Universidade Federal do Rio Grande do Sul

AROLDO AYUB DARGÉL

Níveis séricos de proteína C-reativa e o papel da inflamação crônica no transtorno bipolar

Porto Alegre

22 de dezembro de 2014

AROLDO AYUB DARGÉL

Níveis séricos de proteína C-reativa e o papel da inflamação crônica no transtorno bipolar

Tese apresentada ao Programa de Pós-Graduação em Ciências Médicas: Psiquiatria, da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul, como requisito parcial para obtenção do título de Doutor em Psiquiatria.

Orientador: Flávio Pereira Kapczinski

Porto Alegre

22 de dezembro de 2014

Dados Internacionais de Catalogação na Publicação (CIP)

Dargél, Aroldo Ayub
D217p Níveis séricos de proteína C-reativa e o papel da inflamação crônica no transtorno bipolar / Aroldo Ayub Dargél ; orientador Flávio Pereira Kapczinski. – Porto Alegre, 2014.

Dissertação (Doutorado em Psiquiatria) – Universidade Federal do Rio Grande do Sul. Faculdade de Medicina. Programa de Pós-Graduação em Ciências Médicas : Psiquiatria, 2014.
143 f. : il. color.

1. Transtorno bipolar. 2. Protéina C-reativa. 3. Inflamação crônica. I. Kapczinski, Flávio Pereira, orient. II. Título.

NLM – WM 100

Bibliotecária Luísia Feichas Alves – CRB 10/2121

À Nanucha, minha vida.

The important thing is not to stop questioning. Curiosity has its own reason for existing.

Albert Eisntein

Faites que le rêve dévore votre vie afin que la vie ne dévore pas votre rêve.

Antoine De Saint-Exupery

AGRADECIMENTOS

Inicialmente, agradeço ao meu orientador Prof. Flávio Kapczinski, pela confiança, pelos valiosos ensinamentos clínicos, e pelo incentivo no mundo da pesquisa.

À Profa. Keila Céreser pela amizade, apoio e pelo auxílio incondicional durante todo esse período no Laboratório de Psiquiatria Molecular, o que contribui substancialmente para essa tese acontecer. Muito Obrigado!

À Profa. Adriana Rosa, agradeço pela sua disponibilidade como relatora dessa tese; às Profas. Márcia Sant'Anna e Juliana Tramontina, pelo estímulo e oportunidade de participar do grupo de pesquisa, onde tudo começou.

Aos colegas da bancada, agradeço pela parceria, em especial, à Laura Stertz pelo empenho no preparo das amostras de DNA e ao Gabriel Fries colega e professional exemplar; aos demais colegas e professores do Laboratório de Psiquiatria Molecular, pela oportunidade constante de aprender.

Meus sinceros agradecimentos à Profa. Chantal Henry e ao seu grupo de pesquisa na Universidade de Paris, por acreditar no meu trabalho e pelas novas oportunidades de conhecimento. Agradeço também à Profa. Chantal Henry pelas seus ensinamentos clínicos e, também, sobre a cultura francesa, o que contribui ainda mais para a minha formação como psiquiatra.

Agradeço ainda ao CNPq pela bolsa de doutorado-sanduíche; aos pacientes e suas famílias pela participação nas pesquisas. À Luísia Alves por todo o suporte técnico-editorial em minhas pesquisas.

No meu núcleo familiar, agradeço aos meus irmãos Alexandre e Vinícius pela parceria incondicional e à minha sogra Cristina Schuler pelas conversas em tom sereno e alegre;

Aos meus pais, minha gratidão por todo o amor e carinho, pela paciência e compreensão da distância, e, acima de tudo, por me ensinar a importância de buscar o conhecimento e de nunca desistir.

À minha esposa Anelise, agradeço muito pelo carinho, cuidados, e, sobretudo, pela maior paciência e confiança do mundo e que, ao longo desses 15 anos, esteve sempre ao meu lado em todas às minhas aventuras.

RESUMO

Evidências sugerem o envolvimento de um estado de inflamação crônica de baixo grau na fisiopatologia do transtorno bipolar (TB). Os estudos apresentados nesta tese tiveram como objetivo explorar o papel da inflamação crônica nos mecanismos fisiopatológicos do TB através da avaliação dos níveis séricos de proteína C-reativa (PCR). A PCR é um marcador de inflamação sistêmica comumente utilizado na prática clínica, sendo considerado fator de risco para várias patologias, incluindo câncer e doença cardiovascular. O primeiro artigo, através de um estudo de meta-análise, teve como objetivo avaliar o tamanho de efeito da associação entre níveis de PCR em pacientes bipolares nas diferentes fases de humor (n=730) comparado a indivíduos controles (n=888). Pacientes bipolares apresentaram níveis de PCR significativamente elevados em comparação ao grupo controle, com moderado tamanho de efeito (*effect size*, ES = 0.39; 95% IC, 0.24 – 0.55; $P < 0.0001$). Níveis de PCR foram significativamente maiores em pacientes maníacos (ES = 0.73; 95% IC, 0.44 – 1.02; $P < 0.001$) e em eutímicos (ES = 0.26; 95% IC, 0.01 – 0.51; $P = 0.04$). O segundo artigo se propôs a revisar dados da literatura relacionados a biomarcadores periféricos potencialmente implicados na progressão do TB. Pacientes em diferentes estágios do TB apresentaram níveis alterados de marcadores de estresse oxidativo, neurotrofinas e de inflamação, incluindo a PCR, o que reforça a hipótese da inflamação crônica exercer um papel importante na fisiopatologia do TB. Em seguida, considerando a abordagem multidimensional no TB, o terceiro artigo avaliou a reatividade emocional como uma dimensão relevante para caracterizar pacientes bipolares apresentando sintomas subclínicos de humor durante a fase de remissão (N=613). Apesar de todos pacientes estarem em remissão, a maioria deles (68%) apresentou reatividade emocional anormal (hipo ou hiper-reatividade emocional). Esse estudo avaliou, também, o funcionamento psicossocial nesses pacientes e os níveis de PCR ultra-sensível como um possível marcador objetivo de hiper-reatividade emocional no TB. Os pacientes com hiper-reatividade emocional, em comparação aos pacientes com hipo- ou normal reatividade emocional, apresentaram prejuízo cognitivo e níveis de PCR significativamente mais elevados ($P < 0.001$). Esses resultados provêm de um estudo transversal e, portanto, conclusões sobre causalidade dessas associações não podem ser inferidas, já que outros fatores, além dos níveis de PCR, podem também contribuir para o estado inflamatório crônico observado nesses pacientes.

Em suma, os resultados desta tese sugerem que a inflamação crônica de baixo grau, evidenciada pelas alterações nos níveis de PCR, parece estar implicada na fisiopatologia e na progressão do TB. Novas intervenções terapêuticas com alvo em mecanismos inflamatórios e na modulação dos níveis de PCR devem ser priorizados em estudos futuros.

Palavras-chave: transtorno bipolar. proteína C-reativa. inflamação crônica. abordagem multidimensional. reatividade emocional. funcionamnento cognitivo. funcionamento psicossocial.

ABSTRACT

Evidence suggests that chronic low-grade inflammation appears to be involved in the pathophysiology of bipolar disorder (BD). The studies presented in this thesis aimed at exploring the role of chronic inflammation in the BD pathophysiological mechanisms by assessing serum levels of C-reactive protein (CRP). CRP is a marker of low-grade inflammation widely used in clinical practice, and a risk factor for cardiovascular and malignant diseases. The first article, a meta-analysis, aimed at evaluating the effect size of the association between CRP levels in bipolar patients (n=730) compared to healthy subjects (n=888). Overall, CRP levels were significantly elevated in patients with BD versus controls (effect size, ES = 0.39; 95% CI, 0.24 to 0.55; P < .0001). CRP levels were significantly higher in manic (ES = 0.73; 95% CI, 0.44 to 1.02; P < 0.001) and euthymic (ES = 0.26; 95% CI, 0.01 to 0.51; P = 0.04). The second paper aimed at reviewing the scientific literature regarding peripheral biomarkers potentially implicated in the progression of BD. Bipolar patients within different disease's stages presented altered levels of oxidative stress, neurotrophins and inflammatory markers, including PCR. These findings reinforce the hypothesis of the potential role of the chronic inflammation in BD pathophysiology. Regarding the multidimensional approach in BD, the third article assessed emotional reactivity as a major dimension for better characterizing remitted bipolar patients with subthreshold mood symptoms (N=613). Although all patients were in remission, most of them (68%) showed abnormal emotional reactivity (hipo- or hyper-reactivity). In addition, this study assessed the psychosocial functioning in these patients as well as the levels of high-sensitivty PCR (hsCRP) as an objective marker of emotional hyper-reactivity in BD. Patients with emotional hyper-reactivity had higher levels of PCR and cognitive impairment compared to patients with emotional hypo or normal emotional reactivity (P < 0.001). This was a cross-sectional study of emotional reactivity, hsCRP levels and functional status in remitted bipolar patients, and no conclusions regarding the causality of these associations can be substantiated. Others factors could also be contributing to the chronic inflammatory state in these patients.

In conclusion, the results of this thesis suggest that low-grade chronic inflammation, as evidenced by alteration in CRP levels, may be implicated in the pathophysiology as well as in the BD progression. Novel therapeutic interventions targeting inflammatory mechanisms and the modulation of CRP levels should be prioritized in future studies.

Keywords: bipolar disorder. C-reactive protein. chronic inflammation. multidimensional approach. emotional reactivity. cognitive functioning. psychosocial functioning.

LISTA DE ABREVIATURAS

BDNF	Fator Neurotrófico Derivado do Cérebro
DALYs	*Disability-Adjusted Life Years* = Anos Vividos com Incapacidade
DSM-IV	Quarta edição do Manual Diagnóstico e Estatístico
FAST	Escala de Avaliação do Funcionamento Psicossocial
GDNF	Fator neurotrófico derivado de células gliais
IL-1	Interleucina-1
IL-10	Interleucina-10
IL-1-beta	Interleucina-1 beta
IL-1R	Receptor de interleucina-1
IL-2	Interleucina-2
IL-4	Interleucina-4
IL-6	Interleucina-6
INF-alfa	Interferon alfa
INF-beta	Interferon beta
INF-gama	Interferon gama
MADRS	Escala de avaliação de depressão de Montgomery-Asberg
MAThyS	Escala de avaliação multidimensional dos estados de humor
NMDA	N-metil-d-aspartato
PCR	Proteína C-reativa
hsPCR	Proteína C-reativa ultra-sensível
SCID-I	Entrevista clínica estruturada para transtornos de eixo I
TB	Transtorno Bipolar
TNF-alfa	Fator de necrose tumoral alfa
YMRS	Escala de Avaliação de Mania de Young

SUMÁRIO

1 INTRODUÇÃO 10
2 FUNDAMENTAÇÃO TEÓRICA 14
2.1 Inflamação: aspectos gerais 14
2.2 Inflamação crônica e proteína C-Reativa 16
2.3 Inflamação e alterações comportamentais: aspectos evolutivo-fenomenológicos 17
2.4 Inflamação sistêmica no transtorno bipolar 18
2.5 Proteína C-Reativa e comorbidades clínicas no transtorno bipolar 20
2.6 Neuroinflamação e transtorno bipolar 22
2.7 Funcionamento cognitivo e psicossocial no transtorno bipolar 23
2.8 Abordagem dimensional no transtorno bipolar: reatividade emocional e níveis de proteína C-Reativa 25
2.9 Tratamento e resposta inflamatória no transtorno bipolar 27
3 JUSTIFICATIVA 29
4 OBJETIVOS 30
4.1 Objetivo geral 30
4.2 Objetivos específicos 30
5 MÉTODOS 31
5.1 Revisão sistemática e meta-análise 31
5.2 Mecanismos biológicos associados à progressão do transtorno bipolar 31
5.3 Estudo transversal com pacientes bipolares 32
6 RESULTADOS: ARTIGOS CIENTÍFICOS 35
6.1 Artigo 1: C-Reactive protein alterations in bipolar disorder: a meta-analysis 35
6.2 Artigo 2: Biomarkers in illness progression in bipolar disorder 45
6.3 Artigo 3: Emotional reactivity, functioning, and C-Reactive protein alterations in remitted bipolar patients: clinical relevance of a dimensional approach 63
7 CONSIDERAÇÕES FINAIS 84
7.1 Possíveis implicações clínicas dos achados dessa pesquisa 84
7.1.1 Proteína C-reativa como biomarcador no transtorno bipolar 84
7.1.2 Níveis de proteína C-reativa e comorbidades clínicas no transtorno bipolar: oportunidades para o manejo clínico e prevenção 85
7.1.3 Reatividade emocional e níveis de proteína C-reativa em pacientes bipolares em remissão: relevância clínica de uma abordagem dimensional 87
7.1.4 Reatividade emocional e funcionamento psicossocial no transtorno bipolar 89
7.2 Perspectivas 90
REFERÊNCIAS 91
ANEXO A – BIPOLAR PATIENTS REFERRED TO SPECIALIZED SERVICES OF CARE: NOT RESISTANT BUT IMPAIRED BY SUBSYNDROMAL SYMPTOMS 102
ANEXO B – STAGING AND NEUROPROGRESSION IN BIPOLAR DISORDER 110

ANEXO C – EFFECTIVENESS AND TOLERANCE OF ANTI-INFLAMMATORY DRUGS' ADD-ON THERAPY IN MAJOR MENTAL DISORDERS: A SYSTEMATIC QUALITATIVE REVIEW 119
ANEXO D – POLYMORPHISM OF TOLL-LIKE RECEPTOR 4 GENE IN BIPOLAR DISORDER..... 136

1 INTRODUÇÃO

O transtorno bipolar (TB) é uma doença crônica, de etiologia multifatorial, que afeta em torno de 1-2% da população mundial (World Health Organization, 2008; Ferrari, Baxter, and Whiteford, 2011; Merikangas et al., 2011). O TB é classificado como subtipo I, definido por episódios de elevação de humor (mania) e de depressão, ou subtipo II, determinado pela alternância entre episódios hipomaníacos e depressivos (American Psychiatric Association, 2000; Phillips and Kupfer, 2013). Além da alta prevalência, o TB inicia, em média, em torno dos 20 anos de idade (Merikangas et al., 2011), afetando o indivíduo em uma das fases mais produtivas da vida (Chisholm et al., 2005; Alonso et al., 2011). Dados recentes apontam o TB entre as cinco primeiras causas de "Anos Vividos com Incapacidade" (*Disability-Adjusted Life Years, DALYs*) em pessoas entre 25 e 34 anos (World Health Organization, 2008; Whiteford et al., 2013). O número de anos vividos com incapacidade no TB é maior do que o de doenças clínicas como infarto, asma, epilepsia, demência ou doenças infecciosas, o que contribui para a incapacitação funcional do indivíduo, acarretando considerável prejuízo econômico para a sociedade (Whiteford et al., 2013). No Reino Unido, por exemplo, o custo estimado do TB para a sociedade no ano de 2010 foi de 5,2 bilhões de libras (Abdul Pari et al., 2014).

O diagnóstico do TB pode ser particularmente difícil, tendo em vista a apresentação heterogênea da doença (Hirschfeld, 2014). A sintomatologia pode variar desde alterações do comportamento e do sono até sintomas de humor inespecíficos e desregulação emocional persistente (Phillips and Kupfer, 2013). O tempo médio entre o início dos sintomas clínicos até o estabelecimento do diagnóstico correto de TB pode variar entre 5 e 10 anos (Hirschfeld, 2014). Em atenção primária, por exemplo, estudos relatam que apenas 20% dos indivíduos com

sintomatologia sugestiva de TB avaliados pelo clínico geral recebem um diagnóstico compatível com TB no primeiro ano (Hirschfeld, Lewis, and Vornik, 2003; Gazalle et al., 2005).

Apesar do tratamento farmacológico, a maioria dos pacientes com TB permanece sintomática por mais da metade da vida mesmo aqueles considerados em fase de remissão (Judd et al., 2012). Nessa fase, também denominada período inter-episódio, os pacientes podem apresentar instabilidade emocional transitória ou persistente (Broome et al., 2015) e sintomas de humor subclínicos, principalmente sintomas depressivos (Judd et al., 2012), os quais têm sido fortemente associados ao prejuízo no funcionamento psicossocial, à disfunção cognitiva e à redução na qualidade de vida (Rosa et al., 2008; Bonnín et al., 2012; Henry et al., 2015 (ANEXO A); Strejilevich, Samamé, and Martino, 2015). Contudo, os métodos diagnósticos utilizados na prática clínica para avaliar sintomas de humor são baseados essencialmente em categorias e lista de sintomas (Phillips and Kupfer, 2013), apresentando baixa sensibilidade para detectar variações sutis de humor e da reatividade emocional em pacientes bipolares (Henry and Etain, 2010; Marwaha et al., 2014).

O funcionamento psicossocial está relacionado à habilidade de um indivíduo de viver de maneira independente, de desempenhar atividade laboral e de se relacionar socialmente (Ustün and Kennedy, 2009). Pacientes com TB apresentam, muitas vezes, prejuízo importante em diversas áreas do funcionamento psicossocial como, por exemplo, relacionamento interpessoal, produtividade no trabalho e autonomia (Rosa et al., 2008, 2010; Kauer-Sant'Anna et al., 2009; Strejilevich, Samamé, and Martino, 2015). Um estudo prospectivo conduzido nos Estados Unidos constatou que 98% dos pacientes bipolares atingiram remissão clínica em um período de 02 anos após o primeiro episódio maníaco, ao passo que apenas 38% desses pacientes recuperaram o funcionamento psicossocial nesse mesmo período (Tohen et al., 2000). O prejuízo no funcionamento psicossocial pode aparecer desde os estágios mais precoces do TB, porém tende a

ser mais severo nas fases tardias da doença (Rosa et al., 2014). Isso pode estar relacionado a fatores indicativos de uma maior carga da doença, tais como número episódios prévios, recidivas frequentes e início precoce, os quais parecem impactar o funcionamento (Rosa et al., 2014) além de estarem associados a uma maior probabilidade de comorbidades clínicas (Magalhães et al., 2012).

Evidências demonstram que o TB está intimamente associado com patologias clínicas, dentre as quais a doença cardiovascular e a síndrome metabólica são as mais prevalentes (Roshanaei-Moghaddam and Katon, 2009; Magalhães et al., 2012). A doença cardiovascular, por exemplo, é a primeira causa de excesso de mortalidade em pacientes bipolares (Kupfer, 2005). Ainda que as doenças cardiometabólicas nesses pacientes sejam vistas como consequência de um estilo de vida pouco saudável e, principalmente, dos efeitos colaterais dos medicamentos psicotrópicos (Kupfer, 2005), os mecanismos fisiopatológicos dessa associação ainda não são conhecidos e a inflamação sistêmica parece exercer um papel importante nesse processo (Goldstein et al., 2009; Berk et al., 2011). Tal fato reforça a ideia do TB como uma doença multi-sistêmica (Goldstein et al., 2009; Leboyer et al., 2012).

Indivíduos com infecções severas ou doenças autoimunes apresentam, de forma transitória ou persistente, níveis sanguíneos elevados de marcadores inflamatórios (Benros et al., 2013). Esses indivíduos parecem apresentar risco significativamente elevado de desenvolver patologias psiquiátricas, incluindo TB (Benros et al., 2013). Estudos mostram que, pacientes bipolares nas diferentes fases da doença apresentam níveis alterados de diversos marcadores inflamatórios, incluindo citocinas (Brietzke et al., 2009; Modabbernia et al., 2013) e proteínas de fase aguda, como a proteína C-reativa (PCR) (Dickerson et al., 2007; Cunha et al., 2008). A PCR, um marcador de inflamação crônica comumente utilizado na prática clínica, é fator de risco independente para várias doenças, incluindo câncer e patologia cardiovascular (Pepys and

Hirschfield, 2003; Emerging Risk Factors Collaboration et al., 2010; Allin and Nordestgaard, 2011). Recentemente, estudos prospectivos demonstraram associação entre níveis aumentados de PCR e risco de desenvolver esquizofrenia (Wium-Andersen, Ørsted, and Nordestgaard, 2014) como também ansiedade generalizada (Vogelzangs et al., 2013) em indivíduos da população geral com idade acima de 40 anos . Apesar de alguns estudos reportarem alterações nos níveis de PCR em pacientes bipolares, esses resultados são provenientes de estudos com pequeno tamanho amostral (Wadee et al., 2002; Huang and Lin, 2007; Cunha et al., 2008) ou com grupos heterogêneos de pacientes (Dickerson et al., 2007; Hope et al., 2011; Vuksan-Cusa et al., 2013) o que limita a extrapolação dos resultados. Entretanto, os dados relatados acima apontam a inflamação sistêmica crônica como um componente importante da fisiopatologia do TB.

A inflamação periférica parece atingir o sistema nervoso central, modulando algumas funções cerebrais (Dantzer et al., 2008). Marcadores pró-inflamatórios da periferia (p. ex. citocinas) parecem ativar as células gliais (micróglia) do sistema nervoso central (Dempsey, Vaidya, and Cheng, 2003; Harry and Kraft, 2008). A micróglia, quando sofre ativação crônica e persistente, perde a sua função protetora, o que contribui ainda mais para o aumento de citocinas pro-inflamatórias no cérebro (Harry and Kraft, 2008). A neuroinflamação pode impactar o funcionamento do sistema neuroendócrino e de circuitos neuronais e, consequentemente, a plasticidade do cérebro (Harry and Kraft, 2012). Esses processos podem estar relacionados com o comprometimento progressivo das funções neurocognitivas no TB (Stertz, Magalhães, and Kapczinski, 2013). Contudo, os mecanismos biológicos relacionados à neuroinflamação no TB, incluindo alterações nos níveis de PCR, ainda não foram elucidados (Stertz, Magalhães, and Kapczinski, 2013).

Desse modo, o melhor entendimento do papel da PCR e da inflamação crônica de baixo grau no TB poderá contribuir para elucidação dos mecanismos fisiopatológicos dessa doença.

2 FUNDAMENTAÇÃO TEÓRICA

2.1 Inflamação: aspectos gerais

A inflamação é um dos primeiros mecanismos de defesa do corpo em resposta a uma lesão ou infecção (Abbas, Lichtman, and Pillai, 2015). A inflamação aguda é uma resposta não específica caracterizada por calor, dor e inchaço. Nesse processo, denominado resposta inflamatória, os leucócitos migram para a área da lesão e tornam-se ativados, ocorrendo, também, um aumento da permeabilidade vascular e do fluxo sanguíneo para a área lesada permitindo a passagem de células dos vasos sanguíneos ao tecido lesado. A resposta inflamatória desencadeia a produção local e sistêmica de diferentes citocinas (Abbas, Lichtman, and Pillai, 2015).

As citocinas são componentes-chave do sistema imunológico e regulam diversas funções celulares, como proliferação, sobrevida e maturação celular (Dempsey, Vaidya, and Cheng, 2003). Essas moléculas são produzidas por diversas células do sistema imunológico ou fora desse. Embora diversas citocinas estejam implicadas no processo inflamatório, o fator de necrose tumoral-alfa (TNF-alfa), a interleucina-1 (IL-1) e a interleucina-6 (IL-6), são consideradas os principais mediadores desse processo (Tabela 1) (Dempsey, Vaidya, and Cheng, 2003).

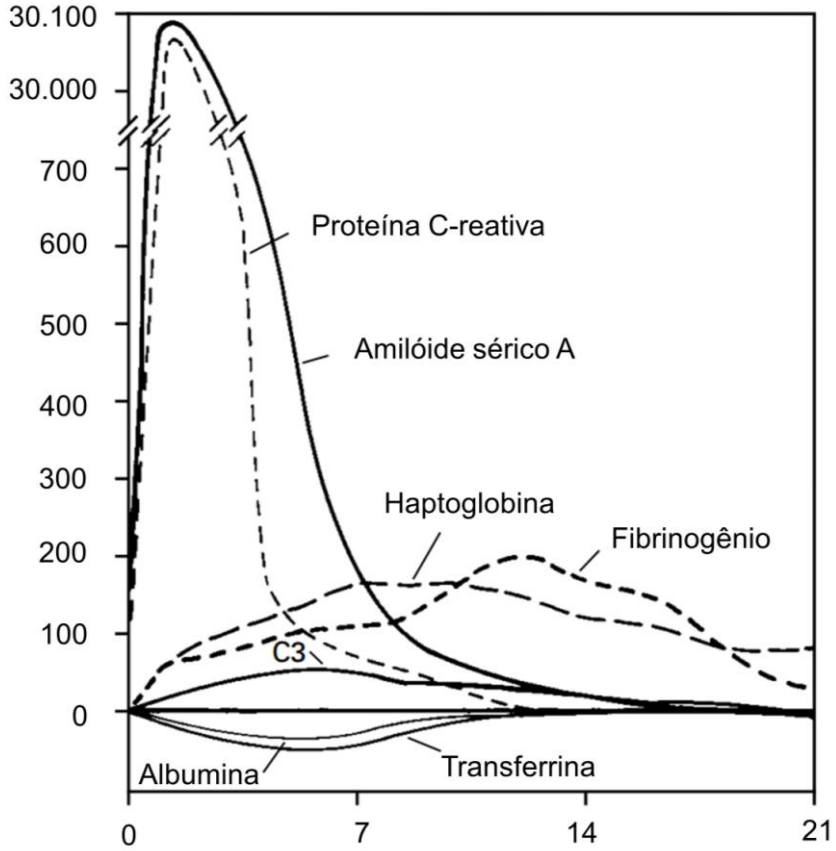
Tabela 1 - Fontes mais importantes e atividades das principais citocinas

Citocina	Fonte primária	Atividade biológica primária
IL-1	Macrófagos	Mediador inflamatório, reagente de fase aguda, amplificação da resposta imune
IL-2	Linfócitos T	Ativação das células T
IL-6	Macrófagos e linfócitos T	Diferenciação de células B, reagente de fase aguda
IL-10	Linfócitos T	Inibição da resposta celular, inibição de citocinas produzidas pelos monócitos e macrófagos
TNF-alfa	Macrófagos, linfócitos T, mastócitos, células natural killers	Sobrepõe-se à atividade da IL-1; expressiva atividade antitumoral
INF-alfa, INF-beta e INF-gama	Linfócitos B, macrófagos, fibroblastos, células epiteliais, linfócitos T	Atividade antiviral e antitumoral, ativa macrófagos, aumenta atividade de linfócitos T citotóxicos e células NK

Fonte: Dempsey, Vaidya, and Cheng, 2003.

Conjuntamente, os eventos da resposta inflamatória caracterizam a “reação de fase aguda” (Gabay and Kushner, 1999). Durante essa fase ocorre a síntese maciça de citocinas e de várias proteínas, denominadas proteínas da fase aguda. Em resposta à inflamação, pode ocorrer um aumento na concentração plasmática dessas proteínas, denominadas proteínas da fase aguda positiva, por exemplo, PCR, fatores do complemento, ferritina e haptoglobina; ou redução na concentração, proteínas da fase aguda negativa, por exemplo, albumina, transferrina, anti-trombina (Figura 1) (Gabay and Kushner, 1999).

Figura 1 - Alterações nas concentrações plasmáticas de algumas proteínas da fase aguda após um estímulo inflamatório moderado



Fonte: Gabay and Kushner, 1999.

A resposta de fase aguda não é específica de uma determinada doença, podendo ocorrer em resposta a vários estados patológicos, como infecções bacterianas, sepse, cirurgias, infarto do

miocárdio, doenças inflamatórias e câncer (Epstein, Gabay, and Kushner, 1999; Gabay and Kushner, 1999; Pepys and Hirschfield, 2003).

Por outro lado, a inflamação crônica subclínica caracteriza-se por uma resposta inflamatória de baixo grau, podendo ser sistêmica em vez de localizada, na qual os sinais de inflamação aguda, geralmente, não são visíveis (Gabay and Kushner, 1999). Esse tipo de inflamação desempenha um papel na fisiopatologia de muitas doenças crônicas, incluindo doenças cardiovasculares, diabetes, doença de Alzheimer e câncer, nas quais a PCR tem sido amplamente utilizada como um biomarcador de inflamação crônica (Pepys and Hirschfield, 2003; Emerging Risk Factors Collaboration et al., 2010; Allin and Nordestgaard, 2011).

2.2 Inflamação crônica e proteína C-reativa

Em 1930, William Tillet and Thomas Francis, observando pacientes com pneumonia pneumocócica durante a fase aguda, detectaram uma proteína plasmática que reagia com o polissacarídeo-C da parede do pneumococos, a qual denominaram proteína C-reativa (Tillett and Francis, 1930).

A PCR, um componente do sistema imune inato, é produzida essencialmente no fígado em resposta às citocinas pró-inflamatórias como a IL-1, o TNF-alfa e, principalmente, a IL-6 (Ballou and Lozanski, 1992). A principal função da PCR, ao ligar-se à fosfocolina, é a sua capacidade de reconhecer alguns patógenos estranhos ao organismo bem como os componentes fosfolipídicos de células lesadas. Outras funções pró-inflamatórias da PCR incluem a indução de citocinas inflamatórias e, em monócitos, do fator tecidual (Ballou and Lozanski, 1992; Cermak et al., 1993).

A PCR é um dos marcadores inflamatórios mais comumente utilizados na prática clínica (Pepys and Hirschfield, 2003; Black, Kushner, and Samols, 2004; Allin and Nordestgaard, 2011).

Durante processos inflamatórios agudos (p. ex. infecção bacteriana) os níveis sanguíneos de PCR podem aumentar significativamente, podendo ultrapassar em até 100 vezes os valores basais. Em indivíduos aparentemente saudáveis, os níveis de PCR variam, geralmente, abaixo de 3 mg/L. Níveis de PCR ligeiramente elevados (> 3mg/mL e < 10 mg/L), refletem inflamação crônica de baixo grau (Gabay and Kushner, 1999). Rotineiramente, a PCR sérica é medida por meio de métodos com limites de detecção entre 3mg/L e 8 mg/L, e o limite de referência para a PCR é de < 10 mg/L. No entanto, métodos com alta sensibilidade para detecção de PCR (PCR ultra-sensível) apresentam limites de detecção entre < 0,3 mg/L e 350mg/L (Roberts et al., 2001).

2.3 Inflamação e alterações comportamentais: aspectos evolutivo-fenomenológicos

Do ponto de vista evolutivo, através de séculos de exposição à infecções virais dos mais variados tipos, a inflamação é um processo vantajoso (Abbas, Lichtman, and Pillai, 2015). Por outro lado, as alterações de comportamento e de humor, muitas vezes, parecem não ter vantagens evolutivamente (Hart, 1988). Portanto, pode-se questionar por que a resposta inflamatória continua sendo um processo vantajoso através de séculos de seleção natural.

Hart (Hart, 1988) foi um dos primeiros autores a postular uma razão para os sintomas psicológicos e comportamentais resultantes de uma resposta inflamatória (Hart, 1988). Esse autor argumentou que os sintomas comportamentais associados à inflamação ou doença "[...] não seriam um processo de mal-adaptação ou um efeito indesejável da doença, mas sim uma estratégia altamente organizada, por vezes fundamental para a sobrevivência do indivíduo se o mesmo fosse viver em estado selvagem" (Hart, 1988). Ele postulou também que os animais e os seres humanos se beneficiariam de sintomas neurovegetativos, tais como letargia, redução do apetite, diminuição do humor, aumento do sono, menor interesse em atividades exploratórias e sexuais, possibilitando, dessa forma, ao organismo concentrar energia no processo de cura e para

proteção contra ataques futuros (Hart, 1988). Posteriormente, este fenômeno foi definido como "*sickness beahvior",* isto é, alterações comportamentais associados à inflamação ou doença (Kent et al., 1992; Dantzer et al., 2008). Em um nível populacional, essas alterações comportamentais podem ser benéficas para evitar a propagação de doenças infecciosas, ou seja, os indivíduos doentes que apresentam sintomas neurovegetativos, muitas vezes, se afastam dos outros indivíduos (Anders, Tanaka, and Kinney, 2013).

Embora os sintomas comportamentais associados à inflamação possam ser úteis no contexto da infecção aguda, no caso das doenças inflamatórias crônicas não relacionadas à infecção, tais como doenças autoimunes, doenças cardiovasculares e diabetes, esses sintomas podem ser prejudiciais (Pepys and Hirschfield, 2003). No caso dos transtornos de humor, a desregulação emocional pode induzir uma resposta inflamatória, o que poderia agravar ainda mais os sintomas de humor do indivíduo (Raison and Miller, 2013). Além disso, se a sintomatologia psico-comportamental (*sickness behavior*) decorrente de uma patologia clínica for mediada por uma resposta inflamatória, o controle dessa resposta poderia auxiliar na redução dos sintomas psicológicos e comportamentais independentemente da resolução da doença clínica (Dantzer et al., 2008; Capuron and Miller, 2011).

2.4 Inflamação sistêmica no transtorno bipolar[1]

Evidências crescentes demonstram que pacientes com TB apresentam disfunções imunológicas, as quais parecem estar relacionadas à severidade dos sintomas, ao número de episódios prévios de humor; à alta prevalência de comorbidades clínicas; aos efeitos adversos do

[1] Texto extraído e adaptado do Artigo 2: Biomarkers in illness progression in bipolar disorder. In: Kapczinski, Flávio ; Vieta, Eduardo ; Magalhães, Pedro ; Berk, Michael. **Neuroporgression and Staging in Bipolar Disorder.** Oxford: Oxford University Press, 2015. P. 175-196.

tratamento farmcológico, e, também, à progressão da doença (Brietzke et al., 2009; Berk et al., 2011; Kapczinski et al., 2011; Fries et al., 2012; Pfaffenseller et al., 2013) .

Recentemente, dois estudos de meta-análise encontraram um aumento significativo dos níveis periféricos de citocinas pró-inflamatórias (IL-2, IL-4, IL-6, IL-1, e TNF-alfa) em pacientes durante episódios agudos do TB (mania ou depressão) (Modabbernia et al., 2013; Munkholm, Vinberg, and Vedel Kessing, 2013). Além disso, esses autores reportaram níveis aumentados de receptores de TNF-alfa e de IL-2 em pacientes maníacos comparado a controles saudáveis respectivamente (Modabbernia et al., 2013; Munkholm, Vinberg, and Vedel Kessing, 2013). Outro estudo demonstrou alterações dos níveis de receptores-1 de TNF-alfa entre os diferentes subtipos de TB (TB-I e TB-II) e, também, entre as diferentes fases de humor (hipomania, eutimia e depressão). Esses autores apontaram o receptor-1 de TNF-alfa como um potencial biomarcador para o estadiamento do TB (Bai et al., 2014). O efeito cumulativo de múltiplos episódios de humor bem como o tempo de duração da doença parecem influenciar os níveis de citocinas pró-inflamatórias, o que parece contribuir para a progressão do TB (Berk et al., 2011; Pfaffenseller et al., 2013). Evidências relatam que os níveis de IL-10, a qual tem atividade anti-inflamatória, reduzem significativamente em estágios tardios do TB (Kauer-Sant'Anna et al., 2009; Remlinger-Molenda et al., 2012). Vale ressaltar que a IL-1-beta, o TNF-alfa e, principalmente, a IL-6 induzem a síntese hepática de PCR (Gabay and Kushner, 1999).

Diversos estudos têm relatado alterações nos níveis de PCR em pacientes com TB (Dickerson et al., 2007; Huang and Lin, 2007; Â. B. Cunha et al., 2008; Vuksan-Ćusa, Šagud, and Jakovljević, 2010; Vuksan-Cusa et al., 2013). No entanto, os resultados de muitos estudos baseiam-se em um pequeno tamanho amostral (Aksoy et al., 2010; Fontoura et al., 2012), em grupos heterogêneos de pacientes (Huang and Lin, 2007; Hope et al., 2011; Tsai et al., 2012) ou não controlaram para fatores que, potencialmente, influenciam os níveis de PCR (p .ex. etnia,

doenças cardiometabólicas e tabagismo) (Cunha et al., 2006; Dickerson et al., 2007). Um estudo prospectivo em pacientes com depressão unipolar demonstrou associação entre níveis elevados de PCR e risco aumentado desses pacientes desenvolverem sintomas maníacos após dois anos de acompanhamento clínico, sugerindo que a inflamação sistêmica de baixo grau poderia ter um papel no deslocamento entre fases do TB bem como na diferenciação entre depressão unipolar e bipolar (Becking et al., 2013). Recentemente, estudos prospectivos em indivíduos da população geral demonstraram associação significativa entre níveis elevados de PCR e risco aumentado de desenvolver TB (Wium-Andersen, Orsted, and Nordestgaard, 2016), esquizofrenia (Wium-Andersen, Ørsted, and Nordestgaard, 2014) ou ansiedade generalizada (Vogelzangs et al., 2013) tardiamente ao longo da vida (após 40 anos de idade).

Contudo, o papel da PCR na fisiopatologia do TB ainda não está esclarecido. Pesquisas futuras são necessárias para explorar vias imuno-inflamatórias subjacentes e as relação entre PCR e outros marcadores inflamatórios a fim de entender melhor o caráter sistêmico do TB (Goldstein et al., 2009; Kapczinski et al., 2010; Berk et al., 2011).

2.5 Proteína C-reativa e comorbidades clínicas no transtorno bipolar[2]

Diversas doenças crônicas como doenças cardiovasculares, diabetes e obesidade – nas quais a inflamação sitêmica exerce um papel fundamental nos mecanismos fisiopatológicos (Couzin-Frankel, 2010) - são altamente prevalentes no TB (Magalhães et al., 2012; Vancampfort et al., 2013; Godin et al., 2014). Dados recentes mostram que mais de 50% dos pacientes avaliados no Programa de Tratamento Sistemático para TB (STEP-BD; *Systematic Treatment Enhancement Program for Bipolar Disorder*) apresentavam pelo menos uma comorbidade clínica associada (Magalhães et al., 2012). Recentemente, um estudo de meta-análise demonstrou que

[2] Texto extraido e adaptado do Artigo 1: C-reactive protein alterations in bipolar disorder: a meta-analysis. **J Clin Psychiatry**. 2015;76(2):142-50.

pacientes bipolares apresentaram risco duas vezes maior de apresentar síndrome metabólica em relação a controles saudáveis (OR = 1,98, 95% IC, 1,74-2,25; $P < 0,0001$) (Vancampfort et al., 2013). Vale ressaltar que a PCR é um marcador independente de risco de doença cardiovascular. Níveis aumentados de PCR (Pepys and Hirschfield, 2003; Emerging Risk Factors Collaboration et al., 2010) têm sido associado a risco aumentado de doença cardiovascular e diabetes em indivíduos com síndrome metabólica (Brooks, Blaha, and Blumenthal, 2010). Além disso, a PCR tem sido considerada como marcador epidemiológico de diabetes do tipo-2 (Spranger et al., 2003), patologia altamente prevalente em pacientes bipolares (Sharma et al., 2014).

A obesidade tem sido caracterizada como um estado inflamatório crônico de baixo grau evidenciado pelos níveis ligeiramente elevados de fatores pró-inflamatórios como fibrinogênio, homocisteína e, principalmente, PCR (Brooks, Blaha, and Blumenthal, 2010). A adiposidade visceral, em particular, está relacionada com níveis elevados de PCR, a qual parece desempenhar um papel importante na fisiopatologia da obesidade (Brooks, Blaha, and Blumenthal, 2010). As células gordurosas (adipócitos) produzem e liberam PCR, a qual se liga à leptina na circulação periférica. Esse processo parece impedir o transporte da leptina por meio da barreira hemato-encefálica, impossibilitando, então, a leptina de exercer uma das suas principais funções no organismo: controlar o apetite e promover a quebra de triglicerídeos nos adipócitos (Hsuchou et al., 2012). A obesidade, principalmente a visceral, é muito frequente em pacientes bipolares o que reforça a hipótese de uma relação bidirecional entre TB e obesidade (McElroy and Keck, 2012; Lackner et al., 2015), potencialmente mediada por mecanismos imuno-inflamatórios (Rosenblat et al., 2014).

Esses achados, conjuntamente, sugerem que TB e comorbidades clínicas compartilham uma base biológica comum, reforçando a ideia de que o TB é uma doença inflamatória multi-sistêmica (Leboyer et al., 2012; Mansur, Brietzke, and McIntyre, 2015) onde a inflamação

crônica subclínica parece exercer um papel importante (Goldstein et al., 2009; Stertz, Magalhães, and Kapczinski, 2013; Rosenblat et al., 2014).

2.6 Neuroinflamação e transtorno bipolar

A presença de marcadores de inflamação na periferia pode estar relacionada com um estado inflamatório no sistema nervoso central. Citocinas pró-inflamatórias produzidas na periferia parecem atravessar a barreira hemato-encefálica, ocorrendo, dessa forma, a propagação dos sinais pró-inflamatórios periféricos para o sistema nervoso central. Tal fato reforça a ideia de uma possível comunicação, via sistema imunológico, entre a periferia e o cérebro (Dantzer et al., 2008; Dantzer, 2012). No cérebro, a resposta imunológica pode ativar a micróglia (macrófagos residentes do cérebro), a qual, através da liberação de mediadores do estresse oxidativo e de inflamação, amplifica a resposta inflamatória. Esse processo acarreta mudança na função astroglial, com redução nos níveis de neurotrofinas, incluindo o fator neurotrófico derivado do cérebro (BDNF) e o fator neurotrófico derivado de células gliais (GDNF); e aumento de metabólitos neurotóxicos (p. ex. glutamato) (Miller et al., 2008; Miller, Maletic, and Raison, 2009; Miller et al., 2013). O glutamato se liga aos receptores N-metil-d-aspartato (NMDA) extra-sinápticos, causando a supressão da síntese e a ativação da cascata pró-apoptótica de BDNF (Maletic and Raison, 2014). Além disso, as citocinas pró-inflamatórias aumentam a expressão dos receptores de serotonina e de dopamina, contribuindo, também, para uma desequilíbrio na sinalização monoaminérgica (Felger and Lotrich, 2013), o qual parece estar relacionado com a gravidade dos sintomas de humor (Lindqvist et al., 2009).

Estudos recentes apontam que a neuroinflamação parece estar envolvida na fisiopatologia do TB (Stertz, Magalhães, and Kapczinski, 2013; Maletic and Raison, 2014). Níveis elevados de IL-1-beta foram encontrados no líquor de pacientes bipolares que

apresentaram episódios (hipo-)maníacos um ano antes do estudo em comparação com pacientes que não tiveram episódios (hipo-)maníacos no mesmo período (Söderlund et al., 2011). Estudo *post-mortem* encontrou aumento da ativação da via do receptor da IL-1 em córtex pré-frontal de pacientes com TB, reforçando a hipótese de haver ativação microglial nessa patologia (Rao et al., 2010). A PCR, ainda que não atravesse a barreira hemato-encefálica, parece aumentar a permeabilidade dessa barreira para moléculas pequenas tais como citocinas pró-inflamatórias e anticorpos, o que tornaria o cérebro mais susceptível aos efeitos da inflamação sistêmica (Kuhlmann et al., 2009). Desse modo, os níveis séricos de PCR poderiam indicar, ainda que indiretamente, um estado inflamatório no cérebro. Além do mais, a inflamação sistêmica no TB parece interferir no mecanismo de plasticidade neuronal (Maletic and Raison, 2014), o que poderia explicar, em parte, a expressão dos sintomas da doença (Grande et al., 2010) e o prejuízo cognitivo-funcional encontrado em pacientes bipolares (Martínez-Arán et al., 2004; Goodwin et al., 2008; Rosa et al., 2010).

2.7 Funcionamento cognitivo e psicossocial no transtorno bipolar

A disfunção cognitiva em pacientes com TB parece estar presente desde o início da doença (Goodwin et al., 2008), podendo persistir, também, durante o período de remissão (Bonnín et al., 2012; Martinez-Aran and Vieta, 2015). Estudos com pacientes bipolares têm constatado prejuízo nas áreas de habilidades executivas, da memória verbal, da atenção sustentada como também em áreas relacionadas com a abstração e com a mudança de contexto (Bonnín et al., 2014; Solé et al., 2016). Os déficits em funções executiva e de memória verbal, por exemplo, indicam danos nos córtices pré-frontal e temporo-medial, respectivamente (Lee et al., 2014). A frequência elevada de episódios de humor e o tempo de duração da doença parecem

agravar o prejuízo cognitivo em pacientes bipolares, o que contribui para a progressão do TB (Cardoso et al., 2015).

Estudos reportam associações entre níveis elevados de PCR e comprometimento cognitivo em indivíduos com doença cardiovascular (Gunstad et al., 2006) como também em indivíduos aparentemente saudáveis (Dimopoulos et al., 2006). Tendo em vista que níveis elevados de PCR parecem induzir disfunção endotelial na barreira hemato-encefálica (Kuhlmann et al., 2009; Hsuchou et al., 2012), tal fato poder estar relacionado com o comprometimento cognitivo apresentado por indivíduos com níveis aumentados de PCR. Recentemente, estudos demonstraram associações significativas entre níveis aumentados de PCR e disfunção cognitiva em pacientes com esquizofrenia (Dickerson et al., 2012) ou com TB (Dickerson et al., 2013). Entretanto, faz-se necessário um maior número de estudos, avaliando cognição e níveis de PCR em pacientes bipolares em diferentes fases da doença a fim de elucidar o papel da PCR na neuroinflamação e a sua relação com o prejuízo cognitivo e psicossocial nesses pacientes.

Prejuízo no funcionamento psicossocial tem sido frequentemente encontrado em pacientes bipolares independentemente do tipo de episódio (mania ou depressão) ou da fase da doença (período de remissão) (Rosa et al., 2008; Solé et al., 2015). Um estudo prospectivo conduzido nos Estados Unidos constatou que, após o primeiro episódio maníaco, 98% dos pacientes bipolares atingiram remissão clínica em um período de 02 anos, ao passo que apenas 38% desses pacientes recuperaram o funcionamento psicossocial nesse mesmo período (Tohen et al., 2000). O prejuízo no funcionamento psicossocial em pacientes bipolares pode aparecer em diferentes áreas do funcionamento psicossocial, como por exemplo, atividade laboral, autonomia, organização financeira e relacionamento interpessoal (Rosa et al., 2007, 2012). Além disso, disfunção psicossocial pode estar presente desde as fases mais precoces do TB, podendo, contudo, agravar-se em estágios mais avançados da doença (Judd et al., 2005; Rosa et al., 2014).

Recentemente, Rosa e colaboradores (Rosa et al., 2014) encontraram correlação inversa entre os níveis de funcionamento psicossocial e os estágios clínicos do TB (Rosa et al., 2014). Esses autores constataram que pacientes em estágios mais avançados da doença apresentavam um declínio funcional significativamente maior em comparação aos pacientes em estágio inicial do TB, os quais apresentaram padrões de funcionamento semelhante ao grupo controle (Rosa et al., 2014). Esse mesmo estudo observou, também, déficit neurocognitivo importante nos pacientes em estágios avançados da doença (Rosa et al., 2014). Esses achados reforçam a hipótese da toxicidade sistêmica no TB (Kapczinski et al., 2010) decorrente do acúmulo de múltiplos episódios de humor e do longo período de doença, o que poderia impactar o funcionamento neurocognitivo e psicossocial dos pacientes, contribuindo com a ideia do TB ser uma doença crônica e progressiva (Berk, 2008; Kapczinski et al., 2008; Pfaffenseller et al., 2013). Até o momento, nenhum estudo avaliou o possível a associação entre níveis de PCR e funcionamento psicossocial em pacientes bipolares.

2.8 Abordagem dimensional no transtorno bipolar: reatividade emocional e níveis de proteína C-reativa[3]

Evidências demonstram que a capacidade de regular as emoções está intimamente correlacionada com a saúde física e psíquica do indivíduo (Kiecolt-Glaser et al., 2002; Kubzansky et al., 2011). Déficits persistentes no processo de regulação emocional bem como reatividade emocional desproporcional são frequentemente observadas em indivíduos com TB (Phillips, Ladouceur, and Drevets, 2008; Gruber, Harvey, and Purcell, 2011). Reatividade emocional é definida pela amplitude de variação de um estado emocional de base em resposta a um estímulo emocional (Gross, 1998). Estudos de neuroimagem em pacientes bipolares

[3] Texto extraído do Artigo 3: Emotional reactivity, functioning, and C-reactive protein alterations in remitted bipolar patients: clinical relevance of a dimensional approach. **J Clin Psychiatry**, submitted.

demonstram instabilidade no mecanismo de regulação emocional, caracterizado por hipo-ativação do córtex pré-frontal (responsável pela regulação voluntária das emoções) e por hiper-ativação do sistema límbico, principalmente da amígdala (responsável pela detecção do estímulo emocional) (Phillips, Ladouceur, and Drevets, 2008; Wessa, Kanske, and Linke, 2014). Esse desequilíbrio entre as regiões cerebrais implicadas na regulação emocional evidencia, clinicamente, a reatividade anormal, a instabilidade de humor e a alteração de motivação frequentemente observadas em pacientes bipolares (Phillips, Ladouceur, and Drevets, 2008; Houenou et al., 2011; Van Rheenen, Meyer, and Rossell, 2014; Wessa, Kanske, and Linke, 2014).

Henry e colaboradores, utilizando uma abordagem multidimensional para avaliar pacientes bipolares, demonstraram existir um *continuum* que varia desde um estado de inibição até um estado de ativação global do cmportamento (i.e.: variando desde episódios depressivos maiores, depressão com sintomas maníacos até episódios maníacos e estados mistos, respectivamente) (Henry et al., 2008; Henry et al., 2010). Esses autores demonstraram também que essa abordagem multidimensional permitiu distinguir dois tipos de depressão bipolar: uma caracterizada por inibição global do comportamento e hipo-reatividade emocional e outra caracterizada por ativação global do comportamento e hiper-reatividade emocional (Henry et al., 2007). A reatividade emocional, portanto, parece ser uma dimensão relevante para melhor caracterizar pacientes com perfil clínico distintos o que poderia implicar em intervenções terapêuticas mais individualizadas para esses pacientes.

Estudos em indivíduos saudáveis demonstraram associação entre a desregulação emocional níveis aumentados de PCR (Steptoe, Hamer, and Chida, 2007; Appleton, et al., 2013). Um estudo reportou associações entre níveis de PCR e alterações anátomo-funcionais em áreas cerebrais como a amígdala, o córtex pré-frontal, e o núcleo accumbens) (Miller et al., 2013).

Essas regiões cerebrais estão diretamente envolvidas na regulação das emoções, do humor e da resposta ao estresse em pacientes bipolares (Kempton et al., 2008; Wessa, Kanske, and Linke, 2014).

2.9 Tratamento e resposta inflamatória no transtorno bipolar

Evidências crescentes relatam que medicamentos comumente utilizados para o tratamento do TB, como os antipsicóticos e os estabilizadores de humor, parecem influenciar os níveis de marcadores inflamatórios (Knijff et al., 2007; Hefner et al., 2016). Estudo *in vitro* demonstrou que antipsicóticos podem suprimir a ativação da micróglia através da inibição de mediadores inflamatórios tais como citocinas e óxido nítrico (Kato et al., 2007). Resultados de estudos pré-clínicos indicam que o lítio e o valproato (estabilizadores de humor) parecem inibir as ciclooxigenases (COX-1 e COX-2), reduzindo assim a degradação do ácido araquidônico em prostaglandinas inflamatórias (Bosetti et al., 2002; Bosetti et al., 2003).

Por outro lado, estudos recentes demonstram o benefício de alguns agentes anti-inflamatórios no tratamento da esquizofrenia e dos transtornos de humor (Berk et al., 2013; Fond et al., 2014 (ANEXO C)). Um ensaio clínico avaliou a eficácia do celecoxib (inibidor da COX-2) como tratamento adjuvante em pacientes bipolares com episódios depressivos ou mistos (Nery et al., 2008). Esse estudo demonstrou que o grupo de pacientes que recebeu o anti-inflamatório associado ao tratamento padrão em uso apresentou melhora sintomática significativa quando comparado ao grupo que recebeu apenas o tratamento padrão (Nery et al., 2008). A minociclina, um antibiótico da classe das tetraciclinas, tem sido bastante investigada como tratamento adjuvante no TB (Savitz et al., 2012). Esse antibiótico, o qual permeia a barreira hemato-encefálica, parece inibir a liberação de citocinas pró-inflamatórias (IL-1b, TNF-alfa, IL-6), e promover a liberação de citocinas anti-inflamatórias (IL-10) (Savitz et al., 2012; Burke et al.,

2013). Outros agentes com propriedades anti-inflamatórias, como, por exemplo, os anticorpos monoclonais, também têm sido explorados como tratamento adjuvantes nos transtornos de humor (Raison et al., 2013). O infliximab, um anticorpo monoclonal TNF-alfa específico, parece estar associado a redução de sintomas depressivos em pacientes em tratamento de condições inflamatórias como por exemplo psoríase, doença de Crohn e artrite reumatoide (Persoons et al., 2005; Ertenli et al., 2012). Raison e colaboradores (Raison et al., 2013), utilizando infliximab como adjuvante no tratamento de pacientes com depressão resistente, relataram melhora significativa dos sintomas depressivos apenas nos pacientes que apresentaram níveis elevados de PCR (> 5mg/L) no início do estudo (Raison et al., 2013). Com base nos achados desse estudo (Raison et al., 2013), a PCR poderia ser útil para estratificar pacientes bipolares apresentando diferentes níveis de sintomas e de resposta terapêutica.

Embora o uso de agentes anti-inflamatórios como adjuvantes ao tratamento padrão parece ser uma alternativa interessante no TB, ainda faltam estudos prospectivos para demonstrar a eficácia e dose adequada desses agentes. Dado que a inflamação sistêmica crônica parece estar envolvida na progressão do TB, os moduladores da resposta inflamatória poderiam ser uma alternativa terapêutica relevante nessa patologia.

3 JUSTIFICATIVA

A investigação sobre as bases biológicas do TB tem avançado consideravelmente na última década (Kapczinski et al., 2008; Berk et al., 2011). Contudo, os resultados das pesquisas ainda são insuficientes para explicar os mecanismos fisiopatológicos dessa patologia e, consequentemente, com um impacto discreto no desenvolvimento de tratamentos mais eficazes para os pacientes. Isso pode estar associado a um conjunto de fatores, incluindo a característica multissistêmica do TB que compromete não somente o sistema nervoso central como também diversos outros sistemas, incluindo o imunológico, o cardiovascular e o endócrino (Leboyer et al., 2012; Stertz, Magalhães, and Kapczinski, 2013). Pacientes com TB apresentam uma série de doenças clínicas, e, frequentemente, um estado inflamatório sistêmico crônico evidenciado por alterações persistentes em marcadores inflamatórios periféricos, como, por exemplo, a PCR (Goldstein et al., 2009; Modabbernia et al., 2013; Munkholm, Vinberg, and Vedel Kessing, 2013).

