UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: PSIQUIATRIA

TESE DE DOUTORADO

ASPECTOS CLÍNICOS E EPIDEMIOLÓGICOS ASSOCIADOS ÀS COMORBIDADES CLÍNICAS EM PACIENTES COM TRANSTORNO BIPOLAR

Fabiano Alves Gomes

Orientador: Prof. Dr. Flávio Kapczinski

Porto Alegre, Janeiro de 2012

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

Porto Alegre, Janeiro de 2012

Ao meu filho Ricardo.

Wisdom begins in wonder.

Sócrates

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LISTA DE ABREVIATURAS

BD – do inglês *bipolar disorder*

BRN-BD – do inglês *Brazilian Research Network in Bipolar Disorder*

BMI – do inglês *body mass index*

CI – do inglês *confidence interval*

CID 10 – Classificação Internacional de Doenças – 10ª. Edição

CIRS – do inglês *Cumulative Illness Rating Scale*

DCNT – doenças crônicas não-transmissíveis

DSM IV – do inglês *Diagnostic and Statistical Manual of Mental Disorders – 4th Edition*

EUA – Estados Unidos da América

PROMAN – Programa de Transtorno Bipolar do IPq-USP

PROTAHBI – Programa de Transtorno Bipolar do HCPA-UFRGS

OR – do inglês *odds ratio*

SD – do inglês *standard deviation*

SM – síndrome metabólica

TB – transtorno bipolar

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RESUMO

O transtorno bipolar (TB) é uma doença crônica e debilitante frequentemente associada a comorbidades psiquiátricas e múltiplas doenças clínicas. Estudos recentes têm apontado para um impacto significativo das condições médicas gerais no curso e prognóstico do TB, bem como há um corpo crescente de evidências demonstrando as influências dos episódios de humor e de seu tratamento na incidência e morbidade das comorbidades físicas. No entanto, os estudos ainda são iniciais e ainda há uma carência de dados epidemiológicos e clínicos acerca dessas associações, particularmente no nosso meio. A presente tese é composta por três estudos: 1) um estudo da prevalência e dos correlatos clínicos associados a fatores de risco cardiovascular em duas amostras de pacientes bipolares; 2) uma avaliação da associação entre obesidade e suicidalidade em pacientes bipolares; 3) um estudo da prevalência e dos fatores associados às comorbidades clínicas em pacientes bipolares. Em conjunto, os resultados dos estudos apontam para uma elevada prevalência de fatores de risco cardiovasculares e condições médicas gerais em pacientes bipolares, além da relação entre doenças físicas e características demográficas, clínicas e fatores de gravidade, tais como idade, gênero, tempo de duração da doença, suicidalidade, padrão de uso de medicação e comorbidades psiquiátricas. Nossos achados fornecem dados adicionais para a compreensão da relação entre transtorno bipolar e comorbidades clínicas, enfatizando a necessidade tanto de uma abordagem mais ampla e integral do transtorno quanto do desenvolvimento de estratégias mais eficazes de prevenção e tratamento.

ABSTRACT

Bipolar disorder (BD) is a chronic and debilitating illness frequently associated to multiple psychiatric comorbidities and clinical diseases. Recent studies have pointed out the significant impact o general medical conditions on BD course and prognosis and there is a growing body of evidence showing the influence of mood episodes and their treatment on incidence and morbidity of medical comorbidities. However, most studies are preliminary and there is still a lack of epidemiological and clinical data about these relationships, particularly in Brazil. This thesis comprises three studies: 1) a study on the prevalence and clinical correlates of cardiovascular risk factors in two samples of BD patients; 2) an evaluation about the association of obesity and suicidality in patients with BD; 3) a study on the prevalence and clinical correlates of clinical comorbidities in BD patients. Taken together, the results show an elevated prevalence of cardiovascular risk factors and general medical conditions in BD patients and stress the associations among physical disease, demographic and clinical variables and correlates of severity such as age, gender, duration of illness, medication prescription pattern and psychiatric comorbidities. Our findings provide additional data to the undestanding of the relationship between BD and clinical comorbidities emphasizing the need for both a comprehensive approach to BD and the development of more effective prevention and treatment strategies.

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1. INTRODUÇÃO

O transtorno bipolar (TB) é uma doença conhecida desde a Antiguidade que tem como característica principal a recorrência dos episódios de humor alterado, particularmente a mania e a hipomania, além dos sintomas depressivos, que dominam o quadro clínico na maioria dos pacientes (Belmaker, 2004).

A prevalência do TB na população em geral é de 1,3 a 1,5%, acometendo ambos os sexos de maneira semelhante, com exceção dos quadros de ciclagem rápida, que parecem ser mais prevalentes em mulheres. A idade de início é variável e o pico de incidência é por volta dos 15 a 24 anos. O número de episódios durante a vida tende a ser superior em comparação ao transtorno depressivo maior e o intervalo entre os episódios tende a diminuir com a idade (Müller-Oerlinghausen et al, 2002).

Os transtornos de humor constituem um grande problema de saúde pública, não somente pela significativa perda de funcionalidade e piora da qualidade de vida associadas a eles, mas também pela estreita relação com outras doenças clínicas (Fenn et al, 2005). O TB não foge a esta regra, apresentando um alto índice de comorbidades, tanto com outros transtornos psiquiátricos quanto com as mais variadas doenças físicas, resultando em aumento significativo da morbi-mortalidade (Kupfer, 2005; Laursen et al, 2007).

Estudos recentes têm apontado para uma significativa redução de anos de vida em pacientes com transtornos mentais. Nos EUA, por exemplo, pode haver uma perda potencial de até 25 anos, um aumento de 10-15 anos quando se compara com os dados do início dos anos 90. Coortes de pacientes

europeus têm mostrado dados semelhantes (Fleischhacker et al, 2008). Assim, o foco de atenção - tanto das pesquisas científicas quanto do cuidado - dos pacientes com transtornos psiquiátricos tem se expandido para uma atenção mais ampla à saúde geral e ao bem estar físico.

Além de maior mortalidade, os diversos transtornos mentais são associados a um alto grau de incapacidade. Particularmente, os pacientes com transtornos de humor costumam apresentar elevados índices de perda de funcionalidade, com múltiplas dificuldades em relação ao desempenho de tarefas simples do dia a dia, interação social e capacidade para o exercício de funções laborativas. Tais disfunções podem ser, em parte, atribuídas às manifestações psíquicas e comportamentais do TB, mas também devem ser considerados outros aspectos relacionados à presença de outras doenças, especialmente condições médicas gerais – tais como as doenças cardiovasculares e endócrino-metabólicas – que por si só são causas de significativa morbidade (Viron & Stern, 2010).

