'attitudes toward lithium treatment' on sensitivity and specificity analysis. The calculated sensitivity and specificity were 69% and 71%, respectively.

Concurrent validity was assessed using plasma lithium concentration and showed a significant negative correlation between the total LAQ score and lithium levels (r=-0.198; p=0.048). The number of patients scoring positively for each LAQ subscore during the test completion is shown in Figure 1.

Figure 1 shows that LAQ's subscore 3, regarding the side effects of lithium, was considered a disadvantage of treatment by the majority of respondents. Patients also reported subscore 5 (denial of illness severity) as a source of noncompliance with Li prophylaxis. Subcultural attitudes, as assessed using subscore 6, was considered as a disadvantage in 44.4% of the positive respondents and dissatisfaction with factual knowledge of Li (subscore 7) was rated as a disadvantage in 42,5% of the positive respondents.

We observed statistically significant differences between the LAQ 1 and scores of patients currently manic or euthymic and significant differences between the LAQ 2 and scores of patients currently manic, depressed or euthymic (Pearson Chi-Square <.05) (see Table 4). This result indicates that acute symptoms interfered in lithium treatment adherence.

Discussion:

Unfortunately, poor adherence to lithium is very common and previous studies have already pointed out that it is the most frequent cause of recurrence during prophylactic lithium treatment [13;14;22]. Therefore, it is reasonable try and identify potential reasons which lead patients to discontinue lithium treatment. The Portuguese version of the LAQ scale may become particularly useful because Portuguese is a language which is spoken by a population of 202 million people, including Brazil and Portugal. Hence, it is reassuring to find that the psychometric assessment of the Portuguese version of LAQ showed good sensitivity and specificity. In a sample of bipolar patients the Portuguese version of the LAQ used the cut-off point of 4, which mirrors the English original version; this indicates that four or more points at LAQ reflect the existence of negative attitudes towards lithium treatment.

The LAQ scale showed very good internal consistency and all items presented a Cronbach's alpha above 0.7, as internationally accepted. In the convergent validity analysis we observed a negative correlation between lithium plasma levels and total scores of LAQ. This was due to the fact that, in non-adherent patients (plasma lithium levels < 0.6mmol L or > 1.2mmol L), negative attitudes about lithium treatment were greater than those observed among adherent patients.

The analysis of each LAQ subscores showed that subscore 3, regarding side effects of lithium, was considered an important disadvantage of treatment by the majority of respondents, which is in line with the original study. This result is important because fear of side effects, and not the side effects themselves seem to pose important barriers for the use of lithium. Indeed, Scott and Pope [15] reported that many patients with affective disorders feared harmful effects of the use of lithium in the long run. Patients also reported that denial of the severity of the illness, negative attitudes toward drugs in general and lack of information about lithium prophylaxis were also identified as caveats of lithium therapy. These results are in accordance with

previous studies which highlighted the fact that non-adherent bipolar patients tend to present negative attitudes towards lithium treatment [14-17;23].

Further, the scale proved to be sensitive to mood changes, as differential scores were captured during depression, mania and euthymia. Euthymic patients showed more positive attitudes than manic and depressed patients. The scores obtained in items such as LAQ 1 (resistance to prophylaxis in general) and LAQ 2 (denial of therapeutic effectiveness of lithium as a prophylactic agent) were the main differences between euthymic patients and those who were either manic or depressed. These results were reported in the original English version, where hypomanic patients showed more resistance to prophylaxis in general [24]. Negative attitudes strengthen the hypothesis that attitudes towards treatment play a major role in the effectiveness of lithium long-term prophylaxis.

Gravel studies [22;24] found a possible effect of education in improving adherence. It is reasonable to suppose that this effect is in some extent mediated via patient's aquisition of a positive attitude towards lithium treatment [16]. LAQ is a rapid, reliable screening instrument which presents a good level of acceptability by patients. The subcategories of items, from which the LAQ subscores derive, describe specific problem areas, most of which are considered by patients to represent noteworthy disadvantages of lithium therapy [18]. The importance of this finding is that all factors can be assessed routinely in day-to-day clinical practice, with no need of long questionnaires. The identification of negative attitudes toward lithium treatment may be an important tool in order to increase adherence and consequently reduce the number of relapses, economic burden and rates of mortality associated with BD.