A PCR é um biomarcador de inflamacão largamente utilizado na prática clínica, sendo considerado um fator de risco isolado para doença cardiovascular (Pepys and Hirschfield, 2003). Níveis elevados de PCR tem sido encontrados em patologias psiquiátricas, incluindo autismo (Brown et al., 2014), esquizofrenia (Wium-Andersen, Ørsted, and Nordestgaard, 2014) e depressão (Wium-Andersen et al., 2013). Além disso, níveis aumentados de PCR têm sido encontrados em indivíduos aparentemente saudáveis, mas que apresentam desregulação emocional (Appleton et al., 2013), a qual é uma das principais características do TB (Henry and Etain, 2010). Nesse sentido, um melhor entendimento do papel da PCR e da inflamação crônica subclínica no TB poderá contribuir, em parte, para elucidação de mecanismos fisiopatológicos do TB e, portanto, para o desenvolvimento de intervenções terapêuticas mais efetivas.

4 OBJETIVOS

4.1 Objetivo geral

O objetivo geral desta tese foi avaliar o papel da proteína C-reativa como um marcador de inflamação crônica em indivíduos com transtorno bipolar.

4.2 Objetivos específicos

A pesquisa teve como objetivos específicos:

a) examinar a associação entre os níveis de proteína C-reativa e transtorno bipolar por meio de um estudo de meta-análise a partir dos dados da literatura.

b) investigar, através de uma revisão sitemática da literatura, os potencias biomarcadores periféricos, incluindo neurotrofinas, marcadores de estresse oxidativo e de inflamação associados a progressão do transtorno bipolar.

c) examinar a concentração sérica de proteína C-reativa em pacientes bipolares com diferentes níveis de reatividade emocional durante a fase de remissão.

d) examinar a associação entre funcionamento psicossocial em pacientes bipolares com diferentes níveis de reatividade emocional durante a fase de remissão;

5 MÉTODOS

5.1 Revisão sistemática e meta-análise[4]

Uma extensa revisão sistemática e meta-análise foi realizada para avaliar o tamanho de efeito da associação entre níveis de PCR e as diferentes fases do TB (mania, depressão e eutimia) comparado a indivíduos saudáveis.

Os *critérios de inclusão* para essa meta-análise foram: i) estudos transversais comparando níveis plasmáticos de PCR em pacientes bipolares e indivíduos saudáveis ambos com idade acima de 18 anos; ii) diagnóstico de TB através de critérios diagnósticos válidos; iii) estudos publicados em língua inglesa.

Os *critérios de exclusão* foram: i) estudos que não incluíram grupo controle ou que não compararam pacientes bipolares e indivíduos controles; ii) estudos onde os níveis de PCR não foram avaliados em mais de 50% da amostra; iii) estudos que não forneceram valores de média e desvio-padrão para os níveis de PCR.

As *análises estatísticas* foram realizadas com o software *R* (versão 2.11.1).

5.2 Mecanismos biológicos associados à progressão do transtorno bipolar[5]

Uma ampla revisão da literatura foi realizada para identificar potenciais biomarcadores periféricos, incluindo neurotrofinas e marcadores de estresse oxidativo e de inflamação associados a progressão do TB.

---

[4] Artigo 1: C-reactive protein alterations in bipolar disorder: a meta-analysis. **J Clin Psychiatry**. 2015;76(2):142-50.

[5] Artigo 2: Biomarkers in illness progression in bipolar disorder. In: Kapczinski, Flávio ; Vieta, Eduardo ; Magalhães, Pedro ; Berk, Michael. **Neuroporgression and Staging in Bipolar Disorder.** Oxford: Oxford University Press, 2015. P. 175-196.

5.3 Estudo transversal com pacientes bipolares[6]

Os *participantes* foram 613 pacientes bipolares ambulatoriais com idade acima de 18 anos selecionados de uma coorte de 1451 pacientes avaliados na Rede Nacional Francesa de Centros Especializados em Transtorno Bipolar (FACE-BD) (Henry et al., 2011, 2015). FACE-BD é um programa nacional, multidisciplinar especializado em avaliação, acompanhamento e tratamento de pacientes bipolares.

Os *critérios de inclusão* para esse estudo foram: i) diagnóstico de TB (tipo I; tipo II ou NOS, não especificado); ii) não ter apresentado episódio agudo de humor (conforme os critérios do DSM (American Psychiatric Association, 2000) pelo menos três meses antes do início do estudo; iii) escores < 15 na escala de avaliação de depressão MADRS (Montgomery-Asberg Depression Rating Scale) (Montgomery and Asberg, 1979), e escores < 8 na escala de avaliação de mania YMRS (Young Mania Rating Scale) (Young et al., 1978). Todos os participantes estavam em período de remissão, apresentando ou não sintomas sub-clínicos de humor (Tohen et al., 2009). Foram *excluídos do estudo* os pacientes: i) com níveis de CRP > 10mg/L; ii) apresentando comorbidades clínica como doenças autoimunes, patologias infecciosas, doenças hepáticas ou câncer tendo em vista que inflamação sistêmica e ativação do sistema imunitário são achados comuns nessas doenças (Gabay and Kushner, 1999); iii) que não tinham dosagem de PCR sérica. A coleta de dados clínicos e sócio-demográficos bem como a aplicação das escalas foram realizadas por psiquiatras treinados. O estudo foi aprovado pelo Comitê de Ética em Pesquisa em seres humanos (CPP-Ile de France IX) e uma carta com informação sobre o estudo foi fornecida a cada participante.

[6] Artigo 3: Emotional reactivity, functioning, and C-reactive protein alterations in remitted bipolar patients: clinical relevance of a dimensional approach. **J Clin Psychiatry,** submitted.

A *avaliação multidimensional dos estados de humor* foi realizada através do instrumento MAThyS (Multidimensional Approach of Thymic States) (Henry et al., 2008). A MAThyS é uma escala de auto-avaliação, composta por 20 itens que avalia, de forma quantitativa, cinco dimensões do comportamento que são: reatividade emocional, rapidez cognitiva, atividade psicomotora, motivação e senso-percepção. O escore total da MAThyS varia entre 0 e 200; escores < 91 indicam inibição global do comportamento, enquanto que escores >108 indicam ativação global do comportamento, através das diferentes fases de humor (Henry et al., 2008). A dimensão reatividade emocional é um sub-score da MAThyS total com escores variando entre 0 e 40. Para o artigo 3 dessa tese, os pacientes foram agrupados de acordo com os pontos de corte (previamente validados (Atzeni et al., 2013)) para os níveis de reatividade emocional: < 16 = hipo-reatividade emocional; 16-24 = reatividade emocional normal > 24 = hiper-reatividade emocional.(Atzeni et al., 2013) A escala MAThyS apresenta boas propriedades psicométricas (Coeficiente alfa de *Cronbach* = 0.95) (Henry et al., 2008).

O *funcionamento psicossocial* foi avaliado através do Escala de Avaliação do Funcionamento Psicossocial (FAST, *Functioning Assessement Short Test*) (Rosa et al., 2007). Esse instrumento é composto de 24 itens, incluindo seis áreas específicas do funcionamento: autonomia, funcionamento ocupacional, lazer, relacionamento interpessoal, auto-gerenciamento de finanças e funcionamento cognitivo. A cotação de cada item é realizada através de uma escala *Likert* de 4 pontos: 0 = sem dificuldade, 1 = dificuldade leve, 2 = dificuldade moderada, 3 = dificuldade severa. O escore global da FAST varia entre 0 e 72, onde escores > 11 indicam prejuízo funcional importante e quanto maior o escore, maior o déficit funcional (Rosa et al., 2007).

As amostras de sangue para a *dosagem de PCR* foram coletadas entre 7h e 9h da manhã, com os pacientes em jejum. Imunoturbidimetria foi o método utilizado para quantificar a

concentração sérica da PCR ultra-sensível via análises bioquímicas realizadas com o equipamento Cobas8000 (Roche Diagnostic, Meylan, France). Reagentes e calibragens foram utilizadas de acordo com o manual do fabricante, o qual indica limites de detecção de PCR ultra-sensível entre 0.3 e 350mg/L.

Os *testes estatísticos* ANOVA e *Qui*-quadrado for utilizados para analisar variáveis contínuas e categóricas, respectivamente. O teste *post-hoc* de Cohen foi utilizado para calcular a diferença de tamanho de efeito nas variáveis do funcionamento entre os três grupos de pacientes. Os tamanhos de efeito foram calculados pela diferença das médias dos três grupos dividida pelo desvio-padrão. Um tamanho de efeito < 0.3 é considerado pequeno; entre 0.3 e 0.8, médio; e > 0.8 grande (Kazis, Anderson, and Meenan, 1989). O programa utilizado para as análises estatísticas foi o SPSS (*Statistical Package for Social Science*, v.21, Chicago, IL). O nível de significância estatística para todos os testes foi $P < 0.05$.

6 RESULTADOS: ARTIGOS CIENTÍFICOS

6.1 Artigo 1: C-reactive protein alterations in bipolar disorder: a meta-analysis

C-reactive protein alterations in bipolar disorder: a meta-analysis

Dargél, Aroldo A.; Godin, Ophelia; Kapczinski, Flávio; Kupfer, David J.; Leboyer, Marion

Publicado em *Journal of Clinical Psychiatry*.

C-Reactive Protein Alterations in Bipolar Disorder: A Meta-Analysis

Aroldo A. Dargél, MD, PhD; Ophelia Godin, PhD; Flávio Kapczinski, MD, PhD; David J. Kupfer, MD; and Marion Leboyer, MD, PhD

ABSTRACT

Objective: There is growing evidence that bipolar disorder (BD) is associated with inflammation, including abnormal levels of acute-phase C-reactive protein (CRP). Our meta-analysis was conducted to estimate the size of the association between CRP levels and BD, accounting also for subgroup differences (mood phases and treatment).

Data Sources: MEDLINE, EMBASE, PsycINFO, and ISI Web of Science and references of identified articles were searched up to June 2013 using the keywords (bipolar disorder) AND (C-reactive protein OR CRP). Study Selection: English language studies measuring blood levels of CRP in patients with BD and control subjects were selected, 136 abstracts were reviewed, 20 articles retrieved, and 11 studies included.

Data Extraction: Two independent reviewers extracted data. All studies were included in the primary analyses, and between-group differences for subanalyses were also reported. This meta-analysis was performed using random-effects models.

Results: Eleven studies comprising 1,618 subjects were eligible for inclusion. Overall, CRP levels were significantly elevated in patients with BD versus controls (standardized mean difference [SMD] = 0.39; 95% CI, 0.24 to 0.55; P < .0001). CRP levels were significantly higher in manic (SMD = 0.73; 95% CI, 0.44 to 1.02; P < .001) and euthymic (SMD = 0.26; 95% CI, 0.01 to 0.51; P = .04), but not in depressed (SMD = 0.28; 95% CI, −0.17 to 0.73; P = .22) patients with BD compared to controls. CRP levels were unrelated to use of lithium or antipsychotic medication.

Conclusions: This meta-analysis supports an association between increased CRP levels and BD. Given that an elevated level of CRP is a marker of low-grade inflammation and a risk factor for cardiovascular and malignant diseases, measurement of CRP level might be relevant to the clinical care of bipolar patients.

Corresponding author: Aroldo A. Dargél, MD, Hôpital A. Chenevier, Pavillon Hartmann, 40, rue de Mesly, F-94000, Créteil, France (aroldodargel@gmail.com)

Individuals su ering from severe infections and autoimmune diseases have acute or persistently increased levels of markers of in ammation in their blood,[1] and such individuals are found to have an increased risk of developing mood disorders, including bipolar disorder (BD).[2] Recently, 2 meta-analyses con rmed that patients with BD, across the di erent mood phases of the disease, have abnormal blood levels of several in ammatory markers, including cytokines.[3,4] Cytokines are multifunctional signaling molecules of the immune system that act as key mediators in both central and peripheral in ammation.[5] Proin ammatory cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and particularly interleukin-6 (IL-6), are the chief inducers of acute-phase proteins, including haptoglobin, brinogen, and C-reactive protein (CRP),[1] which are associated with BD.[6] ese ndings indicate that in ammation may be involved in the pathophysiologic mechanisms of BD.[7]

C-reactive protein, which is synthesized by hepatocytes, is a classic acute-phase protein[1] and one of the most commonly used markers of in ammation. Normal levels of CRP are < 3 mg/L, and the high-sensitivity CRP (hsCRP) assay has a lower limit of detection < 0.1 mg/L.[8] During acute in ammatory processes (eg, bacterial infection), circulating blood levels of CRP can increase up to 1,000-fold.[9] Subjects who are apparently healthy have CRP levels that are usually below 3 mg/L, but such levels can be up to 10 mg/L.[9] Levels of CRP that are slightly elevated (> 3 mg/L to < 10 mg/L) re ect low-grade in ammation,[1] which has been linked with a range of conditions, including vascular and malignant diseases,[10] as well as autism[11] and depression.[12] Furthermore, prospective studies have recently demonstrated an association between elevated levels of CRP and increased risk of late-onset schizophrenia[13] and anxiety disorder.[14]

Growing evidence has been reported that BD is consistently associated with clinical comorbidities[15] in which cardiovascular illness and metabolic syndrome are highly prevalent.[16] Of note, elevated levels of CRP can independently predict several conditions, such as cancers[17] and respiratory illnesses, as well as cardiovascular diseases,[18] which are known to be the leading cause of excess mortality in BD.[19] Although cardiometabolic conditions in BD have been considered as a consequence of an unhealthy lifestyle and/or of psychotropic medications, the systemic mechanisms underlying this relationship are still unclear, and in ammation might be implicated.[7,20]

Several studies have reported an association between elevated levels of CRP and BD,[21–34] however, they have frequently been limited to small[21,25,27,34] and/or heterogeneous samples[24,26,33,34] and have failed to control for relevant confounding factors.[22,25,31,32] Moreover, previous studies were inadequately powered to assess the size of association between CRP levels and the di erent mood phases of BD (mania, depression, and euthymia).[22,25,30] erefore, we conducted a meta-analysis to estimate the overall e ect size of the association between CRP levels and BD. We also examined the in uence of BD phases (mania, depression, or euthymia) and of medication (antipsychotics and lithium)

- Increased levels of C-reactive protein (CRP), a marker of systemic inflammation and an established risk factor for cardiovascular disease, appear to be associated with bipolar disorder.
- Inflammation may be implicated in the pathophysiology of bipolar disorder; thus, healthy lifestyle interventions (smoking cessation, dietary measures, and physical activity), which appear to reduce levels of proinflammatory markers (eg, CRP), might help to assuage severity of bipolar disorder.
- Measurement of CRP levels in patients with bipolar disorder should be considered as a possible strategy to motivate them toward healthy body-brain interventions.

on the levels of CRP in patients with BD and whether the findings corroborate the inflammation hypothesis in BD, including CRP as a biomarker.

METHOD

Data Source and Study Selection

To identify relevant studies, we searched MEDLINE, EMBASE, PsycINFO, and ISI Web of Science from their inception to June 2013. Keywords utilized included (*C-reactive protein* OR *CRP)* AND (*bipolar disorder* OR *bipolar illness* OR *manic depression* OR *manic-depression* OR *manic-depressive illness* OR *bipolar depression* OR *mania* OR *manic episode* OR *hypomania* OR *bipolar affective disorder* OR *bipolar psychosis* OR *manic disorder* OR *manic psychosis* OR *dysphoric mania* OR *hypomanic* OR *mixed mania* OR *cyclothymic disorder* OR *cyclothymia).* The reference lists from identified studies were also hand searched for any additional studies.

A priori criteria for inclusion in the meta-analysis were (1) cross-sectional studies comparing blood levels of CRP in adult BD patients (aged > 18 years) and healthy controls (psychiatrically healthy subjects), (2) diagnosis of BD with well-validated diagnostic criteria, and (3) studies published in English. Exclusion criteria were (1) studies without a control group (ie, not comparing BD patients with control subjects), (2) studies in which CRP levels were not detectable for > 50% of subjects, and (3) unavailability of mean and standard deviation (SD) for CRP levels in the article.

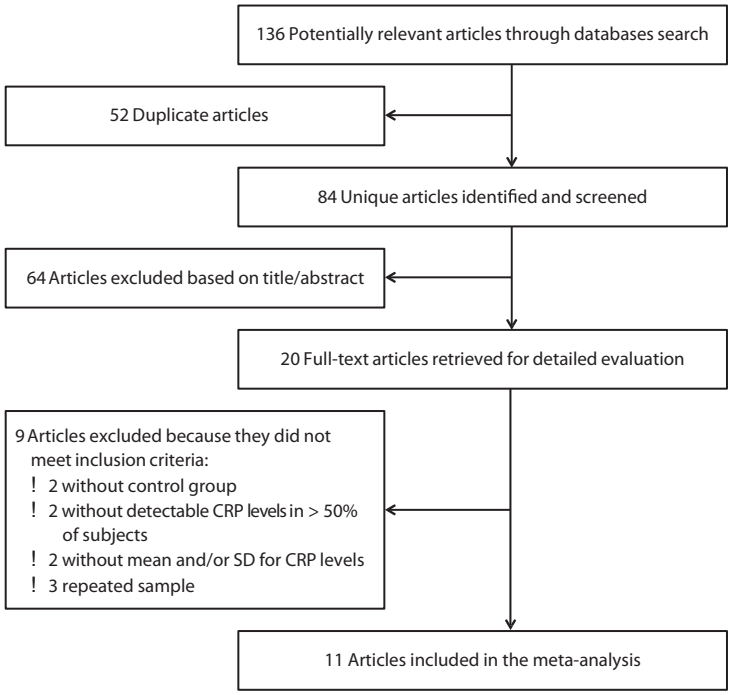
Data Extraction and Meta-Analysis

Two independent authors (A.A.D. and O.G.) screened articles by their titles and abstracts, and those eligible were retrieved. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[35] checklists were used to create the data extraction forms, which were completed for each eligible study. Any difference in abstracted content was discussed with a third author (M.L.) and was resolved by consensus. Extracted data included source (author names, year of publication, and country), study design, participants (sample, control, demographic, and clinical characteristics), assay methods (CRP or hsCRP), and inclusion/exclusion criteria. We also extracted mean and SD for CRP levels in each study. Requests for additional data were sent to authors for original studies, and, of the 9 contacted, a reply was received from 1 author.

For cases in which a sample was repeated (partially or totally) in more than 1 publication, the data from the study with more details on the subgroup of patients (or, if not applicable, the study with larger sample size) were included in the analysis. A study that evaluated symptom severity of BD in outpatients, using the score of Young Mania Rating Scale (YMRS) ≤ 6 versus YMRS > 6 to categorize manic versus euthymic patients, was included.[23] This cutoff is a standard one that has been used in studies of outpatients with BD to distinguish between patients who are euthymic and those who have manic symptoms.[36] For a study that measured CRP levels in psychiatric outpatients in remission (potentially having subsyndromal conditions), the BD population was included in the analysis as euthymic patients.[24] Lastly, in a study including patients in an *elevated* and a *depressed* state, not stating whether these patients fulfilled diagnostic criteria for mood episodes, the symptom rating scale results provided were estimated to fulfill criteria, and the study was included.[26] Considering there were different classifications for euthymic phase and remission (including subsyndromal conditions) among the studies included, we grouped these definitions together under "euthymia" subgroup to avoid increase in the number of subgroups.

To combine studies, the DerSimonian and Laird random-effects model[37] was used in all cases to calculate effect size estimates, considering that individuals in this meta-analytic study tended to be heterogeneous and methodological differences (eg, different assays employed) across studies could generate effect size differences. Since it was considered likely a priori that not all trials would produce exactly equal underlying effect sizes, a random-effects model was considered preferable to a fixed-effects model. The random-effects model includes both within-study and between-study variance and is usually more realistic and conservative than the fixed-effects model.[37] The results are presented as standardized mean difference (SMD) and 95% confidence intervals (CIs). This association measure (SMD) is a useful method that allows the pooling of data measured with different techniques (eg, different CRP assays). An effect size < 0.3 is considered small; from 0.3 to 0.8, medium; and > 0.8, large.[37] We quantified between-study heterogeneity using Cochran Q and the I^2 statistic.[38] I^2 can be interpreted as the proportion of the total variance due to heterogeneity between studies and may be categorized as a low ($I^2 = 25\%$), moderate ($I^2 = 50\%$), or high ($I^2 = 75\%$) degree of heterogeneity.[39] Additionally, we conducted subgroup analyses to assess the influence of BD phases (mania, depression, or euthymia), as well as of medication use (antipsychotics or lithium) on the levels of CRP in patients with BD. We visually inspected funnel plots portraying estimates of SMD from individual studies against their standard error to assess for potential publication bias using Egger regression-based test.[40] Given that statistically nonsignificant findings may have a lower probability of being published, which could lead to an

Figure 1. Flowchart of Study Selection Process



Abbreviations: CRP = C-reactive protein, SD = standard deviation.

overestimation of the effect size, we used the trim-and-fill method that estimates corrected effect sizes after imputing possible lacking effect sizes.[41] Statistical analyses were performed with the metaphor package in R (2.11.1).[42]

RESULTS

Search and Study Characteristics

The computerized search yielded 84 references after 52 duplicates were removed. We excluded 64 studies on the basis of title and abstract review. Of the remaining 20 studies, 9 additional articles were excluded after full-text review (2 studies that had no control group or did not compare BD patients with control subjects,[33,43] 2 studies in which CRP levels were not detectable in > 50% of subjects,[44,45] 2 studies without available mean and SD values of CRP levels in the article,[32,46] and 3 studies that reported results of CRP levels from the same population[47–49]). In total, we included 11 articles[21–31] in the meta-analysis (Figure 1).

Overall, 3 studies were conducted in Taiwan[27–29]; 2 studies each in the United States[23,24] and Brazil[22,25]; and 1 each in Croatia,[30] Norway,[26] South Africa,[31] and Turkey.[21] The available data were too limited to include analysis on ethnicity or geographical differences. The data set comprised 1,618 individuals (730 patients with BD and 888 control subjects), and the studies included in this meta-analysis involved sample sizes that ranged from 13 to 192 bipolar patients, of which 56.7% were female (n = 414; 9 studies). All of the studies included were published between 2007 and 2013 and used *DSM-IV*[50] diagnostic criteria for BD, and most of those used *DSM-IV* criteria to define manic and/or depressive episodes.[22,25,27–31]

Nine studies reported using a clinical protocol to screen control subjects,[22–30] 5 of those used the Structured Clinical Interview for *DSM-IV* Axis I Disorders–Non-Patient Edition.[22–24,27,30] Of the 11 studies included, 5 were conducted among inpatients (n = 166),[27–31] 4 were conducted in outpatient settings (n = 372),[21,23–25] and 2 were conducted in mixed samples (n = 192).[22,26] To avoid multiple hypothesis testing, we decided not to perform a subgroup analysis based on type of setting (inpatient or outpatient). However, we performed subgroup analysis stratified by phases of BD and medication use (antipsychotics and lithium) related to CRP levels that might be more relevant in this clinical context. Seven studies[22–26,29,30] provided data on medication status, although none of them reported CRP levels stratified by type of treatment. The majority of studies measured morning-drawn serum or plasma levels of hsCRP.[21,22,24–29] In fact, low heterogeneity was observed when pooling studies that used different CRP assays (CRP and hsCRP). Overall, the studies included in the meta-analysis reported excluding participants with clinically significant medical disorders, such as neurologic, infectious, and autoimmune diseases. Only 4 studies,[21,25,27,31] however, reported exclusion of individuals with a wide range of medical comorbidities, including metabolic and cardiovascular disorders. Six studies reported controlling for potential confounding factors of CRP levels, such as age, gender, and body mass index.[24,26–30] Three studies were adjusted for age, gender, and smoking[21,24,26]; and 2 of these also accounted for other relevant confounding factors (ie, race, educational level, use of antipsychotics, and alcohol/substance abuse).[24,26] Two studies, however, did not report clearly controlling for any potential confounders related to CRP levels.[25,31] A summary of included studies is shown in Table 1.

CRP Levels

There were significantly higher levels of CRP in BD patients compared with control subjects, with an overall effect size of 0.39 (SMD = 0.39; 95% CI, 0.24 to 0.55; $P < .0001$) (Figure 2). Overall, between-study heterogeneity was moderate ($I^2 = 47.6\%$; $P < .039$).

In the subgroup analysis based on different mood phases of BD, CRP levels were extracted from 7 studies that included 188 manic BD patients and 557 control subjects. Manic bipolar patients had significantly higher levels of CRP compared with control subjects, with a large effect size of 0.73 (SMD = 0.73; 95% CI, 0.44 to 1.02; $P < .001$) (Figure 3A).

There were 399 BD patients in euthymic phase and 735 control subjects from 6 studies for which CRP was measured. CRP levels were significantly increased in euthymic bipolar, albeit with a slight statistical difference (SMD = 0.26; 95% CI, 0.01 to 0.51; $P < .04$) (Figure 3B). Four studies measured CRP levels in depressed bipolar patients (n = 107) and control

Table 1. Characteristics of Studies Included in the Meta-Analysis

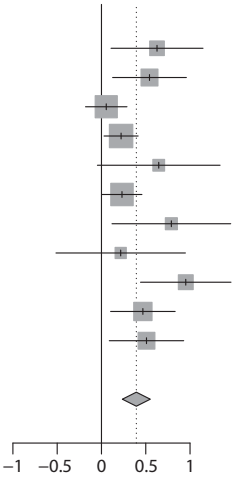
Study, Year Country	N BD/C[a]	Age, y, Mean (SD) BD/C[a]	Female, % BD/C[a]	Illness Duration, y/ Age-at-Onset,[c] y	Current Smoker, % BD/C[a]	BMI (kg/m^2), Mean (SD) BD/C[a]	CRP Assay	Antipsychotic Use,[c] % Any/Typical/ Atypical	Antidepressant Use,[c] %	Lithium Use,[c] %
Aksoy et al, 2010 Turkey[21]	30/30	32.8 (7.55)/ 34.2 (10.29)	60/56.7	NA/25.4 (7.55)	26.7/16.7[b]	NA/NA	hsCRP	NA/NA/NA	NA	NA
Cunha et al, 2008 Brazil[22]	80[d]/32	40.3 (11.26)/ 40.6 (12.12)	57.5/65.6	16.1 (11.90)/ 24.1 (11.97)	NA/NA	NA/NA	hsCRP	NA/NA/NA	63.7	NA
Dickerson et al, 2007 USA[23]	122/165	40.7 (12.34)/ 34.3 (12)	71.3/74	21.1 (12.6)/ 19.8 (9.2)	NA/NA	NA/NA	CRP	49/NA/49	NA	29
Dickerson et al, 2013 USA[24]	192/228	34.8 (13)/ 32.2 (11.4)	71/63	17.2 (12.9)/ 17.2 (8.9)	36/16	28.3 (7.8)/ 27.8 (6.8)	hsCRP	NA/NA/71	40	34
Fontoura et al, 2012 Brazil[25]	28/12	38.67 (7.22)/ 37 (10.39)	78.5/50	NA/NA	NA/NA	NA/NA	hsCRP	73/40/33	NA	83
Hope et al, 2011 Norway[26]	112/239	36.2 (12)/ 36 (10)	60/56	NA/NA	53/20[e]	25.7 (5)/ 24.3 (3)[f]	hsCRP	45/NA/NA	41	60
Huang et al, 2007 Taiwan[27]	13/31	36.9 (10.1)/ 30.5 (3.9)	38.4/42	NA/NA	NA/NA	25.9 (3.0)/ 22.6 (3.7)	hsCRP	NA/NA/NA	NA	NA
Hung et al, 2007 Taiwan[28]	15/14	23.8 (2.71)/ 23.8 (2.24)	NA/NA	NA/NA	NA/NA	22.2 (1.93)/ 22.7 (3)	hsCRP	NA/NA/NA	NA	NA
Tsai et al, 2012 Taiwan[29]	33/33	31.6 (6)/ 28.9 (3.9)	36.4/NA	NA/23.2 (7.0)	36.4/12.1	24.9 (3.9)/ 23.5 (4.4)	hsCRP	48.5/30.3/18.2	NA	33.3
Vuksan-Cusa et al, 2013 Croatia[30]	60/59	44.4 (15.8)/ 42.2 (8.7)	NA/NA	10.9 (9.47)/NA	NA/NA	27.3 (5.0)/ 24.9 (3.3)	CRP	100/NA/100	NA	NA
Wadee et al, 2002 South Africa[31]	45/45	32.7/31.2[g]	46.6/46.6	NA/NA	NA/NA	NA/NA	CRP	NA/NA/NA	NA	NA

[a]Patients without any psychiatric disorder.
[b]Total sample.
[c]Patients with bipolar disorder.
[d]30 euthymic patients, 30 manic patients, 20 depressed patients.
[e]n = 162 C nonsmokers (N = 239).
[f]n = 168 C nonsmokers (N = 239).
[g]SD values unavailable.
Abbreviations: BD = bipolar disorder, BMI = body mass index, C = control subjects, CRP = C-reactive protein, hsCRP = high-sensitivity C-reactive protein, NA = not available, SD = standard deviation.

Figure 2. Meta-Analysis of C-Reactive Protein Levels in Bipolar Disorder

Study	Bipolar Disorder Total	Mean	SD	Control Total	Mean	SD	SMD	95% CI	Weight
Aksoy et al, 2010[21]	30	3.74000	2.70000	30	2.4300	1.10000	0.63	0.11 to 1.15	6.5%
Cunha et al, 2008[22]	80	5.81000	8.99000	32	1.6000	2.24000	0.54	0.13 to 0.96	8.7%
Dickerson et al, 2007[23]	122	4.80000	6.97000	165	4.4000	7.70000	0.05	−0.18 to 0.29	14.9%
Dickerson et al, 2013[24]	192	1.32000	1.80000	228	0.9910	1.15000	0.22	0.03 to 0.41	16.7%
Fontoura et al, 2012[25]	28	0.35700	0.46000	12	0.1000	0.07000	0.65	−0.05 to 1.34	4.2%
Hope et al, 2011[26]	112	1.20000	2.50000	239	0.8000	1.20000	0.23	0.01 to 0.46	15.3%
Huang et al, 2007[27]	13	5.80000	9.60000	31	1.5000	1.80000	0.79	0.12 to 1.46	4.4%
Hung et al, 2007[28]	15	0.50000	0.70000	14	0.3820	0.23000	0.22	−0.51 to 0.95	3.8%
Tsai et al, 2012[29]	33	0.00358	0.00298	33	0.0014	0.00117	0.95	0.44 to 1.46	6.7%
Vuksan-Cusa et al, 2013[30]	60	4.24000	4.09000	59	2.5900	2.79000	0.47	0.10 to 0.83	10.2%
Wadee et al, 2002[31]	45	11.42200	18.24000	45	4.6780	3.67000	0.51	0.09 to 0.93	8.6%
Overall effect	**730**			**888**			**0.39**	**0.24 to 0.55**	**100%**

P = .0001
Heterogeneity: I^2 = 47.6%, tau^2 = 0.0291, *P* = .0394



Abbreviations: CI = confidence interval, SD = standard deviation, SMD = standardized mean difference.

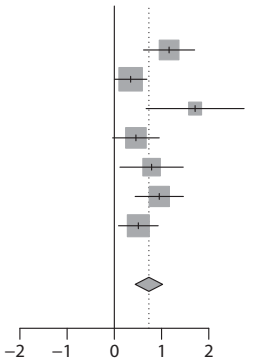
subjects (n = 297), and CRP levels did not differ significantly between such groups (SMD = 0.28; 95% CI, −0.17 to 0.73; *P* = .227) (Figure 3C). However, it is worth mentioning that the SMD was greater in BD depressed patients than in BD euthymic patients (0.28 vs 0.26, respectively), suggesting that the lack of statistical significance for CRP levels may be explained by the smaller sample size in the BD depression group. In the meta-regression to evaluate the influence of use of antipsychotic (any or atypical) or lithium on the CRP levels, no significant associations were identified (data not shown). Nevertheless, the small number of studies that provided data on use of antipsychotic or lithium has potentially limited the analysis. It is important to mention that larger effect sizes were observed in smaller studies with significant asymmetry

Figure 3. Subgroup Analysis of CRP Levels According to Phases of Bipolar Disorder

A. Mania

Study	Bipolar Disorder Total	Mean	SD	Control Total	Mean	SD	SMD	95% CI	Weight
Cunha et al, 2008[22]	30	11.81000	12.29000	32	1.6000	2.24000	1.16	0.62 to 1.70	14.2%
Dickerson et al, 2007[23]	41	7.20000	9.50000	165	4.4000	7.70000	0.35	0.00 to 0.69	20.2%
Fontoura et al, 2012[25]	9	0.80000	0.60000	12	0.1000	0.06920	1.71	0.67 to 2.75	6.1%
Hope et al, 2011[26]	17	1.40000	2.40000	239	0.8000	1.20000	0.46	−0.04 to 0.95	15.5%
Huang et al, 2007[27]	13	5.80000	9.60000	31	1.5000	1.80000	0.79	0.12 to 1.46	11.2%
Tsai et al, 2002[29]	33	0.00358	0.00298	33	0.0014	0.00117	0.95	0.44 to 1.46	15.0%
Wadee et al, 2002[31]	45	11.42200	18.24000	45	4.6780	3.67000	0.51	0.09 to 0.93	17.7%
Overall	**188**			**557**			**0.73**	**0.44 to 1.02**	**100%**

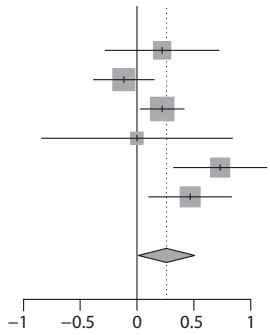
P < .001
Heterogeneity: I^2 = 53.8%, tau^2 = 0.0779, *P* = .0434



B. Euthymia

Study	Bipolar Disorder Total	Mean	SD	Control Total	Mean	SD	SMD	95% CI	Weight
Cunha et al, 2008[22]	30	2.14	2.580	32	1.600	2.2400	0.22	−0.28 to 0.72	13.3%
Dickerson et al, 2007[23]	81	3.60	4.900	165	4.400	7.7000	−0.12	−0.38 to 0.15	21.6%
Dickerson et al, 2013[24]	192	1.32	1.800	228	0.991	1.1500	0.22	0.03 to 0.41	24.5%
Fontoura et al, 2012[25]	10	0.10	0.126	12	0.100	0.0692	0.00	−0.84 to 0.84	6.7%
Hope et al, 2011[26]	26	2.10	4.400	239	0.800	1.2000	0.73	0.32 to 1.14	16.1%
Vuksan-Cusa et al, 2013[30]	60	4.24	4.090	59	2.590	2.7900	0.47	0.10 to 0.83	17.8%
Overall	**399**			**735**			**0.26**	**0.01 to 0.51**	**100%**

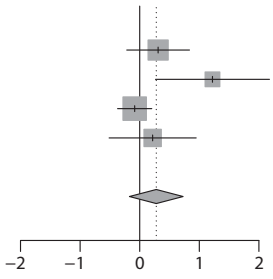
P < .04
Heterogeneity: I^2 = 64.6%, tau^2 = 0.0556, *P* = .0148



C. Depression

Study	Bipolar Disorder Total	Mean	SD	Control Total	Mean	SD	SMD	95% CI	Weight
Cunha et al, 2008[22]	25	2.3	2.23	32	1.600	2.2400	0.31	−0.22 to 0.84	27.5%
Fontoura et al, 2012[25]	9	0.2	0.09	12	0.100	0.0692	1.22	0.26 to 2.18	14.8%
Hope et al, 2011[26]	58	0.7	1.10	239	0.800	1.2000	−0.08	−0.37 to 0.20	37.3%
Hung et al, 2007[28]	15	0.5	0.70	14	0.382	0.2300	0.22	−0.51 to 0.95	20.4%
Overall	**107**			**297**			**0.28**	**−0.17 to 0.73**	**100%**

P = .227
Heterogeneity: I^2 = 60.3%, tau^2 = 0.1201, *P* = .0559



Abbreviations: CI = confidence interval, SD = standard deviation, SMD = standardized mean difference.

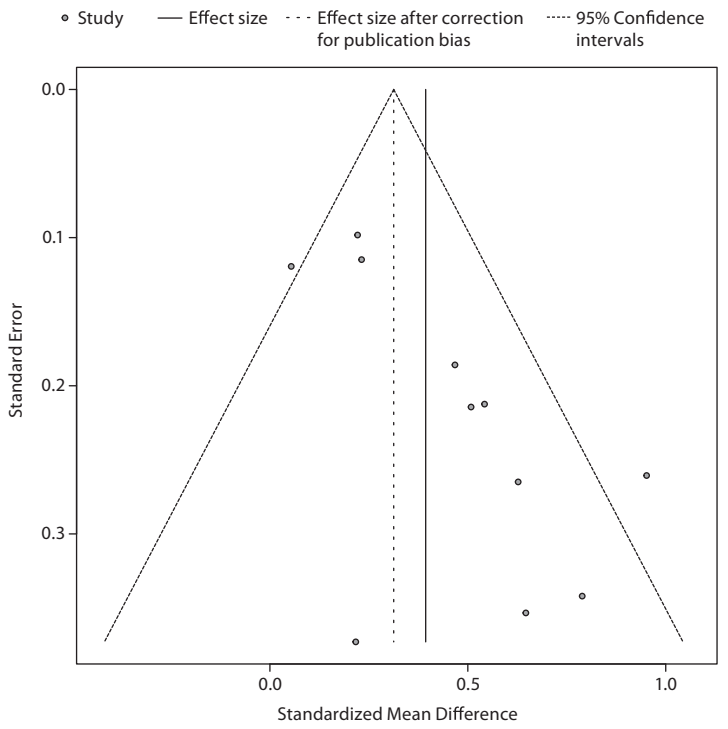
in the funnel plot test (*P* < .006), thus indicating a high probability of publication bias (Figure 4). After adjustment for publication bias, the association between elevated CRP levels in BD patients remained statistically significant with only a slight reduction in the effect size (SMD = 0.28; 95% CI, 0.11 to 0.44; *P* = .001), which reinforces the study findings.

DISCUSSION

We found a significant elevation in CRP levels in patients with BD compared to control subjects, with a small-to-moderate effect size of 0.39. This meta-analytic finding strengthens the evidence that BD is associated with inflammation. However, the mechanisms underlying the relationship between BD and inflammation are still unknown.[20] Consistent evidence has demonstrated elevated levels of cytokines, including IL-1β, IL-6, and TNF-α, in the serum of BD patients.[3,4] As these proinflammatory cytokines are known inducers of CRP,[1] it is reasonable to hypothesize that CRP levels would also be increased in BD patients. Three studies included in this meta-analysis simultaneously measured blood levels of CRP and cytokines.[26,28,29] Altogether, these data reinforce the hypothesis of peripheral inflammation in BD.[51]

Furthermore, a recent study reported the involvement of central inflammation in BD by demonstrating that markers of neuroinflammation are significantly increased in postmortem frontal cortex from BD patients.[52] In particular, this study found an important activation of the IL-1 receptor cascade,[52] which is involved in several regulatory process of inflammation.[52] Importantly, CRP itself seems to play a causal role in neuroinflammation. Elevated levels of CRP may induce a disruptive effect in the blood-brain-barrier,

Figure 4. Publication Bias Assessment for Studies of C-Reactive Protein Levels in Bipolar Disorder



as shown in animals.[53] This barrier-disrupting effect of CRP may increase the permeability of the blood-brain-barrier, making the brain susceptible to the effects of proinflammatory cytokines and/or autoantibodies, both of which are associated with BD.[2] Although the interrelationship between different inflammatory markers is complex, level of CRP may be a marker of inflammation to be considered in everyday practice in BD. Since it is a relatively low-cost biomarker and widely available in clinical settings, measurement of CRP levels might be an easy, cost-effective way to obtain information about the inflammatory pattern in BD patients, and, indirectly, on alterations in proinflammatory cytokines, which are known to modulate CRP levels. Further research pooling CRP with other markers of inflammation is needed to better elucidate the relationship between these markers across the different phases of the disease.

In BD, immune dysregulation has been associated with severity of symptoms and mood episodes. Acutely ill bipolar patients have an activation of immune response accompanied by increased levels of inflammatory markers, including proinflammatory cytokines[54] and hsCRP,[22] particularly during manic episodes. Our meta-analysis adds to the literature that shows that manic BD patients have significantly higher levels of CRP than control subjects (SMD = 0.73; 95% CI, 0.44 to 1.02; $P < .001$). Of note, a recent study demonstrated an association between elevated CRP and manic symptoms in patients having a depressive disorder.[55] Additionally, these authors, in prospective analyses, found that CRP was an important risk factor for the onset of manic symptoms in depressed men during 2 years of follow-up.[55] A proinflammatory state, thus, seems to be strongly related to manic symptoms, contributing to the idea that CRP could be a marker of state in BD. Although explanatory mechanisms of this relationship are still unclear, one possible mechanism might be linked to sleep dysfunction, which is often present in manic[56] BD patients, and is known to be associated with elevated cytokines and CRP levels.[57]

A very interesting finding in our study was also that CRP levels were significantly elevated in euthymic BD patients compared to controls, indicating there is an inflammatory component in nonacutely ill BD patients. Our meta-analysis, therefore, reinforces evidence showing that activation of the inflammatory response persists after remission,[58] suggesting that CRP could also be a trait marker in BD. However, it is important to bear in mind that many studies included in our subgroup analysis used different criteria to characterize the different mood phases of BD, raising the idea that some BD patients categorized as euthymic had subsyndromal symptoms, which could also influence CRP levels. However, the small number of studies providing data on subsyndromal conditions did not allow more in-depth subgroup analysis. Further studies stratifying patients by clinical status (including subsyndromal conditions) are needed to better evaluate the potential impact of mood symptoms on CRP levels.

Inflammation is thought to underlie the pathogenesis of several chronic diseases, such as coronary artery disease, diabetes mellitus, and obesity,[59] that are highly prevalent in patients with BD.[16] Strong evidence has shown that CRP is an independent predictor of cardiovascular disease,[18] the leading cause of excess mortality in BD patients.[19] In addition, CRP levels are associated with increased risk of cardiovascular disease and diabetes among subjects with metabolic syndrome.[60] A recent meta-analysis found that BD patients had almost twice the risk of developing metabolic syndrome compared to age- and gender-matched healthy controls (OR = 1.98; 95% CI, 1.74 to 2.25; $P < .0001$), and approximately one-half of these patients had at least 1 component of metabolic syndrome, including abdominal obesity, hypertension, fasting hyperglycemia, or an abnormal lipid profile.[61] Four studies included in our meta-analysis reported significant associations between hsCRP levels and metabolic syndrome components. In a study by Vuksan-Cusa et al,[30] the prevalence of metabolic syndrome was 31% in the BD group of patients (versus 15% in the control group), and hsCRP levels were significantly positively correlated with waist circumference and diastolic blood pressure in the euthymic BD patients. In the 3 other studies, elevated hsCRP levels were significantly associated with higher body mass index in manic[27,29] and euthymic[24] BD patients compared to control subjects. Because we

had limited metabolic syndrome data on CRP levels, we were not able to draw any conclusions on the association between levels of CRP and cardiometabolic risk in this population. Although metabolic syndrome components and cardiovascular diseases have been strongly associated with persistent low-grade inflammation, reflected by increased CRP levels,[62] the mechanisms are still unknown. Visceral adiposity triggers inflammatory cascades that in turn yield increased secretion of proinflammatory factors, including IL-1β, IL-6, and TNF-α, and appear to be a potential mechanism linking abdominal obesity and cardiovascular disease.[62] In addition, unhealthy diet and physical inactivity also contribute to the accumulation of abdominal obesity predisposing subjects to chronic conditions, such as mood disorders and cardiometabolic diseases. In contrast, growing literature has shown that physical exercise[63] and dietary habits,[64] both related to significant decreases in CRP levels, are associated with improvement in depression-like behavior and depressive symptoms.[63,65] Therefore, a substantial overlap seems to exist between psycho-immuno-endocrinologic mechanisms in BD and cardiometabolic illnesses, as well as between mediators of the systemic toxicity and biological changes (eg, dysregulation of the immune-inflammatory response) observed in BD,[66] suggesting that shared psycho-immuno-endocrinologic mechanisms may exist between these diseases. In summary, cardiometabolic risk is a key factor in the long-term health of BD patients, and CRP levels may provide more objective information on the metabolic-inflammatory status of a bipolar patient. Moreover, abdominal obesity is a reversible condition, and simple measurements (eg, waist circumference) associated with CRP levels may help psychiatrists to motivate their BD patients to improve their lifestyles (ie, lose weight and exercise), thus reducing cardiovascular disease risk. Measurement of CRP levels associated with parameters commonly used in clinical care (eg, blood pressure and lipid and glucose levels) may be a useful biomarker in BD patients at risk for cardiovascular disease, as well as in individuals who are otherwise healthy but suffer from BD.

Despite studies that have suggested that antipsychotics and lithium may exert different effects on CRP levels,[6,33,54] we could not draw any conclusions in this meta-analysis as to the association between medication use and CRP, as the available information was limited. Given that increased CRP levels reflect the presence of inflammation, therapeutic regimens to modulate inflammatory response, reducing CRP levels,[67] may be useful in the treatment of BD patients. In keeping with this view, randomized, double-blind, placebo-controlled studies have reported substantial antidepressant effects following adjunctive treatment with celecoxib (an anti-inflammatory drug) in individuals with BD[68] and depression.[69] Remarkably, recent findings suggest that patients with high inflammatory activity may respond less to antidepressants and better to anti-inflammatory medication.[70] Moreover, there is some evidence suggesting beneficial effects for aspirin in mood disorders, as well as in schizophrenia.[71] Disturbances in inflammation, however, are prominent only in a subset of subjects with BD. Recently, a study evaluated the effect of infliximab, a TNF-α antagonist currently used in the treatment of rheumatic and inflammatory bowel diseases,[72] in patients with treatment-resistant depression. Infliximab was superior to placebo in mitigating depressive symptoms only in individuals who exhibited elevated inflammation (hsCRP > 5 mg/L) at baseline.[70] In this vein, measurement of CRP levels in BD patients might be useful to stratify those patients who may respond to a specific immune or anti-inflammatory treatment, reinforcing the idea of CRP as a potential biomarker in BD. This hypothesis is still in its infancy, and studies are lacking.

To the best of our knowledge, this is the first, formal meta-analysis on CRP levels in BD. Our search, focusing on quality and stricter inclusion criteria, potentially contributed to limiting the heterogeneity of results. Given the large sample size of BD patients with measured blood CRP levels (n = 730), our analyses had enough power to find case-control dissimilarities, as well as to estimate a precise effect size. Another potential strength of our study was its 2 series of subgroup analyses (phases of disease and use of antipsychotic or lithium), which reduced heterogeneity in most cases. In addition, most of the studies included used hsCRP assay to measure CRP concentrations. Currently, hsCRP assay is the standard in clinical practice, and it has the ability to measure CRP levels accurately (ie, lower detection limits of 0.1 mg/L), which may be useful to better discriminate states of low-grade inflammation.[60]

Nevertheless, our findings must be interpreted in light of certain limitations. First, CRP alterations in BD do not necessarily reflect an underlying pathophysiologic process and may be secondary to alterations in biological pathways or presence of comorbidities. Second, we could not account for several confounding factors (body mass index, medical comorbidities, alcohol/drug abuse, or smoking) in the meta-analyses. Although all of these factors are known to influence CRP levels,[73] only a few (age, body mass index, smoking, and absence of inflammatory diseases) were controlled in most of the studies. Also, we cannot rule out that other confounding/moderator variables not examined in the included studies, such as health-related behaviors (ie, diet and physical activity),[73] chronic diseases,[17] psychological stress,[74] and sleep disturbances,[56] may also explain the association between elevated levels of CRP and BD. Third, in addition to variations due to age, gender, and lifestyle factors, CRP may also vary across different geographies and ethnic groups (eg, populations of African descent have higher average CRP levels than European-descended populations).[75] However, the available data were too limited to draw meta-analytic conclusions on ethnicity and/or geographical differences associated with CRP levels in BD patients. Taking into account the wide range of potential confounding factors related to CRP levels in BD, these issues need to be addressed in more detail in future studies given their clinical importance. Fourth, because our findings were based on cross-sectional rather than on randomized

or longitudinal data, the directionality of the association between CRP and BD cannot be clearly inferred. It is possible that inflammation, which is known to be associated with increased levels of CRP, might lead to BD. In contrast, BD symptoms, acting as a stimulus for inflammatory response, might predict CRP levels. Fifth, in some cases, heterogeneity was not reduced after subgroup analyses, suggesting that other factors such as clinical features (eg, subsyndromal conditions) or the differences in assays might have yielded heterogeneity. Sixth, there were often missing data on duration of illness and age-at-onset. Importantly, illness duration may reflect the duration of medication exposure and is related to both age-at-onset of BD and patient's age. Finally, the studies available for this meta-analysis included individuals with BD under various therapeutic regimens and did not provide stratified data on concomitant medication (except for antipsychotics, antidepressants, or lithium), also known to influence CRP levels. It is worth mentioning that conventional mood stabilizers (eg, lithium, antipsychotics, and anticonvulsants) act in varying capacities to down-regulate the production of proinflammatory mRNA and protein gene expression that might alter levels of cytokines and CRP.[76]

CONCLUSIONS

Our meta-analysis supports the association between BD and increased levels of CRP, which is a marker of systemic (low-grade) inflammation, as well as an established risk factor for cardiovascular disease. These findings could be clinically relevant, if tested and confirmed by future studies, also combining measurements of CRP levels with other inflammatory biomarkers (eg, cytokines) to obtain a more specific parameter of systemic inflammation in BD patients. Considering that inflammation appears to be implicated in the pathophysiology of BD,[7,20] healthy lifestyle interventions (smoking cessation, dietary measures, and physical activity), which appear to reduce levels of proinflammatory markers (eg, CRP),[73] might help to assuage severity of BD. Therefore, CRP measurement in individuals with BD should be considered as a possible strategy to motivate those patients toward healthy body-brain interventions.

Drug names: celecoxib (Celebrex), lithium (Lithobid and others).

Author affiliations: National Institute for Translational Medicine, Hospital de Clínicas de Porto Alegre, Molecular Psychiatry Laboratory, Graduate Program in Medicine, Department of Psychiatry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil (Drs Dargél and Kapczinski); Université Paris-Est, INSERM, Psychiatrie Génétique, Créteil, France (Drs Dargél, Godin, and Leboyer); Hôpital H. Mondor, Pôle de Psychiatrie, Créteil, France (Drs Dargél and Leboyer); FondaMental Fondation, Fondation de Coopération Scientifique, Groupe Hospitalier Mondor, Créteil, France (Drs Dargél and Leboyer); UPMC Université Paris and INSERM, Paris, France (Dr Godin); and Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Dr Kupfer).

Potential conflicts of interest: **Dr Dargél** and **Ms Godin** report no potential conflicts of interest. **Dr Kapczinski** has received grant/research support from AstraZeneca, Eli Lilly, Janssen-Cilag, Servier, Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), NARSAD, and the Stanley Medical Research Institute; has been a member of the speaker's board for AstraZeneca, Eli Lilly, Jansen-Cilag, and Servier; and has served as a consultant for Servier. **Dr Kupfer** is a consultant for the American Psychiatric Association (as Chair of the *DSM-5* Task Force) and holds joint ownership of copyright for the Pittsburgh Sleep Quality Index (PSQI). He and his spouse, Dr Ellen Frank, are stockholders in Psychiatric Assessments, Inc. Dr Frank also has the following conflicts of interest: received royalties from the American Psychological Association and Guilford Press; is a member of the advisory board of Servier International; is an editorial consultant for the American Psychiatric Press; and has received honoraria from Lundbeck. **Dr Leboyer** has received grant/research support from Sanofi, Roche, Agence Nationale de la Recherche (ANR), and the Stanley Medical Research Institute.

Funding/support: This work was supported by the Institut National de la Santé et de la Recherche Médicale (INSERM), Assistance Publique des Hôpitaux de Paris (AP-HP), Fondation FondaMental (RTRS Santé Mentale), and by the Investissements d'Avenir Program of the Agence Nationale pour la Recherche (ANR-11-IDEX-0004-02). Dr Dargél is supported by scholarship from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil, and a grant from Fondation FondaMental, France. Mrs Godin is supported by grants from INSERM U943 and Fondation FondaMental, France.

Role of sponsors: The funding agencies had no role in the conduct or publication of the study.

Acknowledgments: The authors thank Ms Luísia Alves, BA at Federal University of Rio Grande do Sul, Porto Alegre, Brazil, for her technical support in formatting this manuscript. Ms Alves reported no conflict of interest. We are also indebted to the reviewers for many excellent suggestions and comments.