Desta forma, há uma necessidade crescente de dados sobre a prevalência e os diversos fatores associados às comorbidades clínicas em pacientes bipolares, o que pode contribuir para uma compreensão mais ampla da fisiopatologia, manifestações clínicas, curso e prognóstico da doença. Em nosso meio os estudos são escassos e constituem uma nova e promissora oportunidade de pesquisa.

2. FUNDAMENTAÇÃO TEÓRICA

2.1. O conceito de comorbidade clínica

A coexistência de múltiplas doenças em um mesmo paciente é um desafio para os profissionais de saúde. Tal situação é cada vez mais frequente e tanto o acesso aos serviços quanto os custos necessários para uma atenção integral têm aumentado consideravelmente (van den Akker et al, 1998). Tem havido um maior interesse no estudo do conceito de comorbidade e nos construtos relacionados, pois estão diretamente associados a piores desfechos em saúde, incluindo maiores taxas de mortalidade, pior qualidade de vida e maior incapacidade (Fortin et al, 2004).

A relação que se estabelece entre as várias condições coexistentes pode ser baseada em vários parâmetros, mesmo quando se avalia o paciente apenas em nível individual: 1) na natureza das condições clínicas; 2) na importância relativa das condições coexistentes; 3) na cronologia da apresentação clínica e; 4) na expansão do conceito para situações mais complexas.

A natureza das condições clínicas que são avaliadas varia bastante, incluindo doenças bem definidas, transtornos, síndromes e situações psicossociais, geralmente derivados das classificações diagnósticas como a CID 10 e o DSM IV. A diferenciação entre quais condições clínicas estão sendo consideradas comórbidas é essencial, pois a ocorrência de duas doenças definidas de maneira muito elástica pode estar relacionada simplesmente à ineficiência dos sistemas classificatórios. Um exemplo clássico é a relação entre depressão e ansiedade, que, caso sejam consideradas como parte de um

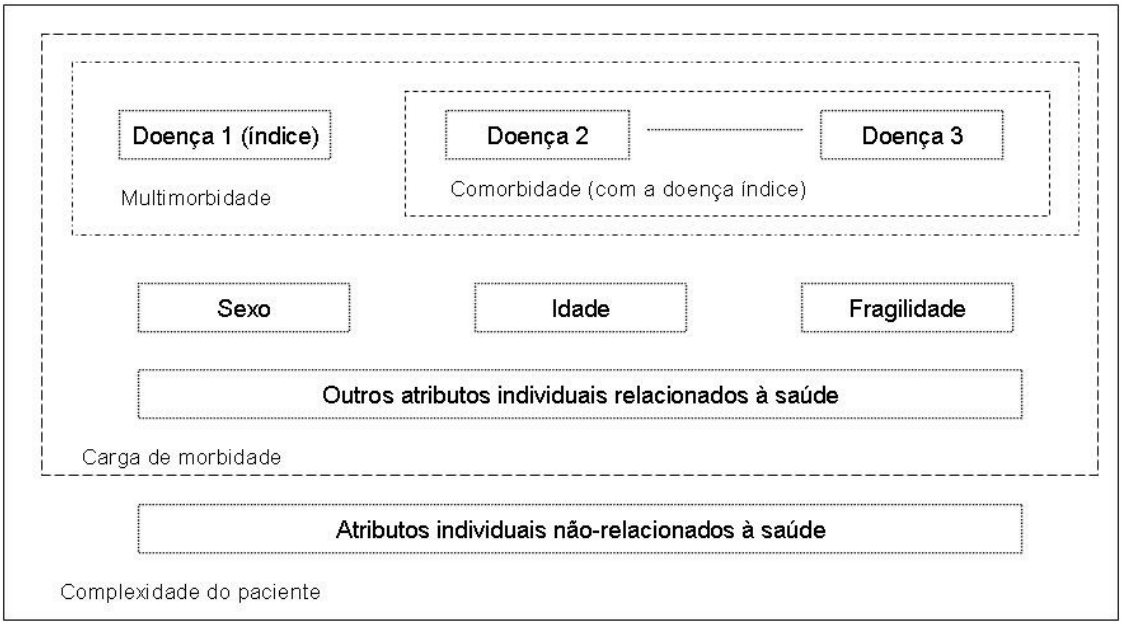
espectro, não devem ser diagnosticadas como comórbidas em um paciente apresentando ambos os transtornos (Valderas et al, 2009).

A segunda distinção está relacionada à importância relativa das condições clínicas. A definição clássica de Feinstein (1970) do termo comorbidade: "*qualquer entidade adicional distinta que existiu ou pode acontecer durante o curso clínico de um paciente que tem a doença índice em estudo*" leva em consideração que há uma doença índice e outras que podem estar relacionadas a ela. Porém, nem sempre há uma definição clara de qual deve ser a doença índice e qual a comórbida, o que pode variar dependendo do contexto – especialidade do médico, por exemplo – ou de qual doença levou o paciente ao tratamento naquele momento específico. O termo multimorbidade (Bayliss et al, 2008), conceituado como "*a ocorrência simultânea de múltiplas doenças agudas ou crônicas em uma mesma pessoa*", tem sido utilizado para essas situações em que não há possibilidade ou mesmo interesse em fazer referência a uma condição índice.

A terceira distinção está relacionada à questão temporal. É comum a tentativa de identificar se ambas as doenças ocorrem simultaneamente ou ao longo da vida do indivíduo ou, ainda, se há uma sequência na qual uma condição clínica surge após a outra. Tal critério é importante devido às implicações diretas quando se consideram fatores etiológicos e associações causais.

Por fim, outro aspecto importante da comorbidade é a relação com o que se costuma chamar de carga da doença (em inglês *burden of disease*). A presença de múltiplas doenças tem um impacto direto na carga total de disfunção fisiológica e na reserva funcional do indivíduo e, consequentemente,

pacientes com múltiplas comorbidades são mais complexos e exigem mais atenção dos serviços de saúde, tanto em relação à utilização dos serviços e aos custos associados, quanto às abordagens terapêuticas realmente efetivas (Valderas et al, 2009). A figura 1 apresenta um resumo da conceituação apresentada acima.