It is important to highlight the fact that individuals who are non-adherent to lithium are also likely to fail to agree to participate or fail to adhere with research protocols. Another point to be considered is that we did not assess current symptom severity and comorbidities. It is also important to mention that this was a crossover

study, as we assessed attitudes about the use of medication in only one occasion. As yet, there is no research on the stability or variability of such beliefs over time.

Conclusion:

In conclusion, the LAQ scale is a rapid and reliable screening instrument which may help to identify negative attitudes towards lithium treatment. The present study showed that the Portuguese version is valid for the assessment of bipolar patients in Portuguese-speaking countries.

Competing Interests:

“The author(s) declare that they have no competing interests”.

Acknowledgements:

** This study was supported in part by CAPES (BrazilI), CNPQ (Brazil) and FIPE-HCPA.

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Table 1: Questionário de Atitudes em relação ao Lítio (LAQ)

Marque com um X as respostas que o Sr considerar correta.	
1. O Sr(a). acha perfeitamente aceitável tomar LÍTIO por vários anos?	(1)S (2) N
2. O Sr(a). toma LÍTIO somente quando sente necessidade?	(1)S (2) N
3. O Sr(a) acha que vale a pena tomar LÍTIO, apesar dos efeitos colaterais?	(1)S (2) N
4. Tomar LÍTIO conforme receitado pelo seu médico é fácil no seu dia-dia?	(1)S (2) N
5. É melhor aliviar o estresse, do que tomar LÍTIO para ficar bem (estável)?	(1)S (2) N
6. Sr(a). considera que a LÍTIO é uma necessidade atual para o seu bem-estar?	(1)S (2) N
7. Sr(a) se preocupa com os efeitos colaterais do LÍTIO mesmo quando sente-se bem?	(1)S (2) N
8. A maioria das pessoas que o Sr(a) conhece acham necessário que tome o LÍTIO?	(1)S (2) N
9. Sr(a). ás vezes tenta esquecer que está doente, e por isso para de tomar os seus comprimidos de LÍTIO?	(1)S (2) N
10. Sr(a). confia tanto nos seus comprimidos de LÍTIO, que se por algum motivo fosse interrompido o seu tratamento, o Sr(a) ficaria preocupado?	(1)S (2) N
11. As pessoas precisam lhe lembrar de tomar o LÍTIO?	(1)S (2) N
12. Sr(a). aceita bem o LÍTIO, mesmo sabendo que é necessário fazer exames de sangue e check up regulares?	(1)S (2) N
13. Sr(a). ás vezes pensa que o LÍTIO é uma maneira artificial de lhe manter bem, e que deveria conseguir viver sem ela?	(1)S (2) N
14. É fácil lembrar as horas certas de tomar LÍTIO?	(1)S (2) N
15. Sr(a). freqüentemente duvida que a sua condição de saúde seja tão seria, que justifique o uso do lítio por vários anos?	(1)S (2) N
16. Sr(a). tem um conhecimento adequado sobre os efeitos da LÍTIO?	(1)S (2) N
17. Se o Sr(a) ficasse bem por vários meses, deixaria de tomar a LÍTIO?	(1)S (2) N
18. Se a sua rotina diária mudar por alguma razão, o Sr(a). terá dificuldade de tomar seus comprimidos de LÍTIO?	(1)S (2) N
19. Sr(a). está convencido dos efeitos benéficos do LÍTIO baseado na sua própria experiência?	(1)S (2) N

Table 2: Demographics and Scores for lithium treatment parameters in 106 bipolar patients

	Average	SD
Age	42,9	9,79
Education level	9,2	3,4
Plasma lithium	0,86	0,25
LAQ TOTAL	4,1	3,37
LAQ1	0,96	1,16
LAQ2	0,13	0,39
LAQ3	0,57	0,6
LAQ4	0,57	0,89
LAQ5	0,67	0,77
LAQ6	0,78	0,82
LAQ7	0,42	0,5