REFERENCES

1. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med*. 1999;340(6):448–454.
2. Benros ME, Waltoft BL, Nordentoft M, et al. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. *JAMA Psychiatry*. 2013;70(8):812–820.
3. Modabbernia A, Taslimi S, Brietzke E, et al. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. *Biol Psychiatry*. 2013;74(1):15–25.
4. Munkholm K, Vinberg M, Vedel Kessing L. Cytokines in bipolar disorder: a systematic review and meta-analysis. *J Affect Disord*. 2013;144(1–2):16–27.
5. Dantzer R, O'Connor JC, Freund GG, et al. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9(1):46–56.
6. Maes M, Delange J, Ranjan R, et al. Acute phase proteins in schizophrenia, mania and major depression: modulation by psychotropic drugs. *Psychiatry Res*. 1997;66(1):1–11.
7. Leboyer M, Soreca I, Scott J, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? *J Affect Disord*. 2012;141(1):1–10.
8. Windgassen EB, Funtowicz L, Lunsford TN, et al. C-reactive protein and high-sensitivity C-reactive protein: an update for clinicians. *Postgrad Med*. 2011;123(1):114–119.
9. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest*. 2003;111(12):1805–1812.
10. Kundu JK, Surh Y-J. Inflammation: gearing the journey to cancer. *Mutat Res*. 2008;659(1–2):15–30.
11. Brown AS, Sourander A, Hinkka-Yli-Salomäki S, et al. Elevated maternal C-reactive protein and autism in a national birth cohort. *Mol Psychiatry*. 2014;19(2):259–264.
12. Wium-Andersen MK, Orsted DD, Nordestgaard BG. Association between elevated plasma fibrinogen and psychological distress, and depression in 73,367 individuals from the general population. *Mol Psychiatry*. 2013;18(8):854–855.
13. Wium-Andersen MK, Ørsted DD, Nordestgaard BG. Elevated C-reactive protein associated with late- and very-late-onset schizophrenia in the general population: a prospective study. *Schizophr Bull*. 2014;40(5):1117–1127.
14. Vogelzangs N, Beekman ATF, de Jonge P, et al. Anxiety disorders and inflammation in a large adult cohort. *Transl Psychiatr*. 2013;3(4):e249.
15. Altamura AC, Serati M, Albano A, et al. An epidemiologic and clinical overview of medical and psychopathological comorbidities in major psychoses. *Eur Arch Psychiatry Clin Neurosci*. 2011;261(7):489–508.
16. Magalhães PV, Kapczinski F, Nierenberg AA, et al. Illness burden and medical comorbidity in the Systematic Treatment Enhancement Program for Bipolar Disorder. *Acta Psychiatr Scand*. 2012;125(4):303–308.
17. Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. *Crit Rev Clin Lab Sci*. 2011;48(4):155–170.
18. Kaptoge S, Di Angelantonio E, Lowe G, et al. Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet*. 2010;375(9709):132–140.
19. Kupfer DJ. The increasing medical burden in bipolar disorder. *JAMA*. 2005;293(20):2528–2530.
20. Goldstein BI, Kemp DE, Soczynska JK, et al. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. *J Clin Psychiatry*. 2009;70(8):1078–1090.
21. Aksoy SN, Saygili EI, Bulbul F, et al. Myeloperoxidase enzyme levels and oxidative stress in bipolar disorders. *Afr J Biotechnol*. 2010;9:3318–3323.

22. Cunha ÂB, Andreazza AC, Gomes FA, et al. Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. *Eur Arch Psychiatry Clin Neurosci*. 2008;258(5):300–304.
23. Dickerson F, Stallings C, Origoni A, et al. Elevated serum levels of C-reactive protein are associated with mania symptoms in outpatients with bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(4):952–955.
24. Dickerson F, Stallings C, Origoni A, et al. C-reactive protein is elevated in schizophrenia. *Schizophr Res*. 2013;143(1):198–202.
25. Fontoura PC, Pinto VLM, Matsuura C, et al. Defective nitric oxide-cyclic guanosine monophosphate signaling in patients with bipolar disorder: a potential role for platelet dysfunction. *Psychosom Med*. 2012;74(8):873–877.
26. Hope S, Dieset I, Agartz I, et al. Affective symptoms are associated with markers of inflammation and immune activation in bipolar disorders but not in schizophrenia. *J Psychiatr Res*. 2011;45(12):1608–1616.
27. Huang T-L, Lin F-C. High-sensitivity C-reactive protein levels in patients with major depressive disorder and bipolar mania. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(2):370–372.
28. Hung Y-J, Hsieh C-H, Chen Y-J, et al. Insulin sensitivity, proinflammatory markers and adiponectin in young males with different subtypes of depressive disorder. *Clin Endocrinol (Oxf)*. 2007;67(5):784–789.
29. Tsai S-Y, Chung K-H, Wu J-Y, et al. Inflammatory markers and their relationships with leptin and insulin from acute mania to full remission in bipolar disorder. *J Affect Disord*. 2012;136(1–2):110–116.
30. Vuksan-Cusa B, Sagud M, Jakovljevic M, et al. Association between C-reactive protein and homocysteine with the subcomponents of metabolic syndrome in stable patients with bipolar disorder and schizophrenia. *Nord J Psychiatry*. 2013;67(5):320–325.
31. Wadee AA, Kuschke RH, Wood LA, et al. Serological observations in patients suffering from acute manic episodes. *Hum Psychopharmacol*. 2002;17(4):175–179.
32. De Berardis D, Conti CM, Campanella D, et al. Evaluation of C-reactive protein and total serum cholesterol in adult patients with bipolar disorder. *Int J Immunopathol Pharmacol*. 2008;21(2):319–324.
33. Dieset I, Hope S, Ueland T, et al. Cardiovascular risk factors during second generation antipsychotic treatment are associated with increased C-reactive protein. *Schizophr Res*. 2012;140(1–3):169–174.
34. Su S-C, Sun M-T, Wen M-J, et al. Brain-derived neurotrophic factor, adiponectin, and proinflammatory markers in various subtypes of depression in young men. *Int J Psychiatry Med*. 2011;42(3):211–226.
35. von Elm E, Altman DG, Egger M, et al; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Bull World Health Organ*. 2007;85(11):867–872.
36. Martínez-Arán A, Vieta E, Colom F, et al. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. *Bipolar Disord*. 2004;6(3):224–232.
37. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–188.
38. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.
39. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, et al. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods*. 2006;11(2):193–206.
40. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.
41. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455–463.
42. The R Development Core Team. R: a language and environment for statistical computing: reference index. Vienna, Austria: R Foundation for Statistical Computing; 2013. http://web.mit.edu/r_v3.0.1/fullrefman.pdf. Accessed October 7, 2014.
43. Vuksan-Cusa B, Sagud M, Jakovljević M. C-reactive protein and metabolic syndrome in patients with bipolar disorder compared to patients with schizophrenia. *Psychiatr Danub*. 2010;22(2):275–277.
44. Legros S, Mendlewicz J, Wybran J. Immunoglobulins, autoantibodies and other serum protein fractions in psychiatric disorders. *Eur Arch Psychiatry Neurol Sci*. 1985;235(1):9–11.
45. Politi P, Brondino N, Emanuele E. Increased proapoptotic serum activity in patients with chronic mood disorders. *Arch Med Res*. 2008;39(2):242–245.
46. Hornig M, Goodman DB, Kamoun M, et al. Positive and negative acute phase proteins in affective subtypes. *J Affect Disord*. 1998;49(1):9–18.
47. Hope S, Melle I, Aukrust P, et al. Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor. *Bipolar Disord*. 2009;11(7):726–734.
48. Hope S, Melle I, Aukrust P, et al. Osteoprotegerin levels in patients with severe mental disorders. *J Psychiatry Neurosci*. 2010;35(5):304–310.
49. Dickerson F, Stallings C, Origoni A, et al. Elevated C-reactive protein and cognitive deficits in individuals with bipolar disorder. *J Affect Disord*. 2013;150(2):456–459.
50. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association 1994.
51. Kapczinski F, Dal-Pizzol F, Teixeira AL, et al. A systemic toxicity index developed to assess peripheral changes in mood episodes. *Mol Psychiatry*. 2010;15(8):784–786.
52. Rao JS, Harry GJ, Rapoport SI, et al. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. *Mol Psychiatry*. 2010;15(4):384–392.
53. Kuhlmann CRW, Librizzi L, Closhen D, et al. Mechanisms of C-reactive protein-induced blood-brain barrier disruption. *Stroke*. 2009;40(4):1458–1466.
54. Kim Y-K, Jung H-G, Myint A-M, et al. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. *J Affect Disord*. 2007;104(1–3):91–95.
55. Becking K, Boschloo L, Vogelzangs N, et al. The association between immune activation and manic symptoms in patients with a depressive disorder. *Transl Psychiatr*. 2013;3(10):e314.
56. Harvey AG. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. *Am J Psychiatry*. 2008;165(7):820–829.
57. Mullington JM, Haack M, Toth M, et al. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. *Prog Cardiovasc Dis*. 2009;51(4):294–302.
58. Potvin S, Stip E, Sepehry AA, et al. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. *Biol Psychiatry*. 2008;63(8):801–808.
59. Couzin-Frankel J. Inflammation bares a dark side. *Science*. 2010;330(6011):1621.
60. Musunuru K, Kral BG, Blumenthal RS, et al. The use of high-sensitivity assays for C-reactive protein in clinical practice. *Nat Clin Pract Cardiovasc Med*. 2008;5(10):621–635.
61. Vancampfort D, Vansteelandt K, Correll CU, et al. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. *Am J Psychiatry*. 2013;170(3):265–274.
62. Brooks GC, Blaha MJ, Blumenthal RS. Relation of C-reactive protein to abdominal adiposity. *Am J Cardiol*. 2010;106(1):56–61.
63. Eyre HA, Papps E, Baune BT. Treating depression and depression-like behavior with physical activity: an immune perspective. *Front Psychiatry*. 2013;4:3.
64. King DE, Egan BM, Geesey ME. Relation of dietary fat and fiber to elevation of C-reactive protein. *Am J Cardiol*. 2003;92(11):1335–1339.
65. Sanchez-Villegas A, Martínez-González MA. Diet, a new target to prevent depression? *BMC Med*. 2013;11(1):3.
66. McIntyre RS, Rasgon NL, Kemp DE, et al. Metabolic syndrome and major depressive disorder: co-occurrence and pathophysiologic overlap. *Curr Diab Rep*. 2009;9(1):51–59.
67. Azar M, Valentin E, Badaoui G, et al. Comparison of the effects of combination atorvastatin (40 mg) + ezetimibe (10 mg) versus atorvastatin (40 mg) alone on secretory phospholipase A2 activity in patients with stable coronary artery disease or coronary artery disease equivalent. *Am J Cardiol*. 2011;107(11):1571–1574.
68. Nery FG, Monkul ES, Hatch JP, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. *Hum Psychopharmacol*. 2008;23(2):87–94.
69. Müller N, Schwarz MJ, Dehning S, et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol Psychiatry*. 2006;11(7):680–684.
70. Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry*. 2013;70(1):31–41.
71. Fond G, Hamdani N, Kapczinski F, et al. Effectiveness and tolerance of anti-inflammatory drugs' add-on therapy in major mental disorders: a systematic qualitative review. *Acta Psychiatr Scand*. 2014;129(3):163–179.
72. Ford AC, Sandborn WJ, Khan KJ, et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106(4):644–659, quiz 660.
73. O'Connor MF, Bower JE, Cho HJ, et al. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. *Brain Behav Immun*. 2009;23(7):887–897.
74. Heath NM, Chesney SA, Gerhart JI, et al. Interpersonal violence, PTSD, and inflammation: potential psychogenic pathways to higher C-reactive protein levels. *Cytokine*. 2013;63(2):172–178.
75. Pankow JS, Folsom AR, Cushman M, et al. Familial and genetic determinants of systemic markers of inflammation: the NHLBI family heart study. *Atherosclerosis*. 2001;154(3):681–689.
76. Haarman BC, Riemersma-Van der Lek RF, Burger H, et al. Relationship between clinical features and inflammation-related monocyte gene expression in bipolar disorder—towards a better understanding of psychoimmunological interactions. *Bipolar Disord*. 2014;16(2):137–150.

6.2 Artigo 2: Biomarkers in illness progression in bipolar disorder

Capítulo de livro aceito para publicação

Dargél, Aroldo A. ; Leboyer, Marion. Biomarkers in illness progression in bipolar disorder. In: Kapczinski, Flávio ; Vieta, Eduardo ; Magalhães, Pedro ; Berk, Michael. **Neuroprogression and Staging in Bipolar Disorder.** Oxford: Oxford University Press, 2015. P. 175-196.

"DUNN, Lauren" <lauren.dunn@oup.com> August 19, 2014 5:57 PM
To: "aroldodargel@gmail.com" <aroldodargel@gmail.com>, "marion.leboyer@inserm.fr" <marion.leboyer@inserm.fr>
Chapter contribution to Neuroprogression and Staging in Bipolar Disorder (Ch10)

1 Attachment, 184 KB

Dear Aroldo A. Dargél and Marion Leboyer,

Many thanks for submitting your chapter on 'Biomarkers in illness progression in bipolar disorder' to be included in *Neuroprogression and Staging in Bipolar Disorder*, edited by Flavio Kápczinski, Eduard Vieta, Pedro Magalhães and Michael Berk.

I have a couple of queries relating to your chapter, which I'm hoping you can help with:

- Please could you provide an Abstract and Keywords. The Abstract should be roughly 250 words and briefly outline the content of your chapter, and please provide 5-10 keywords.
- Please insert a figure placeholder for Figure 10.1 to specify where it should appear in the chapter text.
- Could you confirm that no permission is needed for the figure? Permission is only needed if it has been reproduced or adapted from an existing figure.

I would appreciate it if you could get back to me by 5th September, and I have attached a copy of your chapter for your reference.

Thanks and best wishes,
Lauren

Lauren Dunn
Assistant Commissioning Editor, Medicine
Neurology, Neurosurgery, Psychiatry and Oxford Medical Libraries

Oxford University Press
Great Clarendon Street
Oxford OX2 6DP
UK

e: lauren.dunn@oup.com
t: +44 (0) 1865 354736

Biomarkers in illness progression in bipolar disorder

Aroldo A. Dargél, MD [1,2,3,4,] and Marion Leboyer MD, PhD [2,3,4]

Authors'Affiliations

[1] Laboratório de Psiquiatria Molecular, Instituto Nacional de Ciência e Tecnologia – Translacional em Medicina (INCT), Hospital de Clínicas de Porto Alegre, Programa de Pós-Graduação em Psiquiatria, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
[2] Université Paris-Est, INSERM U955, Psychiatrie Génétique – Eq. 15, F-94000, Créteil, France
[3] AP-HP, Hôpital H. Mondor – A. Chenevier, Pôle de Psychiatrie, F-94000, Créteil, France
[4] Fondation FondaMental, Fondation de Coopération Scientifique, F-94000, Créteil, France

ABSTRACT

Biomarker is an indicator of biological processes (normal or pathogenic) or pharmacologic responses to a therapeutic intervention, which can be measured accurately and reproducibly. In medicine, biomarkers are used to support the presence of a specific disease (diagnostic biomarker), to monitor illness progression (prognostic biomarkers), to measure therapeutic interventions (treatment biomarkers), and to predict the onset of future disease (predictive biomarkers). In psychiatry however, biomarkers with established clinical utility for mental illnesses such as bipolar disorder (BD) are still lacking. With an estimated worldwide prevalence of 2.4%, BD is associated with a wide range of detrimental effects on patient's health and functioning, and is among the top 20 causes of disability worldwide. Currently, BD diagnosis is essentially based on patient interviews and self-report questionnaires, lacking objectivity and biological validation. Growing evidence has shown the frequency of symptomatic recurrence (i.e. mood episodes) have a negative impact in the illness progression, with marked cognitive and functional impairments, lower pharmacological and psychological treatment responsiveness and higher rates of medical comorbidities such as cardiometabolic and neurological diseases. Neuroprogression is a multifactorial, dynamic process, including biological pathways implicated in inflammation, oxidative stress and neuroprotection. Therefore, the aim of this chapter is to summarize the extant literature regarding the relevance of peripheral biomarkers such as neurotrophins, oxidative stress and proinflammatory markers in illness progression in BD. In addition, we outline some future perspectives through which peripheral biomarkers may contribute to better understanding the pathophysiology of BD and to design novel therapeutic strategies.

Keywords: bipolar disorder – biomarkers – illness progression – inflammation – oxidative stress - neurotrophins

INTRODUCTION

Biomarker is an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention, which can be measured accurately and reproducibly.[1] In medicine, biomarkers are used to support the presence of a specific disease (diagnostic biomarker), to monitor illness progression (prognostic biomarkers), to measure therapeutic interventions (treatment biomarkers), and to predict the onset of future disease (predictive biomarkers).[1] Biomarker development is a multi-step process in which improvements in clinical care are evaluated at later stages. In oncology, for example, these phases have been outline as (1) preclinical; (2) assay validation in independent populations; (3) capacity of the biomarker to detect preclinical disease; (4) assessment of effects on patient management and outcomes; (5) biomarker cost-effectiveness.[2] In psychiatry however, biomarkers with established clinical utility for mental illnesses such as bipolar disorder (BD) are still lacking.

Currently, BD diagnosis is essentially based on patient interviews and self-report questionnaires, lacking objectivity and biological validation.[3] With an estimated worldwide prevalence of 2.4%,[4] BD is associated with a wide range of detrimental effects on patient's health and functioning, and is among the top 20 causes of disability worldwide.[5] Growing evidence has shown the frequency of symptomatic recurrence (i.e. mood episodes) have a negative impact in the illness progression, with marked cognitive and functional impairments, lower pharmacological and psychological treatment responsiveness and higher rates of medical comorbidities such as cardiometabolic and neurological diseases.[6] Furthermore, epigenetic mechanisms environmentally mediated could interact with genetic mechanisms that each mediates earlier onset and/or a more severe course of illness.[7]

The notion of neuroprogression in BD is a pathological brain rewiring process that appears to take place when clinical and cognitive deterioration are observed as a result of illness progression.[8] The end-point of such neuroprogressive changes would be tissue injury, structural changes and functional sequelae that are the neural substrate of mood regulation, that has the potential to increase the risk of further recurrence and reduce the potential of treatment response.[8,9] The neuroprogression is a multifactorial, dynamic process, including biological pathways implicated in inflammation, oxidative stress and neuroprotection.[10]

Previous reviews provide a detailed perspective regarding the current state of biomarkers in BD.[3,11] Therefore, the aim of this chapter is to summarize the extant literature regarding the relevance of peripheral biomarkers such as neurotrophins, oxidative stress and proinflammatory markers in illness progression in BD. In addition, we outline some future perspectives through which peripheral biomarkers may contribute to better understanding the pathophysiology of BD and to design novel therapeutic strategies.

PERIPHERAL BIOMARKERS IN BIPOLAR DISORDER

Neurotrophic factors

Neurotrophins are proteins with a crucial role in neuronal development, plasticity and connectivity.[12,13] Growing evidence has demonstrated that patients with BD have abnormal blood levels of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF),[14,15] neurotrophin-3 (NT-3), neurotrophin 4/5 (NT-4/5), glial cell-derived neurotrophic factor (GDNF), and nerve growth factor (NGF).[6,8]

BDNF is a neurotrophin widely distributed in the nervous system, acting as a key-regulator of neuronal growth and synaptic activity/plasticity.[12,13] Preclinical studies reported correlations between serum BDNF levels and BDNF expression in cortical and hippocampal areas,[13,16] which are implicated in regulation of mood and emotion.[14-16] Peripherally, BDNF is expressed at relatively high levels in vascular endothelial cells, lymphocytes, and smooth muscle.[16] The BDNF val66met polymorphism, associated with low BDNF function, has been linked to prefrontal cortical morphometric and metabolic alterations in BD[17,18] as well as with early-onset of the disease.[19,20]

Several studies have shown that circulating levels of BDNF were significantly decreased during mania or depression.[21-24] Pandey *et al*.[25] have found decreased levels of mRNA lymphocyte-derived BDNF as well as of BDNF protein in platelets of drug-free manic children and adolescents compared to controls. Recently, two meta-analyses have shown that BD patients had decreased plasmatic/serum levels of BDNF compared to healthy subjects, particularly during manic or depressive episodes.[15,26] Fernandes *et al*.[26] in a meta-regression analysis (n=548 BD patients; n=565 controls) have found decreased BDNF with large effect sizes (ES) for depression (ES -0.97) and mania (ES -0.81) versus controls.[26] However, BDNF levels among euthymic BD patients compared to controls subjects were not significant, with a small magnitude (ES -0.20). There was a substantial variability in the results in euthymic phase, and both age and illness duration significantly influenced this variability.[26] Of note, decreased BDNF levels have been reported in

euthymic patients at late stages of BD.[27,28] Indeed, associations of lower levels of peripheral BDNF with age, illness duration[29] and late-stage in BD[27] contribute to the hypothesis of BD as a neuroprogressive illness.[8,10]

Other neurotrophic factors have also been studied in BD. Nerve growth factor (NGF) was the first neurotrophin to be discovered, by Rita Levi-Montalcini in 1951. Recently, one study in BD reported a negative correlation between the severity of manic episodes and NGF levels.[30] Increased levels of neurotrophin 3 (NT-3), which share signal transduction pathways with BDNF, have been found in BD patients during mania and depression compared to euthymic patients and healthy controls.[31-33] One study found increased circulating levels of neurotrophin 4/5 (NT-4/5) in BD, but no difference across mood phases.[34] Under stress, astrocytes/microglial cells increase production of glial cell-line derived neurotrophic factor (GDNF) to avoid neuronal loss.[35] Abnormal levels of GDNF have been found across the different BD mood phases.[37–39] Additionally, increased plasma levels of vascular endothelial growth factor (VEGF) were found during major depressive or manic episodes in patients with mood disorders.[40] Other studies have indicated that VEGF could be one of the modulators for the therapeutic effect of mood stabilizers.[41,42] Taken together, these findings reinforce the possibility that alteration in neurotrophin levels may be a compensatory response to restore neurogenesis in turn to the potential toxicity of mood episodes. Although further studies are needed to investigate the applicability of the neurotrophic factors as markers of illness progression in BD, in particular to identify individuals in the earlier stages of the disease, facilitating early intervention and potentially reducing the allostatic load in the early phase.[9]

Inflammatory biomarkers

Growing evidence has shown that inflammatory mechanisms may exert a crucial role in BD pathophysiology,[43] in particular via their regulation of synaptic transmission/plasticity and neuronal survival.[44,45]

In BD patients, immune dysfunctions have been related to the severity and number of mood episodes;[36,46–48] high prevalence of comorbidities;[36,49] medication effects,[50–52] and illness progression.[8,11]

Several studies have reported increased peripheral levels of proinflammatory cytokines, including interleukins (IL-2, IL-4, IL-6 and IL-1) and tumor necrosis factor-α (TNF-α) during mania[28,30,47,48,53–55] and depression.[47,54] Compelling evidence have demonstrated increased levels of soluble receptors of TNF (sTNF-R1 and sTNF-R2) and IL2 (sIL-2) in manic patients compared to euthymic and controls.[28,30,53,56,57] Additionally, increased levels of sTNF-R1 and sTNF-R2 were positively correlated with patients'age and illness duration of BD,[28,30] and BD patients with increased levels of TNFR1 had poor functioning in late adulthood.[58] Preexisting increased levels of Il-1β and Il-1Ra might predict vulnerability for future mood episodes.[47] Furthermore, a recent study have demonstrated that markers of neuroinflammation are significantly increased in postmortem frontal cortex from BD patients.[59] In particular, this study found an important activation of the IL-1 receptor cascade,[59] which is involved in several regulatory process of inflammation.[60] IL-10 exerts a central role in immune response through down-regulation of proinflammatory cytokines, including TNF-a, IL-1β, and IL-6. Elevated levels of Il-10 have been demonstrated in BD patients in remission after manic[50,61] or depressive episodes,[28] while other reports did not find any significantly difference in IL-10 levels.[61] Levels of IL-10 seem to reduce significantly from early to late-stages of BD.[27] Therefore a cumulative effect of successive mood episodes and as well as illness duration appears to influence levels of proinflammatory cytokines, which act as key mediators in both central and peripheral inflammation, and may contribute to neuroprogression in BD.

Its worth mentioning that TNF-α, IL-1β, and particularly IL-6 are the chief inducers of acute-phase proteins, including C-reactive protein.[63] CRP is a marker of systemic, low-grade inflammation as well as an established risk factor for cardiovascular disease. In a recent meta-analysis (including 11 studies; 1618

individuals) to estimate the size of the association between CRP levels and BD, we found a significant elevation in CRP levels in BD patients compared to control subjects, with a moderate effect size (ES=0.39) (95% CI, 0.24-0.55; $P < .0001$).[64] In the subgroup analysis by mood phases, we found that manic BD patients had levels of CRP significantly higher than control subjects with a large ES (0.74) (95% CI, 0.44-1.02; $P < .001$).[64] A 2-years follow-up study demonstrated that increased levels of CRP were an important risk factor for the onset of manic symptoms in depressed men.[65] Another study reported an association between severity of manic symptoms and high-sensitivity CRP as well as a negative association between serum IL-6 and BDNF protein levels in adolescents with BD.[66] A pro-inflammatory state thus seems to be strongly related with manic symptoms, which contribute to the idea of CRP could be a state marker in BD. Although explanatory mechanisms to this relationship are still unclear, one possible mechanism might be linked to sleep dysfunction, which is often in manic[67] BD patients, is known to be associated to elevated cytokines and CRP levels.[68] In the same meta-analysis, differences in CRP levels among euthymic patients vs. controls were significantly higher (ES=0.26), albeit with a slight magnitude (ES=0.26) (SMD = 0.26, 95% CI, 0.01-0.51; $P < .04$)[64], suggesting that there may be an inflammatory component in non-acutely ill BD patients. This meta-analytic results reinforces evidence showing that activation of the inflammatory response persists after remission,[68] suggesting CRP as a potential marker of trait in BD[64]. However, it is important to bear in mind that many studies included in this subgroup analysis used different criteria to characterize the different mood phases of BD, raising the idea that some BD patients categorized as euthymic had residual symptoms (subsyndromal), which could also influence CRP levels.[64] The burden of acute episodes appears to contribute to CVD mortality among individuals with BD.[70] Compelling evidence have shown that CRP is an independent predictor of cardiovascular disease (CVD),[71] which is the leading cause of excess mortality in BD patients.[72] Measurement of CRP levels associated with other parameters commonly used in clinical practice such as blood pressure, waist circumference, lipid and glucose levels may be a useful biomarker in BD patients at risk of CVD as well as in individuals who are otherwise healthy but suffer from BD.

Hypothalamic-pituitary-adrenal (HPA) axis

The HPA is the main system implicated in the response to physical or psychological stress.[73] Various parameters of HPA function such as cortisol levels, dexamethasone suppression test (DST) and DEX/CHR have been related to severity of mood symptoms. In depression, for example, serum cortisol levels measured after the overnight 1 mg dexamethasone suppression test (DST) were related to severity of illness and were thought to discriminate severity of depression.[74] Studies have demonstrated increased activity of the HPA axis and basal cortisol levels during depressive or manic episodes in BD patients.[74–76] as well as a trend to increased levels of cortisol in response to the DEX/CRH test during euthymia.[74,76] Measurements of HPA function, reflecting the severity of a particular disease state, might be putative biomarkers of illness progression in BD.

Oxidative stress biomarkers

The brain is susceptible to oxidative stress damage, due to high oxygen consumption and hence the generation of free radicals, and its low antioxidant capacity.[77] An imbalance between oxidant/antioxidant mechanisms contribute to accumulation of oxidative species, which react with cell components, such as proteins, lipids, mitochondria and nucleic acid, contributing to neuronal degradation and dysfunctional neurogenesis.[78,79] The mechanisms of oxidative injury have been reported in various conditions, including aging,[80] cancer, cardiovascular and neurodegenerative diseases.[81] In BD, significant alterations in antioxidant enzymes, lipid peroxidation, and nitric oxide (NO) levels have been reported.[82] Altered oxidative stress parameters and activated antioxidant defenses have been associated with the different mood phases in BD and/or the number of the manic episodes.[83]

It has been shown that NO levels increase during acute episodes mania[84] and depression[85] as well as in

euthymic BD patients.[83] Altered activity of erythrocyte superoxide dismutase (SOD), an antioxidant enzyme, is another important finding in BD patients. Many studies have demonstrated a significant elevation in SOD concentration in manic and depressed BD patients compared to euthymic patients or controls.[78,86] In contrast, other studies have reported reduced levels of SOD across all mood phases of BD[85,87,88] as well as no significant difference in the SOD activity between BD patients and controls.[89] Despite NO levels have reduced after treatment of BD patients, SOD activity remained high.[85] SOD increasing activity may be a defense-antioxidant mechanism against increased NO levels in BD. Additionally, high SOD activity in mood episodes may reflect a preceding cellular oxidative stress or serve as a compensatory mechanism, suggesting that SOD may be involved in neuroprogression in BD. Increased activity of serum catalase (CAT), another antioxidant enzyme, was found in manic patients[78] including those medication-free,[23] with a reduced activity during euthymia.[78,88] Despite normal levels of glutathione peroxidase were observed during mania,[78] an increased oxidant/anti-oxidant ratio (SOD/GPx + catalase) was found in manic and depressive BD patients compared to euthymic patients and controls.[78] Several conditions related with aging (e.g. higher visceral adiposity, inflammation, abnormal glucose/lipid levels) have been linked to oxidative damage to lipids,[80] which could be assessed by measuring serum/plasma levels of thiobarbituric acid reactive substances (TBARS). Elevated levels of TBARS have been reported across all mood phases of BD.[78,86] Although Kunz et *al.* [86] demonstrated that only manic patients had significantly increased levels of TBARS in comparison to other patient's groups (depressed, euthymic or schizophrenic).[86] Magalhães *et al*.[90] have found an association between current manic episode and abnormal concentrations of protein carbonyl content (PCC), which is a measure of oxidative damage to protein.[90] Higher PCC levels have been associated to apoptosis and necrosis cellular as well as to adverse clinical outcomes (e.g. colorectal cancer).[80] Moreover, oxidative stress may also lead to DNA damage in BD patients mainly in those with severe mood episodes.[78,82] Oxidative damage therefore occurs during acute mood episodes, supporting the idea that mood episodes (mania in particular) might be toxic to patients with BD. However, the lipid and protein damage could be consequence of dysfunction in different pathways and further studies are needed to elucidate of oxidative stress biomarkers in BD illness progression.

PERIPHERAL BIOMARKERS ASSOCIATED WITH THE TREATMENT OF BD

Neurotrophins

Studies reported that manic patients had significant increase in BDNF levels following treatment with mood stabilizers, in particular with lithium.[26,91,92] In addition, BD patients non-responders to lithium had lower plasmatic levels of BDNF than those with a good response to lithium.[93] Another study that examined changes in BDNF levels among BD patients, initially unmedicated, found increased levels of BDNF in depressed patients but a reduced level in patients during manic/mixed episodes after treatment with extended-release quetiapine.[94] Given these findings, peripheral levels of BDNF may also be a potential marker of treatment response in BD. Longitudinal studies are needed to measure BDNF levels in the same patients experiencing different mood episodes as well as in those receiving multiple treatments.

Oxidative stress and antioxidant defense markers

Its important to highlight that the therapeutic effects of mood stabilizers may be related to their regulatory effect on oxidative stress pathways.[82] BD patients medication-free treated with lithium during manic episodes exhibit reduced levels of SOD, CAT and TBARS.[95] Similarly, first-episode psychotic patients treated with olanzapine or risperidone had decreased SOD activity and lipid peroxidation.[82,86,95] Oxidative stress therefore might be implicated in illness progression in BD, and use of antioxidants can be a relevant therapeutic strategy on this disorder.

N-acetyl-cysteine (NAC) is the precursor of glutathione (GSH), the most important nonenzymatic cellular

antioxidant, and is know to maintain the oxidative balance in the cell. Recent clinical trials have shown that adjunctive treatment with NAC to common medication for BD appears to be beneficial in patients with BD,[95,96] in particular improving depressive symptoms[97,98] and functioning.[98] Preclinical evidence has demonstrated some antioxidant/neuroprotective properties of the ω-3 polynsaturated fatty acids (PUFAs).[99] Recently, a meta-analysis of clinical trials using ω-3PUFAs associated with standard treatment in BD reported that ω-3 amended BD depressive symptoms.[100] Of note, add-on supplementation of vitamin C, vitamin E, the combination of vitamin C and vitamin E, or the mixture of fish oil has been shown to reduce oxidative stress markers and improve clinical symptoms in schizophrenic patients.[101] Given these data, development of novel therapeutic approaches to reduce oxidative stress and repair membrane impairments may be useful in early intervention to prevent neuroprogression in BD.

Inflammatory biomarkers

Conventional mood stabilizers (e.g. lithium, antipsychotics, anticonvulsants) act in varying capacities to down-regulate the production of pro-inflammatory mRNA and protein gene expression that potentially alter levels of proinflammatory cytokines and CRP.[102] Dargél *et al*.[64], in a meta-regression analysis to examine the potential influence of lithium and antipsychotics (typical and atypical) in the CRP levels of BD patients did not find significant association, However, the authors could not draw any conclusion on the association between medication use and CRP, as the available data was limited.[64]

Given that inflammatory pathways seem to be involved in illness progression of BD, adjunctive therapies to modulate inflammatory response seem to be another relevant therapeutic strategy to more accurate interventions in BD. In keeping with this view, a randomized, double-blind, placebo-controlled study reported substantial antidepressant effects following adjunctive treatment with celecoxib (cyclooxygenase-2 inhibitor) in BD patients during depressive or mixed episodes[104] beneficial effects of aspirin as an adjunctive treatment in BD.[105] Interestingly, alterations in the arachidonic acid metabolism cascade were found in the postmortem brain of BD.[59]

Disturbances in inflammatory response however can be prominent only in a subset of individuals with BD. Recently, a study have evaluated the effect of a TNF-α antagonist (infliximab) in patients with treatment-resistant depression. Infliximab was superior to placebo in mitigating depressive symptoms only in individuals who exhibited elevated inflammation (hsCRP > 5mg/L) at baseline.[106] This preliminary result support the idea that measurements of CRP levels may be useful to stratify BD patients who respond to a specific immune or anti-inflammatory treatment, suggesting that CRP may be a potential marker for enhancing treatment matching in BD.

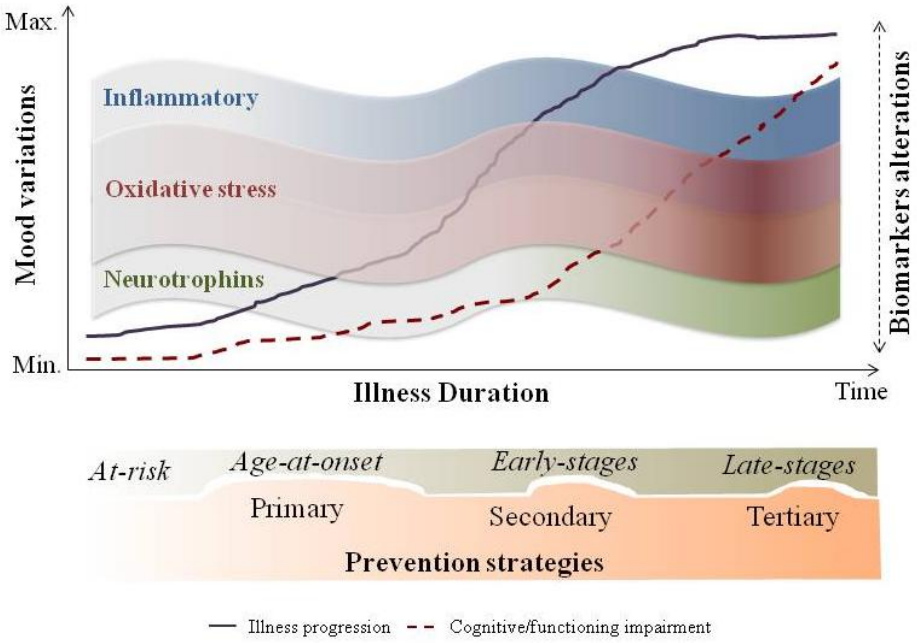
To date, several biomarkers that display potentially information about treatment response overlap with prognostic markers that could predict risk or progression of illness. Moreover, non-pharmacologic therapeutic approaches, such as psychotherapy and healthy behavior may modulate peripheral biomarkers of neuroprogression, including neurotrophins, inflammation and oxidative markers.[107,108]

Evidences have shown that physical exercise[109] and good dietary habits,[110] are associated to significant reduction in CRP levels as well as to improvement in depression-like behavior and depressive symptoms.[109,111] In pediatrics, poor sleep and unhealthy diet habits have been linked to unhealthy growth by modifying the architecture of the plastic brain.[112] Moreover, smoking increases the risk of mood disorders, and appear to affect similar biological pathways.[113]

FUTURE PERSPECTIVES

As discussed in this chapter, a number of neurotrophic, inflammatory and oxidative stress biomarkers are associated with BD.[11] However, a question remains about how to implement these putative biomarkers in the clinical practice to identify individuals at risk or earlier stages of BD and to prevent illness progression.

Figure 1. Peripheral biomarkers in illness progression in bipolar disorder



BD is a heterogeneous disorder, where different peripheral biomarker profile have been linked to particular characteristics of patients, specific mood phases, length of illness, or even different stages of disease thereby making generalised conclusions difficult. Heterogeneous populations used in most of the studies are also another critical point. Examining well-defined groups may enhance accuracy of peripheral biomarkers of illness progression in BD. Moreover, it may be necessary to shift focus away from a one-size-fits-all approach and instead generate biomarkers profiles, highlighting core domains of dysfunction or strengths for each patient toward tailored interventions.

Although BD is associated with several inflammatory or oxidative stress biomarkers, confounding/moderator variables need to be accounted for. For example, despite CRP being commonly used as a marker of inflammation[63] as well as a risk factor for cardiovascular disease,[71] it levels may be influenced by (gender, BMI, medical comorbidities, alcohol/drug abuse, smoking, stressors),[114] with an impact on the results. Further studies including within-subject comparisons and subgroup analyses (e.g., BD subtype, sex, family history of BD) are required to identify useful biomarkers of illness progression in BD. Moreover, it would be interesting to examine whether these peripheral biomarkers can inform our understanding, treatment, and prevention of crucial non-mood conditions in BD as cardiometabolic disorders and cognitive-functioning impairment.[115]

The effect of treating BD on biomarkers has primarily focused on pharmacological treatments. Research into other treatments such as psychological therapies and lifestyle interventions (sleep, diet, and exercise) are still scarce. The influence of more targeted anti-inflammatory treatments and antioxidant therapies on

mood symptoms and biomarkers levels are also required. Finally, while a selection of more commonly assessed biomarkers in BD research, specifically targeting inflammation, oxidative stress and neurotrophins, have been covered in this chapter, there remains an array of other potential options. These include measurements of amino acid levels which are the precursors to neurotransmitters;[116] growth factors such as insulin-like growth factor-1,[117] markers of associated with tryptophan pathways (e.g. kynurenic acid, quinolic acid)[118] genetic polymorphisms associated with dopamine and serotonin transporters and receptors as well as with P450 metabolic pathways.[119,120]

CONCLUSION

BD is complex, and a multidimensional approach its germane to guide disease diagnosis and therapeutic interventions Advances in research have identified promising biomarkers of illness progression, including neurotrophins, oxidative stress and inflammatory markers. However, more work is needed to elucidate the clinical utility of these biomarkers. Future studies combining different approaches, such as integrative omics (e.g. proteomics, epi/genomics, metabolomics), computational models as well as pooling various biomarkers, may contribute to the development of useful biomarkers in BD. Ultimately, more consistent nosology and accurate classification of biomarkers will be crucial to determine how these tests could help us to better understand pathophysiological mechanisms and to identify biological targets, providing individualized treatment and preventing illness progression in BD.

REFERENCES

1. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001 Mar;69(3):89–95.

2. Pepe MS, Etzioni R, Feng Z, Potter JD, Thompson ML, Thornquist M, et al. Phases of biomarker development for early detection of cancer. J Natl Cancer Inst. 2001 Jul 18;93(14):1054–61.

3. Frey BN, Andreazza AC, Houenou J, Jamain S, Goldstein BI, Frye MA, et al. Biomarkers in bipolar disorder: a positional paper from the International Society for Bipolar Disorders Biomarkers Task Force. Aust N Z J Psychiatry. 2013 Apr;47(4):321–32.

4. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. *Arch Gen Psychiatry*. 2011;68(3):241–251.

5. World Health Organization. The Global Burden of Disease: 2004 Update. Geneva:WHO; 2008.

6. Post RM, Fleming J, Kapczinski F. Neurobiological correlates of illness progression in the recurrent affective disorders. J Psychiatr Res. 2012 May;46(5):561–73.

7. Schmitt A, Malchow B, Hasan A, Falkai P. The impact of environmental factors in severe psychiatric disorders. Front Neurosci. 2014;8:19.

8. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev. 2011 Jan;35(3):804–17.

9. Kapczinski F, Vieta E, Andreazza AC, Frey BN, Gomes FA, Tramontina J, et al. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. Neurosci Biobehav Rev. 2008;32(4):675–92.

10. Fries GR, Pfaffenseller B, Stertz L, Paz AVC, Dargél AA, Kunz M, et al. Staging and neuroprogression in bipolar disorder. Curr Psychiatry Rep. 2012 Dec;14(6):667–75.

11. Pfaffenseller B, Fries GR, Wollenhaupt-Aguiar B, Colpo GD, Stertz L, Panizzutti B, et al. Neurotrophins, inflammation and oxidative stress as illness activity biomarkers in bipolar disorder. Expert Rev Neurother. 2013 Jul;13(7):827–42.

12. Lang UE, Hellweg R, Seifert F, Schubert F, Gallinat J. Correlation between serum brain-derived neurotrophic factor level and an in vivo marker of cortical integrity. Biol Psychiatry. 2007 Sep 1;62(5):530–5.

13. Klein AB, Williamson R, Santini MA, Clemmensen C, Ettrup A, Rios M, et al. Blood BDNF concentrations reflect brain-tissue BDNF levels across species. Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacol CINP. 2011 Apr;14(3):347–53.

14. Post RM. Role of BDNF in bipolar and unipolar disorder: clinical and theoretical implications. J Psychiatr Res. 2007 Dec;41(12):979–90.

15. Lin P-Y. State-dependent decrease in levels of brain-derived neurotrophic factor in bipolar disorder: a meta-analytic study. Neurosci Lett. 2009 Dec 11;466(3):139–43.

16. Schmidt HD, Duman RS. Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2010 Nov;35(12):2378–91.

17. Matsuo K, Walss-Bass C, Nery FG, Nicoletti MA, Hatch JP, Frey BN, et al. Neuronal correlates of brain-derived neurotrophic factor Val66Met polymorphism and morphometric abnormalities in bipolar disorder. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2009 Jul;34(8):1904–13.

18. Frey BN, Walss-Bass C, Stanley JA, Nery FG, Matsuo K, Nicoletti MA, et al. Brain-derived neurotrophic factor val66met polymorphism affects prefrontal energy metabolism in bipolar disorder. Neuroreport. 2007 Oct 8;18(15):1567–70.

19. Geller B, Badner JA, Tillman R, Christian SL, Bolhofner K, Cook EH Jr. Linkage disequilibrium of the brain-derived neurotrophic factor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. Am J Psychiatry. 2004 Sep;161(9):1698–700.

20. Tang J, Xiao L, Shu C, Wang G, Liu Z, Wang X, et al. Association of the brain-derived neurotrophic factor gene and bipolar disorder with early age of onset in mainland China. Neurosci Lett. 2008 Mar 12;433(2):98–102.

21. Cunha ABM, Frey BN, Andreazza AC, Goi JD, Rosa AR, Gonçalves CA, et al. Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. Neurosci Lett. 2006 May 8;398(3):215–9.

22. Grande I, Fries GR, Kunz M, Kapczinski F. The role of BDNF as a mediator of neuroplasticity in bipolar disorder. Psychiatry Investig. 2010 Dec;7(4):243–50.

23. Vieira RM, Dietrich MO, Leke R, Cereser VH, Zanatto V, Kapczinski F, et al. Decreased plasma brain derived neurotrophic factor levels in unmedicated bipolar patients during manic episode. Biol Psychiatry. 2007 Jan 15;61(2):142–4.

24. Oliveira GS, Ceresér KM, Fernandes BS, Kauer-Sant'Anna M, Fries GR, Stertz L, et al. Decreased brain-derived neurotrophic factor in medicated and drug-free bipolar patients. J Psychiatr Res. 2009 Sep;43(14):1171–4.

25. Pandey GN, Rizavi HS, Dwivedi Y, Pavuluri MN. Brain-derived neurotrophic factor gene expression in pediatric bipolar disorder: effects of treatment and clinical response. J Am Acad Child Adolesc Psychiatry. 2008 Sep;47(9):1077–85.

26. Fernandes BS, Gama CS, Ceresér KM, Yatham LN, Fries GR, Colpo G, et al. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J Psychiatr Res. 2011 Aug;45(8):995–1004.

27. Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Young LT, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacol CINP. 2009 May;12(4):447–58.

28. Barbosa IG, Rocha NP, de Miranda AS, Magalhães PV da S, Huguet RB, de Souza LP, et al. Increased levels of adipokines in bipolar disorder. J Psychiatr Res. 2012 Mar;46(3):389–93.

29. Yatham LN, Kapczinski F, Andreazza AC, Trevor Young L, Lam RW, Kauer-Sant'anna M. Accelerated age-related decrease in brain-derived neurotrophic factor levels in bipolar disorder. Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacol CINP. 2009 Feb;12(1):137–9.

30. Barbosa IG, Huguet RB, Sousa LP, Abreu MNS, Rocha NP, Bauer ME, et al. Circulating levels of GDNF in bipolar disorder. Neurosci Lett. 2011 Sep 15;502(2):103–6.

31. Fernandes BS, Gama CS, Walz JC, Ceresér KM, Fries GR, Colpo G, et al. Increased neurotrophin-3 in drug-free subjects with bipolar disorder during manic and depressive episodes. J Psychiatr Res. 2010 Jul;44(9):561–5.

32. Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PVS, Kauer-Sant'Anna M, Klamt F, et al. Peripheral biomarkers and illness activity in bipolar disorder. J Psychiatr Res. 2011 Feb;45(2):156–61.

33. Walz JC, Andreazza AC, Frey BN, Cacilhas AA, Ceresér KMM, Cunha ABM, et al. Serum neurotrophin-3 is increased during manic and depressive episodes in bipolar disorder. Neurosci Lett. 2007 Mar 19;415(1):87–9.

34. Walz JC, Magalhães PV, Giglio LM, Cunha AB, Stertz L, Fries GR, et al. Increased serum neurotrophin-4/5 levels in bipolar disorder. J Psychiatr Res. 2009 Apr;43(7):721–3.

35. Miller CA. Stressed and depressed? Check your GDNF for epigenetic repression. Neuron. 2011 Jan 27;69(2):188–90.

36. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. J Clin Psychiatry. 2009 Aug;70(8):1078–90.

37. Rosa AR, Frey BN, Andreazza AC, Ceresér KM, Cunha ABM, Quevedo J, et al. Increased serum glial cell line-derived neurotrophic factor immunocontent during manic and depressive episodes in individuals with bipolar disorder. Neurosci Lett. 2006 Oct 23;407(2):146–50.

38. Zhang X, Zhang Z, Sha W, Xie C, Xi G, Zhou H, et al. Effect of treatment on serum glial cell line-derived neurotrophic factor in bipolar patients. J Affect Disord. 2010 Oct;126(1-2):326–9.

39. Takebayashi M, Hisaoka K, Nishida A, Tsuchioka M, Miyoshi I, Kozuru T, et al. Decreased levels of whole blood glial cell line-derived neurotrophic factor (GDNF) in remitted patients with mood disorders. Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacol CINP. 2006 Oct;9(5):607–12.

40. Lee B-H, Kim Y-K. Increased plasma VEGF levels in major depressive or manic episodes in patients with mood disorders. J Affect Disord. 2012 Jan;136(1-2):181–4.

41. Gupta A, Schulze TG, Nagarajan V, Akula N, Corona W, Jiang X, et al. Interaction networks of lithium and valproate molecular targets reveal a striking enrichment of apoptosis functional clusters and neurotrophin signaling. Pharmacogenomics J. 2012 Aug;12(4):328–41.

42. Sugawara H, Iwamoto K, Bundo M, Ishiwata M, Ueda J, Kakiuchi C, et al. Effect of mood stabilizers on gene expression in lymphoblastoid cells. J Neural Transm Vienna Austria 1996. 2010 Feb;117(2):155–64.

43. Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? J Affect Disord. 2012 Dec 1;141(1):1–10.

44. Yirmiya R, Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain Behav Immun. 2011 Feb;25(2):181–213.

45. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008 Jan;9(1):46–56.

46. Tsai SY, Yang YY, Kuo CJ, Chen CC, Leu SJ. Effects of symptomatic severity on elevation of plasma soluble interleukin-2 receptor in bipolar mania. J Affect Disord. 2001 May;64(2-3):185–93.

47. Ortiz-Domínguez A, Hernández ME, Berlanga C, Gutiérrez-Mora D, Moreno J, Heinze G, et al. Immune variations in bipolar disorder: phasic differences. Bipolar Disord. 2007 Sep;9(6):596–602.

48. Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'anna M, Mascarenhas M, Escosteguy Vargas A, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J Affect Disord. 2009 Aug;116(3):214–7.

49. Magalhães PV, Kapczinski F, Nierenberg AA, Deckersbach T, Weisinger D, Dodd S, et al. Illness burden and medical comorbidity in the Systematic Treatment Enhancement Program for Bipolar Disorder. Acta Psychiatr Scand. 2012 Apr;125(4):303–8.

50. Boufidou F, Nikolaou C, Alevizos B, Liappas IA, Christodoulou GN. Cytokine production in bipolar affective disorder patients under lithium treatment. J Affect Disord. 2004 Oct 15;82(2):309–13.

51. Knijff EM, Breunis MN, Kupka RW, de Wit HJ, Ruwhof C, Akkerhuis GW, et al. An imbalance in the production of IL-1beta and IL-6 by monocytes of bipolar patients: restoration by lithium treatment. Bipolar Disord. 2007 Nov;9(7):743–53.

52. Guloksuz S, Altinbas K, Aktas Cetin E, Kenis G, Bilgic Gazioglu S, Deniz G, et al. Evidence for an association between tumor necrosis factor-alpha levels and lithium response. J Affect Disord. 2012 Dec 20;143(1-3):148–52.

53.Hope S, Dieset I, Agartz I, Steen NE, Ueland T, Melle I, et al. Affective symptoms are associated with markers of inflammation and immune activation in bipolar disorders but not in schizophrenia. J Psychiatr Res. 2011 Dec;45(12):1608–16.

54.O'Brien SM, Scully P, Scott LV, Dinan TG. Cytokine profiles in bipolar affective disorder: focus on acutely ill patients. J Affect Disord. 2006 Feb;90(2-3):263–7

55.Kim Y-K, Jung H-G, Myint A-M, Kim H, Park S-H. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J Affect Disord. 2007 Dec;104(1-3):91–5.

56.Tsai S-Y, Chung K-H, Wu J-Y, Kuo C-J, Lee H-C, Huang S-H. Inflammatory markers and their relationships with leptin and insulin from acute mania to full remission in bipolar disorder. J Affect Disord. 2012 Jan;136(1-2):110–6.

57.Cetin T, Guloksuz S, Cetin EA, Gazioglu SB, Deniz G, Oral ET, et al. Plasma concentrations of soluble cytokine receptors in euthymic bipolar patients with and without subsyndromal symptoms. BMC Psychiatry. 2012;12:158.

58.Hope S, Ueland T, Steen NE, Dieset I, Lorentzen S, Berg AO, et al. Interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder. Schizophr Res. 2013 Apr;145(1-3):36–42. 56.

59.Rao JS, Harry GJ, Rapoport SI, Kim HW. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. Mol Psychiatry. 2010 Apr;15(4):384–92.

60.Buttner N, Bhattacharyya S, Walsh J, Benes FM. DNA fragmentation is increased in non-GABAergic neurons in bipolar disorder but not in schizophrenia. Schizophr Res. 2007 Jul;93(1-3):33–41.

61.Remlinger-Molenda A, Wojciak P, Michalak M, Karczewski J, Rybakowski JK. Selected cytokine profiles during remission in bipolar patients. Neuropsychobiology. 2012;66(3):193–8.

62.Liu H-C, Yang Y-Y, Chou Y-M, Chen K-P, Shen WW, Leu S-J. Immunologic variables in acute mania of bipolar disorder. J Neuroimmunol. 2004 May;150(1-2):116–22.

63.Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999 Feb 11;340(6):448–54

64.Dargél AA, Godin O, kapczinski F, Kupfer D, Leboyer M. C-reactive protein alterations in bipolar disorder: a and meta-analysis. J Clin Psyc. 2014;in press.

65.Becking K, Boschloo L, Vogelzangs N, Haarman BCM, Riemersma-van der Lek R, Penninx BWJH, et al. The association between immune activation and manic symptoms in patients with a depressive disorder. Transl Psychiatry. 2013 Oct 22;3(10):e314.

66.Goldstein BI, Collinger KA, Lotrich F, Marsland AL, Gill M-K, Axelson DA, et al. Preliminary findings regarding proinflammatory markers and brain-derived neurotrophic factor among adolescents with bipolar spectrum disorders. J Child Adolesc Psychopharmacol. 2011 Oct;21(5):479–84.

67.Harvey AG. Sleep and Circadian Rhythms in Bipolar Disorder: Seeking Synchrony, Harmony, and Regulation. Am J Psychiatry. 2008 Jul 1;165(7):820–9.

68. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, Inflammatory, and Metabolic Consequences of Sleep Deprivation. Prog Cardiovasc Dis. 2009 Jan;51(4):294–302.

69. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry. 2008 Apr 15;63(8):801–8.

70. Fiedorowicz JG, Solomon DA, Endicott J, Leon AC, Li C, Rice JP, et al. Manic/hypomanic symptom burden and cardiovascular mortality in bipolar disorder. Psychosom Med. 2009 Jul;71(6):598–606.

71. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010 Jan 9;375(9709):132–40.

72. Kupfer DJ. The Increasing Medical Burden in Bipolar Disorder. JAMA. 2005 May 25;293(20):2528.

73. Teixeira AL, Barbosa IG, Machado-Vieira R, Rizzo LB, Wieck A, Bauer ME. Novel biomarkers for bipolar disorder. Expert Opin Med Diagn. 2013 Mar;7(2):147–59.

74. Maes M, De Ruyter M, Hobin P, Suy E. Repeated dexamethasone suppression test in depressed patients. J Affect Disord. 1986 Oct;11(2):165–72.

75. Schmider J, Lammers CH, Gotthardt U, Dettling M, Holsboer F, Heuser IJ. Combined dexamethasone/corticotropin-releasing hormone test in acute and remitted manic patients, in acute depression, and in normal controls: I. Biol Psychiatry. 1995 Dec 15;38(12):797–802.

76. Watson S, Gallagher P, Ritchie JC, Ferrier IN, Young AH. Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. Br J Psychiatry J Ment Sci. 2004 Jun;184:496–502.

77. Olmez I, Ozyurt H. Reactive oxygen species and ischemic cerebrovascular disease. Neurochem Int. 2012 Jan;60(2):208–12.

78. Andreazza AC, Cassini C, Rosa AR, Leite MC, de Almeida LMV, Nardin P, et al. Serum S100B and antioxidant enzymes in bipolar patients. J Psychiatr Res. 2007 Sep;41(6):523–9.

79. Zhang XY, Yao JK. Oxidative stress and therapeutic implications in psychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2013 Oct 1;46:197–9.

80. Poulose N, Raju R. Aging and Injury: Alterations in Cellular Energetics and Organ Function. Aging Dis. 2014 Apr;5(2):101–8.