Comorbidade: presença de doenças adicionais em relação a uma doença índice em um indivíduo

Multimorbidade: presença de múltiplas doenças em um indivíduo

Carga de morbidade: impacto total da diferentes doenças em um indivíduo, levando em consideração a gravidade de cada uma

Complexidade do paciente: impacto total das diferentes doenças em um indivíduo levando em consideração a gravidade de cada uma e outros atributos não relacionados diretamente à saúde.

Figura 1. Construtos relacionados à comorbidade

2.2. Doenças clínicas e morbi-motalidade dos transtornos psiquiátricos

Os estudos recentes que buscaram avaliar a carga global das doenças têm apontado para uma significativa contribuição dos transtornos mentais para a incapacidade e perda de anos de vida produtiva da população mundial. Apesar de variar de acordo com o nível de desenvolvimento do país, as doenças cardiovasculares, endócrinas e vários transtornos mentais graves são listados entre as principais causas de morbi-mortalidade, com uma tendência de crescimento ainda maior destes últimos nas próximas décadas (WHO, 2008). No Brasil, cerca de 72% das mortes em 2007 foram associadas às doenças crônicas não-transmissíveis (DCNT); em relação à morbidade, os dados são ainda mais impressionantes, pois os transtornos neuropsiquiátricos - especialmente os transtornos de humor, as psicoses e os transtornos relacionados ao uso de álcool - são os maiores responsáveis pela incapacidade e anos de vida perdidos associados às DCNT (Schmidt et al, 2011).

Pacientes com transtornos mentais mais graves são negligenciados em termos de assistência médica geral, embora apresentem taxas elevadas de outras doenças. O comparecimento às consultas e a adesão ao tratamento são em geral baixos e doenças clínicas não-detectadas ou diagnosticadas em estágios avançados são mais comuns (Bruga et al, 1989; McIntyre et al, 2007; Oud & Meyboom-de-Jong, 2009). Em extensa revisão bibliográfica, Harris e Barraclough (1988) concluíram que todos os transtornos mentais apresentam risco aumentado de morte prematura. Um estudo sueco encontrou expectativa de vida diminuída em todas as nove categorias diagnósticas psiquiátricas pesquisadas; o achado deu-se em ambos os sexos e em praticamente todas as faixas etárias (Hannerz et al, 2001). Os transtornos do humor também se

associam a taxas de mortalidade elevadas, sendo que uma revisão recente da literatura concluiu que, em estudos com amostras superiores a 2500 indivíduos, a taxa de mortalidade padronizada por causas naturais encontra-se elevada de 35% a duas vezes (Roshanaei-Moghaddam & Katon, 2009).

Considerando-se que o aumento da mortalidade em pacientes psiquiátricos se deve principalmente a causas naturais, é de se esperar que a prevalência de doenças não-psiquiátricas seja elevada nessa população. Em pacientes esquizofrênicos e bipolares, a prevalência de um largo espectro de doenças, como diabetes, síndrome metabólica, doenças coronarianas e doença pulmonar obstrutiva crônica é elevada (Oud & Meyboom-de-Jong, 2009; McIntyre et al, 2007; Krishnan, 2005; Carney & Jones, 2006). Assim, além da significativa carga de doença associada ao transtorno mental, a presença de comorbidades clínicas confere um prejuízo adicional a esses pacientes (Guo et al, 2008).

2.3. Transtorno bipolar e comorbidades clínicas

A elevada prevalência de doenças clínicas em pacientes bipolares tem sido amplamente documentada na literatura (Krishnan, 2005). A maior parte dos estudos tem demonstrado um aumento significativo dos fatores de risco para outras doenças, tais como sedentarismo, tabagismo e dieta inadequada, além de diversas condições médicas, particularmente alterações metabólicas, doenças cardiovasculares e neurológicas, em pacientes bipolares, quando comparados a controles sem a doença.

2.3.1. Obesidade

Estudos epidemiológicos realizados com a população geral têm evidenciado uma epidemia de obesidade nas últimas décadas. Da mesma forma, a alta prevalência da obesidade está documentada nos pacientes com transtorno bipolar e frequentemente é um complicador para o tratamento. Estudos recentes têm apontado que mesmo pacientes bipolares que nunca receberam tratamento farmacológico apresentam taxas mais elevadas de sobrepeso e obesidade quando comparados a outras populações de pacientes psiquiátricos e à população geral (Maina et al, 2008; Taylor et al, 2008). Além disso, o ganho de peso associado ao tratamento é um importante fator de não-adesão e a presença de obesidade está associada à maior morbidade clínica e piores desfechos psiquiátricos (Wildes et al, 2006; Calkin et al, 2009).

Pacientes bipolares obesos têm maiores riscos de apresentar outros correlatos de obesidade, tais como hipertensão e diabetes (McElroy et al, 2002), apresentam maior número de episódios de humor, episódios mais difíceis de tratar e maiores riscos de recaída (Fagiolini et al, 2003), além de maior número de tentativas de suicídio ao longo da vida e mais ideação suicida no momento da avaliação (Fagiolini et al, 2004; Wang et al, 2006). Apesar das causas exatas da obesidade em pacientes bipolares ainda permanecerem obscuras, há evidência suficiente da relevância dos fatores biológicos, psicológicos e sócio-demográficos no desencadeamento e manutenção do quadro. Mesmo que para um paciente em particular haja uma maior relevância de um fator sobre outro, em última instância serão afetados o comportamento alimentar e a atividade física, principais determinantes da obesidade (Wildes et al, 2006).

2.3.2. Diabetes

Assim como o transtorno bipolar, o diabetes é uma doença conhecida há séculos, com um impacto bastante significativo nos dias atuais. De uma maneira geral, pode ser conceituado como um conjunto de alterações no metabolismo nutricional resultando em anormalidades nos níveis circulantes de glicose e, frequentemente, de lipídeos. A doença é causada por basicamente dois mecanismos: diminuição da secreção de insulina acompanhada ou não de resistência à ação da insulina. O tipo mais comum de diabetes, chamado de diabetes tipo 2, está intimamente relacionado à obesidade e é visto como um dos mais significativos problemas de saúde pública atual (Campbell, 2009).