Table 3: Internal Consistency Reliability

	Scale Mean	Scale Variance	Corrected item	Alpha
Question 1	3,7453	9,4107	0,5778	0,7543
Question 2	4,0283	10,904	0,2149	0,7803
Question 3	4	10,2667	0,5044	0,7654
Question 4	4,0094	10,4666	0,42	0,7703
Question 5	3,9717	10,4659	0,3496	0,7732
Question 6	4,066	10,9385	0,2968	0,7779
Question 7	3,6415	10,5179	0,1792	0,7882
Question 8	3,8679	10,8014	0,1311	0,7886
Question 9	3,8585	10,1417	0,3713	0,7715
Question 10	3,8386	9,6788	0,5355	0,7588
Question 11	3,9245	10,0704	0,4628	0,7654
Question 12	3,9811	10,3806	0,4058	0,7701
Question 13	3,6887	9,6069	0,4884	0,7619
Question 14	3,9434	10,1491	0,4538	0,7664
Question 15	3,7547	10,0726	0,3451	0,774
Question 16	3,6792	10,9247	0,547	0,7979
Question 17	3,8868	10,0442	0,4325	0,7671
Question 18	3,9717	10,7135	0,2343	0,7798
Question 19	4,0094	10,3523	0,4828	0,7671

The internal consistency coefficient (Cronbach's alpha) obtained was 0.78 for the total scale and was superior to 0.7 for each of the 24 items, indicating sufficiently homogeneous.

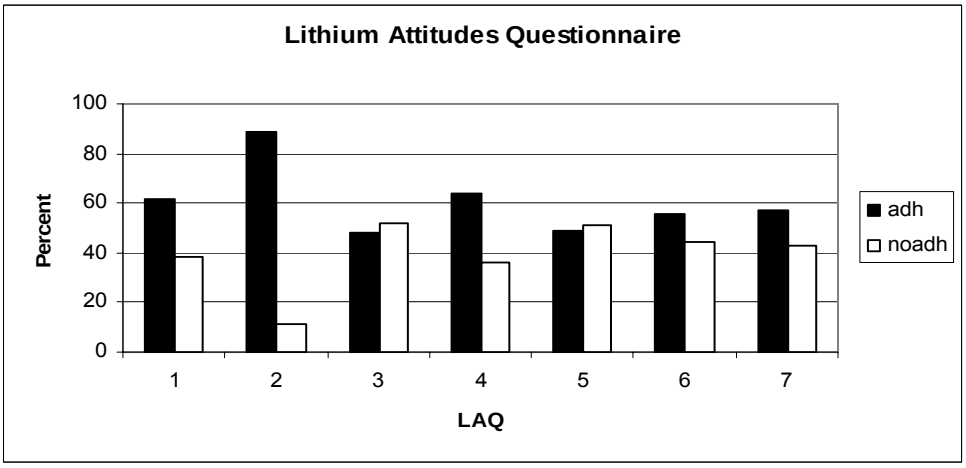
Table 4: Clinical state an scores of LAQ

	LAQ 1			LAQ 2		
			p			p
Clinical state	Adherent	no adherent		adherent	No adherent	
Euthymic	52 (80%)	23 (57,5%)	0,011	73 (77,7%)	3 (25%)	0,001
Manic	3 (4,6%)	9 (22,5%)	0,012	8 (8,5%0	4 (33,3%)	0,001
Depressive	10 (15,4%)	8 (20%)	0,081	13 (13,8%)	5 (41,7%)	0,001

A Pearson Chi-Square showed significant differences between the LAQ 1 scores of patients currently euthymic or manic. There were also significant differences between the LAQ 2 scores of patients currently euthymic, manic or depressive.

Figure 1: Percent of adherent (adh) and nonadherent (noadh) patients scoring positively for each LAQ subscore

(1) resistance to prophylaxis in general; (2) denial of therapeutic effectiveness of lithium as a prophylactic agent; (3) fear of side effects (LAQ 3); (4) difficulties with the daily routine medication intake; (5) denial of the severity of the illness; (6) negative attitudes toward drugs in general; (7) lack of information about lithium prophylaxis (LAQ 7)



10.4. Anexo IV:

Adaptation and Validation of the Portuguese version of the Lithium Knowledge Test (LKT) of Bipolar Patients treated with Lithium: Cross-over study

"Clin Pract Epidemol Ment Health. 2006 Dec 5;2:34"

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Abstract:

Objective: Adherence problems are a common feature among bipolar patients. A recent study showed that lithium knowledge was the main difference between adherent and non adherents bipolar patients. The Lithium Knowledge Test (LKT), a brief questionnaire, was developed as a means of identifying aspects of patients' practical and pharmacological knowledge which are important if therapy is to be safe and effective. The original English version is validated in psychiatric population, but a validated Portuguese one is not yet available.