81. Friese MA, Schattling B, Fugger L. Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis. Nat Rev Neurol. 2014 Mar 18;10(4):225–38.

82. Andreazza AC, Kauer-Sant'anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, et al. Oxidative stress markers in bipolar disorder: a meta-analysis. J Affect Disord. 2008 Dec;111(2-3):135–44.

83. Savas HA, Gergerlioglu HS, Armutcu F, Herken H, Yilmaz HR, Kocoglu E, et al. Elevated serum nitric oxide and superoxide dismutase in euthymic bipolar patients: impact of past episodes. World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry. 2006;7(1):51–5.

84. Savaş HA, Herken H, Yürekli M, Uz E, Tutkun H, Zoroğlu SS, et al. Possible role of nitric oxide

and adrenomedullin in bipolar affective disorder. Neuropsychobiology. 2002;45(2):57–61.

85. Selek S, Savas HA, Gergerlioglu HS, Bulbul F, Uz E, Yumru M. The course of nitric oxide and superoxide dismutase during treatment of bipolar depressive episode. J Affect Disord. 2008 Apr;107(1-3):89–94.

86. Kunz M, Gama CS, Andreazza AC, Salvador M, Ceresér KM, Gomes FA, et al. Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2008 Oct 1;32(7):1677–81.

87. Gergerlioglu HS, Savas HA, Bulbul F, Selek S, Uz E, Yumru M. Changes in nitric oxide level and superoxide dismutase activity during antimanic treatment. Prog Neuropsychopharmacol Biol Psychiatry. 2007 Apr 13;31(3):697–702.

88. Ranjekar PK, Hinge A, Hegde MV, Ghate M, Kale A, Sitasawad S, et al. Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients. Psychiatry Res. 2003 Dec 1;121(2):109–22.

89. Raffa M, Barhoumi S, Atig F, Fendri C, Kerkeni A, Mechri A. Reduced antioxidant defense systems in schizophrenia and bipolar I disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2012 Dec 3;39(2):371–5.

90. Magalhães PV, Jansen K, Pinheiro RT, Colpo GD, da Mota LL, Klamt F. Peripheral oxidative damage in early-stage mood disorders: a nested population-based case-control study. Int J Neuropsychopharmacol. 2012 Oct 15:1043-1050.

91. Tramontina JF, Andreazza AC, Kauer-Sant'anna M, Stertz L, Goi J, Chiarani F, et al. Brain-derived neurotrophic factor serum levels before and after treatment for acute mania. Neurosci Lett. 2009 Mar 13;452(2):111–3.

92. Sousa RT, van de Bilt MT, Diniz BS, Ladeira RB, Portela LV, Souza DO, et al. Lithium increases plasma brain-derived neurotrophic factor in acute bipolar mania: a preliminary 4-week study. Neurosci Lett. 2011 Apr 20;494(1):54–6.

93. Rybakowski JK, Suwalska A. Excellent lithium responders have normal cognitive functions and plasma BDNF levels. Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacol CINP. 2010 Jun;13(5):617–22.

94. Grande I, Kapczinski F, Stertz L, Colpo GD, Kunz M, Cereser KM, et al. Peripheral brain-derived neurotrophic factor changes along treatment with extended release quetiapine during acute mood episodes: an open-label trial in drug-free patients with bipolar disorder. J Psychiatr Res. 2012 Nov;46(11):1511–4.

95. Vieira RM, Andreazza AC, Viale CI, Zanatto V, Cereser V Jr, da Silva Vargas R, et al. Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: a possible role for lithium antioxidant effects. Neurosci Lett. 2007 Jun 21;421(1):33–6.

95. Sarris J, Mischoulon D, Schweitzer I. Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials. Bipolar Disord. 2011 Sep;13(5-6):454–65.

96. Magalhães PV, Dean OM, Bush AI, Copolov DL, Malhi GS, Kohlmann K, et al. N-acetylcysteine

for major depressive episodes in bipolar disorder. Rev Bras Psiquiatr São Paulo Braz 1999. 2011 Dec;33(4):374–8.

97. Magalhães PV, Dean OM, Bush AI, Copolov DL, Malhi GS, Kohlmann K, et al. N-acetyl cysteine add-on treatment for bipolar II disorder: a subgroup analysis of a randomized placebo-controlled trial. J Affect Disord. 2011 Mar;129(1-3):317–20.

98. Berk M. Neuroprogression: pathways to progressive brain changes in bipolar disorder. Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacol CINP. 2008;12(4):441–5.

99. Wu A, Ying Z, Gomez-Pinilla F. Dietary omega-3 fatty acids normalize BDNF levels, reduce oxidative damage, and counteract learning disability after traumatic brain injury in rats. J Neurotrauma. 2004 Oct;21(10):1457–67.

100. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry. 2012 Jan;73(1):81–6.

101. Pandya CD, Howell KR, Pillai A. Antioxidants as potential therapeutics for neuropsychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2013 Oct 1;46:214–23.

102. Haarman BBC, Riemersma-Van der Lek RF, Burger H, Netkova M, Drexhage RC, Bootsman F, et al. Relationship between clinical features and inflammation-related monocyte gene expression in bipolar disorder - towards a better understanding of psychoimmunological interactions. Bipolar Disord. 2014 Mar;16(2):137–50.

104. Nery FG, Monkul ES, Hatch JP, Fonseca M, Zunta-Soares GB, Frey BN, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. Hum Psychopharmacol. 2008 Mar;23(2):87–94.

105. Savitz J, Preskorn S, Teague TK, Drevets D, Yates W, Drevets W. Minocycline and aspirin in the treatment of bipolar depression: a protocol for a proof-of-concept, randomised, double-blind, placebo-controlled, 2x2 clinical trial. BMJ Open. 2012;2(1):e000643.

106. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013 Jan;70(1):31–41.

107. Brietzke E, Kapczinski F, Grassi-Oliveira R, Grande I, Vieta E, McIntyre RS. Insulin dysfunction and allostatic load in bipolar disorder. Expert Rev Neurother. 2011 Jul;11(7):1017–28.

108. Conus P, Ward J, Hallam KT, Lucas N, Macneil C, McGorry PD, et al. The proximal prodrome to first episode mania a new target for early intervention. Bipolar Disord. 2008 Aug;10(5):555–65.

109. Eyre HA, Papps E, Baune BT. Treating Depression and Depression-Like Behavior with Physical Activity: An Immune Perspective. Front Psychiatry [Internet]. 2013 [cited 2014 Jun 3];4. Available from: http://www.frontiersin.org/Journal/10.3389/fpsyt.2013.00003/full

110. King DE, Egan BM, Geesey ME. Relation of dietary fat and fiber to elevation of C-reactive protein. Am J Cardiol. 2003 Dec;92(11):1335–9.

111. Sanchez-Villegas A, Martínez-González MA. Diet, a new target to prevent depression? BMC Med. 2013;11(1):3.

112. Garner AS, Shonkoff JP, Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, Section on Developmental and Behavioral Pediatrics. Early childhood adversity, toxic stress, and the role of the pediatrician: translating developmental science into lifelong health. Pediatrics. 2012 Jan;129(1):e224–231.

113. Moylan S, Eyre HA, Maes M, Baune BT, Jacka FN, Berk M. Exercising the worry away: how inflammation, oxidative and nitrogen stress mediates the beneficial effect of physical activity on anxiety disorder symptoms and behaviours. Neurosci Biobehav Rev. 2013 May;37(4):573–84.

114. O'Connor M-F, Bower JE, Cho HJ, Creswell JD, Dimitrov S, Hamby ME, et al. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. Brain Behav Immun. 2009 Oct;23(7):887–97.

115. Barbosa IG, Rocha NP, Huguet RB, Ferreira RA, Salgado JV, Carvalho LA, et al. Executive dysfunction in euthymic bipolar disorder patients and its association with plasma biomarkers. J Affect Disord. 2012 Mar;137(1-3):151–5.

116. Miller CL, Llenos IC, Cwik M, Walkup J, Weis S. Alterations in kynurenine precursor and product levels in schizophrenia and bipolar disorder. Neurochem Int. 2008 May;52(6):1297–303.

117. Kim Y-K, Na K-S, Hwang J-A, Yoon H-K, Lee H-J, Hahn S-W, et al. High insulin-like growth factor-1 in patients with bipolar I disorder: A trait marker? J Affect Disord. 2013 Nov;151(2):738–43.

118. Olsson SK, Sellgren C, Engberg G, Landén M, Erhardt S. Cerebrospinal fluid kynurenic acid is associated with manic and psychotic features in patients with bipolar I disorder: KYNA correlates to mania and psychosis. Bipolar Disord. 2012 Nov;14(7):719–26.

119. Singh AB, Bousman CA, Ng CH, Byron K, Berk M. ABCB1 polymorphism predicts escitalopram dose needed for remission in major depression. Transl Psychiatry. 2012;2:e198.

120. Patel SD, Le-Niculescu H, Koller DL, Green SD, Lahiri DK, McMahon FJ, et al. Coming to grips with complex disorders: genetic risk prediction in bipolar disorder using panels of genes identified through convergent functional genomics. Am J Med Genet Part B Neuropsychiatr Genet Off Publ Int Soc Psychiatr Genet. 2010 Jun 5;153B(4):850–77.

6.3 Artigo 3: Emotional reactivity, functioning, and C-reactive protein alterations in remitted bipolar patients: clinical relevance of a dimensional approach

Emotional reactivity, functioning, and C-reactive protein alterations in remitted bipolar patients: clinical relevance of a dimensional approach

Dargél, Aroldo A. Dargél; Godin, Ophelia ; Etain, Bruno; Azorin, Jean-Michel ; M'Bailara, Katia; Bellivier, Frank ; Bougerol, Thierry ; Kahn, Jean-Pierre ; Passerieux, Christine ; Aubin, Valerie ; Courtet, Philippe ; Leboyer, Marion ; Henry, Chantal

Submetido ao The Journal of Clinical Psychiatry.

From : jclinpsych@psychiatrist.com
Subject : J16-M10930 Receipt of New Paper by The Journal of Clinical Psychiatry.
Date : May 10, 2016 at 5:38 PM
To : aroldo.ayub-dargel@pasteur.fr

May 10, 2016

Prof. Dargél
40 rue de Mesly
Pavillon Hartmann
Créteil, ile de france 94000
France

Dear Prof. Dargél:

We are in receipt of your manuscript J16-M10930:

"Emotional reactivity, functioning, and C-reactive protein alterations in remitted bipolar patients: clinical relevance of a dimensional approach"

We have sent your manuscript to our Editor-in-Chief for review. You will be advised of his decision in the near future.

Thank you for your submission.

With kind regards,

The Editorial Staff
The Journal of Clinical Psychiatry

Alan J. Gelenberg, MD
Editor-in-Chief

Anna Kwapien
Publications Manager

The Journal of Clinical Psychiatry

Phone: 901-273-2711
Fax: 901-273-2752
jclinpsych@psychiatrist.com

7 CONSIDERAÇÕES FINAIS

A inflamação sistêmica crônica parece estar implicada na fisiopatologia do TB. Com base nos resultados dos artigos que compõem esta tese, os indivíduos com TB parecem apresentar um estado de inflamação crônica de baixo grau, evidenciado pelo aumento dos níveis séricos de PCR.

7.1 Possíveis implicações clínicas dos achados dessa pesquisa

Os resultados dos estudos dessa tese parecem ter implicações relevantes para a prática clínica do TB.

7.1.1 Proteína C-reativa como biomarcador no transtorno bipolar

Com base nos achados do artigo 1 dessa tese, pacientes bipolares apresentaram níveis de PCR significativamente maiores que os indivíduos controles com moderado tamanho de efeito (*effect size*, ES = 0.39; 95% IC, 0.24 – 0.55; $P < 0.0001$). Níveis de PCR foram significativamente maiores em pacientes maníacos (ES = 0.73; 95% IC, 0.44 – 1.02; $P < 0.001$) e em eutímicos (ES = 0.26; 95% IC, 0.01 – 0.51; $P = 0.04$).

O primeiro artigo, através de um estudo de meta-análise, teve como objetivo avaliar o tamanho de efeito da associação entre níveis de PCR em pacientes bipolares nas diferentes fases de humor (n=730) comparado a indivíduos controles (n=888). Pacientes bipolares apresentaram níveis de PCR significativamente elevados em comparação ao grupo controle. Esses resultados confirmam haver um estado de inflamação crônica persistente no TB não somente nas fases agudas (mania ou depressão) mas também nos períodos inter-episódios da doença, indicando que a resposta inflamatória persiste ativada mesmo após remissão sintomática (Padmos et al., 2008). Isso reforça a ideia de existir um estado inflamatório crônico no TB. Ainda que os mecanismos

dessa associação não sejam totalmente conhecidos, a desregulação imunológica levando à inflamação crônica pode estar associada com o número de episódios e severidade dos sintomas, colaborando com a progressão da doença (Berk et al., 2011; Fries et al., 2012; Pfaffenseller et al., 2013).

Tendo em vista a PCR ser um biomarcador inflamatório largamente disponível, de custo relativamente baixo, e muito utilizado na prática clínica (Pepys and Hirschfield, 2003; Black, Kushner, and Samols, 2004; Ridker et al., 2008), a medida dos níveis de PCR parece ser uma forma acessível e custo-efetiva de obter informação sobre o perfil inflamatório sistêmico em pacientes com TB. Além disso, os níveis de PCR podem indicar, ainda que de maneira indireta, alterações nos níveis de citocinas pró-inflamatórias, as quais modulam os níveis séricos de PCR (Gabay and Kushner, 1999).

Embora seja tentadora a ideia de considerar a PCR como um potencial biomarcador no TB, diversos fatores podem, também, influenciar os níveis de PCR, incluindo sexo, idade, etnia, dieta, tabagismo, uso de medicações, etc. Além do mais, os diferentes métodos de dosagem de PCR, podem, também, contribuir para resultados heterogêneos em relação à PCR. Estudos prospectivos utilizando métodos mais acurados de dosagens de PCR (p. ex. PCR ultrassensível) bem como a medida de outros marcadores inflamatórios, são necessários para elucidar o papel da PCR como biomarcador no TB.

7.1.2 Níveis de proteína C-reativa e comorbidades clínicas no transtorno bipolar: oportunidades para o manejo clínico e prevenção

Evidências recentes argumentam que o TB parece ser uma doença multissistêmica (Goldstein, Kemp, Soczynska, and McIntyre, 2009; Leboyer et al., 2012; Stertz, Magalhães, and Kapczinski, 2013). Vale ressaltar que cerca de um terço dos pacientes incluídos no estudo de

meta-análise (artigo 1 dessa tese) apresentou síndrome metabólica. Ao longo da vida, o risco cardiometabólico parece ser um fator crucial para a saúde dos pacientes com TB (Vancampfort et al., 2013; Godin et al., 2014). Além disso, a PCR é um marcador de risco independente para doença cardiovascular e para alguns tipos de câncer (Pepys and Hirschfield, 2003; Ridker et al., 2008; Emerging Risk Factors Collaboration et al., 2010), além de apresentar alto valor prognóstico para doenças como síndrome metabólica e hipertensão arterial sistêmica (Albert, Glynn, and Ridker, 2003; Ridker et al., 2008).

Esses dados reforçam a necessidade de implementação e consolidação de condutas já bem estabelecidas em medicina para o manejo clínico de pacientes: exame clínico detalhado associado a perfil laboratorial de rotina. Por exemplo, medidas dos níveis tensionais e da circunferência abdominal associadas a testes laboratoriais comuns, como glicemia de jejum, perfil lipídico e PCR poderiam ser condutas úteis no manejo não apenas de pacientes com TB com risco elevado para doença cardiometabólica, mas também de indivíduos aparentemente saudáveis que apresentam risco elevado para TB.

O estilo de vida sedentário e hábitos alimentares pouco saudáveis, os quais são muito frequentes em pacientes bipolares, parecem estar relacionados com sintomas de humor e níveis aumentados de PCR (Alsuwaidan, Kucyi, Law, and McIntyre, 2009; Eyre, Papps, and Baune, 2013). Por outro lado, estudos recentes demonstram que atividade física e dieta saudável auxiliam na redução de sintomas depressivos como também dos níveis PCR (King, Egan, and Geesey, 2003; Alsuwaidan, Kucyi, Law, and McIntyre, 2009; Rees and Sabia, 2010; Cooney et al., 2013). O uso de um parâmetro objetivo como a PCR poderia auxiliar, ainda mais, os psiquiatras a motivarem seus pacientes para adoção de um estilo de vida saudável.

Desse modo, intervenções relativamente simples, de baixo custo poderiam auxiliar no manejo e na prevenção do TB, tratando, de uma forma integrada, o corpo e o cérebro.

7.1.3 Reatividade emocional e níveis de proteína C-reativa em pacientes bipolares em remissão: relevância clínica de uma abordagem dimensional

Evidência crescente mostra que a maioria dos pacientes bipolares durante a fase de remissão permanece com sintomas subclínicos de humor (Judd et al., 2012; Marwaha, Balbuena, Winsper, and Bowen, 2015), os quais estão associados com prejuízo funcional e cognitivo (Rosa et al., 2008; Bonnín et al., 2012; Van Rheenen and Rossell, 2014*a*). Contudo, os instrumentos utilizados atualmente para o diagnóstico de TB baseiam-se, essencialmente, em categorias de sintomas (Phillips and Kupfer, 2013), apresentando baixa sensibilidade para detectar sintomatologia subclínica de humor (Henry and Etain, 2010).

Conforme os resultados do artigo 3 dessa tese, a reatividade emocional pareceu ser uma dimensão sensível para discriminar pacientes bipolares apresentando sintomas subclínicos de humor. Apesar de todos os pacientes estarem em remissão, eles apresentaram níveis de reatividade emocional significativamente diferentes, os quais não foram detectados pelos escalas tradicionais de avaliação de humor, as quais baseiam-se em lista de sintomas. Os pacientes com reatividade emocional anormal (hipo- ou hiper-) apresentaram níveis significativamente elevados de sintomas subclínicos de humor, os quais contribuem para a desregulação emocional, levando à hipo- ou hiper-reatividade emocional crônica. Os resultados desse artigo reforçam a nossa hipótese de que o TB não é uma doença caracterizada apenas por episódios recorrentes de humor, mas sobretudo por alteração global do comportamento que oscila desde a inibição até a ativação, variando desde alterações sutis e transitórias até episódios agudos de humor.

Dessa forma, uma abordagem diagnóstica multidimensional parece ser útil no TB, pois permite capturar informações clínicas relevantes tais como variações sutis no humor e em dimensões comportamentais (p. ex. cognição, reatividade emocional e motivação), o que poderia

contribuir para diagnósticos mais próximos da fisiopatologia da doença e, consequentemente, à intervenções terapêuticas mais adequadas.

No artigo 3 dessa tese investigamos, também, a PCR como um potencial marcador objetivo da reatividade emocional como uma dimensão importante no TB. Os pacientes com reatividade emocional anormal tiveram níveis de PCR significativamente mais elevados do que os pacientes com reatividade emocional normal. Entre os pacientes com reatividade emocional anormal, os pacientes com hiper-reatividade emocional apresentaram níveis de PCR significativamente mais elevados do que pacientes com hipo-reatividade emocional. Apesar de ter sido um estudo transversal, esse foi o primeiro estudo a avaliar a associação entre níveis de PCR e de reatividade emocional em uma grande amostra de pacientes bipolares em fase de remissão. Os achados desse estudo reforçaram nossa hipótese da PCR como um marcador da hiper-reatividade emocional em pacientes bipolares. O “proxy” reatividade emocional-PCR, se testado e confirmado em estudos futuros, poderia ser útil na prática clínica para discriminar, com mais precisão, pacientes bipolares com perfis clínicos diferentes. Clinicamente, a utilização de biomarcadores simples e de custo relativamente baixo como a PCR associados à dimensões relevantes como, por exemplo, a reatividade emocional poderia tornar o diagnóstico tradicional (baseado unicamente em categorias de sintomas) mais flexível.

A implementação de uma abordagem integrada no TB, incluindo dimensões fundamentais do comportamento e marcadores biológicos, poderia contribuir para a melhor caracterização dos sintomas de humor em pacientes bipolares e, possivelmente, para identificar mecanismos fisiopatológicos comuns entre indivíduos com perfis clínicos distintos, onde a inflamação crônica de baixo grau parece ser um estado biológico.

7.1.4 Reatividade emocional e funcionamento psicossocial no transtorno bipolar

Estudos relatam que o prejuízo no funcionamento psicossocial e cognitivo persiste durante a fase de remissão do TB (Rosa et al., 2008; Bonnín et al., 2012; Van Rheenen and Rossell, 2014*b*). Os resultados do artigo 3 dessa tese demonstraram que, apesar dos pacientes estarem em remissão, aqueles com desregulação emocional apresentaram maior prejuízo no funcionamento psicossocial. Pacientes com hipo-reatividade emocional apresentaram déficit no funcionamento global bem como em subdomínios de funcionamento, tais como autonomia, finanças e relações interpessoais. Por outro lado, os pacientes com hiper-reatividade emocional apresentaram prejuízo significativo no funcionamento cognitivo comparado aos pacientes com hipo-reatividade ou com reatividade emocional normal ($P < 0.001$). É importante lembrar que os pacientes com hiper-reatividade foram, também, os que apresentaram os níveis de PCR mais elevados em comparação aos outros pacientes incluídos no estudo. Se essa relação entre a reatividade emocional e funcionamento for confirmada em estudos futuros, um aspecto importante do tratamento dos pacientes bipolares seria, por um lado, a remediação emocional a fim de melhorar o funcionamento e, por outro, a remediação funcional (através da psicoterapia, suporte de serviço social, etc.) a fim de melhorar o controle emocional.

Apesar do artigo 3 dessa tese ter sido um estudo transversal, esse foi o primeiro estudo a demonstrar uma associação entre níveis aumentados de PCR, desregulação emocional e prejuízo no funcionamento cognitivo em pacientes bipolares durante a fase de remissão. As razões dessa associação ainda não são conhecidas, mas poderiam estar relacionadas aos processos inflamatórios que ocorrem na vasculatura do sistema nervoso central, especialmente, na barreira hemato-encefálica (Kuhlmann et al., 2009; Hsuchou et al., 2012). Ainda que não atravesse a

barreira hemato-encefálica, a PCR parece aumentar a permeabilidade dessa barreira para moléculas tais como autoanticorpos e citocinas pró-inflamatórias (Kuhlmann et al., 2009; Hsuchou, Kastin, Mishra, and Pan, 2012). Seguindo esse racional, os níveis aumentados de PCR na periferia poderiam indicar, ainda que indiretamente, um estado inflamatório cerebral. Estudos prospectivos são necessários para elucidar o papel da inflamação sistêmica crônica na progressão do TB, incluindo o prejuízo cognitivo e funcional encontrado nesses pacientes.

7.2 Perspectivas

O papel do sistema imune do cérebro ainda é controverso, contudo parece ser afetado pelo sistema imune periférico. A vasculatura cerebral, especialmente a barreira hemato-encefálica, é uma interface importante entre inflamação sistêmica periférica e o cérebro. Contudo, o papel dos níveis de PCR e, de maneira geral, da inflamação crônica no funcionamento da barreira hemato-encefálica ainda precisa ser elucidado.

A ideia de que apenas um gene específico, um único mecanismo biológico como, por exemplo, a inflamação crônica persistente, ou ainda o cérebro *per se*, não representam a doença como um todo, parece ser um passo extremamente importante para uma perspectiva integrada no TB. Se, essa perspectiva irá traduzir-se na descoberta de formas mais homogêneas do TB é uma das grandes questões que desafiam o campo e poderá ter implicações importantes no que diz respeito ao tratamento dos pacientes bipolares, dado o fato de que tal descoberta poderia aumentar sensivelmente a nossa capacidade de individualizar e, por conseguinte, melhorar as intervenções terapêuticas no TB.

A elucidação do papel da inflamação sistêmica crônica e da PCR no TB poderá oferecer intervenções inovadoras, integrando o manejo dos sintomas, das alterações sistêmicas e neuropatológicas, pondo em causa a persistente dicotomia cartesiana entre mente e corpo.

REFERÊNCIAS

Abbas AK, Lichtman AH, Pillai S. Cellular and molecular immunology. 8th ed. Philadelphia: Elsevier-Saunders; 2015.

Abdul Pari AA, Simon J, Wolstenholme J, Geddes JR, Goodwin GM. Economic evaluations in bipolar disorder: a systematic review and critical appraisal. Bipolar Disord. 2014 Sep;16(6):557–82.

Aksoy SN, Saygili EI, Bulbul F, Bahar A, Savas H, Vini O, et al. Myeloperoxidase enzyme levels and oxidative stress in bipolar disorders. Afr. J. Biotechnol. 2010;9(22):3318–23.

Albert MA, Glynn RJ, Ridker PM. Plasma concentration of C-reactive protein and the calculated Framingham Coronary Heart Disease Risk Score. Circulation. 2003 Jul 15;108(2):161–5.

Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. Crit. Rev. Clin. Lab. Sci. 2011 Aug;48(4):155–70.

Alonso J, Petukhova M, Vilagut G, Chatterji S, Heeringa S, Üstün TB, et al. Days out of role due to common physical and mental conditions: results from the WHO World Mental Health surveys. Mol. Psychiatry. 2011 Dec;16(12):1234–46.

Alsuwaidan MT, Kucyi A, Law CWY, McIntyre RS. Exercise and Bipolar Disorder: A Review of Neurobiological Mediators. NeuroMolecular Med. 2009 Dec;11(4):328–36.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). 4th ed. New York: APA; 2000.

Anders S, Tanaka M, Kinney DK. Depression as an evolutionary strategy for defense against infection. Brain. Behav. Immun. 2013 Jul;31:9–22.

Appleton AA, Buka SL, Loucks EB, Gilman SE, Kubzansky LD. Divergent associations of adaptive and maladaptive emotion regulation strategies with inflammation. Health Psychol. 2013;32(7):748–56.

Atzeni T, Henry C, Minois I, Gard S, Desage A, Zanouy L, et al. From inhibition to activation, from emotional hyporeactivity to emotional hyperreactivity: Two pathways to discriminate mood in bipolar disorders. Psychiatry Res. 2013 Aug;209(1):50–4.

Bai Y-M, Su T-P, Tsai S-J, Wen-Fei C, Li C-T, Pei-Chi T, et al. Comparison of inflammatory cytokine levels among type I/type II and manic/hypomanic/euthymic/depressive states of bipolar disorder. J. Affect. Disord. 2014 Sep;166:187–92.

Ballou SP, Lozanski G. Induction of inflammatory cytokine release from cultured human monocytes by C-reactive protein. Cytokine. 1992 Sep;4(5):361–8.

Becking K, Boschloo L, Vogelzangs N, Haarman BCM, Riemersma-van der Lek R, Penninx BWJH, et al. The association between immune activation and manic symptoms in patients with a depressive disorder. Transl. Psychiatry. 2013 Oct 22;3(10):e314.

Benros ME, Waltoft BL, Nordentoft M, Ostergaard SD, Eaton WW, Krogh J, et al. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. JAMA Psychiatry. 2013 Aug;70(8):812–20.

Berk M. Neuroprogression: pathways to progressive brain changes in bipolar disorder. Int. J. Neuropsychopharmacol. Off. Sci. J. Coll. Int. Neuropsychopharmacol. CINP. 2008;12(4):441–5.

Berk M, Dean O, Drexhage H, McNeil JJ, Moylan S, O'Neil A, et al. Aspirin: a review of its neurobiological properties and therapeutic potential for mental illness. BMC Med. 2013;11:74.

Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci. Biobehav. Rev. 2011 Jan;35(3):804–17.

Black S, Kushner I, Samols D. C-reactive Protein. J. Biol. Chem. 2004 Nov 19;279(47):48487–90.

Bonnín C del M, González-Pinto A, Solé B, Reinares M, González-Ortega I, Alberich S, et al. Verbal memory as a mediator in the relationship between subthreshold depressive symptoms and functional outcome in bipolar disorder. J. Affect. Disord. 2014 May;160:50–4.

Bonnín CM, Sánchez-Moreno J, Martínez-Arán A, Solé B, Reinares M, Rosa AR, et al. Subthreshold symptoms in bipolar disorder: impact on neurocognition, quality of life and disability. J. Affect. Disord. 2012 Feb;136(3):650–9.

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

Bosetti F, Rintala J, Seemann R, Rosenberger TA, Contreras MA, Rapoport SI, et al. Chronic lithium downregulates cyclooxygenase-2 activity and prostaglandin E(2) concentration in rat brain. Mol. Psychiatry. 2002;7(8):845–50.

Bosetti F, Weerasinghe GR, Rosenberger TA, Rapoport SI. Valproic acid down-regulates the conversion of arachidonic acid to eicosanoids via cyclooxygenase-1 and -2 in rat brain. J. Neurochem. 2003 May;85(3):690–6.

Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'anna M, Mascarenhas M, Escosteguy Vargas A, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J. Affect. Disord. 2009 Aug;116(3):214–7.

Brooks GC, Blaha MJ, Blumenthal RS. Relation of C-Reactive Protein to Abdominal Adiposity. Am. J. Cardiol. 2010 Jul;106(1):56–61.

Broome MR, Saunders KEA, Harrison PJ, Marwaha S. Mood instability: significance, definition and measurement. Br. J. Psychiatry. 2015 Oct 1;207(4):283–5.

Brown AS, Sourander A, Hinkka-Yli-Salomäki S, McKeague IW, Sundvall J, Surcel H-M. Elevated maternal C-reactive protein and autism in a national birth cohort. Mol. Psychiatry. 2014 Feb;19(2):259–64.

Burke NN, Geoghegan E, Kerr DM, Moriarty O, Finn DP, Roche. Altered neuropathic pain behaviour in a rat model of depression is associated with changes in inflammatory gene expression in the amygdala. Genes Brain Behav. 2013 Oct;12(7):705–13.

Capuron L, Miller AH. Immune system to brain signaling: Neuropsychopharmacological implications. Pharmacol. Ther. 2011 May;130(2):226–38.

Cardoso T, Bauer IE, Meyer TD, Kapczinski F, Soares JC. Neuroprogression and Cognitive Functioning in Bipolar Disorder: A Systematic Review. Curr. Psychiatry Rep. 2015 Sep;17(9):75.

Cermak J, Key NS, Bach RR, Balla J, Jacob HS, Vercellotti GM. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. Blood. 1993 Jul 15;82(2):513–20.

Chisholm D, van Ommeren M, Ayuso-Mateos J-L, Saxena S. Cost-effectiveness of clinical interventions for reducing the global burden of bipolar disorder. Br. J. Psychiatry J. Ment. Sci. 2005 Dec;187:559–67.

Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, et al. Exercise for depression. Cochrane Database Syst. Rev. 2013;(9):CD004366.

Couzin-Frankel J. Inflammation bares a dark side. Science. 2010 Dec 17;330(6011):1621.

Cunha AB, Andreazza AC, Gomes FA, Frey BN, da Silveira LE, Gonçalves CA, et al. Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci. 2008 Aug;258(5):300–4.

Cunha ÂB, Andreazza AC, Gomes FA, Frey BN, da Silveira LE, Gonçalves CA, et al. Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci. 2008 Aug;258(5):300–4.

Cunha ABM, Frey BN, Andreazza AC, Goi JD, Rosa AR, Gonçalves CA, et al. Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. Neurosci. Lett. 2006 May 8;398(3):215–9.

Dantzer R. Depression and Inflammation: An Intricate Relationship. Biol. Psychiatry. 2012 Jan;71(1):4–5.

Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 2008 Jan;9(1):46–56.

Dempsey PW, Vaidya SA, Cheng G. The art of war: Innate and adaptive immune responses. Cell. Mol. Life Sci. CMLS. 2003 Dec;60(12):2604–21.

Dickerson F, Stallings C, Origoni A, Boronow J, Yolken R. Elevated serum levels of C-reactive protein are associated with mania symptoms in outpatients with bipolar disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2007 May 9;31(4):952–5.

Dickerson F, Stallings C, Origoni A, Vaughan C, Khushalani S, Yolken R. Additive effects of elevated C-reactive protein and exposure to Herpes Simplex Virus type 1 on cognitive impairment in individuals with schizophrenia. Schizophr. Res. 2012 Jan;134(1):83–8.

Dickerson F, Stallings C, Origoni A, Vaughan C, Khushalani S, Yolken R. Elevated C-reactive protein and cognitive deficits in individuals with bipolar disorder. J. Affect. Disord. 2013 Sep 5;150(2):456–9.

Dimopoulos N, Piperi C, Salonicioti A, Mitropoulos P, Kallai E, Liappas I, et al. Indices of low-grade chronic inflammation correlate with early cognitive deterioration in an elderly Greek population. Neurosci. Lett. 2006 May 1;398(1-2):118–23.

Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010 Jan 9;375(9709):132–40.

Epstein FH, Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N. Engl. J. Med. 1999;340(6):448–54.

Ertenli I, Ozer S, Kiraz S, Apras SB, Akdogan A, Karadag O, et al. Infliximab, a TNF-α antagonist treatment in patients with ankylosing spondylitis: the impact on depression, anxiety and quality of life level. Rheumatol. Int. 2012 Feb;32(2):323–30.

Eyre HA, Papps E, Baune BT. Treating Depression and Depression-Like Behavior with Physical Activity: An

Immune Perspective. Front. Psychiatry [Internet]. 2013 [cited 2014 Jun 3];4. Available from: http://www.frontiersin.org/Journal/10.3389/fpsyt.2013.00003/full

Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience. 2013 Aug 29;246:199–229.

Ferrari AJ, Baxter AJ, Whiteford HA. A systematic review of the global distribution and availability of prevalence data for bipolar disorder. J. Affect. Disord. 2011 Nov;134(1-3):1–13.

Fond G, Hamdani N, Kapczinski F, Boukouaci W, Drancourt N, Dargel A, et al. Effectiveness and tolerance of anti-inflammatory drugs' add-on therapy in major mental disorders: a systematic qualitative review. Acta Psychiatr. Scand. 2014 Mar;129(3):163–79.

Fontoura PC, Pinto VLM, Matsuura C, Resende A de C, de Bem GF, Ferraz MR, et al. Defective nitric oxide-cyclic guanosine monophosphate signaling in patients with bipolar disorder: a potential role for platelet dysfunction. Psychosom. Med. 2012 Oct;74(8):873–7.

Fries GR, Pfaffenseller B, Stertz L, Paz AVC, Dargél AA, Kunz M, et al. Staging and neuroprogression in bipolar disorder. Curr. Psychiatry Rep. 2012 Dec;14(6):667–75.

Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N. Engl. J. Med. 1999 Feb 11;340(6):448–54.

Gazalle FK, Andreazza AC, Ceresér KM, Hallal PC, Santin A, Kapczinski F. Clinical impact of late diagnose of bipolar disorder. J. Affect. Disord. 2005 Jun;86(2-3):313–6.

Godin O, Etain B, Henry C, Bougerol T, Courtet P, Mayliss L, et al. Metabolic syndrome in a French cohort of patients with bipolar disorder: results from the FACE-BD cohort. J. Clin. Psychiatry. 2014 Oct;75(10):1078–85; quiz 1085.

Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. J. Clin. Psychiatry. 2009 Aug;70(8):1078–90.

Goodwin GM, Martinez-Aran A, Glahn DC, Vieta E. Cognitive impairment in bipolar disorder: neurodevelopment or neurodegeneration? An ECNP expert meeting report. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 2008 Nov;18(11):787–93.

Grande I, Fries GR, Kunz M, Kapczinski F. The role of BDNF as a mediator of neuroplasticity in bipolar disorder. Psychiatry Investig. 2010 Dec;7(4):243–50.

Gross JJ. The emerging field of emotion regulation: An integrative review. Rev. Gen. Psychol. 1998;2(3):271–99.

Gruber J, Harvey AG, Purcell A. What goes up can come down? A preliminary investigation of emotion reactivity and emotion recovery in bipolar disorder. J. Affect. Disord. 2011 Oct;133(3):457–66.

Gunstad J, Bausserman L, Paul RH, Tate DF, Hoth K, Poppas A, et al. C-reactive protein, but not homocysteine, is related to cognitive dysfunction in older adults with cardiovascular disease. J. Clin. Neurosci. Off. J. Neurosurg. Soc. Australas. 2006 Jun;13(5):540–6.

Harry GJ, Kraft AD. Neuroinflammation and microglia: considerations and approaches for neurotoxicity assessment. Expert Opin. Drug Metab. Toxicol. 2008 Oct;4(10):1265–77.

Harry GJ, Kraft AD. Microglia in the developing brain: a potential target with lifetime effects. Neurotoxicology. 2012 Mar;33(2):191–206.

Hart BL. Biological basis of the behavior of sick animals. Neurosci. Biobehav. Rev. 1988;12(2):123–37.

Hefner G, Shams MEE, Unterecker S, Falter T, Hiemke C. Inflammation and psychotropic drugs: the relationship between C-reactive protein and antipsychotic drug levels. Psychopharmacology (Berl.). 2016 May;233(9):1695–705.

Henry C, Etain B. New ways to classify bipolar disorders: going from categorical groups to symptom clusters or dimensions. Curr. Psychiatry Rep. 2010 Dec;12(6):505–11.

Henry C, Etain B, Godin O, Dargel AA, Azorin J-M, Gard S, et al. Bipolar patients referred to specialized services of care: Not resistant but impaired by sub-syndromal symptoms. Results from the FACE-BD cohort. Aust. N. Z. J. Psychiatry. 2015 Oct;49(10):898–905.

Henry C, Etain B, Mathieu F, Raust A, Vibert J-F, Scott J, et al. A French network of bipolar expert centres: A model to close the gap between evidence-based medicine and routine practice. J. Affect. Disord. 2011 Jun;131(1-3):358–63.

Henry C, M'Bailara K, Lépine J-P, Lajnef M, Leboyer M. Defining bipolar mood states with quantitative measurement of inhibition/activation and emotional reactivity. J. Affect. Disord. 2010 Dec;127(1-3):300–4.

Henry C, Mbailara K, Mathieu F, Poinsot R, Falissard B. Construction and validation of a dimensional scale exploring mood disorders: MAThyS (Multidimensional Assessment of Thymic States). BMC Psychiatry. 2008;8(1):82.

Henry C, M'Baïlara K, Poinsot R, Casteret A-A, Sorbara F, Leboyer M, et al. Evidence for two types of bipolar depression using a dimensional approach. Psychother. Psychosom. 2007;76(6):325–31.

Hirschfeld RM. Differential diagnosis of bipolar disorder and major depressive disorder. J. Affect. Disord. 2014 Dec;169 Suppl 1:S12–6.

Hirschfeld RMA, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. J. Clin. Psychiatry. 2003 Feb;64(2):161–74.

Hope S, Dieset I, Agartz I, Steen NE, Ueland T, Melle I, et al. Affective symptoms are associated with markers of inflammation and immune activation in bipolar disorders but not in schizophrenia. J. Psychiatr. Res. 2011 Dec;45(12):1608–16.

Houenou J, Frommberger J, Carde S, Glasbrenner M, Diener C, Leboyer M, et al. Neuroimaging-based markers of bipolar disorder: evidence from two meta-analyses. J. Affect. Disord. 2011 Aug;132(3):344–55.

Hsuchou H, Kastin AJ, Mishra PK, Pan W. C-Reactive Protein Increases BBB Permeability: Implications for Obesity and Neuroinflammation. Cell. Physiol. Biochem. 2012;30(5):1109–19.

Huang T-L, Lin F-C. High-sensitivity C-reactive protein levels in patients with major depressive disorder and bipolar mania. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2007 Mar;31(2):370–2.

Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. Arch. Gen. Psychiatry. 2005 Dec;62(12):1322–30.

Judd LL, Schettler PJ, Akiskal H, Coryell W, Fawcett J, Fiedorowicz JG, et al. Prevalence and clinical significance of subsyndromal manic symptoms, including irritability and psychomotor agitation, during bipolar major depressive episodes. J. Affect. Disord. 2012 May;138(3):440–8.

Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PVS, Kauer-Sant'Anna M, Klamt F, et al. A systemic toxicity index developed to assess peripheral changes in mood episodes. Mol. Psychiatry. 2010 Aug;15(8):784–6.

Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PVS, Kauer-Sant'Anna M, Klamt F, et al. Peripheral biomarkers and illness activity in bipolar disorder. J. Psychiatr. Res. 2011 Feb;45(2):156–61.

Kapczinski F, Vieta E, Andreazza AC, Frey BN, Gomes FA, Tramontina J, et al. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. Neurosci. Biobehav. Rev. 2008;32(4):675–92.

Kato T, Monji A, Hashioka S, Kanba S. Risperidone significantly inhibits interferon-gamma-induced microglial activation in vitro. Schizophr. Res. 2007 May;92(1-3):108–15.

Kauer-Sant'Anna M, Bond DJ, Lam RW, Yatham LN. Functional outcomes in first-episode patients with bipolar disorder: a prospective study from the Systematic Treatment Optimization Program for Early Mania project. Compr. Psychiatry. 2009 Jan;50(1):1–8.

Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Young LT, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int. J. Neuropsychopharmacol. Off. Sci. J. Coll. Int. Neuropsychopharmacol. CINP. 2009 May;12(4):447–58.

Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med. Care. 1989 Mar;27(3 Suppl):S178–89.

Kempton MJ, Geddes JR, Ettinger U, Williams SCR, Grasby PM. Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. Arch. Gen. Psychiatry. 2008 Sep;65(9):1017–32.

Kent S, Bluthé RM, Kelley KW, Dantzer R. Sickness behavior as a new target for drug development. Trends Pharmacol. Sci. 1992 Jan;13(1):24–8.

Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. Annu. Rev. Psychol. 2002;53:83–107.

King DE, Egan BM, Geesey ME. Relation of dietary fat and fiber to elevation of C-reactive protein. Am. J. Cardiol. 2003 Dec;92(11):1335–9.

Knijff EM, Breunis MN, Kupka RW, de Wit HJ, Ruwhof C, Akkerhuis GW, et al. An imbalance in the production of IL-1beta and IL-6 by monocytes of bipolar patients: restoration by lithium treatment. Bipolar Disord. 2007 Nov;9(7):743–53.

Kubzansky LD, Park N, Peterson C, Vokonas P, Sparrow D. Healthy psychological functioning and incident coronary heart disease: the importance of self-regulation. Arch. Gen. Psychiatry. 2011 Apr;68(4):400–8.

Kuhlmann CRW, Librizzi L, Closhen D, Pflanzner T, Lessmann V, Pietrzik CU, et al. Mechanisms of C-Reactive Protein-Induced Blood-Brain Barrier Disruption * Supplemental Methods. Stroke. 2009 Apr 1;40(4):1458–66.

Kupfer DJ. The Increasing Medical Burden in Bipolar Disorder. JAMA. 2005 May 25;293(20):2528.

Lackner N, Mangge H, Reininghaus EZ, McIntyre RS, Bengesser SA, Birner A, et al. Body fat distribution and associations with metabolic and clinical characteristics in bipolar individuals. Eur. Arch. Psychiatry Clin. Neurosci. 2015 Jun;265(4):313–9.

Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? J. Affect. Disord. 2012 Dec 1;141(1):1–10.

Lee M-S, Anumagalla P, Talluri P, Pavuluri MN. Meta-analyses of developing brain function in high-risk and emerged bipolar disorder. Front. Psychiatry. 2014;5:141.

Lindqvist D, Janelidze S, Hagell P, Erhardt S, Samuelsson M, Minthon L, et al. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. Biol. Psychiatry. 2009 Aug 1;66(3):287–92.

Magalhães PV, Kapczinski F, Nierenberg AA, Deckersbach T, Weisinger D, Dodd S, et al. Illness burden and medical comorbidity in the Systematic Treatment Enhancement Program for Bipolar Disorder. Acta Psychiatr. Scand. 2012 Apr;125(4):303–8.

Maletic V, Raison C. Integrated Neurobiology of Bipolar Disorder. Front. Psychiatry [Internet]. 2014 Aug 25 [cited 2015 Jan 18];5. Available from: http://journal.frontiersin.org/Journal/10.3389/fpsyt.2014.00098/full

Mansur RB, Brietzke E, McIntyre RS. Is there a "metabolic-mood syndrome"? A review of the relationship between obesity and mood disorders. Neurosci. Biobehav. Rev. [Internet]. 2015 Jan [cited 2015 Feb 23]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0149763415000020

Martinez-Aran A, Vieta E. Cognition as a target in schizophrenia, bipolar disorder and depression. Eur. Neuropsychopharmacol. 2015 Feb;25(2):151–7.

Martínez-Arán A, Vieta E, Colom F, Torrent C, Sánchez-Moreno J, Reinares M, et al. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar Disord. 2004 Jun;6(3):224–32.

Marwaha S, Balbuena L, Winsper C, Bowen R. Mood instability as a precursor to depressive illness: A prospective and mediational analysis. Aust. N. Z. J. Psychiatry. 2015 Jun;49(6):557–65.

Marwaha S, He Z, Broome M, Singh SP, Scott J, Eyden J, et al. How is affective instability defined and measured? A systematic review. Psychol. Med. 2014 Jul;44(09):1793–808.

McElroy SL, Keck PE. Obesity in bipolar disorder: an overview. Curr. Psychiatry Rep. 2012 Dec;14(6):650–8.

Merikangas KR, Jin R, He J-P, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch. Gen. Psychiatry. 2011 Mar;68(3):241–51.

Miller AH, Haroon E, Raison CL, Felger JC. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depress. Anxiety. 2013 Apr;30(4):297–306.

Miller AH, Maletic V, Raison CL. Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression. Biol. Psychiatry. 2009 May;65(9):732–41.

Miller CL, Llenos IC, Cwik M, Walkup J, Weis S. Alterations in kynurenine precursor and product levels in schizophrenia and bipolar disorder. Neurochem. Int. 2008 May;52(6):1297–303.

Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biol. Psychiatry. 2013 Jul 1;74(1):15–25.

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br. J. Psychiatry J. Ment. Sci. 1979 Apr;134:382–9.

Munkholm K, Vinberg M, Vedel Kessing L. Cytokines in bipolar disorder: a systematic review and meta-analysis. J. Affect. Disord. 2013 Jan 10;144(1-2):16–27.

Nery FG, Monkul ES, Hatch JP, Fonseca M, Zunta-Soares GB, Frey BN, et al. Celecoxib as an adjunct in the

treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. Hum. Psychopharmacol. 2008 Mar;23(2):87–94.

Padmos RC, Hillegers MHJ, Knijff EM, Vonk R, Bouvy A, Staal FJT, et al. A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. Arch. Gen. Psychiatry. 2008 Apr;65(4):395–407.

Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J. Clin. Invest. 2003 Jun 15;111(12):1805–12.

Persoons P, Vermeire S, Demyttenaere K, Fischler B, Vandenberghe J, Van Oudenhove L, et al. The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. Aliment. Pharmacol. Ther. 2005 Jul 15;22(2):101–10.

Pfaffenseller B, Fries GR, Wollenhaupt-Aguiar B, Colpo GD, Stertz L, Panizzutti B, et al. Neurotrophins, inflammation and oxidative stress as illness activity biomarkers in bipolar disorder. Expert Rev. Neurother. 2013 Jul;13(7):827–42.

Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. The Lancet. 2013;381(9878):1663–71.

Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol. Psychiatry. 2008 Sep;13(9):829, 833–57.

Raison CL, Miller AH. Malaise, melancholia and madness: The evolutionary legacy of an inflammatory bias. Brain. Behav. Immun. 2013 Jul;31:1–8.

Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013 Jan;70(1):31–41.

Rao JS, Harry GJ, Rapoport SI, Kim HW. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. Mol. Psychiatry. 2010 Apr;15(4):384–92.

Rees DI, Sabia JJ. Exercise and adolescent mental health: new evidence from longitudinal data. J. Ment. Health Policy Econ. 2010 Mar;13(1):13–25.

Remlinger-Molenda A, Wojciak P, Michalak M, Karczewski J, Rybakowski JK. Selected cytokine profiles during remission in bipolar patients. Neuropsychobiology. 2012;66(3):193–8.

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto Jr AM, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N. Engl. J. Med. 2008;359(21):2195.

Roberts WL, Moulton L, Law TC, Farrow G, Cooper-Anderson M, Savory J, et al. Evaluation of nine automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. Part 2. Clin. Chem. 2001 Mar;47(3):418–25.

Rosa AR, Franco C, Martínez-Aran A, Sánchez-Moreno J, Reinares M, Salamero M, et al. Functional impairment in patients with remitted bipolar disorder. Psychother. Psychosom. 2008;77(6):390–2.

Rosa AR, González-Ortega I, González-Pinto A, Echeburúa E, Comes M, Martínez-Àran A, et al. One-year psychosocial functioning in patients in the early vs. late stage of bipolar disorder: Functioning in patients with first- vs. multiple-episode bipolar disorder. Acta Psychiatr. Scand. 2012 Apr;125(4):335–41.

Rosa AR, Magalhaes PV, Czepielewski L, Sulzbach MV, Goi PD, Vieta E, et al. Clinical staging in bipolar disorder:

focus on cognition and functioning. J. Clin. Psychiatry. 2014;75(5):e450–6.

Rosa AR, Reinares M, Michalak EE, Bonnin CM, Sole B, Franco C, et al. Functional impairment and disability across mood states in bipolar disorder. Value Health J. Int. Soc. Pharmacoeconomics Outcomes Res. 2010 Dec;13(8):984–8.

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

Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: A review of the interactions between inflammation and mood disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2014 Aug;53:23–34.

Roshanaei-Moghaddam B, Katon W. Premature mortality from general medical illnesses among persons with bipolar disorder: a review. Psychiatr. Serv. Wash. DC. 2009 Feb;60(2):147–56.

Savitz J, Preskorn S, Teague TK, Drevets D, Yates W, Drevets W. Minocycline and aspirin in the treatment of bipolar depression: a protocol for a proof-of-concept, randomised, double-blind, placebo-controlled, 2x2 clinical trial. BMJ Open. 2012;2(1):e000643.

Sharma AN, Bauer IE, Sanches M, Galvez JF, Zunta-Soares GB, Quevedo J, et al. Common biological mechanisms between bipolar disorder and type 2 diabetes: Focus on inflammation. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2014 Oct;54:289–98.

Söderlund J, Olsson SK, Samuelsson M, Walther-Jallow L, Johansson C, Erhardt S, et al. Elevation of cerebrospinal fluid interleukin-1ß in bipolar disorder. J. Psychiatry Neurosci. JPN. 2011 Mar;36(2):114–8.

Solé B, Bonnin CM, Mayoral M, Amann BL, Torres I, González-Pinto A, et al. Functional remediation for patients with bipolar II disorder: Improvement of functioning and subsyndromal symptoms. Eur. Neuropsychopharmacol. 2015 Feb;25(2):257–64.

Solé B, Jiménez E, Martinez-Aran A, Vieta E. Cognition as a target in major depression: New developments. Eur. Neuropsychopharmacol. 2015 Feb;25(2):231–47.

Spranger J, Kroke A, Möhlig M, Hoffmann K, Bergmann MM, Ristow M, et al. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Diabetes. 2003 Mar;52(3):812–7.

Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain. Behav. Immun. 2007 Oct;21(7):901–12.

Stertz L, Magalhães PVS, Kapczinski F. Is bipolar disorder an inflammatory condition? The relevance of microglial activation. Curr. Opin. Psychiatry. 2013 Jan;26(1):19–26.

Strejilevich SA, Samamé C, Martino DJ. The trajectory of neuropsychological dysfunctions in bipolar disorders: A critical examination of a hypothesis. J. Affect. Disord. 2015 Apr;175:396–402.

Tillett WS, Francis T. SEROLOGICAL REACTIONS IN PNEUMONIA WITH A NON-PROTEIN SOMATIC FRACTION OF PNEUMOCOCCUS. J. Exp. Med. 1930 Sep 30;52(4):561–71.

Tohen M, Frank E, Bowden CL, Colom F, Ghaemi SN, Yatham LN, et al. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. Bipolar Disord. 2009;11(5):453–73.

Tohen M, Hennen J, Zarate CM, Baldessarini RJ, Strakowski SM, Stoll AL, et al. Two-year syndromal and

functional recovery in 219 cases of first-episode major affective disorder with psychotic features. Am. J. Psychiatry. 2000 Feb;157(2):220–8.

Tsai S-Y, Chung K-H, Wu J-Y, Kuo C-J, Lee H-C, Huang S-H. Inflammatory markers and their relationships with leptin and insulin from acute mania to full remission in bipolar disorder. J. Affect. Disord. 2012 Jan;136(1-2):110–6.

Ustün B, Kennedy C. What is "functional impairment"? Disentangling disability from clinical significance. World Psychiatry Off. J. World Psychiatr. Assoc. WPA. 2009 Jun;8(2):82–5.

Vancampfort D, Vansteelandt K, Correll CU, Mitchell AJ, De Herdt A, Sienaert P, et al. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. Am. J. Psychiatry. 2013 Mar 1;170(3):265–74.

Van Rheenen TE, Meyer D, Rossell SL. Pathways between neurocognition, social cognition and emotion regulation in bipolar disorder. Acta Psychiatr. Scand. 2014 Nov;130(5):397–405.

Van Rheenen TE, Rossell SL. Objective and subjective psychosocial functioning in bipolar disorder: An investigation of the relative importance of neurocognition, social cognition and emotion regulation. J. Affect. Disord. 2014 Jun;162:134–41.

Van Rheenen TE, Rossell SL. Objective and subjective psychosocial functioning in bipolar disorder: An investigation of the relative importance of neurocognition, social cognition and emotion regulation. J. Affect. Disord. 2014 Jun;162:134–41.

Vogelzangs N, Beekman ATF, de Jonge P, Penninx BWJH. Anxiety disorders and inflammation in a large adult cohort. Transl. Psychiatry. 2013 Apr;3(4):e249.

Vuksan-Ćusa B, Šagud M, Jakovljević M. C-reactive protein and metabolic syndrome in patients with bipolar disorder compared to patients with schizophrenia. Psychiatr. Danub. 2010;22(2):275–7.

Vuksan-Cusa B, Sagud M, Jakovljevic M, Peles AM, Jaksic N, Mihaljevic S, et al. Association between C-reactive protein and homocysteine with the subcomponents of metabolic syndrome in stable patients with bipolar disorder and schizophrenia. Nord. J. Psychiatry. 2013 Oct;67(5):320–5.

Wadee AA, Kuschke RH, Wood LA, Berk M, Ichim L, Maes M. Serological observations in patients suffering from acute manic episodes. Hum. Psychopharmacol. 2002 Jun;17(4):175–9.