Os dados disponíveis indicam uma prevalência aumentada de alterações no metabolismo da glicose em algumas populações psiquiátricas, particularmente os pacientes com transtornos do humor e psicose. Tais observações são anteriores aos modernos estudos epidemiológicos e à ampla disponibilidade de tratamento psicofarmacológico, indicando um possível mecanismo fisiopatológico comum. Os relatos dessas alterações não se limitaram apenas aos pacientes, mas também aos parentes de primeiro grau, que apresentavam maiores taxas de resistência à insulina, intolerância à glicose e diabetes mellitus quando comparados a controles (De Hert et al, 2009).

Estudos com populações clínicas e comunitárias que utilizaram diversas técnicas de avaliação do metabolismo da glicose confirmaram os achados dos estudos iniciais (McIntyre et al, 2005). Além disso, o diabetes mellitus e o transtorno bipolar apresentam características fisiopatológicas

comuns em nível genético, molecular, celular, fisiológico e comportamental, as quais podem ajudar a explicar o alto grau de comorbidade entre as duas entidades clínicas (Brietzke et al, 2011a).

2.3.3. Síndrome metabólica

O conceito de síndrome metabólica (SM) é relativamente antigo, mas tem despertado interesse crescente nos últimos anos. O conjunto de alterações metabólicas, todos fatores de risco para doença cardiovascular, tem aumentado sua prevalência de forma importante nas duas últimas décadas, associado à epidemia global de obesidade e diabetes (Eckel et al, 2005).

Apesar das diversas definições correntes da síndrome, suas manifestações incluem intolerância à glicose (diabetes tipo 2, diminuição da tolerância à glicose e alteração na glicemia de jejum), resistência à insulina, obesidade central, dislipidemia e hipertensão. Estudos iniciais relataram uma alta prevalência da SM em pacientes bipolares em diversas populações clínicas, variando entre 18,3% e 49%, porcentagens consideravelmente maiores do que as da população de referência nos diversos países em que foram realizados os inquéritos (Fagiolini et al, 2005; Yumru et al, 2007; Teixeira e Rocha, 2007; Cardenas et al, 2008; Garcia-Portilla et al, 2008; Van Winkel et al, 2008, Gomes et al, 2010). Uma revisão recente de McIntyre e colaboradores (2010) apontou que além da maior prevalência de SM em pacientes bipolares, a circunferência da cintura costuma ser o parâmetro metabólico mais comumente alterado. Além disso, pacientes com a comorbidade apresentam doenças com apresentação mais complexa, menor resposta ao tratamento e

curso e prognóstico menos favoráveis. Desta forma, a presença de SM parece ser um marcador de gravidade da doença bipolar. Na maioria dos estudos, o uso de antipsicóticos atípicos e o uso de múltiplas medicações psiquiátricas estiveram associados à maior prevalência de síndrome metabólica.

2.3.4. Doenças cardiovasculares

A associação entre doenças cardiovasculares e transtornos do humor, particularmente a depressão, é bem estabelecida (Musselman et al, 1998). Evidências crescentes indicam que a população de pacientes bipolares também é afetada de forma diferenciada, tanto da população em geral quanto de outros transtornos psiquiátricos, por doenças cardiovasculares (Newcomer, 2006). A combinação transtorno bipolar/doença cardiovascular está intimamente relacionada não somente a um pior prognóstico clínico de ambas as condições, mas também a maior mortalidade (Tsai et al, 2005; Laursen et al, 2007).

Como já foi dito anteriormente, os principais estudos relacionados às comorbidades clínicas têm priorizado os chamados transtornos mentais graves. Nessas populações, têm sido identificadas elevadas prevalências de fatores de risco para doenças cardiovasculares, bem como uma alta taxa de doença já estabelecida, principalmente acidente vascular cerebral, doença coronariana, dislipidemia e hipertensão arterial (Newcomer, 2006). Em um estudo recente utilizando uma amostra representativa da população americana, pacientes bipolares do tipo I apresentaram risco quase cinco vezes maior de doença cardiovascular quando comparados a controles sadios e 1,8 vezes maior

quando comparados com pacientes com depressão maior. Em relação à hipertensão arterial, os pacientes bipolares apresentaram risco 2,38 vezes maior que os controles e 1,44 vezes maior que pacientes deprimidos (Goldstein et al, 2009).

Apesar do importante influência do uso de antipsicóticos, principalmente de segunda geração, na associação transtornos mentais graves/doença cardiovascular (Correl et al, 2006; Mackin et al, 2007), cabe ressaltar que estudos comparativos têm demonstrado que pacientes bipolares apresentam risco tão grande, se não maior, de apresentarem eventos cardiovasculares adversos quanto pacientes esquizofrênicos (Birkenaes et al, 2007, Kilbourne et al, 2007).

2.3.5. Outras doenças clínicas

Apesar das pesquisas atuais terem seu foco nas doenças metabólicas e cardiovasculares, os pacientes com transtorno bipolar estão, como qualquer indivíduo, propensos a desenvolver os mais diversos tipos de problemas clínicos. Existem, porém, estudos que demonstram uma maior prevalência de algumas doenças na população bipolar. Algumas dessas doenças estão listadas na tabela 1.

Tabela 1. Doenças clínicas comumente comórbidas com o transtorno bipolar

Doença clínica	Prevalência atual (%)	Variação entre os estudos (%)
Artrite	14	12 - 16
Asma	3	-
Doenças cardiovasculares	23	11 - 35
Neoplasias	2	1 - 3
Doença pulmonar obstrutiva cônica	9	8 - 11
Demência	3	-
Doenças dermatológicas	7	-
Diabetes mellitus	10	4 - 17
Dislipidemias	29	23 - 41
Doenças endócrinas	23	-
Doenças gastrointestinais	12	7 - 18
Doenças genito-urinárias	9	-
Enxaqueca	4	-
Doença hepática	17	-
Hepatite C	7	2 - 14
Infecção pelo HIV/AIDS	21	-
Hipertensão arterial	26	2 - 39
Dor lombar	15	-
Doenças músculo-esqueléticas	23	-
Obesidade	31	19 - 49
Pancreatite	2	1 - 4
Doença de Parkinson	0,05	-
Doenças pulmonares	7	1 - 13
Doenças renais	2	1 - 2
Acidente vascular cerebral	2	1 - 2
Doenças tireoidianas	12	7 - 19

Adaptado de McIntyre et al, 2007

Além dos efeitos metabólicos das medicações utilizadas no tratamento do transtorno bipolar – antipsicóticos, antidepressivos e estabilizadores do humor – tais medicações têm alguns efeitos particulares em determinados sistemas. Existem algumas evidências de que alterações tireoidianas podem fazer parte do mecanismo fisiopatológico do transtorno bipolar, mas, além disso, o tratamento com lítio está relacionado à disfunção da tireóide, usualmente resultando em hipotireoidismo. Doenças renais, incluindo insuficiência renal crônica, também podem resultar dos efeitos nefrotóxicos do lítio (McIntyre et al, 2007).