Methods: One hundred six patients selected were diagnosed with bipolar disorder (I or II) according to DSM-IV criteria and had to be on lithium treatment for at least one month. The LKT was administered on only one occasion. We analysed the internal consistency, concurrent validity, sensitivity and specificity of the LKT for the detection of the knowledge about lithium treatment of bipolar patients.

Results: The internal consistency, evaluated by Cronbach's alpha was 0.596. The mean of total score LKT by bipolar patients was 9.0 (SD: 0.75) for men and 8.74 (SD: 0.44) for women. Concurrent validity based on serum lithium concentration showed a significant correlation between the total LKT score and plasma lithium (r=0,232; p=0.020). The sensitivity was 84% and specificity was 81%.

Conclusion: LKT is a rapid, reliable instrument which appears to be as effective as a lengthier standard interview with a lithium clinic doctor, and which has a high level of acceptability to lithium patients. We found that the psychometric assessment of the Portuguese version of LKT showed good internal consistency, sensitivity and specificity.

Key words: adherence, knowledge, lithium, bipolar patients, psychicoeducation.

Introduction

To date, lithium is probably still the gold standard for the long term treatment of bipolar disorder, as shown in classical papers [1], newer studies [2] and a recent and thoughtful meta analysis [3]. However, a marked gap has been noted between the efficacy of lithium in clinical trials and its effectiveness in ordinary clinical practice [4;5], this difference being almost certainly due to poor treatment adherence [4;6;7]. A survey conducted in the United States showed that the average time of lithium intake was as start as 76 days [8].

Adherence problems are a common feature among bipolar patients. A recent study showed that lithium knowledge was the main difference between adherent and non-adherent bipolar patients [9]. Gravel studies have shown that psychoeducative interventions are associated with high adherence rates, stabilization of serum lithium levels, reduction of the total number of episodes and total number of patients needing to hospitalization ([10-12]. The fact that patients are informed about the disease, the treatment and the risks of not treating it positively, influences adherence, because it facilitates their acceptance of the disease and maintenance therapy [13-15].

The Lithium Knowledge Test (LKT) a brief questionnaire, was developed as a means of identifying aspects of patients' practical and pharmacological knowledge which are important if therapy is to be safe and effective. One point is scored for each correct answer and one is deducted for each wrong answer, giving a total Lithium Knowledge Score. Some incorrect answers, since they constitute potential hazards to patients on lithium, are added up to give a Lithium Hazard Score (LHS). The original English version has been validated in psychiatric population and has shown good reliability [16]

Methods:

2.1. Subjects:

The study was conducted in two psychiatric outpatient services specialized in mood disorders in the city of Porto Alegre, Brazil. The psychiatric patients selected were diagnosed with bipolar disorder, I and II according to DSM-IV criteria. The study was approved by the Ethics Committees on Research of the hospital where the research took place, where the research took place and was carried out in compliance with the Helsinki Declaration.

The patient selection criteria included a well-established diagnosis, being on lithium treatment for at least one month, and regularly complying with the weekly visits scheduled in two psychiatric outpatients who agreed in take part in the survey.

In the weekly consultations, the patients were evaluated for both their symptoms and general state. The patients participated in psycho-educational groups about lithium with a specialized nurse and support groups with psychiatrists to discuss topics related to the disease.

The patients who agreed to participate in the study gave informed consent, were interviewed and had blood drawn immediately for comparison between the concentrations of lithium in the plasma with the LKT responses.

2.2. Variables:

Demographical Data

Every subject gave information about marital status, work, age, gender and education level.

Current clinical status

Bipolar patients were diagnosed using the Structured Clinical Interview for DSM-IV (SCID) and all patients were followed up prospectively using mood charts.