Wessa M, Kanske P, Linke J. Bipolar disorder: A neural network perspective on a disorder of emotion and motivation. Restor. Neurol. Neurosci. 2014;32(1):51–62.

Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, others. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. The Lancet. 2013;382(9904):1575–86.

Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet Lond. Engl. 2013 Nov 9;382(9904):1575–86.

Wium-Andersen MK, Ørsted DD, Nielsen SF, Nordestgaard BG. Elevated C-Reactive Protein Levels, Psychological Distress, and Depression in 73 131 Individuals. JAMA Psychiatry. 2013 Feb 1;70(2):176.

Wium-Andersen MK, Ørsted DD, Nordestgaard BG. Elevated C-reactive protein associated with late- and very-late-onset schizophrenia in the general population: a prospective study. Schizophr. Bull. 2014 Sep;40(5):1117–

27.

Wium-Andersen MK, Orsted DD, Nordestgaard BG. Elevated C-reactive protein and late-onset bipolar disorder in 78 809 individuals from the general population. Br. J. Psychiatry. 2016 Feb 1;208(2):138–45.

World Health Organization. The Global Burden of Disease: 2004. Geneva: WHO; 2008.

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

ANEXO A – BIPOLAR PATIENTS REFERRED TO SPECIALIZED SERVICES OF CARE: NOT RESISTANT BUT IMPAIRED BY SUBSYNDROMAL SYMPTOMS

Bipolar patients referred to specialized services of care: not resistant but impaired by sub-syndromal symptoms

Henry, C.; Etain, B.; Godin, O.; Dargel, A. A.; Azorin, J-M.; Gard, S.; Bellivier, F.; Bougerol, T.; Kahn, J-P.; Passerieux, C.; Aubin, V.; Courtet, P.; Leboyer, M.

Publicado em Australian and New Zealand Journal of Psychiatry.

Bipolar patients referred to specialized services of care: Not resistant but impaired by sub-syndromal symptoms. Results from the FACE-BD cohort

Chantal Henry[1,2,3,4], Bruno Etain[1,2,3,4], Ophelia Godin[4,5], Aroldo Ayub Dargél[2,3,4,6,7], Jean-Michel Azorin[4,8,9] Sébastien Gard[4,10], Frank Bellivier[4,11], Thierry Bougerol[1,4,12,13,14], Jean-Pierre Kahn[1,4,15], Christine Passerieux[4,16,17], Valerie Aubin[4,18], Philippe Courtet[4,19,20] and Marion Leboyer[1,2,3,4]; FACE-BD group

Abstract

Objective: A national network of expert centers for bipolar disorders was set up in France to provide support, mainly for psychiatrists, who need help for managing bipolar disorder patients. The aims of this article are to present the main characteristics of the patients referred to an expert center in order to highlight the major disturbances affecting these patients and to understand the most significant difficulties encountered by practitioners dealing with bipolar disorder patients.

Methods: Patients were evaluated by trained psychiatrists and psychologists, with standardized and systematic assessment using interviews and self-report questionnaires.

Results: All patients (n=839) met Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition criteria for bipolar disorder I (48.4%), bipolar disorder II (38.1%) or bipolar disorder–not otherwise specified (13.5%). Mean illness duration was 17 years (±11.3), with 41.9% of patients having a history of suicide attempts. Lifetime comorbidities were 43.8% for anxiety disorders and 32.8% for substance abuse. At the point of inclusion, most patients (76.2%) were not in an acute phase, being considered to have a syndromal remission, but which still required referral to a tertiary system of care. Among these patients, 37.5% had mild to moderate residual depressive symptoms (Montgomery and Asberg Depression Rating Scale ranging from 7 to 19) despite 39% receiving an antidepressant. However, 47.8% were considered to be poorly adherent to medication; 55% showed evidence of sleep disturbances, with half being overweight; 68.1% of patients showed poor functioning (Functioning Assessment Short Test 12) with this being linked to residual depressive symptoms, sleep disturbances and increased body mass index.

Conclusions: It appears that bipolar disorder patients referred to an expert center in most cases do not suffer from a severe or resistant illness but they rather have residual symptoms, including subtle but chronic perturbations that have a major impact on levels of functioning. The longitudinal follow-up of these patients will enable a better understanding of the evolution of such residual symptoms.

Keywords

Bipolar disorders, expert center, residual depressive symptoms, remitted phase, functioning

[1]Université Paris-Est, UMR_S955, UPEC, Créteil, France
[2]Inserm, U955, Equipe 15 Psychiatrie génétique, Créteil, France
[3]AP-HP, Hôpital H. Mondor—A. Chenevier, Pôle de psychiatrie, Créteil, France
[4]Fondation FondaMental, fondation de cooperation scientifique, Créteil, France
[5]UPMC Université Paris 06, UMRS 943, Paris, France
[6]Instituto Nacional de Ciência e Tecnologia—Translacional em Medicina (INCT) e Laboratório de Psiquiatria Molecular, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil
[7]Programa de Pós Graduação em Ciências Médicas: Psiquiatria, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil
[8]Pôle de psychiatrie, Hôpital Sainte Marguerite, Assistance Publique Hôpitaux de Marseille, Marseille, France
[9]Aix-Marseille Université, CNRS, CRN2M UMR 7286, Marseille, France
[10]Hôpital Charles Perrens, Centre Expert Trouble Bipolaire, Service de psychiatrie adulte, Bordeaux, France
[11]AP-HP, GH Saint-Louis—Lariboisière—Fernand Widal, Pôle Neurosciences, Paris, France
[12]Université Joseph Fourier, Grenoble, France
[13]CHU de Grenoble, Grenoble, France
[14]Grenoble Institut des Neurosciences (GIN) Inserm U836, La Tronche, France
[15]Centre Hospitalier Universitaire de Nancy, Hôpitaux de Brabois, Université de Lorraine, Nancy, France
[16]Centre Hospitalier de Versailles, Le Chesnay, France
[17]Université Versailles-Saint-Quentin-en-Yvelines, Versailles, France
[18]Centre Hospitalier Princesse Grace, Monaco
[19]Psychiatric Emergency Department, CHRU Montpellier, Montpellier, France
[20]Inserm U1061, Université Montpellier, Montpellier, France

Corresponding author:
Chantal Henry, Université Paris-Est, UMR_S955, UPEC, Hôpital A. Chenevier, Pavillon Hartmann, 40, rue de Mesly, F-94000 Créteil, France
Email: chantal.henry@inserm.fr

Introduction

A national network of expert centers for bipolar disorders (BDs) (FondaMental Advanced Centres of Expertise for Bipolar Disorders; FACE-BD) was set up in France to provide support for psychiatrists who need help for managing BD patients. In some cases, patients can also be referred by general practitioners (GPs), when BD is suspected, allowing their orientation to a specialized care system (Henry et al., 2011). The goals are to provide advice about potential treatment targets that is based on an accurate evaluation and which enhances concordance between evidence-based medicine guidelines and clinical practice, thereby promoting a personalized medicine approach. The network represents a tertiary system of care open to all BD sub-types allowing a large spectrum of patients to be included. Traditionally, specialized services of care are usually considered only for severe and/or complex or resistant presentations meaning that research based on such severe BD presentations will not be representative of the population of BD patients.

However, several elements can influence access to specialized care. First, guidelines have become more complex, meaning that clinicians may become more prone to referrals to a specialized care system. Moreover, even if guidelines exist for prophylactic treatment that are built on evidence-based medicine, we lack information on very long-term management of BD patients, given the frequent complexity of presenting cases.

Second, patients have access to medical information from a wide array of sources, including consumer medicines information, media reports and Internet web sites. It is hoped that improved 'medicine health information' will help with patient compliance, reduce adverse events and result in better health outcomes. In turn, this may also change exigency levels of BD patients and their willingness to utilize specialized care.

Finally, there is now evidence that the manifestations of BD are not restricted to recurrent episodes of (hypo)mania or depression, but that there is also a more subtle chronic course than initially conceptualized (Leboyer et al., 2012). In most cases, the inter-episodic periods are characterized by residual symptoms (Judd et al., 2003), subtle cognitive impairment (Martínez-Arán et al., 2004), increased impulsivity (Etain et al., 2013; Swann et al., 2009) and emotional hyper reactivity (Henry et al., 2008), as well as sleep and circadian rhythm abnormalities (Harvey et al., 2005). All these disturbances seem to be strongly linked to long-term prognosis and significantly impact on functioning (Soreca et al., 2009). Specialized care can be perceived as a system that can help achieve functional recovery by offering solutions for these chronic course elements (Henry and Etain, 2010).

To better understand the role of these specialized care services, there is a need to better know the nature of BD patients referred to them. The aim of this report is to assess the global characteristics of the BD patients referred to expert centers, in turn indicating the main difficulties that practitioners face in the management of BD patients.

Method

Design of FACE-BD

The methods are presented briefly below and have been described in more detail elsewhere (Henry et al., 2011). The network of expert centers dedicated to BD is an innovative health care system in France. Until now, mental health care in France has been based essentially on catchment areas. Because of the complexity of diagnosis and care of BD disorders, this network was created to provide support to clinicians for the management of BD patients and, in parallel, to generate clinically relevant research.

Site selection

Sites must be affiliated to an academic center that is actively involved in BD care and research, and have the motivation to integrate into the network. Currently, there are nine expert centers in France. Members of the clinical teams from each center have joint monthly meetings to ensure inter-rater reliability, to receive or provide training in new therapeutic interventions, to develop research protocols and to maintain the levels of expertise required in this tertiary care system that is associated with specialized care and research.

Participant enrollment

Patients are referred by a GP or psychiatrist (mainly a psychiatrist), who subsequently receives a detailed evaluation report that outlines potential therapeutic interventions. Although patients are re-assessed and followed at the expert center, routine care and treatment is still managed by the referring physician.

There are no exclusion criteria for referral, and all patients who appear to meet the diagnostic criteria for any BD subtype (I, II or not otherwise specified [NOS]) can be assessed. Patients are only outpatients and are not referred to us in emergency. The assessment protocol was approved by the relevant ethical review board and requires only a letter of information for patients (CPP-Ile de France IX, 18 January 2010). A web-based application, e-bipolar© was developed to collate data for clinical monitoring and research purposes. Access to the system is carefully regulated and approval was obtained from the body overseeing the safety of computerized databases (CNIL) (DR-2011-069).

Assessments

In this study, we have focused on the general characteristics of the referred BD presentations allowing the assessment of

their current state to better clarify why patients are referred to us. The Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition* (DSM-IV) Axis I Disorders (SCID) was used to confirm BD diagnosis, as well as to evaluate the course of the disease (First, 1996). SCID was also used to identify comorbid psychiatric disorders. Current mood state was assessed using the Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Young Mania Rating Scale (Young et al., 1978).

In the first part of the study, we have included all patients referred to us and meeting a BD diagnosis. In the second part, we keep only the patients who are not in an acute episode, being normothymic or with sub-syndromal symptoms.

Current psychotropic treatments were recorded and adherence to treatment is checked using the French version of the Medication Adherence Rating Scale (MARS) (Misdrahi et al., 2004). MARS is a 10-yes/no item questionnaire, which includes reverse items, being a self-reporting multidimensional instrument along three dimensions that were determined by two previous principal component factor analyses and has been utilized in previous studies. The three dimensions are 'medication adherence behavior' (items 1–4), 'attitude toward medication' (items 5–8) and 'negative side effects and attitudes to psychotropic medication' (item 9 and 10). The total score and the three sub-scores are obtained by summing the items. A low score is correlated with a low likelihood of medication adherence and a total score ≥ 8 is associated with a higher likelihood of medication adherence.

Global social functioning was evaluated using the Global Assessment of Functioning scale (GAF) and the Functioning Assessment Short Test (FAST) (Rosa et al., 2007). The FAST is an interview developed to evaluate disability in BD patients and includes items on autonomy, work, cognitive functioning, financial issues and interpersonal relationships. This scale provides a total score of functioning and also six specific domain sub-scores.

Sleep disturbance was assessed with the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), which is a 19-item self-completed questionnaire requiring the participant to describe patterns of sleep, such as typical bedtime and wake time, sleep latency and actual sleep time. The patient is also asked about sleeping habits and quality. The French version of this questionnaire has been validated by Blais et al. (1997).

The same package of evaluations has been adopted by all centers, and the full assessment is performed by members of a specialized multidisciplinary team: a nurse, a clinical psychologist, a neuro-psychologist and a psychiatrist.

Statistical methods

Socio-demographic characteristics and the principal clinical feature of the disease and comorbidities for the first 839 BD patients included in the cohort are presented. Measures of means and dispersion (standard deviation, SD) were used for continuous data and frequency distribution for categorical variables.

Since a high proportion of patients are referred to us in a non-acute episode ($n = 588$), we present disease characteristics and comorbidities of this sub-sample and we have explored the links between these characteristics and functioning. To evaluate the association between functioning and various factors (clinical characteristics and comorbidities), we performed a multivariate linear regression analysis. SAS software (release 9.1; SAS Statistical Institute, Cary, NC) was used for the statistical analyses.

Results

Demographic characteristics

The sample included 839 BD patients. The mean age of the participants was 41.6 (±12.9) years and 57.7% were female (see Table 1). Approximately half of the patients (50.9%) were married, with one-third (34.4%) being single.

A large proportion of the patients (83%) had a high school diploma. Unemployment was prevalent, with 21.1% of the patients unemployed (double the French national unemployment rate).

Clinical features and treatment

In our sample, 48.4% of patients met criteria for BD I disorder, 38.1% BD II and the remaining patients were classified as BD NOS. The mean age at onset was 24.7 (±10.4) years: the age at first pharmacological treatment, irrespective of the pharmaceutical class, was 27.2 (±10.8) years, and the mean age at first hospitalization was 30.7 (±12.1) years.

The polarity of the first episode was a major depressive episode in most cases (73.8%) and the first manifestation of the disorder was manic or hypomanic states for only 23.2% of the patients. The predominant polarity of all episodes was depressive, with means of 4.6 (±3.7) depressive episodes, 1.3 (±2.0) manic episodes and 2.5 (±3.2) hypomanic episodes.

For lifetime comorbidities, the rates of anxiety disorders was 43.8% and substance abuse 32.8%; 41.9% of the patients had a history of suicide attempts; 15.5% of the patients fulfilled criteria of rapid cycling. The mean number of medication received was 2.4 (±1.3) (Table 2), with 42% of patients receiving an antidepressant. The most frequently prescribed class of mood stabilizers was anticonvulsants (57.5%) followed by atypical antipsychotics (APA) (32.4%) and lithium (31.5%).

Most patients (76.2%) were not in an acute phase when referred to us. The clinical characteristics in this sub-sample are presented in Table 3. Although the patients were

Table 1. Demographic and illness characteristics of the entire cohort.

	FACE-BD (%), n=839
Demographic characteristics	
Gender	
Female	57.7
Male	42.3
Age (years) mean (SD)	41.6 (12.9)
Marital status	
Married	50.9
Separated/divorced	13.5
Widowed	1.1
Single	34.4
High level of education (≥Baccalaureat)	
No	16.8
Yes	83.2
Occupational status	
Full-time	48.0
Part-time	
Unemployed	21.1
Pension	3.6
Retired	8.3
Other	19.1
Illness characteristics	
Bipolar sub-types	
Bipolar I	48.4
Bipolar II	38.1
Bipolar NOS	13.5
Duration of illness, mean (SD)	17.0 (11.3)
Age of onset, mean (SD)	24.7 (10.4)
Age of first treatment, mean (SD)	27.2 (10.8)
Age of first hospitalization, mean (SD)	30.7 (12.1)
First mood episode	
Depression	73.8
Manic	13.0
Mixed	3.1
Hypomanic	10.2
Number of episodes, mean (SD)	
Depression	4.6 (3.7)
Manic	1.3 (2.0)
Mixed	0.4 (1.1)
Hypomanic	2.5 (3.2)
Total	7.1 (6.1)
Number of episode/year of evolution, mean (SD)	
Depression	0.4 (0.5)
Manic	0.12 (0.2)
Mixed	0.03 (0.09)
Hypomanic	0.2 (0.9)
Rapid cycling (current)	15.5
Lifetime comorbidity	
Anxiety disorders	43.8
Substances misuse	32.8
History of suicide attempt	41.9
Mood state at study entry—not in an acute phase, % (n)	76.2% (588)
Referring doctors	
General practitioner	15.2
Psychiatrist	72.9
Other	12.0

FACE-BD: FondaMental Advanced Centres of Expertise for Bipolar Disorders; SD: standard deviation; NOS: not otherwise specified.

Table 2. Pharmacological treatment (based on 610 patients).

	FACE-BD (%), n=610
Type of medication	
Antidepressant	42.0
Neuroleptics	26.1
APA	32.4
Lithium	31.5
Anticonvulsant	57.5
Anxiolytic/hypnotic	31.8
Number of medication, mean (SD)	2.4 (1.3)
Number of medication	
Monotherapy	29.6
Bi-therapy	33.8
Three	19.4
> Three	17.2

FACE-BD: FondaMental Advanced Centres of Expertise for Bipolar Disorders; APA: atypical antipsychotics; SD: standard deviation.

supposed to be in syndromal remission, most of them had residual symptoms. In particular, 59.7% of patients had at least one depressive symptom, and the scores at the MADRS ranged from 7 to 19 in 37.5% of patients due to mild to moderate depressive symptoms, despite 39% being in receipt of an antidepressant. Manic symptoms were less prevalent than depressive symptoms: 32.1% of patients had one or more manic symptom, although 94.6% of the patients had a YOUNG score below or equal to 8. Almost half of these patients (47.8%) were considered to be non-adherent to medication (MARS score below 8). These patients also showed moderate to serious impairment of global functioning as assessed using the GAF scale (5.4% had a score < 51 and 48.4% a score < 70). Using the FAST, a more specific tool to assess BD patient functioning, we obtained a mean total score of 17.6 (SD = 12.9) corresponding to 68.1% of patient with an impaired functioning (FAST total score ≥12).

Half of these patients also had sleeping disturbances (55.1% had an abnormal PSQI score) and 48.4% were overweight or obese, with a body mass index (BMI) > 25.

We used multivariate linear regression to assess the consequences of these clinical characteristics on the functioning, as assessed with FAST (Table 4). The main factors impacting functioning are residual depressive symptoms (MADRS total score, $p < 0.0001$), sleep disturbances (PSQI total score, $p = 0.005$) and BMI ($p < 0.0003$). Considering the FAST sub-scores, corrected for multiple testing ($p < 0.01$), depressive symptoms assessed with the MADRS had an impact on all sub-scores (autonomy, work, cognitive functioning, financial issues, leisure and interpersonal relationships) ($p < 0.0001$); non-adherence had an negative impact on autonomy ($p < 0.0065$); poor sleep had an impact on leisure ($p = 0.0049$) and interpersonal relationships ($p < 0.003$); a high BMI had a bad impact on all the sub-scores except on work.

Table 3. Characteristics of the sample considered in a remitted phase (n = 588).

Number of depressive symptoms, mean (SD)	1.6 (2.0)
0	40.4
At least one	49.4
MADRS, total score, mean (SD), (range)	6.4 (5.9), (0–31)
0–6: Euthymic	58.1
7–19: Mild depression	37.5
> 20	4.5
Number of manic symptoms, mean (SD)	0.6 (1.3)
0	67.9
At least one	32.1
YOUNG, total score, mean (SD), (range)	2.1 (3.1), (0–17)
≤ 8	94.6
> 8	5.5
GAF, mean (SD), range	70.3 (12.5), (31–100)
100–71	46.2
70–51	48.4
< 51	5.4
MARS	
0–7	47.8
8–10	54.2
PSQI total score, mean (SD)	6.6 (3.6)
Abnormal PSQI score > 5	55.1
Body mass index	
< 25	51.7
25–30	33.7
> 30	14.7
FAST, total score, mean (SD)	17.6 (12.9)
< 12	31.9
≥12	68.1

SD: standard deviation; MADRS: Montgomery and Asberg Depression Rating Scale; GAF: Global Assessment of Functioning scale; MARS: Medication Adherence Rating Scale; PSQI: Pittsburgh Sleep Quality Index; FAST: Functioning Assessment Short Test.

Since sub-syndromal depressive symptoms had a major impact on functioning, we looked at the profile of patients considered truly in a normothymic phase with a MADRS < 7. This sub-group also had poor functioning in 43.9%, with a score at the FAST ≥12. Such poor functioning was associated with residual symptoms even when they are very low (MADRS total score, $p = 0.002$, adherence to treatment, MARS, $p = 0.03$, and the BMI, $p = 0.01$).

Table 4. Factors associated with functioning using the FAST in patients considered in a remitted phase (n = 588).

	Total FAST	
	Beta (SE)	p
Intercept	4.4 (3.7)	0.2361
MADRS score total	0.90 (0.10)	< 0.0001
YOUNG score total	−0.36 (0.16)	0.0272
MARS score total	−0.66 (0.29)	0.0204
PSQI score total	0.53 (0.15)	0.0005
BMI	0.36 (0.10)	0.0003

FAST: Functioning Assessment Short Test; SE: standard error; MADRS: Montgomery and Asberg Depression Rating Scale; MARS: Medication Adherence Rating Scale; PSQI: Pittsburgh Sleep Quality Index; BMI: body mass index.

Discussion

We report a description of the first 839 BD patients included in the FACE-BD cohort, including socio-demographic characteristics and the principal clinical features of the disease, as well as comorbidities and current state. It appears that 76% of patients referred to an expert center were not in an acute episode. Our data highlight the main features presented, giving clarity to the reasons motivating a consultation in an expert center.

The main demographic and clinical characteristics of the FACE-BD patients were comparable to those of other cohorts or data from the literature. For example, the mean age, the slight preponderance of women and the recorded educational level are very close to those of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (Kogan et al., 2004).[AQ: 3] Most of our patients reported depression as their first mood episode, with presentations of comorbid anxiety disorders and a history of suicide attempts being very common (respectively 43.8% and 41.9%) (Kogan et al., 2004; Popovic et al., 2013).

The age at onset, 24.7 years in our cohort, is consistent with previous studies in Europe but higher than in the United States (Etain et al., 2012). Several explanations for this difference have been suggested (Bellivier et al., 2011), including cultural factors, clinical differences, genetic mechanisms (Lange and McInnis, 2002), differences in the approaches to treatment (Da Silva Magalhães et al., 2009; Reichart and Nolen, 2004) or differences in access to specialized mental health care (Carlson, 2011).

A high proportion of patients in our cohort met the criteria for BD II (38%) and BD NOS (13.5%). This may be due in part to the fact that a substantial proportion of patients (42.4%) included in the FACE-BD cohort were referred by private psychiatrists often in charge of less severe patients.

Another particular feature of FACE-BD cohort is the high proportion of patients who are considered in syndromal remission (defined as 'not currently in an acute episode' using the DSM-IV criteria) (76.2%). It appears that approximately 40% of these patients had residual depressive symptoms, in spite of 39% receiving an antidepressant. Previous studies have shown that BD patients have sub-syndromal and minor depressive symptoms nearly three times more frequent than full episodes (Judd and Akiskal, 2003; Judd et al., 2002, 2003) and that subthreshold depressive symptoms are good markers of rapid and frequent relapse and/or recurrence of a clinically depressive episode (De Dios et al., 2012; Judd et al., 2008). Regarding the great impact on functioning of these depressive symptoms, further studies are needed to better characterize them and to understand their poor response to antidepressant. The next step is to characterize them with a dimensional approach, which seems more appropriate to capture the heterogeneity of mild symptoms (article in preparation).

We also found that patients had sleep disturbances, were overweight and showed only partial adherence to treatment. Other studies have found that symptoms of insomnia and circadian rhythm disturbances are frequent in remitted patients with BD (Milhiet et al., 2011). A more systematic assessment of sleep and circadian rhythms in patients with BD may help to define appropriate personalized treatment. Light-therapy (Sit et al., 2007) and specific psycho-social interventions, such as Interpersonal and Social Rhythms Therapy (Frank et al., 2005), could be preferentially proposed to patients with such disturbances.

Almost half of our patients were overweight or obese. Being overweight and obesity are both more prevalent in patients with BD than individuals with no psychiatric condition (adjusted odd ratio of 3.9) (Gurpegui et al., 2012). As a consequence, life expectancy is reduced by around 10 years, due in part to cardiovascular and metabolic disease (Roshanaei-Moghaddam and Katon, 2009). In addition to somatic complications, high BMI has a negative

effect on functioning, including impairing quality of life (Kolotkin et al., 2008); it is also linked to a poorer response to classical mood stabilizers (Kemp et al., 2010).

Beyond direct adverse effects, all these elements impact the functioning of patients. In fact, our data highlight that depressive residual symptoms, sleep disturbances and a high BMI are associated with a poor functioning (Table 3).

All together, these data reveal that a high proportion of patients are referred to an expert center as a consequence of residual depressive symptoms, poor functioning, moderate adherence to treatment and sleep disturbances. The recruitment into the FACE-BD cohort seems not based on refractory or severe cases but on more subtle, but chronic disturbances.

The strengths of the FACE-BD study include its multisite patient sample, the uniformity of diagnostic and evaluation procedures and its broad spectrum of multidimensional assessments. The non-restrictive criteria for entering the cohort favor wide inclusion, limited only by the willingness of patients and recruitment capacity.

However, it is a cross-sectional study, giving an overview of the main disturbances evident in patients who are referred to an expert center during a remitted phase, and requires longitudinal follow-up data to better understand the evolution of such disabling features.

Large longitudinal cohorts of BD patients are essential for studying the progression of the disease, individual differences, relapse factors and treatment effectiveness. The establishment of specialized care and treatment based on guidelines should improve the management and consequently change the course of the disease (Bauer et al., 2009; Kessing et al., 2013). With this prospective cohort, we will be able to generate data about outcomes from the patients followed up within the network. Our data highlight the need to focus on subtle and chronic disturbances of the disease.

Specialized care is inherent to the progress of medicine and is particularly important for psychiatric diseases, as the nosology is changing: this is due to a better understanding of psychopathological mechanisms and should be further refined in the light of responses to treatments (Berk et al., 2013; Vieta, 2013). These data reinforce that mood instability and sub-syndromal symptoms rather than mood episodes might be the key feature of BD, reinforcing the idea that classical psychiatric diagnosis would benefit from being completed along a dimensional perspective.

Acknowledgements

[AQ: 4] This research received the support of the Foundation FondaMental. We would like to thank George Anderson, CRC Scotland & London, for English editing of this article. FACE-BD group: AP-HP, Hôpital H. Mondor—A. Chenevier, Pôle de Psychiatrie, Créteil: C. Boudebesse, A. Raust; AP-HP, GH Saint-Louis—Lariboisière—Fernand Widal, Pôle Neurosciences, Paris: M. Leroux, S. Sportiche; Hôpital C Perrens, Centre Expert Trouble Bipolaire, Service de psychiatrie adulte, Pôle 3-4-7, Bordeaux: S. Gard, K. M'Bailara; Département d'Urgence et Post Urgence Psychiatrique, CHRU Montpellier, Montpellier: E. Olié, F. Molière; Département de Psychiatrie, Hôpital Sainte Marguerite, Marseille: N. Viglianaise, L. Lescalier; Service de Psychiatrie et Psychologie Clinique, CHU de Nancy, Hôpitaux de Brabois, Vandoeuvre Les Nancy: O. Wajsbrot-Elgrabli, R. Cohen; Clinique Universitaire de Psychiatrie, CHU de Grenoble, Grenoble: M. Polosan, M.A. De Pourtales; Centre Hospitalier de Versailles, Service de Psychiatrie Adulte, Le Chesnay: N. Kayser, I. Grevin; Centre Hospitalier Princesse Grace, 98000 Monaco: J. Loftus, I. Médecin.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding

This work was supported (in part) by the Investissements d'Avenir programs managed by the ANR under references ANR-11-IDEX-0004- and ANR-10-COHO-10-01.

References

Bauer MS, Biswas K and Kilbourne AM (2009) Enhancing multiyear guideline concordance for bipolar disorder through collaborative care. *American Journal of Psychiatry* 166: 1244–1250.

Bellivier F, Etain B, Malafosse A, et al. (2011) Age at onset in bipolar I affective disorder in the USA and Europe. *World Journal of Biological Psychiatry* 15: 369–376.

Berk M, Scott J, Macmillan I, et al. (2013) The need for specialist services for serious and recurrent mood disorders. *Australian and New Zealand Journal of Psychiatry* 47: 815–818.

Blais FC, Gendron L, Mimeault V, et al. (1997) Evaluation of insomnia: Validity of 3 questionnaires. *L'Encéphale* 23: 447–453.

Boudebesse C, Etain B, Goldstein T, et al. (2013) Sleep and circadian profiles of bipolar disorder: From chronobiology to noveltherapeutic strategies. *Current Psychiatry Reviews* 10: 1573–4005.[AQ: 5]

Buysse DJ, Reynolds CF, Monk TH, et al. (1989) The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research* 28: 193–213.

Carlson GA (2011) Will the child with mania please stand up? *British Journal of Psychiatry* 198: 171–172.

Da Silva Magalhães PV, Gomes FA, Kunz M, et al. (2009) Birth-cohort and dual diagnosis effects on age-at-onset in Brazilian patients with bipolar I disorder. *Acta Psychiatrica Scandinavica* 120: 492–495.

De Dios C, Ezquiaga E, Agud JL, et al. (2012) Subthreshold symptoms and time to relapse/recurrence in a community cohort of bipolar disorder outpatients. *Journal of Affective Disorders* 143: 160–165.

Drancourt N, Etain B, Lajnef M, et al. (2013) Duration of untreated bipolar disorder: Missed opportunities on the long road to optimal treatment. *Acta Psychiatrica Scandinavica* 127: 136–144.[AQ: 6]

Etain B, Lajnef M, Bellivier F, et al. (2012) Clinical expression of bipolar disorder type I as a function of age and polarity at onset: Convergent findings in samples from France and the United States. *Journal of Clinical Psychiatry* 73: e561–e566.

Etain B, Mathieu F, Liquet S, et al. (2013) Clinical features associated with trait-impulsiveness in euthymic bipolar disorder patients. *Journal of Affective Disorders* 144: 240–247.

Fagiolini A and Goracci A (2009) The effects of undertreated chronic medical illnesses in patients with severe mental disorders. *Journal of Clinical Psychiatry* 70: 22–29.[AQ: 7]

First M (1996) *Structured Clinical Interview for the DSM-IV Axis I Disorders*. Washington, DC: American Psychiatric Association.

Frank E, Kupfer DJ, Thase ME, et al. (2005) Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Archives of General Psychiatry* 62: 996–1004.

Goldstein BI, Kemp DE and Soczynska JK (2009) Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: A systematic review of the literature. *Journal of Clinical Psychiatry* 70: 1078–1090.[AQ: 8]

Gurpegui M, Martínez-Ortega JM, Gutiérrez-Rojas L, et al. (2012) Overweight and obesity in patients with bipolar disorder or schizophrenia compared with a non-psychiatric sample. *Progress in Neuropsychopharmacology and Biological Psychiatry* 37: 169–175.

Harvey AG, Schmidt DA, Scarnà A, et al. (2005) Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. *American Journal of Psychiatry* 162: 50–57.

Henry C and Etain B (2010) New ways to classify bipolar disorders: Going from categorical groups to symptom clusters or dimensions. *Current Psychiatry Reports* 12: 505–511.

Henry C, Andreassen O and Barbato A (2013) European Network of Bipolar Research Centres (ENBREC): A network to foster research and promote innovative care. *Internal Journal of Bipolar Disorder* 1: 2.[AQ: 9]

Henry C, Etain B, Mathieu F, et al. (2011) A French network of bipolar expert centres: A model to close the gap between evidence-based medicine and routine practice. *Journal of Affective Disorders* 131: 358–363.

Henry C, Van den Bulke D, Bellivier F, et al. (2008) Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period. *Psychiatry Research* 159: 1–6.

Judd LL, Akiskal HS, Schettler PJ, et al. (2003) A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Archives of General Psychiatry* 60: 261–269.

Judd LL and Akiskal HS (2003) Depressive episodes and symptoms dominate the longitudinal course of bipolar disorder. *Current Psychiatry Reports* 5: 417–418.

Judd LL, Schettler PJ and Akiskal HS (2002) The prevalence, clinical relevance, and public health significance of subthreshold depressions. *Psychiatric Clinics of North America* 25: 685–698.

Judd LL, Schettler PJ and Akiskal HS (2008) Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. *Archives of General Psychiatry* 65: 386–394.

Kemp DE, Gao K, Chan PK, et al. (2010) Medical comorbidity in bipolar disorder: Relationship between illnesses of the endocrine/metabolic system and treatment outcome. *Bipolar Disorders* 12: 404–413.

Kessing LV, Hansen HV, Hvenegaard A, et al. (2013) Treatment in a specialised out-patient mood disorder clinic v. standard out-patient treatment in the early course of bipolar disorder: Randomised clinical trial. *British Journal of Psychiatry* 202: 212–219.

Kolotkin RL, Corey-Lisle PK, Crosby RD, et al. (2008) Impact of obesity on health-related quality of life in schizophrenia and bipolar disorder. *Obesity* 16: 749–754.

Lange Kezia J and McInnis MG (2002) Studies of anticipation in bipolar affective disorder. *CNS Spectrums* 7: 196–202.

Leboyer M, Soreca I, Scott J, et al. (2012) Can bipolar disorder be viewed as a multi-system inflammatory disease? *Journal of Affective Disorders* 141: 1–10.

Martínez-Arán A, Vieta E, Colom F, et al. (2004) Cognitive impairment in euthymic bipolar patients: Implications for clinical and functional outcome. *Bipolar Disorders* 6: 224–232.

Merikangas KR, Akiskal HS, Angst J, et al. (2007) Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Archives of General Psychiatry* 64: 543–552.[AQ: 10]

Milhiet V, Etain B, Boudebesse C, et al. (2011) Circadian biomarkers, circadian genes and bipolar disorders. *Journal of Physiology* 105: 183–189.

Misdrahi D, Verdoux H, Llorca PM, et al. (2004) Therapeutic adherence and schizophrenia: The interest of the validation of the French translation of Medication Adherence Rating Scale (MARS). *L'Encéphale* 30: 409–410.

Montgomery SA and Asberg M (1979) A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* 134: 382–389.

Popovic D, Torrent C, Goikolea JM, et al. (2013) Clinical implications of predominant polarity and the polarity index in bipolar disorder: A naturalistic study. *Acta Psychiatrica Scandinavica* 129: 366–374.

Reichart CG and Nolen WA (2004) Earlier onset of bipolar disorder in children by antidepressants or stimulants? An hypothesis. *Journal of Affective Disorders* 78: 81–84.

Rosa AR, Sánchez-Moreno J, Martínez-Arán A, et al. (2007) Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clinical Practice and Epidemiology in Mental Health* 3: 5.

Roshanaei-Moghaddam B and Katon W (2009) Premature mortality from general medical illnesses among persons with bipolar disorder: A review. *Psychiatric Services* 60: 147–156.

Sachs GS, Thase ME, Otto MW, et al. (2003) Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biological Psychiatry* 53: 1028–1042.[AQ: 11]

Sit D, Wisner KL, Hanusa BH, et al. (2007) Light therapy for bipolar disorder: A case series in women. *Bipolar Disorders* 9: 918–927.

Soreca I, Frank E and Kupfer DJ (2009) The phenomenology of bipolar disorder: What drives the high rate of medical burden and determines long-term prognosis? *Depression and Anxiety* 26: 73–82.

Swann AC, Lijffijt M, Lane SD, et al. (2009) Increased trait-like impulsivity and course of illness in bipolar disorder. *Bipolar Disorders* 11: 280–288.

Thompson K1, Kulkarni J and Sergejew AA (2000) Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. *Schizophrenia Research* 42: 241–247.[AQ: 12]

Vieta E (2013) Pros and cons of specialised care in bipolar disorder: An international perspective. *British Journal of Psychiatry* 202: 170–171.

Young RC, Biggs JT and Ziegler VE (1978) A rating scale for mania: Reliability, validity and sensitivity. *British Journal of Psychiatry* 133: 429–435.

ANEXO B – STAGING AND NEUROPROGRESSION IN BIPOLAR DISORDER

Staging and neuroprogression in Bipolar Disorder
Fries, G. R.; Pfaffenseller, B.; Stertz, L.; Paz, A. V.; Dargel, A. A.; Kunz, M.; Kapczinski, F.
Publicado em Current Psychiatry Reports.

Staging and Neuroprogression in Bipolar Disorder

Gabriel Rodrigo Fries & Bianca Pfaffenseller & Laura Stertz & André Vinicius Contri Paz & Aroldo Ayub Dargél & Maurício Kunz & Flávio Kapczinski

Abstract The apparently progressive nature of a considerable proportion of cases of bipolar disorder (BD) has been acknowledged in recently proposed clinical staging models. This has been part of an attempt to facilitate and refine diagnosis, treatment selection, and establish a prognosis. The study of the progressive nature of some cases of BD has given raise to the hypothesis of neuroprogression, which postulates that different stages of BD are associated with distinct neurobiological underpinnings. Given that BD may be intimately associated with chronic stress response and coping mechanisms over the course of illness, we propose that cellular resilience mechanisms may play a key role in the neuroprogression in BD. In the present study, we review neuroanatomical evidence of the progression that occurs in many cases of BD, as well as cellular resilience mechanisms and peripheral biomarkers associated with distinct stages of this disorder. In summary, cellular resilience mechanisms seem to be less efficient at later stages of BD, especially mitochondrial and endoplasmic reticulum-related responses to stress. These insights may help in developing staging models of BD, with a special emphasis on the search for biomarkers associated with illness progression.

Keywords Bipolar disorder · BD · Staging · Clinical staging model · Neuroprogression · Cellular resilience · Neuroplasticity · Biomarkers · Allostatic load · Treatment · Remission · Psychiatry

Introduction

A growing body of evidence has suggested that bipolar disorder (BD) may present a progressive course [1, 2, 3]. As reviewed elsewhere [4], the duration of interepisode intervals seems to be reduced with the recurrence of acute episodes [5,6], and progression of BD may also be associated with several unfavorable clinical outcomes: lower responsiveness to treatment, especially with lithium and cognitive behavioral therapy [7–9], worse treatment outcome of family psychoeducation

G. R. Fries · B. Pfaffenseller · L. Stertz · A. V. C. Paz · A. A. Dargél · M. Kunz · F. Kapczinski (*)
Laboratory of Molecular Psychiatry, Centro de Pesquisas Experimentais, Hospital de Clínicas de Porto Alegre, and INCT for Translational Medicine,
Rua Ramiro Barcelos,
2350, Porto Alegre, RS, Brazil
e-mail: flavio.kapczinski@gmail.com

G. R. Fries
e-mail: gabrielrfries@gmail.com

B. Pfaffenseller
e-mail: bianca.pfaffenseller@gmail.com

L. Stertz
e-mail: laurastertz@gmail.com

A. V. C. Paz
e-mail: andrecontri@hotmail.com

A. A. Dargél
e-mail: aroldodargel@gmail.com

M. Kunz
e-mail: maukunz@gmail.com

G. R. Fries · B. Pfaffenseller · L. Stertz · F. Kapczinski
Programa de Pós-Graduação em Ciências Biológicas: Bioquímica,
Universidade Federal do Rio Grande do Sul, UFRGS,
Rua Ramiro Barcelos,
2350, Porto Alegre, RS, Brazil

A. A. Dargél · M. Kunz · F. Kapczinski
Programa de Pós-Graduação em Medicina: Psiquiatria,
Universidade Federal do Rio Grande do Sul, UFRGS,
Rua Ramiro Barcelos,
2350, Porto Alegre, RS, Brazil

[10], higher rates of comorbidity [11], functional impairment [12], increased cognitive dysfunction [1 ,13,14], and an augmented risk of suicide [15] and hospitalization [16].

Different hypotheses have been proposed to explain the mechanisms underlying the recurrence of mood episodes and the progressive nature of a significant percentage of cases of BD. Post (1992) [17] suggested that multiple episodes may lead to permanent alterations in neuronal activity, possibly resulting in a greater liability to relapse and a poorer response to medication [18]. In this same vein, BD progression has been compared to stress sensitization models and to electrophysiological kindling of seizures, used in providing a possible explanation for the increased vulnerability to episode occurrence and the transition from triggered to spontaneous episodes at later stages of illness [1]. Moreover, an allostatic load theory has been proposed to account for the cumulative damage associated with BD [3,19]. According to that theory, the chronicity involved in activating allostatic mechanisms to restore parameters after stressful events leads to a physiological wear-and-tear, which has been described as allostatic load [20]. These effects are normally observed during aging and exposure to chronic stress, and seem to play a role in adaptive functions. In contrast, the progressive neural and physical dysfunction resulting from multiple mood episodes in BD could be seen as affecting allostatic responses, leading to an allostatic overload in a non-adaptive way. More recently, the allostatic load paradigm has been incorporated into a new concept of neuroprogression [2], focused on identifying the pathways associated with oxidative stress, inflammation, and neurotrophin expression, which may provide explanations for the progressive nature of BD. Neuroprogression will be used in this review as the pathological rewiring of the brain that takes place when a clinical and cognitive deterioration occurs in the context of the progression of psychiatric disorders.

Several neurobiological studies have linked chronic social stress with distinct biological features possibly underlying BD neuroprogression and its consequences. Therefore, this review aims to discuss neuroanatomical and neurobiological and genetic findings associated with BD staging and progression, emphasizing the potential role of dysfunctions in cellular resilience mechanisms as one of the pathways to neuroprogression. The clinical implications of these studies are discussed in light of the concept of clinical staging in BD.

Neuroanatomical Changes in BD

Different stages of BD have been associated with specific brain abnormalities related to cognitive and emotional functions. Due to the heterogeneity of groups and methodologies used in the studies available, it remains unclear whether changes predate the illness or are related to the consequences of illness progression [21].

Reductions of the gray [22–24] and white matter [23–25] in the prefrontal cortex have been described in first manic episode patients, becoming more pronounced after multiple episodes. Consistent results have been also obtained in the anterior cingulate cortex, pointing to a reduction of its volume [26] and also of gray matter volume [27] in BD patients, regardless of their stages. In particular, the subgenual prefrontal cortex has attracted special interest, because of its mood-regulating role, integrating cognitive and emotional information [28]. A study involving patients with a family history of BD has reported reductions in the volume, blood flow and glucose metabolism of this region [28]. A reduced number of glial cells at the same area has also been reported in mood disorders' patients [25]. This latter finding is especially interesting because the subgenual prefrontal cortex has connections with the amygdala, hypothalamus and midbrain periaqueductal structures that are related to emotional behavior and stress responses [25]. As a result, changes in the prefrontal cortex may partly explain the impairment of executive functions [13] and the emotional instability observed in patients with BD.

The limbic system is another neuroanatomical area of interest in BD due to its relationship with emotional responses. Some studies have suggested that the amygdala tends to increase in volume with the progression of illness [29], although results obtained at initial stages have shown reduced amygdala volumes [30]. Interestingly, the hippocampus appears to increase in volume in early stage BD, but progressively decreases with illness duration and number of episodes experienced by patients, ultimately becoming smaller than the hippocampus of healthy controls [31,32]. Some studies have also shown that V2 and V3 regions of the cerebellar vermis are reduced in BD patients who have experienced multiple episodes when compared to first-episode patients [33].

The basal ganglia in general and the striatum in particular have also been shown to present altered shape [34] and volume [29, 35] in BD patients. These structural changes seem to take place at the onset of BD and to remain at later stages [35]. The corpus callosum also seems to be affected from illness onset. Studies involving first-episode bipolar patients [36], bipolar adolescents [37], and bipolar adults [38] have reported abnormalities in the white matter of the corpus callosum, possibly indicating altered myelination and ultimately leading to problems in interhemispheric communication in BD patients [38].

Finally, other studies have shown that total brain gray matter is reduced in BD patients [39,40], and that the ventricles increase in size with illness duration [41]. As a

consequence, total brain volume is smaller in multiple-episode patients compared to first-episode patients and control subjects [40].

In sum, it seems that neuroanatomical alterations already present at the onset of BD are aggravated by the ocurrence off urther episodes. However, other abnormalities seem to appear only with illness progression and may be characteristic ofl ater stages of BD. Further studies are required to clarify these issues. Nonetheless, the findings above, along with additional evidence coming from neuroimaging and post-mortem brain studies that associate BD with structural anatomical changes in the size, number, and density of neurons and glia in specific brain areas [21, 42], suggest that BD neuroprogression may be associated with impairments of cellular resilience and neuroplasticity mechanisms.

Cellular Resilience

Considering cellular resilience as the ability of cells to adapt to different insults or stress episodes, an impaired resilience at the cellular level may be one possible explanation for the increased vulnerability ofBD patients when exposed to stressful environmental conditions.

Evidence suggests that abnormalities in several intracellular signaling pathways may affect neuroplasticity and cellular resilience in BD. This would include neurotransmitters, glutamatergic and glucocorticoid signaling, neurotrophic cascades, anti-apoptotic factors, cell survival pathways, and calcium signaling, among others [43–45]. For instance, elevated and calcium levels have been found in peripheral blood cells of BD patients [46], and an increased vulnerability to cell death in cells of the olfactory neuroepithelium has also been observed [47]. Neuroimaging studies reporting decreased levels of N-acetylaspartate in the living brain [48] also support the hypothesis that BD patients present impaired neuronal viability and function, possibly causing alterations in cell number and density and changing gray matter volumes. The mechanisms leading to this reduced resilience are most likely involve specific cell signaling pathways and organelles typically responsible for maintaining cell homeostasis, such as the ER [49, 50] and the mitochondrion [51]. In vitro and animal model studies have reported that chronic stress and chronic exposure to glucocorticoids can induce mitochondrial dysfunction, causing reductions in oxygen consumption, mitochondrial membrane potential and calcium holding capacity, ultimately leading to apoptosis [52, 53]. Of note, BD patients present mitochondrial dysfunction and an impaired hypothalamus-pituitary-adrenal (HPA) axis [54], as evidenced by decreased levels of high-energy phosphates and mitochondrial respiration, alterations in mitochondrial morphology, and downregulation of proteins involved in mitochondrial metabolism [51]. These findings may be related to an impaired regulation of Ca^{2+} cascades [46], as apoptosis in BD is manifested by an increased expression of apoptotic genes [55]. No study has assessed mitochondrial functions in early- vs. late-stage BD patients, but the evidence ofi mpaired mitochondrial functioning strongly supports a key role of this organelle in synaptic functioning, thus contributing to the atrophic changes underlying BD neuroprogression.

It remains unclear whether such alterations in cellular resilience pathways occur as a result of developmental abnormalities, illness progression toxicity of mood episodes, or due to treatment (or the lack of it). Few studies have examined resilience at the cell level in BD to determine whether illness duration and number of episodes may affect this process. One of such studies reported that the levels of synaptic subcellular markersof neuroplasticity were not only reduced in the anterior cingulate cortex of BD patients, but also negatively correlated with illness duration [56], suggesting progressive alterations in synaptic plasticity in BD. Another recent study showed that lymphocytes from early-stage-patients responded better to in vitro-induced ER stress (with induction of glucose-regulated protein of 78 kDa (GRP78) and phosphorylated eukaryotic initiation factor 2 (eIF2α-P), both essential in activating ER stress response signaling) when compared to patients at late stages of BD [57]. These findings suggests that protective cell mechanisms may become less efficient at more advanced stages of BD.

The loss of cell plasticity in BD is thought to be the result of a deficiency in trophic support or survival factors along with an impaired regulation of intracellular signaling cascades [58]. In fact, brain-derived neurotrophic factor (BDNF) levels have been shown to be reduced in postmortem brain from BD patients when compared to controls [59], and alterations in peripheral neurotrophic factors have been reported in BD during acute episodes, e.g., BDNF [60], neurotrophin-3 and 4/5 (NT-3 and NT-4/5) [61, 62], and glial-derived neurotrophic factor (GDNF) [63]. Furthermore, increased peripheral oxidative stress and higher levels ofi nflammatory markers have also been observed in BD patients [64]. As discussed below, these alterations in biochemical markers may be related to different stages of the disorder [65, 66].

Neuronal atrophy and reduced cellular resilience make certain neurons more vulnerable to insults and may be related to stress and chronic activation of the HPA axis [67] and/or a decreased expression of BDNF in some brain regions [67]. BDNF, as well as other neurotrophic factors, are necessary for neuronal survival and function, and are involved in neurogenesis and brain maturation during neurodevelopment. In adults, BDNF activates important intracellular pathways implicated in synaptic

plasticity and dendritic growth, especially in the cortex and hippocampus [68]. Therefore, reduced BDNF levels in late-stage BD may indicate decreased neuronal viability [66] resulting from illness progression.

Additional evidence comes from studies showing the effects of mood stabilizers on signaling pathways involved in the regulation of cell plasticity [69], such as mitogen-activated protein kinases, cyclic adenosine monophosphate (cAMP) response element-binding (CREB) protein, BDNF, and B-cell lymphoma 2 (Bcl-2) protein. Those studies have suggested long-term benefits associated with mood stabilizers as a result of their neurotrophic effects. In this same vein, the increased vulnerability to stress associated with disease progression may be explained by the progressive loss of neuronal resilience. These cell cascades are therefore considered important targets in the treatment of BD. Likewise, impairments in signal transduction pathways suggest that effective treatments will need to provide both trophic and neurochemical support, mainly in patients refractory to conventional medications. Because cell changes may progress over the course of BD, avoiding impairments by enhancing resilience mechanisms could probably delay or prevent illness progression. Further studies should focus on identifying resilience and susceptibility factors, and also on elucidating how such factors could contribute to treatment and to improve both staging of BD and interventions aimed at earlier stages of the disorder. In this sense, if we consider that these impairments provoke changes to different peripherally detectable molecules, the use of biomarkers could be a useful tool in optimizing clinical staging.

The use of biomarkers as a potential tool for staging BD

An ideal biomarker assay for BD staging should be sensitive, specific, cost-effective, fast, easily detected, and robust against inter-operator and inter-institutional variability [70]. It should also be clinically more relevant than the information already available at the time of diagnosis [70]. In addition, it is reasonable to consider that biomarkers for BD staging should be used after the stabilization of an acute episode (i.e., during euthymia), in order to avoid bias from episode-induced alterations. To the best of our knowledge, none of the biomarkers studied so far has adequately fulfilled these characteristics.

Therefore, we decided to review the main peripheral biomarkers in euthymic BD patients, including neurotrophins, inflammatory markers, oxidative stress, and telomere length. Given the lack of studies designed to evaluate these biomarkers in relation to the clinical staging of BD findings were divided into in early-stage alterations (stages I or II) and late-stage alterations (stages III or IV). The main findings are reported in Table 1.

Neurotrophins

Alterations in neurotrophic factors are well documented in BD [59], especially in association with acute mood symptomatology. During euthymia, decreased BDNF levels have been reported at late stages of BD, but not at early stages [66]. Recently, some studies have reported increased plasma levels of BDNF in patients with long-term BD [71, 72]. However, meta-analytic studies seem to agree that BDNF levels are reduced during mood episodes but not during euthymia, suggesting a decrease of this protein with age and length of illness [60, 73]. Another possible target is neurotrophin 4/5, which was found to be increased in euthymic BD patients at late stages [62]. In summary, along with the evidence of reduced neuroplasticity resulting from illness progression, the measure of peripheral neurotrophic factors may be useful to determine the stage of BD.

Inflammatory Markers

We found only two studies assessing inflammatory markers at early stages of BD, which reported increased serum levels of tumor necrosis factor alpha (TNF-alpha) [66, 74], as well as of interleukin-6 (IL-6) and interleukin-10 (IL-10) [66], in patients when compared to controls. Moreover, several studies report a pro-inflammatory imbalance at late stages of BD. The main inflammatory markers which seem to be increased are IL-6 [66, 75], TNF-alpha [66, 76, 77], high sensitive C-reactive protein (hs-CRP) [75, 76], IL-10 [78], and IL-1β [79]. Recently, increased plasma levels of CCL11, CCL24, and CXCL10, and decreased plasma levels of CXCL8 have been reported in late BD when compared to healthy controls [80]. In a peripheral profiling analysis for BD, approximately 60 differentially expressed molecules involved predominantly in cell death/survival pathways were identified. In peripheral blood mononuclear cells, this was manifested in cytoskeletal and stress response-associated proteins, whereas most serum analyses were associated withinflammatory response [81]. Therefore, the imbalance toward a pro-inflammatory state seems to be prominent at late stages of BD. More studies are warranted to further assess inflammatory markers in early stages of BD.

Oxidative Stress Markers

Many lines of evidence link BD with a fundamental abnormality in oxidative energy metabolism [82]. In early stages, increased lactate levels in the cerebrospinal fluid of patients possibly indicate increased extra-mitochondrial, anaerobic glucose metabolism, which is consistent with

Table 1 Peripheral biomarkers in early and late-stage euthymic BD patients

	Early	Late
Neurotrophins	-	↓BDNF [66] ↑NT-4/5 [62]
Inflammatory markers	↑IL-6 [66] ↑IL-10 [66] ↑TNF-alpha [66, 74]	↑IL-6 [66, 75] ↑TNF-alpha [66, 76] ↑IL-10 [78] ↑hs-CRP [75, 76] ↑IL-1 β[79] ↑CCL11, CCL24, CXCL10 [80] ↓CXCL8 [80]
Oxidative stress	↑3-Nitrotyrosine [65] ↑PCC [85]	↑Glutathione reductase [65] ↑Glutathione S-transferase [65] ↑3-Nitrotyrosine [65] ↑TBARS [86] ↑NO [86] ↑Lactate [83] ↑Total oxidants status [88]
Telomere length	-	Shorter telomeres [89, 90]

the impaired mitochondrial metabolism observed in some patients with schizophrenia and BD [83]. Impaired mitochondrial metabolism could lead to excess free radicals, causing an imbalance between oxidants and antioxidant mechanisms [84]. Two studies point to oxidative alterations in proteins in early BD, such as increased 3-nitrotyrosine [65] and protein carbonyl content [85]; some of these alterations seem to be maintained at late stages [65]. Nonetheless, the main findings have been reported for late stages of BD. Increased levels of thiobarbituric acid-reactive substances (TBARS) [86, 87], glutathione reductase, glutathione S-transferase [65],nitric oxide [86], and total oxidant status [88] point toward an increase in oxidative stress along with the progression of BD.