Cabe, ainda, ressaltar a importância de algumas doenças clínicas tais como os distúrbios respiratórios e neurológicos. A prevalência de doença pulmonar obstrutiva crônica e de asma, por exemplo, é significativa, tendo em vista o grande número de pacientes bipolares tabagistas e que fazem uso de substâncias ilícitas como maconha, cocaína e crack. Doenças neurológicas como a enxaqueca, esclerose múltipla e epilepsia também são mais prevalentes em pacientes bipolares (Krishnan, 2005; Brietzke et al 2011b).

2.4. Impacto das comorbidades clínicas no transtorno bipolar

A maior parte dos cuidados recebidos pelos pacientes com transtornos mentais tem como foco o controle dos sintomas psiquiátricos, o que pode ser responsável pela alta taxa de não-reconhecimento dessas doenças nessa população (Evans & Charney, 2003). Os pacientes bipolares têm uma alta taxa de utilização de serviços de saúde, incluindo-se consultas ambulatoriais, internações, uso de psicofármacos e intervenções psicossociais

(Frye et al, 2005; Ohsfeldt et al, 2007). Estudos têm demonstrado que boa parte dos custos de tratamento está relacionada às comorbidades, particularmente às doenças crônicas apresentadas pelos pacientes, tais como diabetes, hipertensão e doenças cardiovasculares. (Guo et al, 2008).

Evidências recentes indicam que o uso de antipsicóticos de segunda geração e a polifarmacoterapia estão mais associados ao diagnóstico de comorbidades clínicas, principalmente de natureza metabólica. Outros fatores associados a uma maior prevalência de doenças físicas são: idade avançada, menor escolaridade e maior tempo de duração da doença (Thompson et al, 2006; Soreca et al, 2008). Os estudos tiveram seu foco inicial na esquizofrenia, mas a expansão do uso de antipsicóticos atípicos no tratamento do transtorno bipolar trouxe consigo não só os benefícios, mas também os riscos associados a essas medicações.

Além do potencial efeito das medicações, estudos recentes com pacientes bipolares têm indicado um papel importante de mediadores fisiológicos, principalmente os hormônios e as citocinas, na fisiopatologia da doença. Disfunções nestes sistemas também estão presentes nas principais comorbidades clínicas – particularmente cardiometabólicas - e parecem ser responsáveis tanto pela gênese quanto pela perpetuação de processos patológicos tanto celulares quanto sistêmicos (Grande et al, 2011).

Diversos estudos têm destacado a associação entre as comorbidades clínicas e marcadores de gravidade, tais como suicidalidade – principalmente em pacientes obesos (Fagiolini et al, 2004); sintomatologia mais grave (Kemp et al, 2010); e pior curso da doença – ex. início precoce, ciclagem rápida, maior prevalência de comorbidades psiquiátricas e uso de substâncias

(Kemp et al, 2009; Magalhães et al, 2011). Embora ainda incipientes, esses resultados apontam para a necessidade de se considerar não somente as variáveis clínicas da doença, mas também a presença e o impacto das doenças físicas na avaliação global do paciente com TB.

Apesar dos múltiplos avanços em relação à fisiopatologia e clínica do transtorno bipolar, incluindo a contribuição significativa dos grupos de pesquisa brasileiros, ainda há poucos dados sobre a prevalência e os fatores associados às comorbidades clínicas em pacientes bipolares no nosso país. Além das diferenças regionais em relação ao acesso a tratamento, uso de medicações e curso clínico do TB (Kapczinski & Gentil, 2005), a prevalência dos fatores de risco e das próprias comorbidades clínicas também tende a ser diferente em relação aos países desenvolvidos, onde é realizada a maioria dos estudos até o momento.

3. OBJETIVOS

3.1. Objetivo Geral

- Estudar os aspectos clínicos e epidemiológicos associados às comorbidades clínicas em uma amostra de pacientes brasileiros com transtorno bipolar.

3.2. Objetivos Específicos

- Avaliar a prevalência e as variáveis clínicas associadas a fatores de risco cardiovascular em pacientes com transtorno bipolar.

- Estudar a associação entre obesidade e suicidalidade em pacientes com transtorno bipolar.

- Avaliar a prevalência e as variáveis clínicas associadas à presença de múltiplas comorbidades em pacientes com transtorno bipolar.

4. CONSIDERAÇÕES ÉTICAS

Todos os pacientes assinaram termo de consentimento informado previamente ao início dos estudos.

Foi assegurada a ausência de vinculação da concordância em participar do estudo com a continuidade do atendimento no programa de atendimento de transtorno de humor bipolar (PROTAHBI) no Hospital de Clínicas de Porto Alegre.

Os estudos foram aprovados pelos Comitês de Ética em Pesquisa das instituições envolvidas – Hospital de Clínicas de Porto Alegre, Faculdade de Medicina da Universidade de São Paulo e Universidade Federal de Santa Maria.

5. METODOLOGIA

Os estudos foram realizados no Laboratório de Psiquiatria Molecular do Hospital de Clínicas de Porto Alegre. Por meio de parcerias com outros grupos de pesquisa, incluindo a Rede Brasileira de Pesquisa em Transtorno Bipolar, foi possível aumentar o tamanho das amostras para o primeiro e segundo estudos. Promoveu-se, ainda, intercâmbio com pesquisadores de outras instituições, incluindo colegas da Universidade de Santa Maria, Universidade de São Paulo e Universidade de Melbourne- Austrália. A descrição dos materiais e métodos utilizados em cada estudo será apresentada na seção metodologia de cada artigo.

6. ARTIGOS

6.1. Artigo 1

Cardiovascular risk factors in outpatients with bipolar disorder: a report from the Brazilian Research Network in Bipolar Disorder.

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TITLE PAGE

Title: Cardiovascular risk factors in outpatients with bipolar disorder: a report from the Brazilian Research Network in Bipolar Disorder.