LKT

LKT is a brief questionnaire to identify aspects of patients' practical and pharmacological knowledge which are important if therapy is to be safe and effective. The LKT comprises 20 questions, which 1 point to be added for every correct answer and 1 point to be deducted for every wrong one. The correct answers are: 1-b; 2-b-c-f-h; 3-a-d-f; 4-a-b; 5-a-d; 6-c-e-f-g-i-k; 7-a-c-e. The total LKT score is obtained by adding together the responses to the 20 points. The mean LKT scores were close to 6. The mean LKT scores were > 6 indicating more knowledgeable. The LKT Hazard comprises of 3, 4, 6 and 7 questions for rating of identify aspects of intoxication symptoms about lithium. The total LKT Hazard score was obtained by adding together the responses to the 9 points. The mean LKT Hazard score was close to 4 or more indicating more hazard.

The linguistic adaptation of the LKT started with document in Portuguese obtained by a translation back translation method [17;18]). The items resulting in optimal word equivalence with the original text were analysed by the five of psychiatric investigators that agreed upon translation. Subsequently, bilingual people evaluated the degree of equivalence between the English original and the Portuguese version, as shown table 1. Finally, the comprehension of each item was assessed with a sample of 106 bipolar patients.

The LKT was administered on one occasion, when venous blood to determine lithium concentration was collected from each patient. The time to application of LKT was 10 minutes. We analysed the internal consistency, concurrent validity in relation to plasma lithium concentration, sensitivity and specificity. Internal consistency was assessed with Cronbach's Alpha for the total scale.

Concurrent validity was studied considering plasma lithium concentration and the score obtained on the LKT by means of Pearson's correlation.

To study the sensitivity, specificity and positive and negative values of the LKT, we calculated the proportion of fully adherent bipolar patients by plasma lithium concentration and the proportion of non-adherent bipolar patients identified as such.

Lithium plasma concentration

The subjects were contacted seven days before the scheduled appointment and were instructed to be at the hospital early in the morning, without having taken their lithium dose in the morning because the lithium blood levels were to be measured, respecting a 12-hour interval between the last dose of lithium and the blood sampling. Venous blood was collected from each patient into Vacutainer tube containing edetic acid. The whole blood was then centrifuged 1600x g for 10 minutes and the plasma removed by aspiration. A 1/20 dilution in water was made of 99µl of plasma. Lithium concentrations were measured on the plasma dilutions by the indirect method, using an Instrumentation Laboratory CELM Flame Photometer. Assays were performed in duplicate [19].

Statistical analysis:

Statistical analysis was performed using SPSS for Windows - Version 12.0 (SPSS Inc., Chicago, IL, USa). The Kolmogorov-Smirnov test was used to compare an observed

cumulative distribution to a theoretical cumulative distribution function. ANOVA test was used for compare LKT scores and plasmatic levels of lithium. Pearson's correlation coefficient was performed to examine the relationship between plasma lithium concentration and LKT scores. The binomial variables (clinical state and LKT scores) were compared using Chi-Square test. Validity was assessed with Cronbach's alpha.

Results:

The sample included 73 (68.9%) women, mean age 43.56±9.83 and 33 31.1% men with a mean age of 41.61±9.72. At the time when the present study was carried out, there were 77 (71.7%) euthymic, 12 (11.1%) manic and 17 (17.2%) depressed patients, according to the mood charts and physician is assessment. Habits showed 40 (37.7%) were smokers, 70 (66%) used coffee on a regular basis, and 68 (64.2%) had tea on a regular basis.

The answers to the LKT were obtained from 106 bipolar patients and the mean score on the LKT was 9.0 ±0.75 for men and 8.74±0.44 for woman and LKT HAZARD was 4.06±0.19 for men and 3.96±0.15 for woman. Table 2 describes the principal sociodemographic and clinical characteristics of the study sample.

The internal consistency coefficient obtained to 43 items and the mean Cronbach's alpha of 0.596, for the total scale indicating that the items are sufficiently homogeneous.

Concurrent validity based on diagnosis according to plasma lithium concentration showed a significant correlation between the total LKT score and plasma lithium levels (r=0.232; p=0.020). The patients with higher LKT scores are more likely to have plasma levels within the therapeutic range.