Telomere Length

Telomere length has been reported to be significantly shorter in patients with mood disorders, corresponding to as much as 10 years of accelerated aging when compared to controls [89]. Moreover, the load of short telomeres was found to be increased in patients with BD type II compared to healthy controls, possibly representing 13 years of accelerated aging. In this study, the authors found that the load of short telomeres and mean telomere length were associated with lifetime number of depressive episodes, but not with illness duration. Depressive episode-related stress may accelerate telomere shortening and aging. Longitudinal studies are needed to fully clarify the role of telomere shortening and its relationship with clinical variables in BD [90].

Clinical Staging Models

Different clinical staging models have been proposed for BD [91–93] (Table 2). Their common feature is placing the illness in a continuum progressing from a latent or asymptomatic form (stage 0 or latent) to a chronic, unremitting presentation (stage IV or unremitting). That is to say researchers agree that there is a great clinical need of selecting treatment interventions that are able to match patients' illnesses in terms of natural course, severity and underlying biology. This is the basis of staging models [93]. Effective staging methods should be able to predict what treatments should be used according to illness characteristics, and this would benefit the patient in terms of efficacy and tolerability. Nonetheless, at this point staging models proposed for BD specifically differ regarding emphasis on mood symptomatology and patterns of recurrence, functional disability and cognitive decline.

Simply using the total number of previous episodes, Berk and colleagues have been able to demonstrate the potential of clinical staging [4]. When people with BD have had over ten previous episodes, for instance, they tend to have a more treatment-resistant illness, and their risk of relapse is much higher when compared to people with fewer than ten episodes [4]. Furthermore, an analysis using data from STEP-BD shows that people with more than ten episodes tend to have worse outcomes across the board, having worse longitudinal functioning and quality-of-life measures in addition to traditional symptom outcomes [94]. In this same dataset, staging also predicted the likelihood of having a comorbid clinical condition, which is also in accordance with the notion of neuroprogression and staging [95]. While an

Table 2 Proposed clinical staging models for BD

Berk et al., 2007 [91]		Kapczinski et al., 2009 [92]		Reinares et al., 2012 [96]	
Stage	Description	Stage	Description	Stage	Description
0	at-risk, asymptomatic period, where a range of risk factors may be operating	Latent	mood and anxiety symptoms and increased risk for developing threshold BD; no cognitive impairment but polymorphisms that confer susceptibility		
1a 1b	mild or non-specific symptoms range of prodromal patterns	1	well-established periods of euthymia and absence of overt psychiatric morbidity between episodes, without cognitive impairment. High serum levels of tumor necrosis factor alpha (TNF-alpha) and 3-nitrotyrosine (3-NT) as biomarkers	Good outcome	low subsyndromal depressive symptoms, increased inhibitory control and estimated verbal intelligence
2	first threshold episode of illness, which can be of either polarity, but more commonly depressive	2	rapid cycling or current axis I or II comorbidities, transient impairment and high serum levels of TNF-alpha and 3-NT and low brain-derived neurotrophic factor (BDNF) as biomarkers		
3a 3b 3c	first relapse, subthreshold threshold illness subsequent pattern of remission and recurrences	3	clinically relevant pattern of cognitive and functioning deterioration as well as altered biomarkers (morphometric changes in brain may be persistent, high serum levels of TNF-alpha and 3-NT and low BDNF levels)	Poor outcome	residual depressive symptoms, increased episode density, low inhibitory control and estimated verbal intelligence
4	unremitting or treatment refractory course	4	cognitive and functioning impairment, unable to live autonomously and altered brain-scans and biomarkers (ventricular enlargement and/or white matter hyperintensities, high levels of TNF-alpha and 3-NT and low BDNF levels, increased levels of glutathione reductase and transferase)		

estimate of a quantity of episodes is possibly too simplistic to realistically reflect individual treatment needs, this line of research demonstrates how people with recent illness can differ from people with chronic illness in a number of features related to course and outcome. Taking into account interepisode functioning may be one viable alternative to create more realistic models [92, 96]. Table 2 demonstrates some features of one such model. What is hypothesized is that having a measure of disability and cognitive decline, for instance, would be a more direct measure of underlying neuroprogression that would be able to more accurately predict treatment needs [92]. This has been tested in a sample of people that underwent a course of psychoeducation. As predicted, being on a late stage predicted a worse outcome to this simple intervention [10], as would be predicted by the notion of staging [93].

Certainly, there is a large cross-over between current models. That is, possibly most people characterized to be in a late stage by chronicity would only be placed in a late stage using functioning measures. Nevertheless, the clinical implications of using these staging models need to be clarified, so models can be refined. Ideally, the utility of staging BD – as well as the utility of employing a specific model – should be demonstrated in randomized controlled trials. That would be the test of whether staging truly has heuristic potential for improving the treatment of BD.

Conclusions

Some cases of patients with BD seem to progress with the course of illness. As an attempt to explain the progression reported in BD without the kind of degeneration reported in patients with neurodegenerative diseases, we propose the hypothesis of neuroprogression. This progression has been acknowledged by different clinical staging systems, which all categorize the disorder in prodromal, early, and late stages of BD. In this vein, neuroprogression may help explain clinical, functional and cognitive alterations that occur with the course of illness. However, it is crucial to extend staging beyond clinical features to include biological correlates. In this light, a stage-specific treatment regimen might work not only to promote

regression to an earlier stage but also to prevent progression to more advanced stages, ultimately allowing the patient to obtain sustained full remission [97].

Based on available data, it is reasonable to assume that neuroprogression may occur along with a loss of cellular resilience. As discussed earlier, we consider that impairment of cellular resilience may play a key role in the pathological rewiring of specific brain areas, possibly accounting for the impaired resilience to stress observed in these patients. Chronic stress and increased allostatic load associated with neuroprogression may be implicated in cellular resilience impairments most likely by interfering with mitochondrial functions and trophic cell signaling pathways. In order to prevent these alterations, the identification of staging biomarkers becomes a priority. Although only longitudinal studies can confirm most of these alterations and their association with different stages of BD, the present findings strongly support the inclusion of biological underpinnings of BD neuroprogression in an effective and useful clinical staging model. Moreover, these data point toward new possible targets in the research for novel drugs potentially effective in treating later stages of BD, such as mitochondrial enhancers. Within this scenario, we believe that the modulation of mechanisms such as mitochondrial resilience and ER unfolded-protein response may allow for patients to effectively re-set stress-activated mechanisms, ultimately decreasing the allostatic load and possibly achieving sustained full remission.

Disclosure G. R. Fries: none; B. Pfaffenseller: none; L. Stertz: none; A. V. C. Paz: none; A. Ayub Dargél: none; M. Kunz: travel/accommodations/meeting expenses reimbursed by Eli Lilly and Company; F. Kapczinski: grants from NARSAD, Stanley Medical Research Institute, CNPq (National Council for Scientific and Technological Development), and CAPES, and payment for lectures including service on speakers bureaus from Eli Lilly and Company, Lundbeck, AstraZeneca, Servier, and Janssen.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. • Post RM, Fleming J, Kapczinski F. Neurobiological correlates of illness progression in the recurrent affective disorders. J Psychiatr Res. 2012;46(5):561–73. This is a full review regarding progression of bipolar disorder, including data on clinical aspects, effects of medications and neurobiological findings.
2. •• Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev. 2011;35(3):804–17. This review discuss the several biological mechanisms responsible for bipolar disorder progression, including oxidative stress, neurotrophic factors, among others
3. Kapczinski F, Vieta E, Andreazza AC, et al. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. Neurosci Biobehav Rev. 2008;32(4):675–92.
4. • Berk M, Brnabic A, Dodd S, et al. Does stage ofi llness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. Bipolar Disord. 2011;13(1):87–98. This study employs a staging model to classify the patients and shows that individuals at the earliest stages ofi llness have a more favourable response to treatment when compared to later stages
5. Kessing LV, Andersen PK, Mortensen PB. Predictors of recurrence in affective disorder. A case register study. J Affect Disord. 1998;49(2):101–8.
6. Roy-Byrne P, Post RM, Uhde TW, Porcu T, Davis D. The longitudinal course of recurrent affective illness: life chart data from research patients at the NIMH. Acta Psychiatr Scand Suppl. 1985;317:1–34.
7. Ketter TA, Houston JP, Adams DH, et al. Differential efficacy of olanzapine and lithium in preventing manic or mixed recurrence in patients with bipolar I disorder based on number of previous manic or mixed episodes. J Clin Psychiatry. 2006;67(1):95-101.
8. Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD. Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. Am J Psychiatry. 1999;156(8):1264–6.
9. Scott J, Paykel E, Morriss R, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. Br J Psychiatry. 2006;188:313–20.
10. Reinares M, Colom F, Rosa AR, et al. The impact of staging bipolar disorder on treatment outcome off amily psychoeducation. J Affect Disord. 2010;123(1–3):81–6.
11. Matza LS, Rajagopalan KS, Thompson CL, de Lissovoy G. Misdiagnosed patients with bipolar disorder: comorbidities, treatment patterns, and direct treatment costs. J Clin Psychiatry. 2005;66(11):1432–40.
12. Rosa AR, González-Ortega I, González-Pinto A, et al. One-year psychosocial functioning in patients in the early vs. late stage of bipolar disorder. Acta Psychiatr Scand. 2012;125 (4):335–41.
13. Torres IJ, Boudreau VG, Yatham LN. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatr Scand Suppl. 2007;434:17-26.
14. Kessing LV, Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? J Neurol Neurosurg Psychiatry. 2004;75(12):1662–6.
15. Hawton K, Sutton L, Haw C, Sinclair J, Harriss L. Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. J Clin Psychiatry. 2005;66(6):693–704.
16. Goldberg JF, Ernst CL. Features associated with the delayed initiation of mood stabilizers at illness onset in bipolar disorder. J Clin Psychiatry. 2002;63(11):985–91.
17. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry. 1992;149 (8):999–1010.
18. Vieta E, Reinares M, Rosa AR. Staging bipolar disorder. Neurotox Res. 2011;19(2):279–85.
19. Vieta E, Popovic D, Rosa AR, et al. The clinical implications of cognitive impairment and allostatic load in bipolar disorder. Eur Psychiatry 2012. doi:10.1016/j.eurpsy.2011.11.007.
20. McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. Horm Behav. 2003;43(1):2–15.
21. Strakowski SM, Delbello MP, Adler CM. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. Mol Psychiatry. 2005;10(1):105–16.

22. Lyoo IK, Sung YH, Dager SR, et al. Regional cerebral cortical thinning in bipolar disorder. Bipolar Disord. 2006;8(1):65 –74.
23. Rajkowska G, Halaris A, Selemon LD. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. Biol Psychiatry. 2001;49(9):741–52.
24. López-Larson MP, DelBello MP, Zimmerman ME, Schwiers ML, Strakowski SM. Regional prefrontal gray and white matter abnormalities in bipolar disorder. Biol Psychiatry. 2002;52(2):93–100.
25. Ongür D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci USA. 1998;95(22):13290–5.
26. Sassi RB, Brambilla P, Hatch JP, et al. Reduced left anterior cingulate volumes in untreated bipolar patients. Biol Psychiatry. 2004;56(7):467–75.
27. Doris A, Belton E, Ebmeier KP, Glabus MF, Marshall I. Reduction of cingulate gray matter density in poor outcome bipolar illness. Psychiatry Res. 2004;130(2):153–9.
28. Drevets WC, Price JL, Simpson JR, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature. 1997;386 (6627):824–7.
29. Bora E, Fornito A, Yücel M, Pantelis C. Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. Biol Psychiatry. 2010;67(11):1097–105.
30. Rosso IM, Killgore WD, Cintron CM, et al. Reduced amygdala volumes in first-episode bipolar disorder and correlation with cerebral white matter. Biol Psychiatry. 2007;61(6):7439.
31. Javadapour A, Malhi GS, Ivanovski B, et al. Hippocampal volumes in adults with bipolar disorder. J Neuropsychiatry Clin Neurosci. 2010;22(1):55–62.
32. Berk M, Hallam K, Malhi GS, et al. Evidence and implications for early intervention in bipolar disorder. J Ment Health. 2010;19 (2):113–26.
33. Mills NP, Delbello MP, Adler CM, Strakowski SM. MRI analysis of cerebellar vermal abnormalities in bipolar disorder. Am J Psychiatry. 2005;162(8):1530–2.
34. Hwang J, Lyoo IK, Dager SR, et al. Basal ganglia shape alterations in bipolar disorder. Am J Psychiatry. 2006;163(2):276–85.
35. Strakowski SM, DelBello MP, Sax KW, et al. Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. Arch Gen Psychiatry. 1999;56(3):254–60.
36. Atmaca M, Ozdemir H, Yildirim H. Corpus callosum areas in first-episode patients with bipolar disorder. Psychol Med. 2007;37 (5):699–704.
37. Barnea-Goraly N, Chang KD, Karchemskiy A, Howe ME, Reiss AL. Limbic and corpus callosum aberrations in adolescents with bipolar disorder: a tract-based spatial statistics analysis. Biol Psychiatry. 2009;66(3):238–44.
38. Brambilla P, Nicoletti M, Sassi RB, et al. Corpus callosum signal intensity in patients with bipolar and unipolar disorder. J Neurol Neurosurg Psychiatry. 2004;75(2):221–5.
39. Moorhead TW, McKirdy J, Sussmann JE, et al. Progressive gray matter loss in patients with bipolar disorder. Biol Psychiatry. 2007;62(8):894–900.
40. Frey BN, Zunta-Soares GB, Caetano SC, et al. Illness duration and total brain gray matter in bipolar disorder: evidence for neurodegeneration? Eur Neuropsychopharmacol. 2008;18(10):717– 22.
41. Strakowski SM, DelBello MP, Zimmerman ME, et al. Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. Am J Psychiatry. 2002;159 (11):1841–7.
42. Rajkowska G. Cell pathology in bipolar disorder. Bipolar Disord. 2002;4(2):105–16.
43. Hunsberger JG, Austin DR, Chen G, Manji HK. Cellular mechanisms underlying affective resiliency: the role of glucocorticoid receptor- and mitochondrially-mediated plasticity. Brain Res. 2009;1293:76–84.
44. Schloesser RJ, Huang J, Klein PS, Manji HK. Cellular plasticity cascades in the pathophysiology and treatment of bipolar disorder. Neuropsychopharmacology. 2008;33(1):110– 33.
45. Kato T. Molecular neurobiology of bipolar disorder: a disease of 'mood-stabilizing neurons'? Trends Neurosci. 2008;31(10):495 –503.
46. Perova T, Wasserman MJ, Li PP, Warsh JJ. Hyperactive intracellular calcium dynamics in B lymphoblasts from patients with bipolar I disorder. Int J Neuropsychopharmacol. 2008;11(2):185 –96.
47. McCurdy RD, Féron F, Perry C, et al. Cell cycle alterations in biopsied olfactory neuroepithelium in schizophrenia and bipolar I disorder using cell culture and gene expression analyses. Schizophr Res. 2006;82(2–3):163–73.
48. Stork C, Renshaw PF. Mitochondrial dysfunction in bipolar disorder: evidence from magnetic resonance spectroscopy research. Mol Psychiatry. 2005;10(10):900–19.
49. So J, Warsh JJ, Li PP. Impaired endoplasmic reticulum stress response in B-lymphoblasts from patients with bipolar-I disorder. Biol Psychiatry. 2007;62(2):141 –7.
50. Hayashi A, Kasahara T, Kametani M, et al. Aberrant endoplasmic reticulum stress response in lymphoblastoid cells from patients with bipolar disorder. Int J Neuropsychopharmacol. 2009;12 (1):33 –43.
51. •• Manji H, Kato T, Di Prospero NA, et al. Impaired mitochondrial function in psychiatric disorders. Nat Rev Neurosci. 2012;13 (5):293–307. This study reviews data on mitochondrial function in psychiatric disorders, including clinical and preclinical data
52. • Du J, Wang Y, Hunter R, et al. Dynamic regulation of mitochondrial function by glucocorticoids. Proc Natl Acad Sci USA. 2009;106(9):3543–8. This study shows that glucocorticoids have a biphasic effect on mitochondrlafunctions, relating chronic stress to reduced mitochondrial membrane potential, calcium holding capacity and oxygen consumption
53. Gong Y, Chai Y, Ding JH, Sun XL, Hu G. Chronic mild stress damages mitochondrial ultrastructure and function in mouse brain. Neurosci Lett. 2011;488(1):76–80.
54. Daban C, Vieta E, Mackin P, Young AH. Hypothalamic-pituitary-adrenal axis and bipolar disorder. Psychiatr Clin North Am. 2005;28(2):469–80.
55. Benes FM, Matzilevich D, Burke RE, Walsh J. The expression of proapoptosis genes is increased in bipolar disorder, but not in schizophrenia. Mol Psychiatry. 2006;11(3):241–51.
56. Eastwood SL, Harrison PJ. Synaptic pathology in the anterior cingulate cortex in schizophrenia and mood disorders. A review and a Western blot study of synaptophysin, GAP-43 and the complexins. Brain Res Bull. 2001;55(5):569 –78.
57. Pfaffenseller B. Disfunção na Resposta ao Estresse do Retículo Endoplasmático em linfócitos de pacientes com Transtorno de Humor Bipolar. Dissertation. Porto Alegre: Universidade Federal do Rio Grande do Sul; 2012.
58. Bachmann RF, Schloesser RJ, Gould TD, Manji HK. Mood stabilizers target cellular plasticity and resilience cascades: implications for the development of novel therapeutics. Mol Neurobiol. 2005;32(2):173–202.
59. Kim HW, Rapoport SI, Rao JS. Altered expression of apoptotic factors and synaptic markers in postmortem brain from bipolar disorder patients. Neurobiol Dis. 2010;37(3):596 –603.
60. Fernandes BS, Gama CS, Ceresér KM, et al. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J Psychiatr Res. 2011;45(8):995–1004.
61. Walz JC, Andreazza AC, Frey BN, et al. Serum neurotrophin-3 is increased during manic and depressive episodes in bipolar disorder. Neurosci Lett. 2007;415(1):87–9.
62. Walz JC, Magalhães PV, Giglio LM, et al. Increased serum neurotrophin-4/5 levels in bipolar disorder. J Psychiatr Res. 2009;43(7):721–3.

63. Rosa AR, Frey BN, Andreazza AC, et al. Increased serum glial cell line-derived neurotrophic factor immunocontent during manic and depressive episodes in individuals with bipolar disorder. Neurosci Lett. 2006;407(2):146–50.
64. Kapczinski F, Dal-Pizzol F, Teixeira AL, et al. Peripheral biomarkers and illness activity in bipolar disorder. J Psychiatr Res. 2011;45(2):156–61.
65. Andreazza AC, Kapczinski F, Kauer-Sant'Anna M, et al. 3-Nitrotyrosine and glutathione antioxidant system in patients in the early and late stages of bipolar disorder. J Psychiatry Neurosci. 2009;34(4):263–71.
66. Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int J Neuropsychopharmacol. 2009;12(4):447–58.
67. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry. 2000;57(10):925–35.
68. Grande I, Fries GR, Kunz M, Kapczinski F. The role of BDNF as a mediator of neuroplasticity in bipolar disorder. Psychiatry Investig. 2010;7(4):243–50.
69. Young LT. Neuroprotective effects of antidepressant and mood stabilizing drugs. J Psychiatry Neurosci. 2002;27(1):8–9.
70. Ludwig JA, Weinstein JN. Biomarkers in cancer staging, prognosis and treatment selection. Nat Rev Cancer. 2005;5(11):845–56.
71. Barbosa IG, Huguet RB, Mendonça VA, et al. Increased plasma levels of brain-derived neurotrophic factor in patients with long-term bipolar disorder. Neurosci Lett. 2010;475(2):95–8.
72. Barbosa IG, Rocha NP, Huguet RB, et al. Executive dysfunction in euthymic bipolar disorder patients and its association with plasma biomarkers. J Affect Disord. 2012;137(1–3):151–5.
73. Lin PY. State-dependent decrease in levels of brain-derived neurotrophic factor in bipolar disorder: a meta-analytic study. Neurosci Lett. 2009;466(3):139–43.
74. Magalhães PV, Jansen K, Pinheiro RT, et al. A nested population-based case-control study on peripheral inflammation markers and brainderived neurotrophic factor in early-stage mood disorders . Istambul: Presented at the 5th Biennial Conference of the International Society for Bipolar Disorders; 2012.
75. Hope S, Dieset I, Agartz I, et al. Affective symptoms are associated with markers ofi nflammation and immune activation in bipolar disorders but not in schizophrenia. J Psychiatr Res. 2011;45 (12):1608–16.
76. Tsai SY, Chung KH, Wu JY, et al. Inflammatory markers and their relationships with leptin and insulin from acute mania to full remission in bipolar disorder. J Affect Disord. 2012;136(12):110–6.
77. Barbosa IG, Huguet RB, Mendonça VA, et al. Increased plasma levels of soluble TNF receptor I in patients with bipolar disorder. Eur Arch Psychiatry Clin Neurosci. 2011;261(2):139–43.
78. Kunz M, Ceresér KM, Goi PD, et al. Serum levels of IL-6, IL-10 and TNF- in patients with bipolar disorder and schizophrenia: differences in pro- and anti-inflammatory balance. Rev Bras Psiquiatr. 2011;33(3):268–74.
79. Söderlund J, Olsson SK, Samuelsson M, et al. Elevation of cerebrospinal fluid interleukin-1ß in bipolar disorder. J Psychiatry Neurosci. 2011;36(2):114–8.
80. Barbosa IG, Rocha NP, Bauer ME, et al. Chemokines in bipolar disorder: Trait or state? Eur Arch Psychiatry Clin Neurosci. 2012. doi:10.1007/s00406-012-0327-6
81. Herberth M, Koethe D, Levin Y, et al. Peripheral profiling analysis for bipolar disorder reveals markers associated with reduced cell survival. Proteomics. 2011;11(1):94–105.
82. Kato T. Mitochondrial dysfunction as the molecular basis of bipolar disorder: therapeutic implications. CNS Drugs. 2007;21(1):1–11.
83. Regenold WT, Phatak P, Marano CM, et al. Elevated cerebrospinal fluid lactate concentrations in patients with bipolar disorder and schizophrenia: implications for the mitochondrial dysfunction hypothesis. Biol Psychiatry. 2009;65(6):489–94.
84. Halliwell B. Free radicals and antioxidants: updating a personal view. Nutr Rev. 2012;70(5):257–65.
85. Magalhães PV, Jansen K, Pinheiro RT, et al. Peripheral oxidative damage in early-stage mood disorders: a nested population-based case-control study. Int J Neuropsychopharmacol. 2011;19:1 – 8.
86. Andreazza AC, Kauer-Sant'anna M, Frey BN, et al. Oxidative stress markers in bipolar disorder: a meta-analysis. J Affect Disord. 2008;111(2–3):135–44.
87. Kunz M, Gama CS, Andreazza AC, et al. Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(7): 1677–81.
88. Yumru M, Savas HA, Kalenderoglu A, et al. Oxidative imbalance in bipolar disorder subtypes: a comparative study. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(6):1070–4.
89. Simon NM, Smoller JW, McNamara KL, et al. Telomere shortening and mood disorders: preliminary support for a chronic stress model of accelerated aging. Biol Psychiatry. 2006;60(5):432–5.
90. Elvsåshagen T, Vera E, Bøen E, et al. The load of short telomeres is increased and associated with lifetime number of depressive episodes in bipolar II disorder. J Affect Disord. 2011;135(1–3):43–50.
91. Berk M, Hallam KT, McGorry PD. The potential utility of a staging model as a course specifier: a bipolar disorder perspective. J Affect Disord. 2007;100(1–3):279–81.
92. Kapczinski F, Dias VV, Kauer-Sant'Anna M, et al. Clinical implications of a staging model for bipolar disorders. Expert Rev Neurother. 2009;9(7):957–66.
93. McGorry PD, Purcell R, Hickie IB, et al. Clinical staging: a heuristic model for psychiatry and youth mental health. Med J Aust. 2007;187(7 Suppl):S40–2.
94. Magalhães PV, Dodd S, Nierenberg AA, Berk M. Cumulative morbidity and prognostic staging ofi llness in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Australian & New Zealand Journal of Psychiatry. Aust N Z J Psychiatry. 2012. doi:10.1177/0004867412460593
95. Magalhães PV, Kapczinski F, Nierenberg AA, Deckersbach T, Weisinger D, Dodd S, Berk M. Illness burden and medical comorbidity in the Systematic Treatment Enhancement Program for Bipolar Disorder. Acta Psychiatr Scand. 2012;125(4):303–308.
96. Reinares M, Papachristou E, Harvey P, Mar Bonnín C, Sánchez-Moreno J, Torrent C, Ayuso-Mateos JL, Ploubidis GB, Vieta E, Frangou S. Towards a clinical staging for bipolar disorder: Defining patient subtypes based on functional outcome. J Affect Disord. doi:10.1016/j.jad.2012.06.005.
97. McGorry PD. Staging in neuropsychiatry: a heuristic model for understanding, prevention and treatment. Neurotox Res. 2010;18 (3–4):244–55.

ANEXO C – EFFECTIVENESS AND TOLERANCE OF ANTI-INFLAMMATORY DRUGS' ADD-ON THERAPY IN MAJOR MENTAL DISORDERS: A SYSTEMATIC QUALITATIVE REVIEW

Effectiveness and tolerance of anti-inflammatory drugs' add-on therapy in major mental disorders: a systematic qualitative review

Fond, G.; Hamdani, N.; Kapczinski, F; Boukouaci, W.; Drancourt, N.; Dargel, A. A.; Oliveira, J.; Le Guen, E.; Marlinge, E.; Tamouza, R. Leboyer, M.

Publicado em Acta Psychiatrica Scandinavica

Effectiveness and tolerance of anti-inflammatory drugs' add-on therapy in major mental disorders: a systematic qualitative review

Fond G, Hamdani N, Kapczinski F, Boukouaci W, Drancourt N, Dargel A, Oliveira J, Le Guen E, Marlinge E, Tamouza R, Leboyer M.

Objective: To provide a systematic review of the literature regarding the efficacy of anti-inflammatory drugs in three major mental disorders [major depressive disorder (MDD), schizophrenia and bipolar disorders].
Method: Four databases were explored, without any year or language restrictions. The baseline search paradigm was limited to open-labelled clinical and randomized controlled trials (RCTs).
Results: Four major classes of anti-inflammatory drugs were identified, namely polyunsaturated fatty acids (PUFAs), cyclooxygenase (COX) inhibitors, anti-TNFalpha and minocycline. Effectiveness and benefit/risk ratio of each class in MDD, bipolar disorders and schizophrenia was detailed when data were available. Several meta-analyses indicated effectiveness of PUFAs in MDD with a good tolerance profile. One meta-analysis indicated that COX-2 specific inhibitors showed effectiveness in schizophrenia. Anti-TNFalpha showed important effectiveness in resistant MDD with blood inflammatory abnormalities. Minocycline showed effectiveness in schizophrenia.
Conclusion: Polyunsaturated fatty acids seem to have the best benefit/risk ratio profile but proved their effectiveness only in MDD. A number of anti-inflammatory drugs are available as adjunct treatment for treatment-resistant patients with MDD, schizophrenia and bipolar disorder. If used with caution regarding their possible side-effects, they may be reasonable therapeutic alternatives for resistant symptomatology.

G. Fond,[1] N. Hamdani,[1] F. Kapczinski,[2] W. Boukouaci,[3] N. Drancourt,[1] A. Dargel,[2,3] J. Oliveira,[3] E. Le Guen,[1] E. Marlinge,[1] R. Tamouza,[3,*] M. Leboyer[1,*]

[1]Pôle de psychiatrie des hôpitaux universitaires H Mondor, University Paris Est-Créteil, INSERM U955, Eq Psychiatrie Génétique, Fondation FondaMental Fondation de coopération scientifique en santé mentale, Créteil, France, [2]Laboratory of Molecular Psychiatry, Centro de Pesquisas Experimentais, Hospital de Clínicas de Porto Alegre, and INCT for Translational Medicine, Porto Alegre, Brazil and [3] Jean Dausset Laboratory & INSERM, UMRS 940, Hôpital Saint Louis, Paris, France

Key words: anti-inflammatory; cyclooxygenase-1; cyclooxygenase-2; non-steroidal anti-inflammatory drugs; celecoxib; salicylate; tumor necrosis factor; infliximab; minocycline; depression; schizophrenia; bipolar disorders

Dr Guillaume Fond, Pole de Psychiatrie, Hôpital A. Chenevier, 40 rue de Mesly, Créteil F-94010, France.
E-mail: guillaume.fond@gmail.com

*Both authors equally directed the present work.

Summations

- One of the most promising research fields is the inflammatory component of major psychiatric diseases (depression, bipolar disorders and schizophrenia).
- Patients with high hs-CRP (>5 mg/l) in cases of early episodes of mood or psychotic disorders (<2 years) may be particularly responsive to anti-inflammatory drugs.

Considerations

- Further studies are warranted to identify more precisely the biomarkers that could identify potential responders and orientate some specific treatment.
- The benefit/risk ratio of add-on-anti-inflammatory drugs should always be discussed Omega-3 may have the better benefit/risk ratio in depressive disorders as no severe side-effects have been described to date.

Introduction

Mental, neurological and substance-use disorders still constitute 13% of the global disease burden, surpassing both cardiovascular diseases and cancers (1–3). Major psychiatric disorders such as major depressive disorders (MDD), schizophrenia and bipolar disorders are among the four most disabling MNS illnesses worldwide with a global social cost of respectively 66.5, 23.7 and 16.8 millions disability-adjusted life years (DALYs) (1). While forecasts predict an increase in the prevalence of mental disorders worldwide, the response rate to classical psychiatric treatments still remains unsatisfactory (4).

The contribution of chronic inflammation to major mental disorders has received increased attention, which revealed a host of pharmacological targets. Indeed, multiple recent reviews clearly demonstrate that MDD, schizophrenia and bipolar disorder are associated with a dysregulation of immune responses as reflected by the observed abnormal profiles of circulating pro- and anti-inflammatory cytokines in affected patients [see for MDD (5 –8), for bipolar disorder (9 –11) and for schizophrenia (12–17)]. Considering the high rate of associated somatic comorbidity, major mental illnesses, especially bipolar disorders, have been proposed as multisystemic inflammatory diseases affecting the brain as well as other organs (18–20). In parallel, chronic inflammatory diseases are known to have a high psychiatric comorbidity rate (especially with MDD) (21 –26).

The same overlap is also found in pharmacological drug properties as several antidepressants [especially selective serotonin reuptake inhibitors (SSRIs)], several antipsychotics and mood stabilizers have shown intrinsic anti-inflammatory properties (27–34), while some anti-inflammatory drugs have shown effectiveness in the treatment of major psychiatric disorders (35 –41). Some specific reviews focused either on one anti-inflammatory drug (celecoxib and minocycline) or on one mental disorder (schizophrenia or depression) (42 –45), but no comprehensive review summarized the effectiveness of anti-inflammatory drugs in major psychiatric disorders to date.

Aim of the study

To provide a systematic review of the literature regarding the efficacy and benefit/risk ratio of anti-inflammatory drugs (classified according to their mechanisms of action) in three major mental disorders (major depressive disorder, schizophrenia and bipolar disorders).

In a purpose of consistency and coherence, the strictly speaking neuroprotective and antioxidant mechanisms, nor the non-pharmacological interventions such as treatments focused on weight loss or nutritional factors will not be mentioned in this review even if they are intertwinned with anti-inflammatory ones. However, PUFAs were included as they showed some anti-inflammatory properties.

Material and methods

The present work was based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Medline (1966-janv 2013), Web of Science (1975-janv 2013), www.clinicaltrials.org and google scholar databases were explored, without any year or language restrictions. The search paradigm was limited to open-labelled clinical and randomized controlled trials (RCTs) with the following terms: (depression, bipolar disorders, schizophrenia) and respectively anti-inflammatory drugs, non-steroidal anti-inflammatory drugs (NSAID), ibuprofen, diclofenac, naproxen sodium, acetylsalicylic acid, cyclooxygenase (COX)-2 inhibitors, celecoxib, anti-TNF- a, etanercept, infliximab, adalimumab, minocycline). Last search was conducted on January 2013. Duplicates were discarded. Additionally, the reference list of the retrieved articles and relevant review articles were examined for cross-references (Fig. 1).

Results

Polyunsaturated fatty acids

The eicosanoids derived from n-3 (omega 3) PUFAs curb the production of arachidonic acid (AA)-derived eicosanoids that have proinflammatory properties (46). Add-on omega-3 therapy has been recently observed to lower the inflammatory status in healthy middle-aged and old adults (47) and to improve anxiety symptoms (but not depressive symptoms) in healthy young adults (48). For recent reviews of omega 3 in psychiatric disorders, see (49–52).

n-3 PUFAs in MDD. Several meta-analyses evaluated the effectiveness of n-3 PUFAs supplementation in adults with MDD. Most of them found that such supplementation was beneficial in adult patients with MDD and that this effect was strongly dependent on the eicosapentaenoic acid (EPA) content of nutritional regimens with a

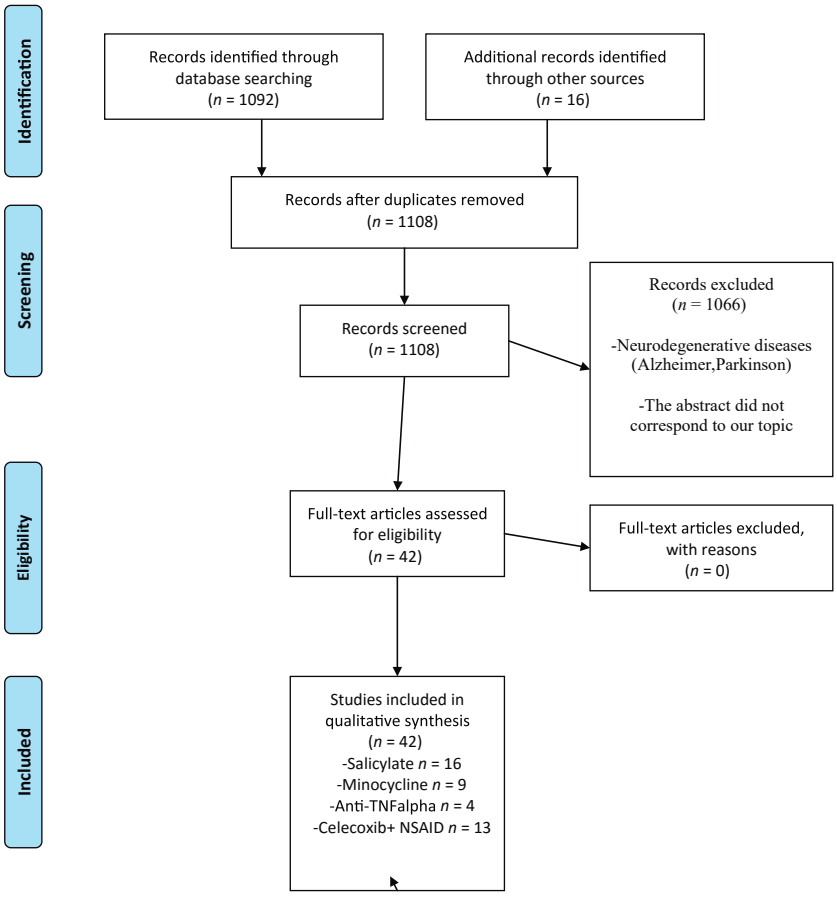


Fig. 1. PRISMA 2009 Flow Diagram. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

standard mean difference of 0.62 ($P < 0.001$) for those containing >60% EPA (53 –57).

n-3 PUFAs in bipolar disorders. Mixed evidence was found for omega-3 therapy in bipolar depression, while no argument was found for their use in mania (for a systematic review, see (58). Omega-3 administration during 4 –26 weeks revealed significant positive results on depression in two of seven RCTs (N = 14 to 121) and no significant effect in mania (59 –64). These differences could be due to analysed small sample sets and/or to the heterogeneity of omega-3 pharmaceutical preparation.

n-3 PUFAs in schizophrenia. An interesting hypothesis suggests that schizophrenic symptoms may result from altered neuronal membrane structure and metabolism in which fatty acids play an important role (65, 66). A recent meta-analysis including 168 patients with schizophrenia receiving EPA along with 167 others receiving placebo did not allow to note any statistically significant effect of EPA on psychotic symptomatology (67). Another meta-analysis including 11 RCTs and 1246 subjects found that EPA administration may have a preventing effect against the transition to psychosis at 12 months, but the quality of evidence remains poor to date (68).

PUFAs benefit/risk ratio. The most frequently reported side-effects during PUFAs administration are gastrointestinal side-effects [including eructation (4.9%) and dyspepsia (3.1%)], infection (4.4%), back pain (2.2%), pain (1.8%), rashes (1.8%), angina pectoris (1.3%), arthralgia and dizziness (69). High blood PUFAs concentrations have been associated with increased prostate cancer risk (70). A meta-analysis of 12 studies found that high serum level of docosapentaenoic acid was associated with reduced total prostate cancer risk, while high blood level of EPA and DHA was possibly associated with increased high-grade prostate tumour risk (71). No clear relation between PUFAs consumption and gastric cancer risk was found in a meta-analysis of 17 trials and 5323 patients and more than 130 000 controls (72). No

relation was found between PUFAs high consumption and bleeding in a large, multicenter cohort of 1524 patients with acute myocardial infarction, suggesting that concerns about bleeding should not preclude the use of omega-3 supplements when clinically indicated (73, 74).

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs are a well-known and broad class of anti-inflammatory drugs that inhibit the conversion of AA to prostaglandins (75) and thromboxanes by blocking the enzyme cyclooxygenase-1 (COX-1) or 2 (COX-2) (76, 77). The arguments for targeting respectively COX-1 or COX-2 are summarized in Table 1.

COX-2 inhibitors (celecoxib) and NSAID other than low-dose aspirin. Celecoxib accesses easily the central nervous system (CNS), and its central effects have not been yet fully elucidated.

COX-2 inhibitors in MDD. In three RCTs, celecoxib (200 mg 9 2/day) was found to improve depressive outcomes in an add-on therapy (to respectively reboxetine 4 mg/day, and fluoxetine 40 mg/day, sertraline 200 mg/day) (N = 40 for each RCT) (98 –100) (Table 2).

A recent pharmacovigilance study (104) including 1528 patients with major depression found a positive association between exposure to chronic use of NSAID (excluding COX-2 inhibitors and salicylates) and resistant depression (OR = 1.55, 95% CI = 1.21–2.00), after adjustment for comorbidities and sociodemographic variables. Interestingly, this association was not found with COX-2 inhibitors and salicylates alone. It was stressed that authors were not able to adjust the association with pain and suggest to avoid classical NSAID in patients with depression and to prefer other inflammatory mechanism-related actions such as COX-2 inhibitors and salicylates among these patients.

COX-2 inhibitors in bipolar disorders. A preliminary study comparing adjunction of celecoxib 200 mg 9 2/day vs. placebo for 6 weeks in 28 patients with bipolar disorders (depressive or mixed phase) did not find a significant difference between the groups except for the first week (105). These results contrasted with those obtained using celecoxib in unipolar depression, however.

No specific study on ibuprofen, diclofenac or naproxen sodium in mood disorders was published to date.

COX-2 inhibitors in schizophrenia. A recent meta-analysis (113) studied the effect of the addition of a NSAID to antipsychotic treatment in patients with stabilized schizophrenia (Table 3).

This meta-analysis included five RCTs [four with celecoxib 400 mg/day and one with acetylsalicylic acid (ASA) 1000 mg/day] (N = 264). The authors found an effect size of 0.43 (P = 0.02) on

Table 1. Summary of physiological properties of cyclooxygenase 1 and 2 (COX-1/2) and rodent studies of anti-COX selective drugs to dress arguments for targeting each COX in major psychiatric disorders associated with inflammatory disorders (for human studies, see Table 2 for unipolar depressive disorders, Table 3 for schizophrenia and the manuscript for depressive bipolar disorders). Arguments are majorly in favour of COX-2 given that it was the predominant target hypothesis over COX-1 for decades, but this hypothesis has recently been suggested to be reviewed. PG, prostaglandin

Target	COX-2	COX-1
Physiology	Is mainly induced in response to inflammatory stimuli Is constitutively expressed in central nervous system, mainly in hippocampus, amygdala (78, 79) , in cortical glutamatergic neurons where it has a pivotal role in synaptic activity and long-term synaptic plasticity (80–82) PG play an important role in cytokines and TNF-a metabolism, as well as with N-methyl-D-aspartate acid (NMDA) receptors, important in glutamate transmission (83). The prostaglandin PGE2 (the product of arachidonic acid by COX-2) is increased in depression (84) COX-2, but not COX-1, enhances glucocorticoid receptor function, which may be another therapeutic pathway in psychiatric disorders (85)	Is constitutively expressed in most tissues, has been classically considered as the isoform primarily responsible for homeostatic PG synthesis (86) Is the major player in mediating the inflammatory microglia activation (87) Plays a recently recognized proinflammatory role in the pathophysiology of acute and chronic neurological disorders (88, 89)
Rodent studies	Anti-COX-2 drugs Access easily the central nervous system but their effects are not fully elucidated Can reduce inflammation without affecting the physiological functions of COX-1-derived PGs have been linked to neuroprotective properties (90, 91) Balance the type-1/type-2 immune response by inhibition of PGE2 (and IL-10) and by stimulating the type-1 immune response (92) Antagonize IL-1 and other proinflammatory interleukins production (93) and prevent the anxiety- and cognitive-associated decline (94) Prevent the dysregulation of the HPA axis (95), in particular the increase of cortisol, one of the key hormones associated with depression (96), contrary to anti-COX-1	Anti-COX-1 activity is neuroprotective, whereas anti-COX-2 activity is detrimental, during a primary neuroinflammatory response (reviewed in (97))

Table 2. Summary of clinical trials (open-label and double-blind randomized placebo controlled trials (RCT)) on add-on therapy of anti-inflammatory drugs in major depressive disorder (MDD). All diagnoses were carried out according to the DSM-IV or DSM-IV-TR (Chronic inflammatory diseases were excluded). HAM-D Hamilton Depression Rating Scale. CGI clinical Global Impression score. BPRS Brief Psychiatric Rating Scale

Author	Study design	TTreatment + trial duration	Outcome measures	Results
Abbasi (98)	RCT N= 40 patients with HAM-D score> 17	Sertraline 200 mg/day (celecoxib 400 mg or placebo) 6 weeks	Serum IL-6 concentrations at baseline and week 6, HAM-D scores at baseline and weeks 1, 2, 4, and 6	The celecoxib group showed significantly greater reduction in serum IL-6 concentrations (mean difference (95% CI) = 0.42(0.30–0.55) pg/ml, t(35) = 6.727, P < 0.001) as well as HAM-D scores (mean difference (95% CI) = 3.35(1.08–5.61), t(38) = 2.99, P = 0.005) than the placebo group. The patients in the celecoxib group experienced more response (95%) and remission (35%) than the placebo group (50% and 5%, P = 0.003 and 0.04 respectively). Baseline serum IL-6 levels were significantly correlated with baseline HAM-D scores (r = 0.378, P = 0.016). Significant correlation was observed between reduction of HAM-D scores and reduction of serum IL-6 levels at week 6 (r = 0.673, P < 0.001)
Müller (99)	RCT N= 40 patients with acute MDD	Reboxetine 4 mg+ (Celecoxib 400 mg or placebo) 6 weeks	HAM-D	The celecoxib group showed significantly greater improvement compared to the reboxetine-alone group. (F = 3.220; df 2.434; P = 0.035)
Akhondzadeh (100)	RCTN = 40 out-patient with MDD (baseline HAM-D score> 17)	Fluoxetine 40 mg+ (Celecoxib 400 mg or placebo) 6 weeks	HAM-D (weeks 0,1,2,4,6)	The combination of fluoxetine and celecoxib showed a significant superiority over fluoxetine alone in the treatment of symptoms of major depression. The difference between the two treatments was significant at the endpoint (week 6) (t = 3.35, df = 38, P < 0.001). There was a significant difference between two treatments in terms of the percentage of responders (at least 50% reduction in the HAM-D score) (celecoxib group: 90%, 18 of 20 and placebo group: 50%, 10 of 20; P < 0.01). Thirty-five per cent of the patients in the celecoxib group and 5% in the placebo group were remitted after 6 weeks (HAM-D < 7). The difference was significant (P = 0.04). There were no significant differences in the two groups in terms of observed side-effects
Mendlewicz (101)	Open-label N = 24 non-responder patients with MDD	SSRI + aspirin 160 mg/day 4 weeks	HAM-D	The combination SSRI-ASA was associated with a response rate of 52.4%. Remission was achieved in 43% of the total sample and 82% of the responder sample. In the responder group, a significant improvement was observed within week 1 (mean HAM-D at day 0 = 29.3± 4.5, at day 7 = 14.0± 4.1; P < 0.0001) and remained sustained until day 28. These preliminary results are in favour of an accelerating effect of ASA in combination with SSRIs in the treatment of major depression
Raison (102)	RCTN= 60 out-patients with stable depression (37 with antidepressant and 23 medication free)	Three administrations (week 0,2,6) 12 weeks	HAM-D at weeks 0 (baseline), 1, 2, 3, 4, 6, 8, 10 and 12. -high-sensitivity C-reactive protein (hs-CRP), TNF, and its soluble receptors at weeks 0 (baseline), 1, 2, 3, 4, 6, 8, 10 and 12	No overall difference in change of HAM-D scores between treatment groups across time was found. However, there was a significant interaction between treatment, time, and log baseline hs-CRP concentration (P = 0.01), with change in HAM-D scores (baseline to week 12) favouring infliximab-treated patients at a baseline hs-CRP concentration >5 mg/l and favouring placebo-treated patients at a baseline hs-CRP concentration of 5 mg/l or less. Exploratory analyses focusing on patients with a baseline hs-CRP concentration >5 mg/l revealed a treatment response (≥50% reduction in HAM-D score at any point during treatment) of 62% (eight of 13 patients) in infliximab-treated patients vs. 33% (three of nine patients) in placebo-treated patients (P = 0.019). Baseline concentrations of TNF and its soluble receptors were significantly higher in infliximab-treated responders vs nonresponders (P < 0.05), and infliximab-treated responders exhibited significantly greater decreases in hs-CRP from baseline to week 12 compared with placebo-treated responders (P < 0 .01). Drop-outs and adverse events were limited and did not differ between groups. This proof-of-concept study suggests that TNF antagonism does not have generalized efficacy in treatment resistant depression but may improve depressive symptoms in patients with high baseline inflammatory biomarkers
Miyaoka (103)	Open-label N = 25 adult in-patients with major depression with psychotic features (psychotic depression) according to DSM-IV-TR	Fluvoxamine, paroxetine, or sertraline+ minocycline 150 mg/day 6 weeks	HAM-D (baseline and week 6) CGI (baseline and week 6) BPRS (baseline and week 6)	Minocycline in combination with antidepressants provided significant improvement in depression. Mean (±SD) HAM-D was reduced to 6.7± 1.9 at week 6 from a baseline value of 40.4± 2.5. Significant improvement of psychotic symptoms (mean± SD) was indicated by the decrease in BPRS scores from baseline (63.3± 8.7) to week 6 (4.6± 2.4) (P < 0.001). No serious adverse events occurred

Hs-CRP, highly sensitive C-reactive protein; 95% CI, 95% e interval.

Table 3. Summary of clinical trials on add-on therapy of anti-inflammatory drugs in schizophrenia (open-label and double-blind randomized placebo-controlled trials (RCT)). All diagnoses were carried out according to the DSM-IV or DSM-IV-TR ASA acetylsalicylic acid. PANSS Positive and Negative Syndrome Scale. CGI clinical Global Impression. SANS Scale for the Assess ment of Negative Symptoms, GAF Global Assessment of Functioning Scale

Author	Study design	Duration ofi llness (mean, years)	PANSS score	Treatment + trial duration	Outcome measures	Results
Müller (106)	RCT N=50 patients with acute exacerbation of schizophrenia	5,9	Not provided	Risperidone flexible dose ± Celecoxib 400 mg 5 weeks	PANSS (weekly)	The celecoxib add-on therapy had a significant effect on the mean improvement in total PANSS score, as indicated by the effect of group, the between-subjects factor (F = 3.80, df = 1, 47, P = 0.05). The difference between the two treatment groups was not homogeneous across time (multivariate group-by-time interaction: F = 3.91, df = 4, 44, P = 0.008). The main effects of celecoxib were seen in the middle of the treatment period (quadratic interaction component: F = 12.50, df = 1, 47, P = 0.001). In simple post hoc t tests, the difference between the two treatment groups was significant from week 2 to week 4 (week 2: t = 2.06, df = 48, P = 0.05; week 3: t = 2.64, df = 48, P = 0.01; week 4: t = 2.54, df = 48, P = 0.01). The celecoxib add-on treatment did result in earlier improvement in all subscale scores
Rapaport (107)	RCT N=38 out-patients with chronic schizophrenia	<10 (no mean provided)	84,2	Risperidone or Olanzapine fixed dose± Celecoxib 400 mg 9 weeks	PANSS (weekly) SANS (weekly) CGI (weekly)	The treatment cohorts did not differ on any of the clinical outcome measures. (P > 0.05)
Akhondzadeh 2007 (108)	RCT N=60 in-patients with chronic schizophrenia	7,9	Not provided	Risperidone fixed dose± Celecoxib 400 mg 8 weeks	PANSS (weeks 0,2,4,6,8)	The combination of risperidone and celecoxib showed a significant superiority over risperidone alone in the treatment of positive symptoms (P < 0.05 at week 8), general psychopathology symptoms (P < 0.001 at week 8) as well as PANSS total scores (P < 0.01 at week 8)
Müller (109)	Randomized double-blind controlled N=49 patients with first episode schizophrenia	1,3	95,2	Amisulpride flexible dose± Celecoxib 400 mg 6 weeks	PANSS (weekly) CGI (weekly)	A significantly better outcome was observed in the patient group treated with amisulpride plus celecoxib compared with the group with amisulpride plus placebo (PANSS negative: P = 0.03; PANSS global; P = 0.05 and PANSS total: P = 0.02). In addition, ratings by the CGI scale during therapy with amisulpride and celecoxib showed a significantly better result (P ≤ 0.001). A significantly superior therapeutic effect could be observed in the celecoxib group compared with placebo in the treatment of early stage schizophrenia.
Laan 2010 (110)	RCTN=70 in-patients and out-patients with schizophrenia or schizoaffective disorder with PANSS score >60	3,7	72,2	Risperidone olanzapine or clozapine fixed dose± ASA 1000 mg 3 months all patients received gastric protection (pantoprazole 40 mg daily)	PANSS (monthly)	Mixed-effect models showed a 4.86-point (95% CI, 0.91–8.80) and 1.57-point (95% CI, 0.06–3.07) larger decrease in the aspirin group compared with the placebo group on the total and positive PANSS score respectively. Similar but not statistically significant results were observed for the other PANSS subscale scores. Treatment efficacy on total PANSS score was substantially larger in patients with the more altered immune function (P = .018). Aspirin did not significantly affect cognitive function. No substantial side-effects were recorded
Miyaoka (111)	Open-label n=22	Not provided	Not provided	Atypical antipsychotics fixed dose± minocycline 300 mg/day 4 weeks	PANSS	Significant improvement on PANSS score (maintained 4 weeks after discontinuation)

Table 3. (Continued)

Author	Study design	Duration of illness (mean, years)	PANSS score	Treatment + trial duration	Outcome measures	Results
Levkovitz (112)	Randomized double-blind controlledN=54 patients with early phase schizophrenia	Not provided	Not provided	The patients were randomly allocated in a 2:1 ratio to minocycline 200 mg/day. All patients had been initiated on treatment with an atypical antipsychotic ≤14 days prior to study entry (risperidone, olanzapine, quetiapine or clozapine; 200–600 mg/day chlorpromazine-equivalent doses)	SANS (primary outcome) PANSS CGI GAF All clinical measures were evaluated weekly during the leadin phase and the first 2 weeks of the study and then once a month for the remaining 5 months (weeks 6, 10, 14, 18, 22)	Minocycline was well tolerated, with few adverse events. It showed a beneficial effect on negative symptoms and general outcome (evident in SANS, Clinical Global Impressions scale). A similar pattern was found for cognitive functioning, mainly in executive functions (working memory, cognitive shifting and cognitive planning)

the PANSS total score in favour of NSAIDs, 0.34 (P = 0.02) on positive symptoms and more moderate on negative symptoms (0.26, P = 0.03). The longest trial lasted only 12 weeks, and the authors suggested that longer treatment may potentiate the NSAID-antipsychotic association and that treatment would be more effective ifi nitiated early in the illness progression, especially in the first 2 years (114). The optimization in doses and duration of celecoxib treatment in schizophrenia cannot still be determined at the moment because of the lack of data on the degree of CNS penetration and the required time period for the efficient effect of celecoxib on CNS.

No specific study on ibuprofen, diclofenac or naproxen sodium in psychotic disorders was published to date.

Celecoxib and NSAID benefit/risk ratio. The following adverse events of celecoxib were reported in controlled trials: headache, dizziness, constipation, nausea, abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, bronchitis, coughing, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, arthralgia, back pain, insomnia, myalgia, pain, peripheral pain, pruritus, tooth disorder, accidental injury, allergy aggravated, flu-like symptoms, peripheral oedema, rash and urinary tract infection.

There has been much concern about the possibility ofi ncreased risk of heart attack and stroke in users of NSAID drugs, particularly COX-2-selective NSAIDs such as celecoxib, since the withdrawal of the COX-2 inhibitor rofecoxib (Vioxx) in 2004. Like all NSAIDs on the US market, celecoxib carries an FDA-mandated 'black box warning' for cardiovascular and gastrointestinal risk. Celecoxib may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. Celecoxib is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. NSAIDs, including Celecoxib, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk of serious gastrointestinal events. Other potential side-effects of celecoxib include borderline elevations of one or more liver-associated enzymes may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with

NSAIDs. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including celecoxib. Long-term administration of NSAIDs may also have renal effects and result in renal papillary necrosis and other renal injury. As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to celecoxib. Celecoxib is a sulphonamide and can cause serious skin adverse events such as exfoliative dermatitis, Stevens–Johnson syndrome and toxic epidermal necrolysis, which can be fatal. Celecoxib should be avoided in late pregnancy, starting at 30-week gestation, because it may cause premature closure of the ductus arteriosus.

To establish more conclusively the true cardiovascular risk profile of celecoxib, Pfizer agreed to fund a large, randomized trial specifically designed for that purpose. The trial is not scheduled to be completed until May 2014 (115).