Running Title: Cardiovascular risk factors in BD.

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ABSTRACT

BACKGROUND: Bipolar disorder (BD) is associated with significant morbidity and mortality due to comorbid general medical conditions, particularly cardiovascular disease. This study is the first report of the Brazilian Research Network in Bipolar Disorder (BRN-BD) that aims to evaluate the prevalence and clinical correlates of cardiovascular risk factors among Brazilian patients with BD.

METHODS: A cross-sectional study of 159 patients with DSM-IV BD, 18 years or older, consecutively recruited from the Bipolar Research Program (PROMAN) in São Paulo and the Bipolar Disorder Program (PROTAHBI) in Porto Alegre. Clinical, demographic, anthropometrical and metabolic variables were systematically assessed.

RESULTS: High rates of smoking (27%), physical inactivity (64.9%), alcohol use disorders (20.8%), elevated fasting glucose (26.4%), diabetes (13.2%), hypertension (38.4%), hypertrygliceridemia (25.8%), low HDL-cholesterol (27.7%), general (38.4%) and abdominal obesity (59.1%) were found in the sample. Male patients were more likely to present alcohol use disorders, diabetes and hypertrygliceridemia and female patients showed higher prevalence of abdominal obesity. Variables such as medication use pattern, alcohol use disorder and physical activity were associated with selected cardiovascular risk factors in the multivariate analysis.

CONCLUSION: This report from the BRN-BD provides new data regarding prevalence rates and associated cardiovascular risk factors in Brazilian

outpatients with BD. There is a need for increasing both awareness and recognition of metabolic and cardiovascular diseases in this patient population.

KEYWORDS: bipolar disorder; cardiovascular risk factors; comorbidity

RESUMO

INTRODUÇÃO: O Transtorno Bipolar (TB) é associado a uma significativa morbi-mortabildade devido a comorbidades médicas gerais, particularmente doenças cardiovasculares. Este estudo é o primeiro relato da Rede Brasileira de Pesquisa em Transtorno Bipolar que tem por objetivo avaliar a prevalência e os correlatos clínicos de fatores de risco cardiovascular entre pacientes brasileiros com TB.

MÉTODOS: Foi realizado um estudo transversal com 159 pacientes bipolares diagnosticados pelos critérios do DSM IV, com idade acima de 18 anos, recrutados de forma consecutiva no PROMAN em São Paulo e no PROTAHBI em Porto Alegre. Variáveis clínicas, demográficas, antropométricas e metabólicas foram avaliadas de maneira sistemática.

RESULTADOS: Foram encontradas altas taxas de tabagismo (27%), sedentarismo (64,9%), transtorno por uso de álcool (20,8%), hiperglicemia (26,4%), diabetes (13,2%), hipertensão arterial (38,4%), hipertrigliceridemia (25,8%), níveis baixos de colesterol HDL (27,7%), obesidade geral (38,4%) e abdominal (59,1%). Pacientes do sexo masculino apresentaram maior prevalência de transtorno por uso de álcool, diabetes e hipertrigliceridemia, enquanto pacientes do sexo feminino apresentaram taxas mais elevadas de obesidade abdominal. Variáveis como padrão de uso de medicação, transtornos por uso de álcool e atividade física foram associadas aos fatores de risco cardiovascular estudados na análise multivariada.

CONCLUSÃO: Este relato da Rede Brasileira de Pesquisa em Transtorno Bipolar apresenta dados novos a respeito da prevalência e dos fatores

associados a fatores de risco cardiovasculares em pacientes brasileiros ambulatoriais com TB. Existe uma necessidade crescente tanto de conscientização quanto de reconhecimento das doenças metabólicas e cardiovasculares nessa população de pacientes.

PALAVRAS-CHAVE: transtorno bipolar; fatores de risco cardiovasculares; comorbidade.

INTRODUCTION

Bipolar disorder (BD) is a chronic and disabling illness associated with significant morbidity and mortality[1]. Patients with BD are subject to premature death from all causes when compared to the general population[2] and usually present several comorbid general medical conditions which are associated with worse outcomes and higher burden of disease[3-5].

Increased rates of obesity[6-7], diabetes[8], hypertension[9], dyslipidemia[10] and the metabolic syndrome[11-13] have been reported in recent studies. In addition to being exposed to the weight gaining effects of pharmacological treatment, BD patients are more likely to present sedentary lifestyles and poor dietary habits[14], which are well-established cardiovascular risk factors[15].

Most of the abovementioned data come from developed countries which have somewhat distinct realities from the developing world. In Brazil, together with an increase in the absolute prevalence of obesity and the metabolic syndrome, there is a trend for shifting toward the lower income population[16]. This is of particular interest for the field of BD since most patients are consumers of the public health system and prescription patterns may be different from the rest of the world, particularly regarding the use of atypical antipsychotics[17].

Despite being a leader in psychiatric research among developing countries[18], one of the shortcomings that may constrain the progress of clinical research in Brazil is the relatively limited number of patients enrolled in most studies and a natural step to overcome these limitations is to establish research networks[19]. In 2005, the Brazilian Association for Bipolar Disorder (ABTB)

created the Brazilian Research Network in Bipolar Disorder (BRN-BD) as a means to promote the integration of bipolar disorder research centers and to develop collaborative studies.

In this context, the present study is a report of the BRN-BD that aims to evaluate the prevalence and clinical correlates of cardiovascular risk factors among patients with bipolar disorder from two research centers in São Paulo (PROMAN) and Porto Alegre (PROTAHBI), Brazil.

METHODS

1. Subjects

The study is a cross-sectional analysis of outpatients with BD, 18 years or older, consecutively recruited from the Bipolar Research Program (PROMAN) at the University of São Paulo Medical School, São Paulo, Brazil, and the Bipolar Disorder Program (PROTAHBI) at the Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. The study was approved by both sites Institutional Review Boards (FMUSP 1326/06 and GPPG-HCPA 06-245) and patients gave written informed consent before entering the study. All patients met DSM-IV criteria for BD, diagnosed with the SCID-I.