We analysed the scale's discriminative capacity for bipolar patients by means of the knowledge about lithium treatment performance on sensitivity and specificity analysis. The sensitivity was 84% and specificity was 81%.

There were no significant differences between the total LKT scores among manic, depressive and euthymic patients (Pearson Chi-Square <.05). Date not shown.

We analysed the frequency of positive/negative answers on the LKT test by bipolar patients in comparison with standard answers offered by the original scale, as shown in table 3.

There was a significantly negative correlation between age and LKT scores (r= -0.2; p=0.04). Age was positively correlated with LKT HAZARD scores (r= 0.366; p=0.001).

Discussion:

Psychometric tests may be useful tools for the assessment of bipolar patients, not only in research protocols, but also in clinical practice [20]. LKT is a rapid, reliable instrument which appears to be as effective as a lengthier standard interview with a lithium clinic doctor, and which has a high level of acceptability to lithium patients. We found that the psychometric assessment of the Portuguese version of LKT showed good internal consistency, sensitivity and specificity. In Brazilian bipolar patients, the Portuguese version of LKT showed total scores which were similar of those described by *Dharmendra et al.[21]*, in Scottish bipolar patients (total scores 9.6). Indeed, there was a significant negative correlation age and LKT scores and a significant positive correlation between LKT and Hazard scores, as shown in previous studies [21;22]). In the convergent analysis the total LKT scores were significantly correlated with plasma lithium levels, meaning that, the patients with higher LKT scores were more likely to have plasma levels within the therapeutic levels of lithium. Moreover, sensitivity and specificity tests showed good results, reinforcing the validation of Portuguese version of the LKT.

The LKT scale asked bipolar patients about lithium pharmacology aspects, such as, side effects, lithium interactions, risks of intoxication, food and lithium, necessity of measuring lithium levels, continuation of the lithium dosages and others [23]. Our study indicated that Couldn't you to do while you was taken lithium? Which of these would be sensible actions if you developed acute diarrhoea and vomiting?, Why the regular blood tests are necessary?, Lithium must be taken at exactly the same times each day?, Lithium is not effective if the blood level falls too low?, Stopping lithium altogheter usually leads to a relapse?, Which of the following changes in diet can cause problems with lithium? were mainly difficulties reported by bipolar patients, because of this that patients with lower LKT scores are more uninformed about intoxication risks.

The identification of problems about lithium treatment and bipolar disorder with LKT could contribute to better understanding of the difficulties that bipolar patients have, and offer this specific information in the clinical consultations. Indeed, knowledge about prescribed medication tends to be poor in the ederly and these patients could have higher risks of intoxicacion with lithium than younger patients. While it is possible that patients who have been on lithium for a long time did not receive comprehensive information as did those who commenced treatment more recently and they required some reeducation about lithium for some time [21].

The knowledge level is a predictor of the adherence rates in bipolar patients in according recent reported [9]. In deed, *Colom et al.[24]* had reported that educated bipolar patients showed lower relapses rates, lower number and during hospitalizations. Psychoeducation is important to definitely mean more than providing information to patients and has shown its efficacy in stabilizing lithium serum levels by improving pharmacological treatment adherence.

It is important to highlight gravel methodological issues. First, as with any study of treatment adherence we are hampered by the likelihood that the sample might have included a representative sample. Such methodological problems affect all studies in this field, as individuals who are non- adherent with lithium are also likely to fail to agree to participate or fail to adhere with research protocols. Second, we did not assess current symptom severity or comorbidity of bipolar disorder with other psychiatric or physical disorders. Third, this was a cross-over study, as we assessed attitudes about medication in only one occasion. As yet, there is no research on the stability or variability of such beliefs over time.

Conclusion:

In conclusion, the scale LKT is a brief questionnaire to evaluate the knowledge level in bipolar patients, identify aspects of patients' practical and pharmacological knowledge which are important if therapy is to be safe and effective. The LKT scale may now be used in Portuguese speaking populations as a direct measure of knowledge on lithium as a valid indirect measure of treatment adherence.