Concerning the non-selective COX-2 inhibitors, a study of 3175 participants (116) found a high prevalence of current NSAID (other than low-dose aspirin) use among groups at risk of significant drug-related adverse events or who have major chronic conditions that are relative contraindications to NSAID use. The authors concluded that the potential to make a substantial impact on chronic disease burden via improved use of NSAIDs was considerable.

The benefit/risk ratio of a COX-2 inhibitor in psychiatric patients should therefore be evaluated for each patient and may be rather indicated in the treatment of acute resistant episodes rather than in the long-term relapse prevention, given the potential rare but grave side-effects. Its use in bipolar disorders is not recommended to date regarding the preliminary results and the potential interactions with lithium.

Anti-COX-1 (acetylsalicylic acid). Acetylsalicylic acid is 50- to 100-fold more potent in inhibiting platelet COX-1 than monocyte COX-2 activity (117). Choi et al. (97) proposed in a recent review to reconsider the prevailing hypothesis that, by being the isoform induced in response to inflammatory stimuli, COX-2 is the most appropriate pharmacological target for anti-inflammatory therapy, and suggested that COX-1, owing to its predominant localization in microglia, is the major player in mediating the inflammatory response (Table 1).

Although ASA has a short half-life (15–20 min), ASA's permanent inhibition of COX-1 allows once daily circulating platelets count. In contrast, because nucleated cells rapidly regenerate this enzyme, a shorter dose interval is required to persistently impact COX activity in cells that mediate inflammatory processes (118). In high doses (1000 mg/day), aspirin has been studied as a COX-2 inhibitor and showed effectiveness in schizophrenia (110).

Folk remedies containing salicylic acid have been used for centuries to treat pain and fever. Acetylsalicylic acid was first synthesized in Europe in the mid-19th century. The patent for aspirin, owned by Bayer, expired in 1917 in the United States, and it has been widely available over-the-counter since that time (4).

ASA in MDD. Mendlewicz et al. (101) examined the effect of add-on aspirin (160 mg/day) to conventional antidepressant pharmacotherapy in 24 patients with MDD proven to be non-responsiveness for 4 weeks of SSRI treatment. Participants were treated openly during the subsequent 4 weeks. The combined administration of SSRI and aspirin was associated with a response rate of 52.4%. Remission was achieved in 43% of the total sample and 82% of the responder sample. In the responder group, a significant improvement was observed within week 1 and this benefit persisted through day 28.

ASA in bipolar disorders. It has been hypothesized that NSAIDs would be beneficial in bipolar disorders more specifically because of their ability to downregulate activity in the brain AA cascade by interfering with phospholipase A2 (PLA2) and/or COX function (119–128). The PLA2 and COX enzymes catalyse, respectively, release of AA from membrane phospholipid and AA conversion to eicosanoids such as prostaglandin E2 and thromboxane B2. The AA cascade is involved in neuroreceptor-initiated signalling and can be pathologically upregulated by neuro-inflammation and excitotoxicity. Preliminary data obtained in bipolar disorders suggest beneficial effects on depressive symptoms that are improved using ASA in low doses (in which ASA would inhibit COX-1 but not COX-2). The clinical use ofl ow-dose ASA primarily has been driven by its role as an antithrombotic and thrombolytic agent, given the increased death rate of cardiovascular event in bipolar disorders (18).

In a large pharmaco-epidemiological study, Stolk et al. (129) tested in 5145 patients receiving lithium whether NSAIDs or glucocorticoids would improve bipolar symptoms (based upon the assumption that lithium treatment is relatively specific to individuals with bipolar disorders). The

main outcome measure was a calculated incidence density of medication events (change in the type or numbers of psychotropic medications prescribed or increase (>30%) in the psychotropic drug dose). Subjects receiving low-dose (≤80 mg/day) aspirin were 17% less likely to have a medication event, a finding that remained significant after adjusting for age, sex, chronic disease score and healthcare utilization. Aspirin and lithium may also exert synergistic effects in forming anti-inflammatory brain metabolites (129). These preliminary observations thus appeared consistent with the hypothesis that COX-1 inhibitors can reduce neuro-inflammatory processes with consequent beneficial improvement of bipolar illness.

Benefit/risk ratio of ASA add-on therapy in mood disorders. Aspirin is a relatively safe drug except for individuals who have gastro-intestinal tract fragility or bleeding problems. It should not be used without medical authorization for patients taking inhibitors of blood clotting, such as warfarin (Coumadin) or clopidogrel (Plavix), now proven to be metabolized under an interindividual genetic control (130). These effects are especially common at high doses, and contra-indication combination with other anticoagulant is not absolute.

The low-dose aspirin (<200 mg/day) has been studied in mood disorders, where it could have a very interesting potential effectiveness in terms of pathophysiological hypotheses outlined in the Table 1. No study has examined the effect of adding low-dose aspirin in the treatment of acute manic episodes. As for the COX-2 inhibitors, the prescription of aspirin would be even more interesting in the first episodes of the disease, and the benefit–risk ratio is in favour of the prescription, especially in patients with cardiovascular, addictive or cancer risk factors comorbidities.

Adding a low-dose aspirin to conventional treatments appears a very promising strategy in uni- or bipolar depressive episodes.

Anti-TNFα

TNF- a is a 157 amino acid proinflammatory glycoprotein, which was isolated in 1975 by Carswell et al. (131) as a soluble factor released by host cells that caused necrosis of a transplanted tumour. TNF- a is produced by various immune cellular types including activated macrophages and T-cells and has several different functions. TNF- a was named 'early response cytokine' as it coordinates proinflammatory signals of the early immune response in the innate cellular immune system. Due to this function, TNF- a is assigned to the T helper type-1 (Th1) cytokines and is considered to be one of the most important mediators ofi nflammation and cachexia (132). TNF- a can have mitogenic or apoptotic effects and its synthesis depends on the nuclear factor kappa B (NF-KB) induction (133). TNF- a neutralization has proven to be a potent treatment for rheumatoid arthritis and Crohn disease (134). During inflammation, TNF- a activates HPA axis at the hypothalamic, pituitary and adrenal level resulting in the release of cortisol as the most important negative signal feedback to prevent an overshoot of the ongoing host defence (135). Moreover, Zhu et al. (136) found in an animal model that TNF- a stimulates serotonin uptake and indoleamine 2,3-dioxygenase (137) which results in a peripheral depletion of tryptophan, the precursor of serotonin (138). These three mechanisms may be involved in TNF- a-associated depression.

Currently, four molecules of the anti-TNF- a class were approved by the Food and Drug Administration (69): adalimumab, a fully human monoclonal antibody, infliximab, a chimeric monoclonal antibody, etanercept, a soluble receptor construct, and certolizumab pegol, another monoclonal antibody (139). Infliximab is a monoclonal anti-TNF- a antibody that is too large to cross the blood–brain barrier (BBB) in physiological conditions. It has then been suggested that CNS central effects ofi nfliximab may use indirect pathways or that BBB permeability may be increased in inflammatory processes, which may lead to the CNS penetration ofi nfliximab (140) or merely by reducing the systemic level of TNF a regarding the brain-body cross-talk in terms of inflammatory molecules such as cytokines.

Infliximab in MDD. Many studies have explored the association between TNF-alpha and MDD. However, the results of these studies were not consistent (Table 2). A recent meta-analysis including 15 trials found that the blood levels of TNF- a were significantly higher in MDD patients than controls ($P = 0.01$) and that age, samples source and ethnic origins may play a potential role in heterogeneity (141). Moreover, gene-targeted deletion of TNF receptors in mice leads to an antidepressant-like phenotype and reduced anxiety-like behaviour during immune activation (142, 143). To our knowledge, adalimumab and etanercept have been only studied in somatic inflammatory diseases, but both improve depressive mood and decrease fatigue among treated patients versus controls [for review, see (144)]. Tyring et al. (40) studied in 618 patients the effect of etanercept in the treatment of psoriasis and found a greater proportion of

patients with an improvement of more than 50% of the score of depression self-reported questionnaires treated by falling on etanercept 50 mg twice weekly for 12 weeks compared with the placebo group. The symptom 'fatigue' seemed particularly improved. Peripheral administration ofi nfliximab has been shown to improve depressed mood in patients with Crohn disease (145).

Infliximab is the only anti-TNF a drug that has been tested in psychiatric settings to our knowledge. In a recent double-blind randomized control trial, Raison et al. (146) studied the effect of three peripheral intravenous infliximab administrations (5 mg/kg) (week 0, 2 weeks and 6 weeks) on 12-week depressive symptomatology in 60 patients that were moderately resistant to previous antidepressant therapy. It is important to note that bipolar patients in depressed phase were included as well, but they represented only three of 60 patients. The authors found that infliximab was not associated with a significant decrease in the score of the HAM-D except for patients with high-sensitivity C-reactive protein (hs-CRP) > 5 mg/l (among 22/94 patients = 23.4%) with an effect size of 0.41. Patients lost an average of 3.1 points greater on the HAM-D in the infliximab + antidepressant group, which 'corresponds to the average effect of antidepressants', the authors noted. The same significant association was found using the Clinical Global Impression-Severity Scale (CGI). The number of needed-to-treat patients in the hs-CRP > 5 mg/l group was 3.45 (as opposed to 8–10 for conventional antidepressants) (147). The symptoms that were more responsive to infliximab were anhedonia, psychomotor retardation, psychic anxiety, depressed mood and suicidal ideation (146). The authors suggested that these changes were correlated with brain's eras functional changes that were showed in previous studies, as in basal ganglia for anhedonia and psychomotor retardation (148, 149) and anterior cingulate cortex for anxiety depression and suicidal behaviour (150–152).

No published reports describing infliximab augmentation therapy trials in schizophrenia were found.

Infliximab benefit/risk ratio. The anti-TNF therapy has change the face of chronic inflammatory disorders such as rheumatoid arthritis or bowel diseases in terms of evolution (153, 154). However, several years backwards reveal now that their use in clinical setting could be at risk of developing survival-compromising complications (155, 156). Indeed, large controlled trials collecting safety data for other uses have concluded that anti-TNF-related immunosuppression has caused serious side-effects such as fatal infections caused by viruses, fungi or bacteria that have spread systemically, including tuberculosis and histoplasmosis (157–161). Hence, as recommended by national safety agencies like FDA, patients under such therapies should be monitored for symptoms/biological makers of major infectious events, which could not be easy to do in routine clinical psychiatric practice. Moreover, it has been also proven that TNF-blockade could favour the emergence of uncommon neoplastic processes (162). This is well illustrated by the occurrence in young and teenage patients of lymphomas, usually observed more latter in age (163–165).

Beside these severe complications, physicians have also to consider adverse effects due to their immunogenicity and consequent shortened duration of clinical response, infusion reactions or delayed hypersensitivity-type reactions and the fact that in acute phase patients (whatever the disorder), their restricted intravenous use may pose evident problems (166, 167). Hence, despite the fact that such biotherapies are still at the forefront of severe auto-immune/inflammatory treatments, the benefit/risk in psychiatry need to be carefully evaluated with controlled clinical trials on specific clinical phenotypes including non-responder patients to conventional drugs with a strict monitoring of biological/immunological parameters.

Minocycline

Minocycline is a semisynthetic second-generation tetracycline, which exerts anti-inflammatory effects that are not related to its microbial properties, but rather due to its purported inhibition of microglial activation and reduction of polynuclear cells (168, 169). High-dose minocycline is reported to reduce IL-1 b levels following traumatic brain injury in mice (170), inhibits COX-2 expression and reduces PGE2 production in a dose-dependent manner (171). Rises in brain TNF- a were also attenuated following minocycline treatment following 3-nitropropionic acid administration (an inhibitor of the electron transport enzyme succinate dehydrogenase that induces inflammation) (172). Animal models showed that minocycline administration decreases glutamate-induced neurotoxicity (173) and has antidepressant-like properties among some rodent species (174), but not among others (175). Restoration of dopamine deficits in the amygdala ofl earned-helplessness-paradigm rats has been suggested as the mechanism by which minocycline exerts its antidepressant effects (176, 177).

Dean et al. (42) have published a recent comprehensive review on the CNS effects of minocycline. In a purpose of consistency, the antioxidative, neuroprotective and neurotrophic effects of minocycline will not be discussed here (even if these pathways are intertwined and contribute to pathophysiology of mental illnesses as well as potential therapeutic effects of psychotropic drugs). Furthermore, we have not detailed the effects of minocycline on the gut microbiota, a recent exciting field of pathophysiology research (178).

Minocycline in MDD. Human data on antidepressant effects of minocycline are scarce. Miyaoka et al. reported antidepressant and antipsychotic effects of minocycline add to antidepressant medication (fluvoxamine, paroxetine and sertraline) in 25 patients with psychotic depression in a 6-week, open-label study (Table 2).

No trial on minocycline effects in unipolar or bipolar depression was published to date.

Minocycline in schizophrenia. Given glutamate/N-methyl-D-aspartate acid (NMDA) data among rodents, the majority of clinical studies among humans focused on schizophrenia, as a 'glutamate hypothesis' has been postulated in its pathophysiology (179) (Table 3). Miyaoka et al. (111) showed in an open-label study that 300 mg/day minocycline in 22 patients during 4 weeks significantly decreased PANSS scores and that this improvement was continued through the 4 weeks after discontinuation. In a double-blind RCT, Levkovitz et al. (112) studied the effects of 22 weeks 200 mg/day add-on minocycline treatment in 54 recently diagnosed (<5 years) patients with schizophrenia. They found a significant improvement on negative symptoms on the Scale for the Assessment of Negative Symptoms, on CGI and on the measures of functioning, but not on the PANSS scores. Improvements on cognition tasks (executive functioning, working memory, cognitive shifting and planning) at 22 weeks were reported. The authors also found that minocycline limited antipsychotic weight gain and suggested hypotheses on the mechanism of action (effect on satiety via action on NMDA receptors, decrease of TNF- a and IL-6 microglia release).

Minocycline benefit/risk ratio. The following adverse reactions have been observed in patients receiving tetracyclines: photosensitivity, fever, anorexia, nausea, vomiting, diarrhoea, dyspepsia, stomatitis, glossitis, dysphagia, enterocolitis, pseudomembranous colitis, pancreatitis, inflammatory lesions in the oral and anogenital regions, vulvovaginitis, hepatitis (with fatal cases), alopecia, erythema nodosum, hyperpigmentation of nails, pruritus, common or severe skin rash toxic reactions, cough, dyspnoea, bronchospasm, pneumonitis, renal toxicity, arthralgia, anaphylaxis reaction (including shock and fatalities), anaphylactoid purpura, myoc arditis, pericarditis, agranulocytosis, haemolytic anaemia, thrombocytopenia, leukopenia, neutropenia, pancytopenia, eosinophilia, convulsions, dizziness, paraesthesia, sedation, vertigo, tinnitus. Tooth discoloration in children is a well-described side-effect (tetracyclines are contra-indicated in children <8 years) and has been also reported in adults.

As with other serious adverse reactions, the drug should be discontinued immediately if any of the following syndromes are recognized:

(i) Hypersensitivity syndrome consisting of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis and pericarditis. Fever and lymphadenopathy may be present. This syndrome has led to a restriction of use of minocycline (69, 180).

(ii) Lupus-like syndrome consisting of positive antinuclear antibody; arthralgia, arthritis, joint stiffness or joint swelling; and one or more of the following: fever, myalgia, hepatitis, rash and vasculitis.

(iii) Serum sickness-like syndrome consisting of fever; urticaria or rash; and arthralgia, arthritis, joint stiffness or joint swelling.

It is then not possible to recommend minocycline as first-line add-on therapy in schizophrenia, but minocycline remains a potentially very promising treatment, with multiple mechanisms of action. Studies remain to be carried out in unipolar and bipolar mood disorders, given that a preliminary study showed minocycline effectiveness on mood as well as on psychosis in psychotic depression.

Discussion

Anti-inflammatory drugs represent one of the most interesting add-on therapy in the treatment of chronic major psychiatric disorders such as depression or schizophrenia. Raison et al. found a major result with increased infliximab effectiveness in the subgroup of depressed patients with hs-CRP > 5 mg/l (about one quarter of patients). This demonstration of the benefits of personalized medicine is to encourage research in the characterization of inflammatory profiles of psychiatric patients.

A number of anti-inflammatory drugs are available as adjunct treatment of treatment-resistant patients with MDD, schizophrenia and bipolar disorder. If used with attention to their possible side-effects, they may be reasonable therapeutic alternatives when clinicians are out ofi deas.

Acknowledgements

This work was supported by INSERM, Assistance Publique - H ôpitaux de Paris, RTRS Sant é Mentale (Fondation Fondamental) and by Agence Nationale pour la Recherche (ANR: NEURO 2009, V.I.P. project). This work was supported (in part) by the Investissements d'Avenir program managed by the ANR under reference ANR-11-IDEX-0004-02. No funding source.

Declaration ofi nterest

None.

References

1. Collins PY, Patel V, Joestl SS, et al. Grand challenges in global mental health. Nature 2011; 475:27–30.
2. Olesen J, Leonardi M. The burden of brain diseases in Europe. Eur J Neurol 2003; 10:471–477.
3. Wittchen HU, Jacobi F, Rehm J, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011; 21:655–679.
4. Torrey EF, Davis JM. Adjunct treatments for schizophrenia and bipolar disorder: what to try when you are out of ideas. Clin Schizophr Relat Psychoses 2012; 5:208–216.
5. Leonard B, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. Neurosci Biobehav Rev 2012; 36:764–785.
6. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry 2009; 65:732–741.
7. Dantzer R, O'connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008; 9:46–56.
8. Janssen DG, Caniato RN, Verster JC, Baune BT. A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. Hum Psychopharmacol 2010;25:201–215.
9. Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev 2011; 35:804–817.
10. Drexhage RC, Knijff EM, Padmos RC, et al. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. Expert Rev Neurother 2010; 10:59–76.
11. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. J Clin Psychiatry 2009;70:1078–1090.
12. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 2011; 70:663–671.
13. Meyer U, Feldon J, Yee BK. A review of the fetal brain cytokine imbalance hypothesis of schizophrenia. Schizophr Bull 2009; 35:959–972.
14. Muller N, Myint AM, Schwarz MJ. Inflammation in schizophrenia. Adv Protein Chem Struct Biol 2012;88:49–68.
15. Miller BJ, Culpepper N, Rapaport MH, Buckley P. Prenatal inflammation and neurodevelopment in schizophrenia: A review of human studies. Prog Neuropsychopharmacol Biol Psychiatry 2013; 42:92–100.
16. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry 2008;63:801–808.
17. Drexhage RC, Hoogenboezem TA, Cohen D, et al. An activated set point of T-cell and monocyte inflammatory networks in recent-onset schizophrenia patients involves both pro- and anti-inflammatory forces. Int J Neuropsychopharmacol 2011; 14:746–755.
18. Leboyer M, Soreca I, Scott J, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? J Affect Disord 2012; 141:1–10.
19. Yolken RH, Torrey EF. Viruses, schizophrenia, and bipolar disorder. Clin Microbiol Rev 1995; 8:131–145.
20. Yolken RH, Torrey EF. Are some cases of psychosis caused by microbial agents? A review of the evidence. Mol Psychiatry 2008; 13:470–479.
21. Feinstein A. Multiple sclerosis and depression. Mult Scler 2011; 17:1276–1281.
22. Moll LT, Gormsen L, Pfeiffer-Jensen M. Higher prevalence of depression in patients with rheumatoid arthritis–a systematic review. Ugeskr Laeger 2011; 173:2564–2568.
23. Lisitsyna TA, Kovalevskaia OB, Seravina OF, Vel'tishchev D, Nasonov EL. Systemic lupus erythematosus and depression: pathogenetic interrelations. Ter Arkh 2006; 78:82–85.
24. Rickards H. Depression in neurological disorders: Parkinson's disease, multiple sclerosis, and stroke. J Neurol Neurosurg Psychiatry 2005; 76(Suppl 1):i48 –i52.
25. Torrey EF, Yolken RH. The schizophrenia-rheumatoid arthritis connection: infectious, immune, or both? Brain Behav Immun 2001; 15:401–410.
26. Iacovides A, Andreoulakis E. Bipolar disorder and resembling special psychopathological manifestations in multiple sclerosis: a review. Curr Opin Psychiatry 2011;24:336–340.
27. Bianchi M, Panerai AE. Antidepressant drugs and experimental inflammation. Pharmacol Res 1996; 33:235–238.
28. Vogelzangs N, Duivis HE, Beekman AT, et al. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. Transl Psychiatry 2012; 2:e79.
29. Martelli EA, Toth E, Segre AD, Corsico N. Mechanism ofi nhibition of experimental inflammation by antidepressant drugs. Eur J Pharmacol 1967; 2:229–233.
30. Pollmacher T, Haack M, Schuld A, Kraus T, Hinze-Selch D. Effects of antipsychotic drugs on cytokine networks. J Psychiatr Res 2000; 34:369–382.
31. Nahman S, Belmaker RH, Azab AN. Effects ofl ithium on lipopolysaccharide-induced inflammation in rat primary glia cells. Innate Immun 2012; 18:447–458.

32. Raza M, Dhariwal MA, Ageel AM, Qureshi S. Evaluation of the antiinflammatory activity of sodium valproate in rats and mice. Gen Pharmacol 1996;27:1395–1400.
33. Fornaro M, Martino M, Battaglia F, Colicchio S, Perugi G. Increase in IL-6 levels among major depressive disorder patients after a 6-week treatment with duloxetine 60 mg/day: a preliminary observation. Neuropsychiatr Dis Treat 2011; 7:51–56.
34. Hannestad J, Dellagioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. Neuropsychopharmacology 2011;36:2452–2459.
35. Gniadecki R, Robertson D, Molta CT, et al. Self-reported health outcomes in patients with psoriasis and psoriatic arthritis randomized to two etanercept regimens. J Eur Acad Dermatol Venereol 2012; 26:1436–1443.
36. Kekow J, Moots RJ, Emery P, et al. Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: the COMET trial. Ann Rheum Dis 2010; 69:222–225.
37. Feldman SR, Gottlieb AB, Bala M, et al. Infliximab improves health-related quality ofl ife in the presence of comorbidities among patients with moderate-to-severe psoriasis. Br J Dermatol 2008; 159:704–710.
38. Tookman AJ, Jones CL, Dewitte M, Lodge PJ. Fatigue in patients with advanced cancer: a pilot study of an intervention with infliximab. Support Care Cancer 2008;16:1131–1140.
39. Braun J, McHugh N, Singh A, Wajdula JS, Sato R. Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. Rheumatology (Oxford) 2007; 46:999–1004.
40. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006; 367:29–35.
41. Lichtenstein GR, Bala M, Han C, Dewoody K, Schaible T. Infliximab improves quality ofl ife in patients with Crohn's disease. Inflamm Bowel Dis 2002; 8:237–243.
42. Dean OM, Data-Franco J, Giorlando F, Berk M. Minocycline: therapeutic potential in psychiatry. CNS Drugs 2012;26:391–401.
43. Miyaoka T. Clinical potential of minocycline for schizophrenia. CNS Neurol Disord Drug Targets 2008; 7:376–381.
44. Muller N, Strassnig M, Schwarz MJ, Ulmschneider M, Riedel M. COX-2 inhibitors as adjunctive therapy in schizophrenia. Expert Opin Investig Drugs 2004;13:1033–1044.
45. Muller N. COX-2 inhibitors as antidepressants and antipsychotics: clinical evidence. Curr Opin Investig Drugs 2010;11:31–42.
46. Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Willett WC, Rimm EB. Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among US men and women. Circulation 2003; 108:155–160.
47. Kiecolt-Glaser JK, Belury MA, Andridge R, Malarkey WB, Hwang BS, Glaser R. Omega-3 supplementation lowers inflammation in healthy middle-aged and older adults: a randomized controlled trial. Brain Behav Immun 2012;26:988–995.
48. Kiecolt-Glaser JK, Belury MA, Andridge R, Malarkey WB, Glaser R. Omega-3 supplementation lowers inflammation and anxiety in medical students: a randomized controlled trial. Brain Behav Immun 2011;25:1725–1734.
49. Ravindran AV, da Silva TL. Complementary and alternative therapies as add-on to pharmacotherapy for mood and anxiety disorders: a systematic review. J Affect Disord 2013; 150:707–719.
50. Cerullo MA, Strakowski SM. A systematic review of the evidence for the treatment of acute depression in bipolar I disorder. CNS Spectr 2013; 18:1–10.
51. Ortega RM, Rodriguez-Rodriguez E, Lopez-Sobaler AM. Effects of omega 3 fatty acids supplementation in behavior and non-neurodegenerative neuropsychiatric disorders. Br J Nutr 2012; 107(Suppl 2):S261 –S270.
52. Prior PL, Galduroz JC. (N-3) Fatty acids: molecular role and clinical uses in psychiatric disorders. Adv Nutr 2012;3:257–265.
53. Appleton KM, Rogers PJ, Ness AR. Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. Am J Clin Nutr 2010; 91:757–770.
54. Martins JG. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. J Am Coll Nutr 2009; 28:525–542.
55. Ross BM, Seguin J, Sieswerda LE. Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid? Lipids Health Dis 2007; 6:21.
56. Sublette ME, Hibbeln JR, Galfalvy H, Oquendo MA, Mann JJ. Omega-3 polyunsaturated essential fatty acid status as a predictor off uture suicide risk. Am J Psychiatry 2006; 163:1100–1102.
57. Martins JG, Bentsen H, Puri BK. Eicosapentaenoic acid appears to be the key omega-3 fatty acid component associated with efficacy in major depressive disorder: a critique of Bloch and Hannestad and updated meta-analysis. Mol Psychiatry 2012; 17:1144–1149; discussion 63–67.
58. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry 2012; 73:81–86.
59. Chiu CC, Huang SY, Chen CC, Su KP. Omega-3 fatty acids are more beneficial in the depressive phase than in the manic phase in patients with bipolar I disorder. J Clin Psychiatry 2005; 66:1613–1614.
60. Frangou S, Lewis M, Wollard J, Simmons A. Preliminary in vivo evidence ofi ncreased N-acetyl-aspartate following eicosapentanoic acid treatment in patients with bipolar disorder. J Psychopharmacol 2007; 21:435–439.
61. Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. Br J Psychiatry 2006;188:46–50.
62. Gracious BL, Chirieac MC, Costescu S, Finucane TL, Youngstrom EA, Hibbeln JR. Randomized, placebo-controlled trial of flax oil in pediatric bipolar disorder. Bipolar Disord 2010; 12:142–154.
63. Keck PE Jr, Mintz J, Mcelroy SL, et al. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. Biol Psychiatry 2006;60:1020–1022.
64. Stoll AL, Severus WE, Freeman MP, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. Arch Gen Psychiatry 1999;56:407–412.

65. McNamara RK. Omega-3 fatty acid deficiency: a preventable risk factor for schizophrenia? Schizophr Res 2011;129:215–216.
66. Sethom MM, Fares S, Bouaziz N, et al. Polyunsaturated fatty acids deficits are associated with psychotic state and negative symptoms in patients with schizophrenia. Prostaglandins Leukot Essent Fatty Acids 2010; 83:131–136.
67. Fusar-Poli P, Berger G. Eicosapentaenoic acid interventions in schizophrenia: meta-analysis of randomized, placebo-controlled studies. J Clin Psychopharmacol 2012;32:179–185.
68. Stafford MR, Jackson H, Mayo-Wilson E, Morrison AP, Kendall T. Early interventions to prevent psychosis: systematic review and meta-analysis. BMJ 2013; 346: f185.
69. FDA 2012. http://www.fda.gov (accessed 21 November 2012).
70. Brasky TM, Darke AK, Song X, et al. Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. J Natl Cancer Inst 2013; 105:1132–1141.
71. Chua ME, Sio MC, Sorongon MC, Morales ML Jr. The relevance of serum levels ofl ong chain omega-3 polyunsaturated fatty acids and prostate cancer risk: a meta-analysis. Can Urol Assoc J 2013; 7:E333 –E343.
72. Wu S, Liang J, Zhang L, Zhu X, Liu X, Miao D. Fish consumption and the risk of gastric cancer: systematic review and meta-analysis. BMC Cancer 2011; 11:26.
73. Salisbury AC, Harris WS, Amin AP, Reid KJ, O'keefe JH Jr, Spertus JA. Relation between red blood cell omega-3 fatty acid index and bleeding during acute myocardial infarction. Am J Cardiol 2012; 109:13–18.
74. Kepler CK, Huang RC, Meredith D, Kim JH, Sharma AK. Omega-3 and fish oil supplements do not cause increased bleeding during spinal decompression surgery. J Spinal Disord Tech 2012; 25:129–132.
75. Hepgul N, Mondelli V, Pariante CM. Psychological and biological mechanisms of cytokine induced depression. Epidemiol Psichiatr Soc 2010; 19:98–102.
76. Riedel M, Strassnig M, Schwarz MJ, Muller N. COX-2 inhibitors as adjunctive therapy in schizophrenia: rationale for use and evidence to date. CNS Drugs 2005;19:805–819.
77. Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs–differences and similarities. N Engl J Med 1991;324:1716–1725.
78. Yamagata K, Andreasson KI, Kaufmann WE, Barnes CA, Worley PF. Expression of a mitogen-inducible cyclooxygenase in brain neurons: regulation by synaptic activity and glucocorticoids. Neuron 1993; 11:371–386.
79. Breder CD, Saper CB. Expression ofi nducible cyclooxygenase mRNA in the mouse brain after systemic administration of bacterial lipopolysaccharide. Brain Res 1996;713:64–69.
80. Nogawa S, Zhang F, Ross ME, Iadecola C. Cyclo-oxygenase-2 gene expression in neurons contributes to ischemic brain damage. J Neurosci 1997; 17:2746–2755.
81. Baik EJ, Kim EJ, Lee SH, Moon C. Cyclooxygenase-2 selective inhibitors aggravate kainic acid induced seizure and neuronal cell death in the hippocampus. Brain Res 1999;843:118–129.
82. Yang H, Zhang J, Breyer RM, Chen C. Altered hippocampal long-term synaptic plasticity in mice deficient in the PGE2 EP2 receptor. J Neurochem 2009; 108:295–304.
83. O'Connor SM, Stenger DA, Shaffer KM, Maric D, Barker JL, Ma W. Primary neural precursor cell expansion, differentiation and cytosolic Ca(2 +) response in three-dimensional collagen gel. J Neurosci Methods 2000;102:187–195.
84. Tassoni D, Kaur G, Weisinger RS, Sinclair AJ. The role of eicosanoids in the brain. Asia Pac J Clin Nutr 2008; 17 (Suppl 1):220 –228.
85. Hu F, Wang X, Pace TW, Wu H, Miller AH. Inhibition of COX-2 by celecoxib enhances glucocorticoid receptor function. Mol Psychiatry 2005; 10:426–428.
86. Phillis JW, Horrocks LA, Farooqui AA. Cyclooxygenases, lipoxygenases, and epoxygenases in CNS: their role and involvement in neurological disorders. Brain Res Rev 2006; 52:201–243.
87. Choi SH, Langenbach R, Bosetti F. Genetic deletion or pharmacological inhibition of cyclooxygenase-1 attenuate lipopolysaccharide-induced inflammatory response and brain injury. FASEB J 2008; 22:1491–1501.
88. Gassner EM, Schocke M, Peer S, Schwabegger A, Jaschke W, Bodner G. Persistent median artery in the carpal tunnel: color Doppler ultrasonographic findings. J Ultrasound Med 2002;21:455–461.
89. Pepicelli O, Fedele E, Berardi M, et al. Cyclo-oxygenase-1 and -2 differently contribute to prostaglandin E2 synthesis and lipid peroxidation after in vivo activation of N-methyl-D-aspartate receptors in rat hippocampus. J Neurochem 2005;93:1561–1567.
90. Aid S, Langenbach R, Bosetti F. Neuroinflammatory response to lipopolysaccharide is exacerbated in mice genetically deficient in cyclooxygenase-2. J Neuroinflammation 2008;5:17.
91. Toscano CD, Kingsley PJ, Marnett LJ, Bosetti F. NMDA-induced seizure intensity is enhanced in COX-2 deficient mice. Neurotoxicology 2008; 29:1114–1120.
92. Pyeon D, Diaz FJ, Splitter GA. Prostaglandin E(2) increases bovine leukemia virus tax and pol mRNA levels via cyclooxygenase 2: regulation by interleukin-2, interleukin-10, and bovine leukemia virus. J Virol 2000;74:5740–5745.
93. Cao C, Matsumura K, Ozaki M, Watanabe Y. Lipopolysaccharide injected into the cerebral ventricle evokes fever through induction of cyclooxygenase-2 in brain endothelial cells. J Neurosci 1999; 19:716–725.
94. Catalani A, Casolini P, Cigliana G, et al. Maternal corticosterone influences behavior, stress response and corticosteroid receptors in the female rat. Pharmacol Biochem Behav 2002; 73:105–114.
95. Bugajski AJ, Thor P, Glod R, Gadek-Michalska A, Bugajski J. Influence of cyclooxygenase inhibitors on the central histaminergic stimulations of hypothalamic - pituitary - adrenal axis. J Physiol Pharmacol 2003;54:643–652.
96. Reus VI, Peeke HV, Miner C. Habituation and cortisol dysregulation in depression. Biol Psychiatry 1985;20:980–989.
97. Choi SH, Aid S, Bosetti F. The distinct roles of cyclooxygenase-1 and -2 in neuroinflammation: implications for translational research. Trends Pharmacol Sci 2009;30:174–181.
98. Abbasi SH, Hosseini F, Modabbernia A, Ashrafi M, Akhondzadeh S. Effect of celecoxib add-on treatment on symptoms and serum IL-6 concentrations in patients with major depressive disorder: randomized double-blind placebo-controlled study. J Affect Disord 2012;141:308–314.
99. Muller N, Schwarz MJ, Dehning S, et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in

major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. Mol Psychiatry 2006; 11:680–684.
100. AkhondzadehS, Jafari S, Raisi F, et al. Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. Depress Anxiety 2009; 26:607–611.
101. Mendlewicz J, Kriwin P, Oswald P, Souery D, Alboni S, Brunello N. Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: a pilot open-label study. Int Clin Psychopharmacol 2006; 21:227–231.
102. Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 2013; 70:31–41.
103. Miyaoka T, Wake R, Furuya M, et al. Minocycline as adjunctive therapy for patients with unipolar psychotic depression: an open-label study. Prog Neuropsychopharmacol Biol Psychiatry 2012; 37:222–226.
104. Gallagher PJ, Castro V, Fava M, et al. Antidepressant response in patients with major depression exposed to NSAIDs: A pharmacovigilance study. Am J Psychiatry 2012;169:1065–1072.
105. Nery FG, Monkul ES, Hatch JP, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. Hum Psychopharmacol 2008;23:87–94.
106. Muller N, Riedel M, ScheppachC, et al. Beneficial antipsychotic effects of celecoxib add-on therapy compared to risperidone alone in schizophrenia. Am J Psychiatry 2002;159:1029–1034.
107. Rapaport MH, Delrahim KK, Bresee CJ, Maddux RE, Ahmadpour O, Dolnak D. Celecoxib augmentation of continuously ill patients with schizophrenia. Biol Psychiatry 2005; 57:1594–1596.
108. AkhondzadehS, Tabatabaee M, Amini H, Ahmadi Abhari SA, Abbasi SH, BehnamB. Celecoxib as adjunctive therapy in schizophrenia: a double-blind, randomized and placebo-controlled trial. Schizophr Res 2007; 90:179–185.
109. Muller N, Krause D, Dehning S, et al. Celecoxib treatment in an early stage of schizophrenia: results of a randomized, double-blind, placebo-controlled trial of celecoxib augmentation of amisulpride treatment. Schizophr Res 2010; 121:118–124.
110. Laan W, Grobbee DE, Selten JP, Heijnen CJ, Kahn RS, Burger H. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2010; 71:520–527.
111. Miyaoka T, Yasukawa R, Yasuda H, Hayashida M, Inagaki T, Horiguchi J. Minocycline as adjunctive therapy for schizophrenia: an open-label study. Clin Neuropharmacol 2008;31:287–292.
112. Levkovitz Y, Mendlovich S, Riwkes S, et al. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. J Clin Psychiatry 2010; 71:138–149.
113. SommerIE, de Witte L, BegemannM, Kahn RS. Nonsteroidal anti-inflammatory drugs in schizophrenia: ready for practice or a good start? A meta-analysis J Clin Psychiatry 2012; 73:414–419.
114. Muller N, Ulmschneider M, ScheppachC, et al. COX-2 inhibition as a treatment approach in schizophrenia: immunological considerations and clinical effects of celecoxib add-on therapy. Eur Arch Psychiatry Clin Neurosci 2004;254:14–22.
115. Prospective Randomized Evaluation Of Celecoxib Integrated Safety Vs Ibuprofen Or Naproxen (PRECISION). 2006. http://Clinicaltrials.GOV/CT/SHOW/NCT00346216?ORDER=13.
116. Adams RJ, Appleton SL, Gill TK, Taylor AW, Wilson DH, Hill CL. Cause for concern in the use of non-steroidal anti-inflammatory medications in the community–a population-based study. BMC Fam Pract 2011;12:70.
117. Cipollone F, Patrignani P, Greco A, et al. Differential suppression of thromboxane biosynthesis by indobufen and aspirin in patients with unstable angina. Circulation 1997;96:1109–1116.
118. Savitz J, Preskorn S, Teague TK, Drevets D, Yates W, Drevets W. Minocycline and aspirin in the treatment of bipolar depression: a protocol for a proof-of-concept, randomised, double-blind, placebo-controlled, 2x2 clinical trial. BMJ Open 2012; 2:e000643.
119. Duncan RE, Bazinet RP. Brain arachidonic acid uptake and turnover: implications for signaling and bipolar disorder. Curr Opin Clin Nutr Metab Care 2010; 13:130–138.
120. Rao JS, Rapoport SI. Mood-stabilizers target the brain arachidonic acid cascade. Curr Mol Pharmacol 2009;2:207–214.
121. Bazinet RP. Is the brain arachidonic acid cascade a common target of drugs used to manage bipolar disorder? Biochem Soc Trans 2009; 37:1104–1109.
122. Rapoport SI, Basselin M, Kim HW, Rao JS. Bipolar disorder and mechanisms of action of mood stabilizers. Brain Res Rev 2009; 61:185–209.
123. Rapoport SI. Brain arachidonic and docosahexaenoic acid cascades are selectively altered by drugs, diet and disease. Prostaglandins Leukot Essent Fatty Acids 2008;79:153–156.
124. Rao JS, Lee HJ, Rapoport SI, Bazinet RP. Mode of action of mood stabilizers: is the arachidonic acid cascade a common target? Mol Psychiatry 2008; 13:585–596.
125. Lee HJ, Rao JS, Rapoport SI, Bazinet RP. Antimanic therapies target brain arachidonic acid signaling: lessons learned about the regulation of brain fatty acid metabolism. Prostaglandins Leukot Essent Fatty Acids 2007;77:239–246.
126. van Strater AC, Bouvy PF. Omega-3 fatty acids in the treatment of affective disorders: an overview of the literature. Tijdschrift voor psychiatrie 2007; 49:85–94.
127. Quiroz JA, Gould TD, Manji HK. Molecular effects of lithium. Mol Interv 2004; 4:259–272.
128. Rapoport SI, Bosetti F. Do lithium and anticonvulsants target the brain arachidonic acid cascade in bipolar disorder? Arch Gen Psychiatry 2002; 59:592–596.
129. Stolk P, Souverein PC, Wilting I, et al. Is aspirin useful in patients on lithium? A pharmacoepidemiological study related to bipolar disorder. Prostaglandins Leukot Essent Fatty Acids 2010; 82:9–14.
130. Jorgensen AL, Fitzgerald RJ, Oyee J, PirmohamedM, Williamson PR. Influence of CYP2C9 and VKORC1 on patient response to warfarin: a systematic review and meta-analysis. PLoS One 2012; 7:e44064.
131. Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci USA 1975;72:3666–3670.

132. Perskidskii I u V, Barshtein I u A. Biological manifestations of the tumor necrosis factor effect and its role in the pathogenesis of various diseases. Arkh Patol 1992; 54:5–10.
133. PlumpeJ, Malek NP, Bock CT, RakemannT, Manns MP, Trautwein C. NF-kappaB determines between apoptosis and proliferation in hepatocytes during liver regeneration. Am J Physiol Gastrointest Liver Physiol 2000; 278: G173 –G183.
134. Silva LC, Ortigosa LC, Benard G. Anti-TNF-alpha agents in the treatment ofi mmune-mediated inflammatory diseases: mechanisms of action and pitfalls. Immunotherapy 2010;2:817–833.
135. Kapcala LP, Chautard T, Eskay RL. The protective role of the hypothalamic-pituitary-adrenal axis against lethality produced by immune, infectious, and inflammatory stress. Ann N Y Acad Sci 1995; 771:419–437.
136. Zhu CB, Blakely RD, Hewlett WA. The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. Neuropsychopharmacology 2006; 31:2121–2131.
137. Robinson CM, Hale PT, Carlin JM. The role of IFN-gamma and TNF-alpha-responsive regulatory elements in the synergistic induction ofi ndoleamine dioxygenase. J Interferon Cytokine Res 2005; 25:20–30.
138. Wichers M, Maes M. The psychoneuroimmuno-pathophysiology of cytokine-induced depression in humans. Int J Neuropsychopharmacol 2002; 5:375–388.
139. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther 2008; 117:244–279.
140. TweedieD, SambamurtiK, Greig NH. TNF-alpha inhibition as a treatment strategy for neurodegenerative disorders: new drug candidates and targets. Curr Alzheimer Res 2007; 4:378–385.
141. Liu Y, Ho RC, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-alpha) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord 2012; 139:230–239.
142. Silverman MN, Macdougall MG, Hu F, Pace TW, Raison CL, Miller AH. Endogenous glucocorticoids protect against TNF-alpha-induced increases in anxiety-like behavior in virally infected mice. Mol Psychiatry 2007;12:408–417.
143. SimenBB, DumanCH, SimenAA, DumanRS. TNFalpha signaling in depression and anxiety: behavioral consequences ofi ndividual receptor targeting. Biol Psychiatry 2006;59:775–785.
144. Soczynska JK, Kennedy SH, Goldstein BI, Lachowski A, Woldeyohannes HO, McIntyre RS. The effect of tumor necrosis factor antagonists on mood and mental health-associated quality ofl ife: novel hypothesis-driven treatments for bipolar depression? Neurotoxicology 2009;30:497–521.
145. Persoons P, Vermeire S, Demyttenaere K, et al. The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. Aliment Pharmacol Ther 2005; 22:101–110.
146. Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. Arch Gen Psychiatry 2012; 3:1–11.
147. Undurraga J, Baldessarini RJ. Randomized, placebo-controlled trials of antidepressants for acute major depression: thirty-year meta-analytic review. Neuropsychopharmacology 2012;37:851–864.
148. Capuron L, Pagnoni G, Drake DF, et al. Dopaminergic mechanisms of reduced Basal Ganglia responses to hedonic reward during interferon alfa administration. Arch Gen Psychiatry 2012; 69:1044–1053.
149. Eisenberger NI, Berkman ET, Inagaki TK, RamesonLT, Mashal NM, Irwin MR. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. Biol Psychiatry 2010; 68:748–754.
150. Capuron L, Pagnoni G, Demetrashvili M, et al. Anterior cingulate activation and error processing during interferon-alpha treatment. Biol Psychiatry 2005; 58:190–196.
151. Steiner J, Bielau H, Brisch R, et al. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. J Psychiatr Res 2008; 42:151–157.
152. Torres-Platas SG, Hercher C, Davoli MA, et al. Astrocytic hypertrophy in anterior cingulate white matter of depressed suicides. Neuropsychopharmacology 2011;36:2650–2658.
153. Guidi L, Pugliese D, Armuzzi A. Update on the management ofi nflammatory bowel disease: specific role of adalimumab. Clin Exp Gastroenterol 2011; 4:163–172.
154. Karampetsou MP, Liossis SN, Sfikakis PP. TNF-alpha antagonists beyond approved indications: stories of success and prospects for the future. QJM 2010; 103:917–928.
155. DeepakP, StobaughDJ, Sherid M, Sifuentes H, Ehrenpreis ED. Neurological events with tumour necrosis factor alpha inhibitors reported to the Food and Drug Administration Adverse Event Reporting System. Aliment Pharmacol Ther 2013; 38:388–396.
156. Herrinton LJ, Liu L, Chen L, et al. Association between anti-TNF-alpha therapy and all-cause mortality. Pharmacoepidemiol Drug Saf 2012; 21:1311–1320.
157. Baddley JW, Winthrop KL, Chen L, et al. Non-viral opportunistic infections in new users of tumour necrosis factor inhibitor therapy: results of the SAfety Assessment of Biologic ThERapy (SABER) Study. Ann Rheum Dis 2013; doi:10.1136/annrheumdis-2013-203407.
158. Comar M, Delbue S, Lepore L, et al. Latent viral infections in young patients with inflammatory diseases treated with biological agents: prevalence of JC virus genotype 2. J Med Virol 2013; 85:716–722.
159. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001; 345:1098–1104.
160. Nakelchik M, Mangino JE. Reactivation of histoplasmosis after treatment with infliximab. Am J Med 2002;112:78.
161. Garcia Vidal C, Rodriguez FernandezS, Martinez Lacasa J et al. Paradoxical response to antituberculous therapy in infliximab-treated patients with disseminated tuberculosis. Clin Infect Dis 2005; 40:756–759.
162. Sfikakis PP. The first decade of biologic TNF antagonists in clinical practice: lessons learned, unresolved issues and future directions. Curr Dir Autoimmun 2010;11:180–210.
163. Bader-Meunier B. Tolerance of biological agents in children. Arch Pediatr 2010; 17:962–963.
164. Burger DC, Florin TH. Hepatosplenic T-cell lymphoma following infliximab therapy for Crohn's disease. Med J Aust 2009; 190:341–342.
165. Mackey AC, Green L, Leptak C, Avigan M. Hepatosplenic T cell lymphoma associated with infliximab use in

young patients treated for inflammatory bowel disease: update. J Pediatr Gastroenterol Nutr 2009; 48:386–388.
166. Garces S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis 2012.
167. Fernandes IC, Torres T, Sanches M, Velho G, Lago P, Selores M. Psoriasis induced by infliximab. Acta Med Port 2011; 24(Suppl 3):709 –712.
168. Macdonald H, Kelly RG, Allen ES, Noble JF, Kanegis LA. Pharmacokinetic studies on minocycline in man. Clin Pharmacol Ther 1973; 14:852–861.
169. Kim BJ, Kim MJ, Park JM, et al. Reduced neurogenesis after suppressed inflammation by minocycline in transient cerebral ischemia in rat. J Neurol Sci 2009; 279:70–75.
170. Homsi S, Federico F, Croci N, et al. Minocycline effects on cerebral edema: relations with inflammatory and oxidative stress markers following traumatic brain injury in mice. Brain Res 2009; 1291:122–132.
171. Kim SS, Kong PJ, Kim BS, Sheen DH, Nam SY, Chun W. Inhibitory action of minocycline on lipopolysaccharide-induced release of nitric oxide and prostaglandin E2 in BV2 microglial cells. Arch Pharm Res 2004; 27:314–318.
172. Ahuja M, Bishnoi M, Chopra K. Protective effect of minocycline, a semi-synthetic second-generation tetracycline against 3-nitropropionic acid (3-NP)-induced neurotoxicity. Toxicology 2008; 244:111–122.
173. Morimoto N, Shimazawa M, Yamashima T, Nagai H, Hara H. Minocycline inhibits oxidative stress and decreases in vitro and in vivo ischemic neuronal damage. Brain Res 2005;1044:8–15.
174. Molina-Hernandez M, Tellez-Alcantara NP, Perez-Garcia J, Olivera-Lopez JI, Jaramillo-Jaimes MT. Desipramine or glutamate antagonists synergized the antidepressant-like actions of ntra-nucleus accumbens infusions of minocycline in male Wistar rats. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32:1660–1666.
175. Deak T, Bellamy C, D'agostino LG, Rosanoff M, McElderry NK, Bordner KA. Behavioral responses during the forced swim test are not affected by anti-inflammatory agents or acute illness induced by lipopolysaccharide. Behav Brain Res 2005; 160:125–134.
176. Watanabe T, Sagisaka H, Arakawa S, et al. A novel model of continuous depletion of glutathione in mice treated with L-buthionine (S, R)-sulfoximine. J Toxicol Sci 2003; 28:455–469.
177. Watanabe N, Dickinson DA, Liu RM, Forman HJ. Quinones and glutathione metabolism. Methods Enzymol 2004;378:319–340.
178. Huang TY, Chu HC, Lin YL, et al. Minocycline attenuates 5-fluorouracil-induced small intestinal mucositis in mouse model. Biochem Biophys Res Commun 2009;389:634–639.
179. Tamminga CA, Holcomb HH, Gao XM, Lahti AC. Glutamate pharmacology and the treatment of schizophrenia: current status and future directions. Int Clin Psychopharmacol 1995; 10(Suppl 3):29 –37.
180. Restriction d'utilisation de la minocycline en raison d'un risque de syndromes d'hypersensibilité graves et d'atteintes auto-immunes [French]. http://www.ansm.sante.fr/content/download/41743/543041/version/1/file/lp-120611-Minocycline.pdf.

ANEXO D – POLYMORPHISM OF TOLL-LIKE RECEPTOR 4 GENE IN BIPOLAR DISORDER

Polymorphism of Toll-like receptor 4 gene in bipolar disorder

Oliveira, J.; Busson, M.; Etain, B.; Jamain, S.; Hamdani, N.; Boukouaci, W.; Amokrane, K.; Bennabi, M.; Le Guen, E.; Dargél, Aroldo A.; Houenou, J.; Ivanova, R.; Bellivier, F.; Henry, C.; Kahn, J-P.; Charron, D.; Krishnamoorthy, R.; Vervoitte, L.; Leboyer, M.; Tamouza, R.

Publicado em Journal of Affective Disorders

Polymorphism of Toll-like receptor 4 gene in bipolar disorder

José Oliveira[a,b,f], Marc Busson[a], Bruno Etain[b,d,e,f], Stéphane Jamain[b,d,e,f], Nora Hamdani[b,d,e,f], Wahid Boukouaci[a], Kahina Amokrane[a,c], Mériem Bennabi[a,f], Emmanuel Le Guen[a,b,f], Aroldo Ayub Dargél[a,b,f,g], Josselin Houenou[b,d,e,f], Rayna Ivanova[c], Frank Bellivier[b,d,e,f], Chantal Henry[b,d,e,f], Jean-Pierre Kahn[f,h], Dominique Charron[a,c,f,i], Rajagopal Krishnamoorthy[a,j], Laetitia Vervoitte[k], Marion Leboyer[b,d,e,f,1], Ryad Tamouza[a,c,f,i,n,1]

[a] INSERM, UMRS 940, Hôpital Saint-Louis, Paris F75010, France
[b] INSERM, U 955, IMRB, Psychiatrie Génétique, Créteil F94000, France
[c] Laboratoire Jean Dausset, Hôpital Saint-Louis, 1, avenue Claude Vellefaux, Paris F75010, France
[d] Université Paris-Est Créteil, UMR_S955, UPEC, Créteil F94000, France
[e] AP-HP, Pôle de Psychiatrie, groupe hospitalier Henri Mondor, Créteil F94000, France
[f] Fondation FondaMental, fondation de coopération scienti fique, Créteil, France
[g] Laboratório de Psiquiatria Molecular, Centro de Pesquisas Experimentais, Hospital de Clínicas de Porto Alegre, Programa de Pós-Graduação em Medicina: Psiquiatria, Universidade Federal do Rio Grande do Sul, UFRGS, CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brasil
[h] Service de Psychiatrie et Psychologie Clinique, CHU de Nancy, Hôpitaux de Brabois, F54500 Vandoeuvre Les Nancy, France
[i] Université Paris Diderot, Sorbonne Paris cité, Paris, France
[j] INSERM, U 763, Robert Debré Hospital, Paris F-75019, France
[k] Inserm U955, Centre d 'Investigation Clinique 006 and plateforme de ressources biologiques, Hôpital Henri-Mondor, Creteil F-94000, France

a b s t r a c t

Background: Bipolar disorder (BD) is considered as a multifactorial disorder involving complex interactions between genetic and environmental factors, where immune dysfunction is thought to play a key etiopathogenic role. In particular, excess of winter births associated with early-life infections raise the possibility of the implication ofi nnate immunity. Given the pivotal role of Toll-like receptor 4 (TLR-4), a major innate immune sensor molecule, we hypothesized that genetic variations of TLR-4 may be associated to BD.

Methods: Genomic DNAs from 572 BD patients and 202 healthy controls (HC) were analyzed for the distribution of six single nucleotides polymorphisms (SNPs) scattered along the TLR-4 locus (rs1927914, rs10759932, rs4986790, rs4986791, rs11536889 and rs11536891). Associations between BD and these polymorphisms were examined using the Chi-square test.

Results: We found that rs1927914 AA and rs11536891 TT genotype are more frequent in BD patients than in controls (corrected p; pc¼.02 and .02 respectively) particularly in early-onset BD patients (pc¼.004 and .006) born during the summer season (pc¼.02 and .002 respectively). We also found that rs4986790 AG and rs4986791 CT genotypes were signi ficantly associated with presence of autoimmune thyroiditis (pc¼.002).

Limitations: Our results are to be con firmed by replication in independent BD cohorts.

Conclusions: We report for the first time a genetic association between BD and TLR-4 a major player of innate immunity. Possible mechanisms underlying bipolar disorders linking altered TLR-4 expression and increased susceptibility to infections and/or autoimmunity are discussed.

1. Introduction

Bipolar disorder (BD) is a highly heritable and chronic mood disorder, known to be associated with substantial functional impairment, high health care costs and premature mortality (Leboyer and Kupfer, 2010). Classically described as a cyclical illness, with full blown manic or depressive episodes interspaced with normal euthymic periods, evidence now suggests that patients experience a more subtle chronic course than initially

[n] Corresponding author at: Laboratoire Jean Dausset, Hôpital Saint Louis, 1, avenue Claude Vellefaux, 75010 Paris, France. Tel.: þ 33 1 42 49 48 90; fax: þ 33 1 42 49 46 41.
E-mail address: ryadtamouza@yahoo.fr (R. Tamouza) .
[1] RT and ML are co-senior authors.

thought, characterized by residual symptoms, emotional dysregulation, sleep and circadian rhythm disturbances, cognitive impairment, and increased risk of psychiatric and medical comorbidities including autoimmune thyroid diseases (Leboyer and Kupfer, 2010). Accumulating knowledge tend to view BD as a progressive and multi-systemic disorder in which immune response dysfunctions seem to parallel the onset, progression and occurrence of medical comorbid disorders, in particular cardio-vascular disorders and diabetes (Berk et al., 2011; Leboyer et al., 2012). Such dysimmunity is mainly reflected by chronic low-grade inflammation behaving both as trait and state markers at the systemic level reflecting altered central nervous system (CNS) integrity (Dickerson et al., 2007; Goldstein et al., 2009; Hope et al., 2011; Modabbernia et al., 2013; Rao et al., 2010; Söderlund et al., 2011; Berk et al., 2010) and causal of cognitive decline with progressive atrophy of specific brain areas along disease progression.