2. Clinical and laboratory data

Patient assessment was similar in both sites. Clinical, demographic, anthropometrical and metabolic measures were assessed at the first visit. These included height and weight, body mass index (BMI), waist circumference and blood pressure (measured at two different times during the interview). Mood symptoms were assessed with the 17-item Hamilton Depression Rating Scale (HAM-D) and the Young Mania Rating Scale YMRS). Patients were requested to have a fasting blood sample drawn the next day to evaluate fasting serum glucose, high-density cholesterol (HDL) and triglycerides levels. Patients at PROTAHBI site also had total cholesterol data available. A second study visit was scheduled to provide test results and counseling. Medical referral was provided for those who needed treatment.

3. Determination of cardiovascular risk factors

Cardiovascular risk factors were diagnosed according to recent Brazilian guidelines for diabetes, hypertension and dyslipidemia[20-22]. High glucose was defined as fasting glucose ≥ 100mg/dL; high total cholesterol as fasting total cholesterol ≥ 240mg/dL; low HDL cholesterol as fasting HDL cholesterol < 40mg/dL (men) or < 50mg/dL (women); diabetes as fasting glucose ≥ 126 mg/dL or current use of diabetes medication; hypertrygliceridemia as fasting tryglicerides ≥ 200mg/dL; hypertension as blood pressure ≥ 140/90 mmHg or current use of anti-hypertensive medication; overweight as body mass index (BMI) between 25-29.9 kg/m^2; obesity as BMI ≥ 30; abdominal obesity as waist circumference ≥ 102 cm (men) and ≥ 88 cm (women); physical inactivity as self-report of no regular exercise and smoking as self-report of current use of cigarettes, cigars or pipes.

4. Statistical analysis

Differences between patients from the two sites as well as differences in clinical variables associated with each cardiovascular risk factor were compared using chi-squared tests for dichotomous variables and Student t tests or Mann-Whitney tests for parametric and non-parametric continuous data, respectively. Multilevel logistic regression analyses were used in order to control for confounding factors associated with cardiovascular risk factors. Age, gender and site were included in the first level and other related variables such as smoking, physical activity, alcohol use disorders and medication use (lithium, valproate, other anticonvulsants, antidepressants, typical and atypical antipsychotics) were included in the second level. All tests were two-tailed.

RESULTS

A total of 159 outpatients were enrolled in the study, eighty-four from the PROMAN site and seventy-five from the PROTAHBI site. Demographic and clinical characteristics of the sample are shown in table 1. Patients at the PROMAN site were more likely to be younger (p=0.031), single (p=0.018) and with more years of formal education (p<0.001). There were significant differences in prescription patterns between sites, such as more use of atypical antipsychotics (p=0.001), antidepressants (p=0.002) and lamotrigine (p=0.005) at PROMAN and more lithium (p=0.001) and valproate (p=0.013) at PROTAHBI. Patients at the PROTAHBI site also presented more depressive (p=0.001) and manic (p=0.001) symptoms.

The prevalence of selected cardiovascular risk factors is presented in table 2. In addition to the high rates of the different risk factors we found significant gender differences. Male patients were more likely to present alcohol use disorders (p=0.001), diabetes (p=0.037) and hypertriglyceridemia (p<0.001); female patients showed increased rates of abdominal obesity (p=0.007).

In the multilevel logistic regression - after controlling for site, age and gender - valproate (OR 2.11; CI 1.03-4.35) was associated with obesity. Older age (OR 1.08; CI 1.03-1.13) and male gender (OR 0.29; CI 0.10-0.82) remained associated with diabetes; recruitment from the PROTAHBI site (OR 2.18; 1.04-4.60), older age (OR 1.09; CI 1.05-1.13), physical activity (OR 0.35; CI 0.14-0.87) and lithium use (OR 0.18; CI 0.07-0.46) were factors associated with hypertension. Recruitment from the PROTAHBI site (OR 2.34; CI 1.09-5.03) and alcohol use disorder (OR 0.30; CI 0.09-0.99) were factors associated with

reduced HDL-cholesterol and male gender (OR 4.09; CI 1.92-8.70) remained associated with hypertriglyceridemia.

DISCUSSION

Our study investigated the prevalence and clinical correlates of well-established cardiovascular risk factors in two samples of outpatients with BD. In line with previous studies we found elevated prevalence rates of obesity, smoking, physical inactivity, diabetes, arterial hypertension and dyslipidemia in Brazilian BD outpatients. We also found statistically significant gender differences regarding alcohol use disorders, diabetes, hypertrygliceridemia and abdominal obesity.

BD is associated with substantial morbidity and increased rates of all-cause mortality[23-24] and there has been increasing awareness and recognition about the contribution of cardiovascular risk factors to the medical burden of the illness[25-26]. In addition to general medical conditions such as cardiovascular, endocrine and metabolic diseases[8-27], patients with BD usually present a wide range of modifiable cardiovascular risk factors such as obesity, smoking, physical inactivity and poor eating habits[15].

As expected and in line with recent studies from other countries, patients with bipolar disorder presented higher prevalence of the selected cardiovascular risk factors when compared with data regarding the Brazilian population[20-22]. Previous findings on the prevalence of comorbid general medical conditions in BD have reported alarming high rates in cardiovascular risk factors such as obesity (20-32%)[28]; hypertension (34-60%)[10-29], diabetes (2-26%)[9] and dyslipidemia (23-41%)[8]. Furthermore, studies investigating the prevalence of the metabolic syndrome in BD patients have reported varying rates as low as 18%-25.3% in Belgium[30] and Italy[31], 33.9% in Taiwan[32] and as high as 40-49% in the USA[33; 34]. A recent report on cardiovascular risk factors in

BD patients[35] has also pointed-out differences between prevalence rates not only among different countries but also according to the cardiovascular risk estimation method used. In addition to these findings, our own results underscore the relevance of considering regional differences when studying cardiovascular risk factors in psychiatric patients.

There may be a wide range of confounding factors when studying cardiovascular risk factors in patients with severe mental illnesses[36-37]. Despite individual variables such as age and gender, patients with bipolar disorder are particularly at risk due to both disease and treatment-related factors[33]. Clinical and biological features such as depression with atypical features, anxiety, hypercortisolism, increased oxidative stress and DNA damage[38] as well as treatment with weight gaining medication are related to increased medical burden in BD[39].

In this context, differences in cardiovascular risk factors prevalence rates seen in our study may be explained not only by distinct genetic, lifestyle and dietary backgrounds but also to varying prescription patterns. In order to control for potential confounders - age, gender and treatment site - we used multivariable analysis to explore other associated risk factors. Some variables such as medication use pattern, alcohol use disorder and physical activity were associated with selected cardiovascular risk factors and may represent a possible target for intervention. The multivariate analysis approach is relevant in this study since most of the variables studied are highly correlated[40].