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Table 1: Teste de Conhecimento do Lítio

Marque com um X as respostas que o Sr considerar correta.
1. Na sua opinião o LÍTIO age: (a) Como tranqüilizante; (b) Para prevenir mudanças de humor; (c) Como pílula para dormir; (d) Como tratamento para deficiência de LÍTIO
2. Quais os efeitos colaterais o LÍTIO pode causar? (a) Prisão de ventre (dificuldade de ir aos pés); (b) Mal-estar como enjôos; (c) Tremores; (d) Dor de cabeça; (e) Palpitações; (f) Urinar mais; (g) Insônia; (h) Aumento de peso
3. O que você deve tentar não fazer enquanto estiver tomando LÍTIO? (a) Suar excessivamente; (b) Tomar medicamento para tosse; (c) Climas muito frio; (d) Ficar grávida; (e) Fazer exercícios vigorosos; (f) Tomar diuréticos
4. Se você tivesse uma diarréia aguda e vômitos, o que você faria?(a) Ligaria para o seu médico; (b) Pararia de tomar LÍTIO imediatamente; (c) Iria para a cama e continuaria tomando LÍTIO regularmente; (d) Chamaria uma ambulância; (e) Aumentaria a dose de LÍTIO
5. Para que os exames de sangue regulares são necessários? (a) Para medir a quantidade de LÍTIO em seu sangue; (b) Para verificar se a doença é recorrente; (c) Para verificar se tem anemia; (d) Para testar o funcionamento da glândula tireóide
6. Quais das seguintes afirmações são verdadeiras? (a) O LÍTIO deve ser tomado exatamente no mesmo horário todos os dias (b) Deve-se tomar doses extras de LÍTIO se você se sente deprimido (c) Não deve-se tomar LÍTIO pela manhã quando for fazer exame de sangue (d) É normal não tomar algumas doses de LÍTIO se você se sente bem (e) O LÍTIO não é eficaz se o nível sangüíneo estiver muito baixo (f) O LÍTIO tem efeitos tóxicos se o nível sangüíneo estiver muito alto (g) É comum o LÍTIO ser receitado por vários anos (h) Parar de tomar o LÍTIO por completo geralmente leva a uma recaída (i) O LÍTIO tem sido experimentado e testado por muitos anos (j) O LÍTIO tem sido substituído por medicamentos modernos mais eficazes (k) Uma recaída durante o tratamento com LÍTIO não prova que ele não seja eficaz para o indivíduo
7. Quando você estiver tomando LÍTIO, o que deveria evitar na sua alimentação? (a) Dieta para emagrecimento; (b) Comer queijo; (c) Reduzir o consumo de sal; (d) Comida vegetariana (e) Beber álcool

Table 2: Demographics and clinical characteristics

Euthymic	71.7%	
Manic	11.1%	
Depressed	17.2%	
Smokers	37.7%	
Coffe	66%	
Tea	64.2%	
	Men	Woman
	31.1%	68.9%
Age	41,61±9,72	43,56±9,83
Mean total LKT	9,0 ±0,75	8,74±0,44
Mean LKT Hazard	4,06±0,19	3,96±0,15

Table 3: Frequency of answers from TCL

Questions	% true answer	% false answer
1[a]	81.9	18.1
1b	64.8	35.2
1c	95.2	4.8
1d	77.1	22.9
2[a]	66.7	33.3
2b	41.9	58.1
2c	68.6	31.4
2d	61.9	38.1
2e	66.7	33.3
2f	67.6	32.4
2g	74.3	25.7
2h	83.8	16.2
53[a]	14.3	85.7
53b	91.4	8.6
53c	96.2	3.8
53d	43.8	56.2
53e	96.2	3.8
53f	37.1	62.9
54[a]	68.6	31.4
54b	12.4	87.6
54c	89.5	10.5
54d	93.3	6.7
54e	99.0	1.0
55[a]	89.5	10.5
55b	95.2	4.8
55c	96.2	3.8
55d	7.6	92.4
56[a]	20.0	80.0
56b	95.2	4.8
56c	82.9	17.1
56d	89.5	10.5
56e	52.4	47.6
56f	61.0	39.0
56g	79.0	21.0
56h	16.3	83.7
56i	75.2	24.8
56j	76.2	23.8
56k	73.3	26.7
57[a]	19.0	81.0
57b	89.5	10.5
57c	19.0	81.0
57d	95.2	4.8
57e	81.7	18.3