Given the observed association between BD and environmental factors such as excess of winter births (5.8% winter excess of births) (Torrey et al., 1996), severe psychological stressors including childhood traumatic events observed in more than half of the patients (Etain et al., 2010) and associations with infectious events induced by neurotropic pathogens including Toxoplasma gondii, influenza virus or herpes simplex virus (HSV) (Dickerson et al., 2004, 2006; Gerber et al., 2012; Hamdani et al., 2012; Machón et al., 1997; Moore et al., 2001; Pearce et al., 2012; Tedla et al., 2011), we hypothesized that innate immune responses and their immunogenetic control could participate to the underlying mechanisms associated with BD.

Among the central players of immune first line defense, the Toll-like receptors (TLRs) are of particular interest because of their capacity to recognize and sense a wide range of pathogen-associated molecular patterns (PAMPs) and host-derived damage-associated molecular patterns (DAMPs). Belonging to the pattern recognition receptor (PRR) family, the TLRs consist of eleven functional members (TLR-1–TLR-11) (Mukhopadhyay et al., 2004), classified into two subgroups based on their cellular localization. While the TLR-3, TLR-7, TLR-8, TLR-9, and TLR-10 are expressed exclusively in the intracellular compartments, the TLR-1, TLR-2, TLR-4, TLR-5, TLR-6 and TLR-11 are cell surface molecules (Akira et al., 2006; Venkatasubramanian and Debnath, 2013) and all of them are pivotal molecules for the induction of innate immune responses (Mogensen, 2009).

In this context, the prominent TLR-4 molecules constitute an excellent candidate to be studied in BD given (i) their specificity to recognize lipopolysaccharide (LPS) from gram-negative bacteria and various ligands from viruses, fungus, and mycoplasma as well as products of oxidative stress/inflammation (Piccinini and Midwood, 2010; Sirisinha, 2011), (ii) their capacity to induce specific intra-cellular signaling cascade that activate nuclear factor-kappa B (NF-κB) and other transcription factors which precede the synthesis of pro-inflammatory cytokines and in flammatory mediators (Janeway and Medzhitov, 2002), (iii) their expression in circulating immune cells as well as in brain by microglia, astrocytes, oligodendrocytes and neurons or thyroid cells (Hanke and Kielian, 2011; Nishimura and Naito, 2005; Okun et al., 2011; Suh et al., 2009), and (iv) their implication in CNS homeostasis and CNS immune surveillance (Rivest, 2009) during diseases of infectious or non-infectious origin including neurodegenerative pathological processes (Glass et al., 2010). TLR-4 molecules are encoded by a highly polymorphic gene exhibiting polymorphisms scattered along the promoter, coding and 3′-untranslated regions (3′ UTR) (Netea et al., 2012). Furthermore, polymorphisms of the TLR-4 gene have been studied in a variety of clinical entities, eg. viz increased susceptibility to bacterial infection (Agnese et al., 2002), Alzheimer's disease (Balistreri et al., 2009; Minoretti et al., 2006; Wang et al., 2011), Crohn's disease (Shen et al., 2010), atherosclerosis (den Dekker et al., 2010) or cancer (Kutikhin, 2011) but not yet shown in psychiatric disorders. Only one recent work addressed the impact of various TLRs, including TLR-4, on pro-inflammatory cytokine production in supernatants of cultured blood cells from schizophrenia and BD patients after selective TLR agonist-induction (McKernan et al., 2011).

Given the high likelihood of innate-immune involvement in BD, as discussed above, we investigated, in a case-control study, the potential impact of TLR-4 polymorphism in susceptibility to BD.

2. Methods

2.1. Sample composition

Five hundred and seventy-two BD patients meeting DSM-IV criteria (American Psychiatric Association, 1994) for BD type I or II or not otherwise specified, consecutively admitted into three French university-affiliated psychiatry departments (Paris-Créteil, Bordeaux and Nancy), were interviewed by trained psychiatrists, using the French version of the Diagnostic Interview for Genetic Studies (DIGS version 3.0) (Nurnberger et al., 1994). All patients were euthymic at inclusion [i.e. having a Montgomery-Asberg Depression Rating Scale (Montgomery and Asberg, 1979) score and a Mania Rating Scale (Bech et al., 1978) score no more than five]. A set of demographic and/or clinical variables (Table 1) were assessed and recorded. Two hundred and two healthy controls (HC) were recruited and interviewed with the DIGS to assess personal and familial history of psychiatric disorders using the National Institute for Mental Health Family Interview for Genetic Studies (Maxwell, 1992). Only those, with neither personal nor family history (first degree) of psychiatric disorders, affective disorders or suicidal behavior were included. All patients and controls were of French descent, with at least three grandparents from the mainland of France and were consecutively recruited between February 2006 and January 2010. Among the clinical variables of interest, the age at onset (AAO) of BD was defined as the age at which the first mood episode (depressive, manic or hypomanic) occurred, as determined by reviewing medical records and information obtained with the DIGS. The threshold for early-onset BD (AAO before the age of 22 years) was defined on the basis of previous admixture analyses in four independent samples (Bellivier et al., 2003, 2001; Lin et al., 2006; Manchia et al., 2008) which identified three AAO subgroups: early-, intermediate- and late-onset. In order to have comparable subgroup sample size and taking into consideration the genetic homogeneity (Grigoroiu-Serbanescu et al., 2001) intermediate- and late-onset samples

Table 1
Demographic and clinical characteristics of study subjects.

	BD patients	Healthy controls
Mean age (years, y)	42 y (range: 16–67)	43 y (range: 19–64)
Sex		
Male	42% (216)	62% (101)
Female	58% (297)	38% (61)
Season of birth [a]	n¼513	n¼157
Winter	23% (118)	23% (36)
Spring	27% (138)	25% (39)
Summer	22% (113)	26% (41)
Autumn	28% (144)	26% (41)
Thyroiditis [a]	n¼504	n¼202
Yes	15% (77)	
No	85% (427)	100%

[a] Phenotype data were not available for the whole cohort.

were pooled into a single subgroup, herein referred to as "late-onset" subgroup for statistical comparison against early-onset group. We also recorded clinical variables of interest for the immuno-inflammation paradigm such as season of birth (winter, spring, summer and autumn) and presence of autoimmune thyroiditis. Written informed consent was obtained from all participating subjects and the institutional ethical committee approved the research protocol. The present study is ancillary of a larger National French ongoing program entitled "Genetic and environmental susceptibility factors to bipolar disorders" (RBM0436 and C0829) which began in 2004.

2.2. TLR-4 genotyping

Genomic DNA was extracted from EDTA-treated peripheral blood samples or B-lymphoblastoid cell lines using the Nucleon BACC3 kit (GE HealthCare, Chalfont St Giles, UK). The genotyping of the six single nucleotide polymorphisms (SNPs) herein studied i.e. promoter rs1927914 (−4434) A/G, rs10759932 (−7263) C/T; Exon 3 rs4986790 (+6143, Asp299Gly) A/G, rs4986791 (+8851, Thre399Ile) C/T and 3′-UTR rs11536889 (+5724) C/G, rs11536891 (+8469) C/T by a TaqMan® 5′-nuclease assay (Applied Biosystems®, Foster city, CA, USA) with allele-specific fluorogenic oligonucleotide probes. The following pre-developed TaqMan® assay genotyping kits were used: C_2704048_10, C_31783996_10, C_11722238_20, C_11722237_20, C_31784034_10 and C_31784036_10.

2.3. Statistical analysis

Comparisons of genotype and allele frequencies between patients and controls were performed using the Chi-square testing. The p values (two tailed) were corrected (pc) using the Bonferroni method and findings were considered statistically significant for pc less than .05. Both odds ratio (OR) and confidence interval 95% (CI95%) were calculated to assess the relative risk conferred by a specific allele or genotype. The following demographic/clinical items i.e. seasonality of birth and presence of thyroiditis, were included in the analysis. Deviation from the Hardy–Weinberg equilibrium was analyzed using the Chi-square test testing.

3. Results

Both the phenotype and genotype characteristics of patient and control groups are summarized in Tables 1 and 2 respectively.

The mean age of the BD patients at inclusion was 42 years (range: 16–67 years) while it was 43 years (range: 19–64 years) for controls. The observed genotype distribution satisfied the expected Hardy–Weinberg proportions for both patient and

Table 2
Genetic characteristics of study subjects: TLR4 genotype frequencies among patients and controls.

A. The rs1927914 AA and rs11536891 TT genotypes are more prevalent in BD patients than in controls								
TLR4 rs1927914 A/G TLR4 rs11536891 C/T	Patients (n¼572)		Controls (n¼202)		p	pc	OR	CI 95%
	n	f (%)	n	f (%)				
Genotypes								
TLR4 rs1927914 AA	275/572	48	75/201	37	.008	.02	1.56	1.11–2.20
TLR4 rs1927914 AG + GG	297/572	52	127/201	63				
TLR4 rs11536891 TT	406/572	71	123/202	61	.008	.02	1.57	1.11–2.22
TLR4 rs11536891 CT + CC	166/572	29	79/202	39				
B. The rs1927914 AA and rs11536891 TT genotypes are more prevalent in early onset BD patients than in controls								
TLR4 rs1927914 A/G TLR4 rs11536891 C/T	Early onset patients (n¼231)		Controls (n¼202)		p	pc	OR	CI 95%
	n	f (%)	n	f (%)				
Genotypes								
TLR4 rs1927914 AA	120/231	52	75/201	37	.002	.004	1.82	1.21–2.72
TLR4 rs1927914 AG + GG	111/231	48	126/201	63				
TLR4 rs11536891 TT	172/231	75	123/202	61	.003	.006	1.87	1.22–2.88
TLR4 rs11536891 CT + CC	59/231	25	79/202	39				
C. The rs1927914 AA and rs11536891 TT genotypes are more prevalent in early onset BD patients born during summer season than in controls								
TLR4 rs1927914 A/G TLR4 rs11536891 C/T	Summer born early onset BD (n¼55)		Summer born controls (n¼42)		p	pc	OR	CI 95%
	n	f (%)	n	f (%)				
Genotypes								
TLR4 rs1927914 AA	33/55	60	14/42	33	.009	.02	3	1.20–7.59
TLR4 rs1927914 AG + GG	22/55	40	28/42	67				
TLR4 rs11536891 TT	45/55	82	21/42	50	.001	.002	4.5	1.65–12.6
TLR4 rs11536891 CT + CC	10/55	18	21/42	50				
D. The rs4986790 AG and rs4986791 CT genotypes are more prevalent in BD patients with Thyroiditis than those without (independent of lithium treatment)								
TLR4 rs4986790 A/G TLR4 rs4986791 C/T	Patients with Thyroiditis (n¼44)		Patients without thyroiditis (n¼460)		p	pc	OR	CI 95%
	n	f (%)	n	f (%)				
Genotypes [a]								
TLR4 rs4986790 AA	32/44	73	413/460	90	.001	.002	3.30	1.44–7.10
TLR4 rs4986790 AG	12/44	27	47/460	10				
TLR4 rs4986791 CC	32/44	73	412/460	90	.001	.002	3.22	1.41–6.93
TLR4 rs4986791 CT	12/44	27	48/460	10				

n: number, f: frequency, pc: corrected-p, OR: odds ratio and CI 95%: confidence interval 95%.

[a] The homozygous state for TLR4 rs4986790 G and rs4986791 T alleles were not found in the studied BD and HC groups.

control samples and the overall frequencies were comparable to those previously published in public database (http://www.ncbi.nlm.nih.gov/).

The analysis of TLR-4 genotype distribution revealed that the homozygous state for TLR-4 rs1927914 A and the TLR-4 rs11536891 T alleles were significantly more prevalent in BD patients than in HC (rs1927914 AA vs. AG þ GG: 48% vs. 37%, p¼.008, pc ¼.02; OR ¼1.56, CI95% ¼1.11 –2.20 and rs11536891 TT vs. CT þ CC: 71% vs. 61%, p¼.008, pc ¼.02; OR ¼1.57, CI95% ¼1.11 – 2.22 in patients and HC respectively) (Table 2 A). Further analysis of TLR-4 genotype distribution after stratification for the disease AAO and season of birth revealed that the above-observed susceptibility status was stronger among the early-onset patient subset as compared to HC (rs1927914 AA vs. AG þ GG: 52% vs. 37%, p¼.002, pc¼.004; OR ¼1.82, CI95% ¼1.21 –2.72 and rs11536891 TT vs. CT þ CC: 75% vs. 61%, p¼.003, pc¼.006; OR ¼1.87, CI95% ¼1.22 – 2.88) (Table 2 B) especially in those born during the summer season as compared to HC born during the same season (rs1927914 AA vs. AG þ GG: 60% vs. 33%, p¼.009, pc¼.02; OR ¼3, CI95%¼1.20 –7.59 and rs11536891 TT vs. CT þ CC: 82% vs. 50%, p¼.001, pc¼.002; OR ¼4.5, CI95% ¼1.65 –12.6) (Table 2 C).

Another finding concerns the genotype distribution of the two genetically linked TLR-4 rs4986790 (Asp299Gly) and rs4986791 (Thr399Ile) exonic polymorphisms. Indeed, a patient stratification based on the occurrence of autoimmune thyroiditis revealed that the compound heterozygotes rs4986790 AG and rs4986791 CT were more prevalent in patients with this comorbidity as compared to those without (rs4986790 AG vs. others, 27% vs. 10%, p¼.001, pc¼.002; OR ¼3.30, CI95% ¼1.44 –7.10 and rs4986791 CT vs. others, 27% vs 10%, p ¼.001, pc¼.002; OR ¼3.22, CI95% ¼1.41 – 6.93 in patients with and without thyroiditis respectively) (Table 2 D). It is of interest to note that such association was observed regardless of lithium treatment.

4. Discussion

The presence of an inflammatory background and the implication of various neurotropic pathogens along with an excess of winter births have been associated with BD manifestation indicating a possible contribution for the immunogenetic regulation of immune responses in the etiology of the disorder. Only few, often discrepant, studies have addressed this issue mainly focusing on polymorphisms of cytokine genes (Czerski et al., 2008 ; Papiol et al., 2004 , 2008) or more recently on a functionally-relevant variation in the non-classical HLA-G locus (Debnath et al., 2013).

To explore the genetics of the innate arm of the immune response, a key pathway in the control of infection/inflammation, we studied genetic polymorphisms located in the promoter, exon 3 and the 3′ –UTR of the TLR-4 gene in BD. We found that both promoter TLR-4 rs1927914 A and 3′ UTR TLR-4 rs11536891 T alleles in homozygous state are associated with BD and that this association was restricted to the early-onset subgroup of patients, especially those born during the summer season. These findings could point to potential transcriptional and post-transcriptional alterations in TLR-4 expression.

Indeed, the promoter TLR-4 rs1927914 AA genotype could be considered as a "low expressor" genotype, regarding that the presence of the G nucleotide is predicted to disrupt binding sites for the Oct-1 and C/EBP repressor transcription factors (Heinemeyer et al., 1998) with a probable consequent increase in TLR-4 expression as suggested at functional level (Ragnarsdóttir et al., 2010). Recent studies support that the G allele in a single dose is protective against late-onset Alzheimer's disease (Yu et al., 2012) and severe forms of asthma (Zhang et al., 2011).

Regarding the TLR-4 rs11536891 located in the 3′ UTR, a major post-transcriptional regulatory region at the mRNA level, we searched for possible microRNA (miRNA) binding site alterations using RegRNA (Huang et al., 2006) and found that the T to C variation could abrogate binding sites for has-miR-568 and has-miR-933 which is expected to consequently increase the expression of TLR-4 protein and thereby raise the inflammatory response. Thus, also in this case, the 3′ UTR TLR-4 rs11536891 TT genotype, shown in this study to be significantly more prevalent in BD patients, would be a potential "low expressor" genotype. Although no functional studies have targeted this polymorphism in particular, the TLR-4 3′ -UTR has been shown to regulate gene expression (Song et al., 2006) through various functional polymorphisms (Duan et al., 2007 ; Sato et al., 2012) with some genetic variants already associated with the development of disorders like prostate cancer (Kim et al., 2012), late-onset Alzheimer's disease (Yu et al., 2012) or nasopharyngeal carcinoma (Song et al., 2006) with only one study addressing the herein studied polymorphism in a colorectal cancer case-control study (Tsilidis et al., 2009).

Accordingly, we may hypothesize here that BD patients carrying the promoter TLR-4 rs1927914 A and the 3'UTR TLR-4 rs11536891 T alleles in an homozygous state could potentially be less prone to develop an efficient TLR-4-mediated response than those having the TLR-4 "high expressor" G and C alleles, and thus less able to mount an efficient innate immune response against potential pathogens.

Altogether, these findings and observations are of particular interest given that the immune privilege concept of the CNS is now debated due to evidences such as the implication of activated TLR-4 molecules in CNS injury during several clinical conditions including ischemia (Caso et al., 2008), alcoholism (Alfonso-Loeches et al., 2012), stress exposure and commensal bacterial translocation (Gárate et al., 2011 ; Maes et al., 2012). In terms of gene-environment interactions, the participation of TLR-4 molecules in host defense against Toxoplasma gondii infection (Debierre-Grockiego et al., 2007) deserved to be mentioned regarding the demonstrated association between such parasitic infection and BD (Hamdani et al., 2013; Pearce et al., 2012). In this context, it is worthy to remind that TLR-4 mediates anti-infectious inflammatory responses in the small intestine against this orally acquired infection as demonstrated in mice model after toxoplasmosis induced by peroral administration of cysts (Furuta et al., 2006). In addition, TLR-4 activation, both in intestinal epithelial cells and the lamina propria, is important for healing of injured intestinal epithelium, expression of defensins and recruitment of polynuclear neutrophils (Fukata and Abreu, 2007) but we cannot exclude the potential involvement of other pathogen features including specific strain effects or other pathogen-related compromised immune responses. Furthermore its role in the inflammatory response triggered by LPS from intestinal bacteria translocation is relevant for BD given the recent implication of LPS in psychiatric disorders (Gárate et al., 2011 ; Maes et al., 2012) and the importance of brain-gut axis in neuropsychiatry (Bergstrom et al., 2012 ; Cryan and Dinan, 2012 ; Severance et al., 2012).

Our data suggest that the genetic susceptibility conferred by the promoter TLR-4 rs1927914 AA and the 3′ UTR TLR-4 rs11536891 TT genotypes may be of greater importance in the development of early-onset BD. Early-onset BD is considered to be a more homogeneous subgroup in which genetic factors have a higher weight (Leboyer et al., 2005) and recent evidence suggests that not only it is a more severe form with a longer delay between diagnosis and treatment, poorer response to medication and greater lifetime prevalence of neuropsychiatric comorbidities (Bellivier et al., 2001 ; Leverich et al., 2007 ; Perlis et al., 2004 ; Schürhoffet al., 2000) but it also seems to be associated with the presence of immune system activation and high burden of medical comorbidities (Goldstein

et al., 2011 ; Jerrell et al., 2010). It has been postulated that a common physiopathological pathway mediates the association of several comorbid medical conditions with BD, chronic low-grade in flammation being probably the major culprit (Leboyer et al., 2012). These conditions seem to be highly prevalent in pediatric BD patients, namely obesity, type 2 diabetes mellitus, cardiovascular disorders, endocrine disorders and asthma among others, and that obesity, cardiovascular disease and asthma preceded the diagnosis of adolescent-onset BD (age Z 13 years) (Jerrell et al., 2010). Interestingly, Padmos et al. observed the expression of a set ofi n flammatory genes in monocytes of BD offspring and de fined a pro-in flammatory gene expression signature that was observed among 85% of offspring with mood disorders and even in 45% of the offspring without mood disorders, but only in 19% of control adolescents (Padmos et al., 2008). Bipolar offspring have also been found to be more susceptible to thyroid autoimmunity independently from the susceptibility to develop psychiatric disorders (Hillegers et al., 2007). Thus, it seems that immune system activation precedes the development of BD, and that these dysfunctional traits, in regard of our results, may be present at the innate immunity level under genetic in fluence and contribute to the severity of the early forms of the disorder.

In addition, the observed association between season of birth and TLR-4 genotype distribution could be considered through the admitted relationship between infections by common neurotropic pathogens and psychiatric disorders (Yolken and Torrey, 2008). Indeed, the consequences of such potential infectious insults during pregnancy and/or neonatal period could be modulated by immunogenetically-driven anti-infectious responses to pathogens during speci fic seasonal windows. In this regard, two hypotheses emerge that could help explain our results, (i) infants born during summer could be more exposed to seasonal gastrointestinal infections with persistence of microorganisms and pathogen-related products in neonates due to impaired bacterial clearance (within the concept of the "brain-axis " psychiatric pathway) or (ii) as the first half of pregnancy, for summer-born individuals, takes place during winter months, maternal viral infections could be implicated in BD development since TLR-4 recognizes wide range of viruses (Carty and Bowie, 2010). In this respect, a recent report demonstrates the in fluence of gestational in fluenza on the development of BD in adult offspring (Parboosing et al., 2013).

It is worthy to highlight that the present findings are also in agreement with our recent data describing the genetically-driven immuno-modulatory effects of the HLA-G molecules in BD. Studying the same sample set of BD patients and controls, we observed that in BD patients, the association with normal/high expression of HLA-G molecules could enhance immunosuppressive/tolerogenic functions with consequent inef ficient protection against infectious challenges, particularly among patients born during the winter season (Debnath et al., 2013). Thus by studying both innate immunity (the present study) and immune regulation, the data provided by the two studies are convergent in uncovering an immogenetically-driven susceptibility/sensitivity to infection in BD. The paradigm described here reinforces the importance of the genetic control ofi mmune processes in BD as well as possible gene-environment interactions (Fig. 1).

These hypotheses are further reinforced by the observed association between the exonic TLR-4 rs4986790 AG and TLR-4 rs4986791 CT genotypes and autoimmune thyroiditis in BD patients, independently ofl ithium treatment. Autoimmune thyroiditis is known to be a comorbid condition emerging independently ofl ithium treatment (Kupka et al., 2002 ; Padmos et al., 2004). The non-synonymous TLR-4 Asp299Gly and TLR-4 Thr399Ile amino-acid changes associated respectively with the exonic TLR-4 rs4986790 A/G and TLR-4 rs4986791 C/T polymorphisms, are known to affect the extracellular domain of the receptor and thereby LPS-responsiveness (Arbour et al., 2000).

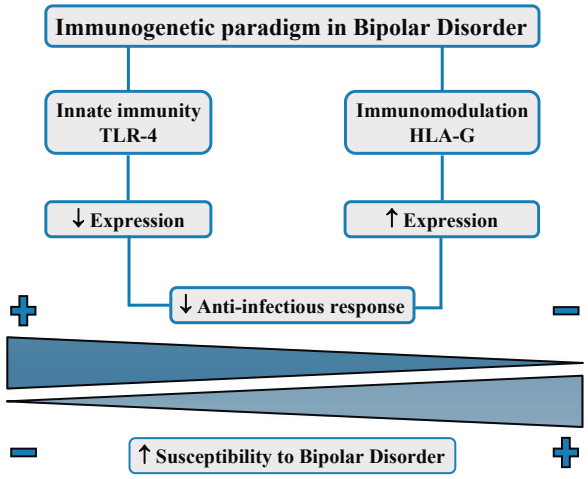


Fig. 1.

These genetically linked changes were previously associated either in terms of susceptibility or protection with a wide range ofi nfectious and chronic in flammatory/autoimmune disorders (Agnese et al., 2002 ; Brand et al., 2005 ; de Oliveira and Silva, 2012 ; Lorenz et al., 2002 ; Mockenhaupt et al., 2006 ; Pabst et al., 2006 ; Tal et al., 2004 ; Török et al., 2004 ; Van der Graaf et al., 2006).

Association of heterozygosity for these exonic variations in BD may implicate a dominant effect of such changes with decreased TLR-4 activity and consequent inef ficient removal of microbial pathogens and/or apoptotic/necrotic thyroid cells. Such situation may promote chronic in flammation, breakdown of tolerance and autoimmunity (thyroiditis) after repeated antigenic challenges dictated by seasonal variations (Desailloud and Hober, 2009 ; Krassas et al., 2007). One of the implicated viruses in autoimmune diseases including autoimmune thyroiditis, is the Parvovirus B19 (Lunardi et al., 2008 ; Wang et al., 2010). Ofi nterest, the Parvovirus B19 was detected in 14.4 to 42.3% of human brain samples (Hobbs, 2006) and was shown to be involved in neuronal disorders (Douvoyiannis et al., 2009) via a potential immune-mediated mechanism (Kerr et al., 2002). Moreover, other data suggest also that this viral infection may be associated with co-morbid bipolar and autoimmune thyroid disorders in females (Hammond and Hobbs, 2007). Although further research is needed, genetically determined differences in immune responses to viral infections, possibly including the TLR4 pathway, may constitute a common background of susceptibility to both bipolar and autoimmune thyroid disorders, at least in a subset of patients.

In conclusion, our results show that inherited variations of TLR-4 are associated with BD. Moreover, season of birth variability implying a gene-environment interaction is in line with the already described pathogenic role of some microorganisms in the etiology of BD.

If con firmed by replication in other BD cohorts, further exploration of the TLR-4 signaling network in BD may allow designing novel therapeutic targets.

Role off unding source

This work was supported by INSERM (UMRS 940 and U955), Assistance Publique des Hôpitaux de Paris, Agence Nationale pour la Recherche (ANR MNP2008 —VIP-Project) and fondation FondaMental.

Con fl ict ofi nterest

The authors declare no competing financial interests.

Acknowledgments

We thank patients with bipolar disorders and controls who agreed to participate in this study. The authors thank the "Plateforme de Ressources Biologiques" (B. Ghaleb) of Mondor Hospital, "l'Etablissement Français du Sang" of Créteil (J.L. Beaumont and B Mignen), the Cochin Hospital cell repository (J. Chelly). We thank Nita Nguyen for data management.

JO acknowledges the financial support of the Foundation for Science and Technology (Portugal) doctoral degree grant (SFRH/BD/76170/2011).

References

Agnese, D.M., Calvano, J.E., Hahm, S.J., Coyle, S.M., Corbett, S.A., Calvano, S.E., Lowry, S.F., 2002. Human toll-like receptor 4 mutations but not CD14 polymorphisms are associated with an increased risk of gram-negative infections. J. Infect. Dis. 186, 1522–1525.

Akira, S., Uematsu, S., Takeuchi, O., 2006. Pathogen recognition and innate immunity. Cell 124, 783–801.

Alfonso-Loeches, S., Pascual, M., Gómez-Pinedo, U., Pascual-Lucas, M., Renau-Piqueras, J., Guerri, C., 2012. Toll-like receptor 4 participates in the myelin disruptions associated with chronic alcohol abuse. Glia 60, 948–964.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Masson, Paris.

Arbour, N.C., Lorenz, E., Schutte, B.C., Zabner, J., Kline, J.N., Jones, M., Frees, K., Watt, J.L., Schwartz, D.A., 2000. TLR4 mutations are associated with endotoxin hyporesponsiveness in humans. Nat. Genet. 25, 187–191.

Balistreri, C.R., Colonna-Romano, G., Lio, D., Candore, G., Caruso, C., 2009. TLR4 polymorphisms and ageing: implications for the pathophysiology of age-related diseases. J. Clin. Immunol. 29, 406–415.

Bech, P., Rafaelsen, O.J., Kramp, P., Bolwig, T.G., 1978. The mania rating scale: scale construction and inter-observer agreement. Neuropharmacology 17, 430–431.

Bellivier, F., Golmard, J.L., Henry, C., Leboyer, M., Schürhoff, F., 2001. Admixture analysis of age at onset in bipolar I affective disorder. Arch. Gen. Psychiatry 58, 510–512.

Bellivier, F., Golmard, J.L., Rietschel, M., Schulze, T.G., Malafosse, A., Preisig, M., McKeon, P., Mynett-Johnson, L., Henry, C., Leboyer, M., 2003. Age at onset in bipolar I affective disorder: further evidence for three subgroups. Am. J. Psychiatry 160, 999–1001.

Bergstrom, K.S., Sham, H.P., Zarepour, M., Vallance, B.A., 2012. Innate host responses to enteric bacterial pathogens: a balancing act between resistance and tolerance. Cell. Microbiol. 14, 475–484.

Berk, M., Conus, P., Kapczinski, F., Andreazza, A.C., Yücel, M., Wood, S.J., Pantelis, C., Malhi, G.S., Dodd, S., Bechdolf, A., Amminger, G.P., Hickie, I.B., McGorry, P.D., 2010. From neuroprogression to neuroprotection: implications for clinical care. Med. J. Aust. 193, S36–40.

Berk, M., Kapczinski, F., Andreazza, A.C., Dean, O.M., Giorlando, F., Maes, M., Yücel, M., Gama, C.S., Dodd, S., Dean, B., Magalhães, P.V.S., Amminger, P., McGorry, P., Malhi, G.S., 2011. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci. Biobehav. Rev. 35, 804–817.

Brand, S., Staudinger, T., Schnitzler, F., Pfennig, S., Hofbauer, K., Dambacher, J., Seiderer, J., Tillack, C., Konrad, A., Crispin, A., Göke, B., Lohse, P., Ochsenkühn, T., 2005. The role of Toll-like receptor 4 Asp299Gly and Thr399Ile polymorphisms and CARD15/NOD2 mutations in the susceptibility and phenotype of Crohn's disease. In flamm. Bowel Dis. 11, 645–652.

Carty, M., Bowie, A.G., 2010. Recent insights into the role of Toll-like receptors in viral infection. Clin. Exp. Immunol. 161, 397–406.

Caso, J.R., Pradillo, J.M., Hurtado, O., Leza, J.C., Moro, M.A., Lizasoain, I., 2008. Toll-like receptor 4 is involved in subacute stress-induced neuroinflammation and in the worsening of experimental stroke. Stroke J. Cereb. Circ. 39, 1314–1320.

Cryan, J.F., Dinan, T.G., 2012. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat. Rev. Neurosci. 13, 701–712.

Czerski, P.M., Rybakowski, F., Kapelski, P., Rybakowski, J.K., Dmitrzak-Weglarz, M., Leszczy ńska-Rodziewicz, A., S łopie ń, A., Skibi ńska, M., Kaczmarkiewicz-Fass, M., Hauser, J., 2008. Association of tumor necrosis factor−308 G/A promoter polymorphism with schizophrenia and bipolar affective disorder in a Polish population. Neuropsychobiology 57, 88–94.

De Oliveira, J.G., Silva, A.E., 2012. Polymorphisms of the TLR2 and TLR4 genes are associated with risk of gastric cancer in a Brazilian population. World J. Gastroenterol. 18, 1235–1242.

Debierre-Grockiego, F., Campos, M.A., Azzouz, N., Schmidt, J., Bieker, U., Resende, M.G., Mansur, D.S., Weingart, R., Schmidt, R.R., Golenbock, D.T., Gazzinelli, R.T., Schwarz, R.T., 2007. Activation of TLR2 and TLR4 by glycosylphosphatidylinositols derived from Toxoplasma gondii. J. Immunol. 179, 1129–1137.

Debnath, M., Busson, M., Jamain, S., Etain, B., Hamdani, N., Oliveira, J., Boukouaci, W., Amokrane, K., Moins-Teisserenc, H., Lajnef, M., Bengoufa, D., Malafosse, A., Bellivier, F., Henry, C., Kahn, J.-P., Krishnamoorthy, R., Charron, D., Leboyer, M., Tamouza, R., 2013. The HLA-G low expressor genotype is associated with protection against bipolar disorder. Hum. Immunol. 74, 593–597.

Den Dekker, W.K., Cheng, C., Pasterkamp, G., Duckers, H.J., 2010. Toll like receptor 4 in atherosclerosis and plaque destabilization. Atherosclerosis 209, 314–320.

Desailloud, R., Hober, D., 2009. Viruses and thyroiditis: an update. Virol. J. 6, 5.

Dickerson, F., Stallings, C., Origoni, A., Boronow, J., Yolken, R., 2007. Elevated serum levels of C-reactive protein are associated with mania symptoms in outpatients with bipolar disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 31, 952–955.

Dickerson, F.B., Boronow, J.J., Stallings, C., Origoni, A.E., Cole, S., Krivogorsky, B., Yolken, R.H., 2004. Infection with herpes simplex virus type 1 is associated with cognitive de ficits in bipolar disorder. Biol. Psychiatry 55, 588–593.

Dickerson, F.B., Boronow, J.J., Stallings, C., Origoni, A.E., Cole, S., Leister, F., Krivogorsky, B., Yolken, R.H., 2006. The catechol O-methyltransferase Val158-Met polymorphism and herpes simplex virus type 1 infection are risk factors for cognitive impairment in bipolar disorder: additive gene-environmental effects in a complex human psychiatric disorder. Bipolar Disord. 8, 124–132.

Douvoyiannis, M., Litman, N., Goldman, D.L., 2009. Neurologic manifestations associated with parvovirus B19 infection. Clin. Infect. Dis. 48, 1713–1723.

Duan, Z., Zhu, P., Dong, H., Gu, W., Yang, C., Liu, Q., Wang, Z., Jiang, J., 2007. Functional signi ficance of the TLR4/11367 polymorphism identified in Chinese Han population. Shock 28, 160–164.

Etain, B., Mathieu, F., Henry, C., Raust, A., Roy, I., Germain, A., Leboyer, M., Bellivier, F., 2010. Preferential association between childhood emotional abuse and bipolar disorder. J. Trauma Stress 23, 376–383.

Fukata, M., Abreu, M.T., 2007. TLR4 signalling in the intestine in health and disease. Biochem. Soc. Trans. 35, 1473–1478.

Furuta, T., Kikuchi, T., Akira, S., Watanabe, N., Yoshikawa, Y., 2006. Roles of the small intestine for induction of toll-like receptor 4-mediated innate resistance in naturally acquired murine toxoplasmosis. Int. Immunol. 18, 1655–1662.

Gárate, I., García-Bueno, B., Madrigal, J.L.M., Bravo, L., Berrocoso, E., Caso, J.R., Micó, J.A., Leza, J.C., 2011. Origin and consequences of brain Toll-like receptor 4 pathway stimulation in an experimental model of depression. J. Neuroinflamm. 8, 151.

Gerber, S.I., Krienke, U.J., Biedermann, N.C., Grunze, H., Yolken, R.H., Dittmann, S., Langosch, J.M., 2012. Impaired functioning in euthymic patients with bipolar disorder —HSV-1 as a predictor. Prog. Neuropsychopharmacol. Biol. Psychiatry 36, 110–116.

Glass, C.K., Saijo, K., Winner, B., Marchetto, M.C., Gage, F.H., 2010. Mechanisms underlying in flammation in neurodegeneration. Cell 140, 918–934.

Goldstein, B.I., Collinger, K.A., Lotrich, F., Marsland, A.L., Gill, M.K., Axelson, D.A., Birmaher, B., 2011. Preliminary findings regarding proin flammatory markers and brain-derived neurotrophic factor among adolescents with bipolar spectrum disorders. J. Child Adolesc. Psychopharmacol. 21, 479–484.

Goldstein, B.I., Kemp, D.E., Soczynska, J.K., McIntyre, R.S., 2009. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. J. Clin. Psychiatry 70, 1078–1090.

Grigoroiu-Serbanescu, M., Martinez, M., Nöthen, M.M., Grinberg, M., Sima, D., Propping, P., Marinescu, E., Hrestic, M., 2001. Different familial transmission patterns in bipolar I disorder with onset before and after age 25. Am. J. Med. Genet. 105, 765–773.

Hamdani, N., Daban-Huard, C., Lajnef, M., Richard, J.-R., Delavest, M., Godin, O., Guen, E.L., Vederine, F.E., Lépine, J.-P., Jamain, S., Houenou, J., Corvoisier, P.L., Aoki, M., Moins-Teisserenc, H., Charron, D., Krishnamoorthy, R., Yolken, R., Dickerson, F., Tamouza, R., Leboyer, M., 2012. Relationship between Toxoplasma gondii infection and bipolar disorder in a French sample. J. Affect. Disord. 148, 444–448.

Hammond, C.J., Hobbs, J.A., 2007. Parvovirus B19 infection of brain: possible role of gender in determining mental illness and autoimmune thyroid disorders. Med. Hypotheses 69, 113–116.

Hanke, M.L., Kielian, T., 2011. Toll-like receptors in health and disease in the brain: mechanisms and therapeutic potential. Clin. Sci. London 121, 367–387.

Heinemeyer, T., Wingender, E., Reuter, I., Hermjakob, H., Kel, A.E., Kel, O.V., Ignatieva, E.V., Ananko, E.A., Podkolodnaya, O.A., Kolpakov, F.A., Podkolodny, N.L., Kolchanov, N.A., 1998. Databases on transcriptional regulation: TRANSFAC, TRRD and COMPEL. Nucleic Acids Res. 26, 362–367.

Hillegers, M.H.J., Reichart, C.G., Wals, M., Verhulst, F.C., Ormel, J., Nolen, W.A., Drexhage, H.A., 2007. Signs of a higher prevalence of autoimmune thyroiditis in female offspring of bipolar parents. Eur. Neuropsychopharmacol. 17, 394–399.

Hobbs, J.A., 2006. Detection of adeno-associated virus 2 and parvovirus B19 in the human dorsolateral prefrontal cortex. J. Neurovirol. 12, 190–199.

Hope, S., Dieset, I., Agartz, I., Steen, N.E., Ueland, T., Melle, I., Aukrust, P., Andreassen, O.A., 2011. Affective symptoms are associated with markers of inflammation and immune activation in bipolar disorders but not in schizophrenia. J. Psychiatr. Res. 45, 1608–1616.

Huang, H.Y., Chien, C.H., Jen, K.H., Huang, H.D., 2006. RegRNA: an integrated web server for identifying regulatory RNA motifs and elements. Nucleic Acids Res. 34, W429–434.

Janeway Jr., C.A., Medzhitov, R., 2002. Innate immune recognition. Annu. Rev. Immunol. 20, 197–216.

Jerrell, J.M., McIntyre, R.S., Tripathi, A., 2010. A cohort study of the prevalence and impact of comorbid medical conditions in pediatric bipolar disorder. J. Clin. Psychiatry 71, 1518–1525.

Kerr, J.R., Barah, F., Chiswick, M.L., McDonnell, G.V., Smith, J., Chapman, M.D., Bingham, J.B., Kelleher, P., Sheppard, M.N., 2002. Evidence for the role of demyelination, HLA-DR alleles, and cytokines in the pathogenesis of parvovirus B19 meningoencephalitis and its sequelae. J. Neurol. Neurosurg. Psychiatry 73, 739–746.

Kim, H.J., Bae, J.S., Chang, I.H., Kim, K.D., Lee, J., Shin, H.D., Lee, J.Y., Kim, W.J., Kim, W., Myung, S.C., 2012. Sequence variants of Toll-like receptor 4 (TLR4) and the risk of prostate cancer in Korean men. World J. Urol. 30, 225 –232.

Krassas, G.E., Tziomalos, K., Pontikides, N., Lewy, H., Laron, Z., 2007. Seasonality of month of birth of patients with Graves' and Hashimoto's diseases differ from that in the general population. Eur. J. Endocrinol. 156, 631 –636.

Kupka, R.W., Nolen, W.A., Post, R.M., McElroy, S.L., Altshuler, L.L., Denicoff, K.D., Frye, M.A., Keck Jr, P.E., Leverich, G.S., Rush, A.J., Suppes, T., Pollio, C., Drexhage, H.A., 2002. High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. Biol. Psychiatry 51, 305 –311.

Kutikhin, A.G., 2011. Impact of Toll-like receptor 4 polymorphisms on risk of cancer. Hum. Immunol. 72, 193 –206.

Leboyer, M., Henry, C., Paillere-Martinot, M.L., Bellivier, F., 2005. Age at onset in bipolar affective disorders: a review. Bipolar Disord. 7, 111 –118.

Leboyer, M., Kupfer, D.J., 2010. Bipolar disorder: new perspectives in health care and prevention. J. Clin. Psychiatry 71, 1689 –1695.

Leboyer, M., Soreca, I., Scott, J., Frye, M., Henry, C., Tamouza, R., Kupfer, D.J., 2012. Can bipolar disorder be viewed as a multi-system inflammatory disease? J. Affect. Disord. 141, 1 –10.

Leverich, G.S., Post, R.M., Keck, P.E., Altshuler, L.L., Frye, M.A, Kupka, R.W., Nolen, W. A., Suppes, T., McElroy, S.L., Grunze, H., Denicoff, K., Moravec, M.K.M., Luckenbaugh, D., 2007. The poor prognosis of childhood-onset bipolar disorder. J. Pediatr. 150, 485 –490.

Lin, P.I., McInnis, M.G., Potash, J.B., Willour, V., MacKinnon, D.F., DePaulo, J.R., Zandi, P.P., 2006. Clinical correlates and familial aggregation of age at onset in bipolar disorder. Am. J. Psychiatry 163, 240 –246.

Lorenz, E., Mira, J.P., Frees, K.L., Schwartz, D.A., 2002. Relevance of mutations in the TLR4 receptor in patients with gram-negative septic shock. Arch. Intern. Med. 162, 1028 –1032.

Lunardi, C., Tinazzi, E., Bason, C., Dolcino, M., Corrocher, R., Puccetti, A., 2008. Human parvovirus B19 infection and autoimmunity. Autoimmun. Rev. 8, 116–120.

Machón, R.A., Mednick, S.A., Huttunen, M.O., 1997. Adult major affective disorder after prenatal exposure to an influenza epidemic. Arch. Gen. Psychiatry 54, 322–328.

Maes, M., Kubera, M., Leunis, J.C., Berk, M., 2012. Increased IgA and IgM responses against gut commensals in chronic depression: further evidence for increased bacterial translocation or leaky gut. J. Affect. Disord. 141, 55 –62.

Manchia, M., Lampus, S., Chillotti, C., Sardu, C., Ardau, R., Severino, G., Del Zompo, M., 2008. Age at onset in Sardinian bipolar I patients: evidence for three subgroups. Bipolar Disord. 10, 443 –446.

Maxwell, M.E., 1992. Manual for the Family Interview for Genetic Studies, NIMH.

McKernan, DP, Dennison, U, Gaszner, G, Cryan, JF, Dinan, TG., 2011. Enhanced peripheral toll-like receptor responses in psychosis: further evidence of a pro-inflammatory phenotype. Transl. Psychiatry 1, e36 .

Minoretti, P., Gazzaruso, C., Vito, C.D., Emanuele, E., Bianchi, M., Coen, E., Reino, M., Geroldi, D., 2006. Effect of the functional toll-like receptor 4 Asp299Gly polymorphism on susceptibility to late-onset Alzheimer's disease. Neurosci. Lett. 391, 147 –149.

Mockenhaupt, F.P., Cramer, J.P., Hamann, L., Stegemann, M.S., Eckert, J., Oh, N.R., Otchwemah, R.N., Dietz, E., Ehrhardt, S., Schröder, N.W.J., Bienzle, U., Schumann, R.R., 2006. Toll-like receptor (TLR) polymorphisms in African children: common TLR-4 variants predispose to severe malaria. J. Commun. Dis. 38, 230 –245.

Modabbernia, A., Taslimi, S., Brietzke, E., Ashra fi, M., 2013. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biol. Psychiatry 74, 15 –25.

Mogensen, T.H., 2009. Pathogen recognition and inflammatory signaling in innate immune defenses. Clin. Microbiol. Rev. 22, 240 –273.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry J. Ment. Sci. 134, 382 –389.

Moore, P.B., El-Badri, S.M., Cousins, D., Shepherd, D.J., Young, A.H., McAllister, V.L., Ferrier, I.N., 2001. White matter lesions and season of birth of patients with bipolar affective disorder. Am. J. Psychiatry 158, 1521 –1524.

Mukhopadhyay, S., Herre, J., Brown, G.D., Gordon, S., 2004. The potential for Toll-like receptors to collaborate with other innate immune receptors. Immunology 112, 521 –530.

Netea, M.G., Wijmenga, C., O'Neill, L.A.J., 2012. Genetic variation in Toll-like receptors and disease susceptibility. Nat. Immunol. 13, 535 –542.

Nishimura, M., Naito, S., 2005. Tissue-specific mRNA expression profiles of human toll-like receptors and related genes. Biol. Pharm. Bull. 28, 886 –892.

Nurnberger Jr, J.I., Blehar, M.C., Kaufmann, C.A., York-Cooler, C., Simpson, S.G., Harkavy-Friedman, J., Severe, J.B., Malaspina, D., Reich, T., 1994. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiat.. Arch. Gen. Psychiatry 51, 849 –859. (discussion 863 –864).

Okun, E., Grif fioen, K.J., Mattson, M.P., 2011. Toll-like receptor signaling in neural plasticity and disease. Trends Neurosci. 34, 269 –281.

Pabst, S., Baumgarten, G., Stremmel, A., Lennarz, M., Knüfermann, P., Gillissen, A., Vetter, H., Grohé, C., 2006. Toll-like receptor (TLR) 4 polymorphisms are associated with a chronic course of sarcoidosis. Clin. Exp. Immunol. 143, 420–426.

Padmos, R.C., Bekris, L., Knijff, E.M., Tiemeier, H., Kupka, R.W., Cohen, D., Nolen, W.A., Lernmark, A., Drexhage, H.A., 2004. A high prevalence of organ-specific auto-immunity in patients with bipolar disorder. Biol. Psychiatry 56, 476 –482.

Padmos, R.C., Hillegers, M.H.J., Knijff, E.M., Vonk, R., Bouvy, A., Staal, F.J.T., de Ridder, D., Kupka, R.W., Nolen, W.A., Drexhage, H.A., 2008. A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of in flammatory genes in monocytes. Arch. Gen. Psychiatry 65, 395–407.

Papiol, S., Molina, V., Desco, M., Rosa, A., Reig, S., Sanz, J., Palomo, T., Fañanás, L., 2008. Gray matter de ficits in bipolar disorder are associated with genetic variability at interleukin-1 beta gene (2q13). Genes Brain Behav. 7, 796 –801.

Papiol, S., Rosa, A., Gutiérrez, B., Martín, B., Salgado, P., Catalán, R., Arias, B., Fañanás, L., 2004. Interleukin-1 cluster is associated with genetic risk for schizophrenia and bipolar disorder. J. Med. Genet. 41, 219 –223.

Parboosing, R., Bao, Y., Shen, L., Schaeffer, C.A., Brown, A.S., 2013. Gestational influenza and bipolar disorser in adult offspring. JAMA Psychiatry 70, 677–685.

Pearce, B.D., Kruszon-Moran, D., Jones, J.L., 2012. The relationship between Toxoplasma gondii infection and mood disorders in the third National Health and Nutrition Survey. Biol. Psychiatry 72, 290 –295.

Perlis, R.H., Miyahara, S., Marangell, L.B., Wisniewski, S.R., Ostacher, M., DelBello, M.P., Bowden, C.L., Sachs, G.S., Nierenberg, A.A., 2004. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol. Psychiatry 55, 875 –881.

Piccinini, A.M., Midwood, K.S., 2010. DAMPening inflammation by modulating TLR signalling. Mediat. In flamm., 2010 .

Ragnarsdóttir, B., Jönsson, K., Urbano, A., Grönberg-Hernandez, J., Lutay, N., Tammi, M., Gustafsson, M., Lundstedt, A.-C., Leijonhufvud, I., Karpman, D., Wullt, B., Truedsson, L., Jodal, U., Andersson, B., Svanborg, C., 2010. Toll-like receptor 4 promoter polymorphisms: common TLR4 variants may protect against severe urinary tract infection. Plos One 5, e10734 .

Rao, J.S., Harry, G.J., Rapoport, S.I., Kim, H.W., 2010. Increased excitotoxicity and neuroin flammatory markers in postmortem frontal cortex from bipolar disorder patients. Mol. Psychiatry 15, 384 –392.

Rivest, S., 2009. Regulation of innate immune responses in the brain. Nat. Rev. Immunol. 9, 429 –439.

Sato, K., Yoshimura, A., Kaneko, T., Ukai, T., Ozaki, Y., Nakamura, H., Li, X., Matsumura, H., Hara, Y., Ogata, Y., 2012. A single nucleotide polymorphism in 3′-untranslated region contributes to the regulation of Toll-like receptor 4 translation. J. Biol. Chem. 287, 25163 –25172.

Schürhoff, F., Bellivier, F., Jouvent, R., Mouren-Siméoni, M.C., Bouvard, M., Allilaire, J.F., Leboyer, M., 2000. Early and late onset bipolar disorders: two different forms of manic-depressive illness? J. Affect. Disord 58, 215 –221.

Severance, E.G., Alaedini, A., Yang, S., Halling, M., Gressitt, K.L., Stallings, C.R., Origoni, A.E., Vaughan, C., Khushalani, S., Leweke, F.M., Dickerson, F.B., Yolken, R.H., 2012. Gastrointestinal inflammation and associated immune activation in schizophrenia. Schizophr. Res. 138, 48 –53.

Shen, X., Shi, R., Zhang, H., Li, K., Zhao, Y., Zhang, R., 2010. The Toll-like receptor 4 D299G and T399I polymorphisms are associated with Crohn's disease and ulcerative colitis: a meta-analysis. Digestion 81, 69 –77.

Sirisinha, S., 2011. Insight into the mechanisms regulating immune homeostasis in health and disease. Asian Pac. J. Allergy Immunol. 29, 1 –14.

Söderlund, J., Olsson, S.K., Samuelsson, M., Walther-Jallow, L., Johansson, C., Erhardt, S., Landén, M., Engberg, G., 2011. Elevation of cerebrospinal fluid interleukin-1ß in bipolar disorder. J. Psychiatry Neurosci. 36, 114 –118.

Song, C., Chen, L.Z., Zhang, R.H., Yu, X.J., Zeng, Y.X., 2006. Functional variant in the 3untranslated region of Toll-like receptor 4 is associated with nasopharyngeal carcinoma risk. Cancer Biol. Ther. 5, 1285 –1291.

Suh, H.S., Zhao, M.L., Choi, N., Belbin, T.J., Brosnan, C.F., Lee, S.C., 2009. TLR3 and TLR4 are innate antiviral immune receptors in human microglia: role of IRF3 in modulating antiviral and inflammatory response in the CNS. Virology 392, 246–259.

Tal, G., Mandelberg, A., Dalal, I., Cesar, K., Somekh, E., Tal, A., Oron, A., Itskovich, S., Ballin, A., Houri, S., Beigelman, A., Lider, O., Rechavi, G., Amariglio, N., 2004. Association between common Toll-like receptor 4 mutations and severe respiratory syncytial virus disease. J. Infect. Dis. 189, 2057 –2063.

Tedla, Y., Shibre, T., Ali, O., Tadele, G., Woldeamanuel, Y., Asrat, D., Aseffa, A., Mihret, W., Abebe, M., Alem, A., Medhin, G., Habte, A., 2011. Serum antibodies to Toxoplasma gondii and Herpesvidae family viruses in individuals with schizophrenia and bipolar disorder: a case-control study. Ethiop. Med. J. 49, 211–220.

Török, H.P., Glas, J., Tonenchi, L., Mussack, T., Folwaczny, C., 2004. Polymorphisms of the lipopolysaccharide-signaling complex in inflammatory bowel disease: association of a mutation in the Toll-like receptor 4 gene with ulcerative colitis. Clin. Immunol. 112, 85 –91.

Torrey, E.F., Rawlings, R.R., Ennis, J.M., Merrill, D.D., Flores, D.S., 1996. Birth seasonality in bipolar disorder, schizophrenia, schizoaffective disorder and stillbirths. Schizophr. Res. 21, 141 –149.

Tsilidis, K.K., Helzlsouer, K.J., Smith, M.W., Grinberg, V., Hoffman-Bolton, J., Clipp, S. L., Visvanathan, K., Platz, E.A., 2009. Association of common polymorphisms in IL10, and in other genes related to inflammatory response and obesity with colorectal cancer. Cancer Causes Control 20, 1739 –1751.

Van der Graaf, C.A.A., Netea, M.G., Morré, S.A., Den Heijer, M., Verweij, P.E., Van der Meer, J.W.M., Kullberg, B.J., 2006. Toll-like receptor 4 Asp299Gly/Thr399Ile polymorphisms are a risk factor for Candida bloodstream infection. Eur. Cytokine Netw. 17, 29 –34.

Venkatasubramanian, G., Debnath, M., 2013. The TRIPS (Toll-like receptors in immuno-inflammatory pathogenesis) hypothesis: a novel postulate to understand schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 44, 301–311.

Wang, J., Zhang, W., Liu, H., Wang, D., Wang, W., Li, Y., Wang, Z., Wang, L., Zhang, W., Huang, G., 2010. Parvovirus B19 infection associated with Hashimoto's thyroiditis in adults. J. Infect. 60, 360 –370.

Wang, L.Z., Yu, J.T., Miao, D., Wu, Z.C., Zong, Y., Wen, C.Q., Tan, L., 2011. Genetic association of TLR4/11367 polymorphism with late-onset Alzheimer's disease in a Han Chinese population. Brain Res. 1381, 202 –207.

Yolken, R.H., Torrey, E.F., 2008. Are some cases of psychosis caused by microbial agents? A review of the evidence. Mol. Psychiatry 13, 470 –479.

Yu, J.T., Miao, D., Cui, W.Z., Ou, J.R., Tian, Y., Wu, Z.C., Zhang, W., Tan, L., 2012. Common variants in toll-like receptor 4 confer susceptibility to Alzheimer's disease in a Han Chinese population. Curr. Alzheimer Res. 9, 458 –466.

Zhang, Q., Qian, F.H., Zhou, L.F., Wei, G.Z., Jin, G.F., Bai, J.L., Yin, K.S., 2011. Polymorphisms in toll-like receptor 4 gene are associated with asthma severity but not susceptibility in a Chinese Han population. J. Investig. Allergol. Clin. Immunol. 21, 370 –377.