Our results must be interpreted in the light of some of limitations. Our samples come from tertiary treatment settings most of them consisting of difficult-to-treat patients, which may limit the generalization of our results to the

whole spectrum of bipolar disorder. Due to the cross-sectional nature of our study we cannot make mechanistic causal explanations and longitudinal studies are necessary to further clarify the abovementioned associations.

Despite these limitations, this report from the BRN-BD provides a significant amount of new data regarding prevalence rates and associated cardiovascular risk factors in Brazilian outpatients with BD. This information may be useful in increasing both awareness and recognition of comorbid metabolic and cardiovascular diseases in this patient population what may potentially reduce the increasing medical burden of bipolar disorder.

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The other authors report no conflict of interest.

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Table 1: Socio-demographic and clinical variables of bipolar disorder outpatients.

Variable	Total sample (n=159) mean ± SD/ n(%)	PROMAN (n=84) mean ± SD/ n(%)	PROTAHBI (n=75) mean ± SD/ n(%)	p-value
Age	43.5 ± 12.0	41.5 ± 11.5	45.8 ± 12.1	0.031
Years of formal education	10.4 ± 4.0	11.6 ± 3.6	9.1 ± 4.0	<0.001
Sex				
Male	52 (32.7)	29 (34.5)	23 (30.7)	0.61
Female	107 (67.3)	55 (65.5)	52 (69.3)	
Marital Status				
Single	58 (36.5)	39 (46.4)	19 (25.3)	0.018
Living with partner	60 (37.7)	27 (32.1)	33 (44.0)	
Separated/divorced	29 (18.2)	15 (17.9)	14 (18.7)	
Widowed	12 (7.5)	03 (3.6)	09 (12.0)	
Bipolar disorder				
Type I	150 (94.3)	78 (92.9)	72 (96.0)	0.50
Type II	09 (5.7)	06 (7.1)	03 (4.0)	
Current medication				
Any mood stabilizer	140 (88.1)	71 (84.5)	69 (92.0)	0.22
Lithium	84 (52.8)	34 (40.5)	50 (66.7)	0.001
Valproate	56 (35.2)	22 (26.2)	34 (45.3)	0.013
Carbamazepine/oxcarbazepine	42 (26.4)	31 (36.9)	11 (14.7)	0.002
Typical antipsychotics	30 (18.9)	13 (15.5)	17 (22.7)	0.31
Atypical antipsychotics	63 (39.6)	44 (52.4)	19 (25.3)	0.001
Risperidone	21 (13.2)	06 (7.1)	15 (20.0)	0.02
Quetiapine	17 (10.7)	17 (20.2)	00 (0.0)	<0.001
Olanzapine	19 (11.9)	16 (19.0)	03 (4.0)	0.003
Clozapine	06 (3.8)	02 (2.4)	04 (5.3)	0.42
Ziprasidone/aripiprazole	12 (7.5)	11 (13.1)	01 (1.3)	0.005
Antidepressants	46 (28.9)	32 (38.1)	12 (16.0)	0.002
Others				
Lamotrigine	24 (15.1)	19 (22.6)	05 (6.7)	0.005
Topiramate	13 (8.2)	13 (15.5)	00 (0.0)	<0.001
Gabapentin	06 (3.8)	05 (6.0)	01 (1.3)	0.21
Benzodiazepines	49 (30.8)	27 (32.1)	22 (29.3)	0.73
Number of current medications*	3 (1)	3 (2)	2 (1)	0.003
HAM-D score*	5.5 (10)	4 (6)	8 (10)	0.001
YMRS score*	1 (4)	0 (2)	2 (5)	0.001

*Median (IQR)

Table 2: Prevalence of cardiovascular risk factors in bipolar disorder outpatients.

Variable	Total sample (n=159) n(%)	Male patients (n=52) n(%)	Female patients (n=107) n(%)	χ^2	p-value
Age (Men ≥ 45 years; women ≥ 55)	36 (22.6)	12 (23.1)	24 (22.4)	0.008	0.539
Smoking	43 (27.0)**	18 (35.3)**	25 (23.6)	2.374	0.090
Physical inactivity	103 (64.9)***	30 (60.0)***	73 (70.2)	1.584	0.141
Alcohol use disorders	33 (20.8)***	19 (36.5)***	14 (13.7)	10.646	0.001
High glucose	42 (26.4)	15 (28.8)	27 (25.2)	0.235	0.381
Diabetes	21 (13.2)	11 (21.2)	10 (9.3)	4.256	0.037
Hypertension	61 (38.4)	23 (44.2)	38 (35.5)	1.124	0.187
Hypertrygliceridemia	41 (25.8)	23 (44.2)	18 (16.2)	13.737	<0.001
High total cholesterol*	34 (45.3)	08 (34.8)	26 (50.0)	1.490	0.166
Low HDL cholesterol	44 (27.7)	13 (25.0)	31 (29.0)	0.276	0.372
Overweight	52 (32.7)	21 (40.4)	31 (29.0)	2.071	0.105
Obesity	61 (38.4)	18 (34.6)	43 (40.2)	0.459	0.309
High waist circumference	94 (59.1)	23 (44.2)	71 (66.4)	7.087	0.007

*Data unavailable for PROMAN patients.

**Data unavailable for 2 PROMAN patients.

***Data unavailable for 5 PROMAN patients.

6.2. Artigo 2

Obesity is associated with previous suicide attempts in bipolar disorder

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Running title: Obesity and suicide attempts in BD

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ABSTRACT

OBJECTIVE: There is a paucity of data about risk factors for suicide attempts in bipolar disorder. The aim of this study is to examine the association between suicide attempts and obesity in people with bipolar disorder.

METHODS: Two hundred fifty-five DSM-IV outpatients with bipolar disorder were consecutively recruited from the Bipolar Disorder Program at Hospital das Clínicas de Porto Alegre and the University Hospital at the Universidade Federal de Santa Maria, Brazil. Diagnosis and clinical variables were assessed with SCID I and Program structured protocol. History of suicide attempts was obtained from multiple information sources including patients, relatives and review of medical records. Patients with body mass index (BMI) ≥ 30 were classified as obese.

RESULTS: Over 30% of the sample was obese and over 50% had a history of suicide attempt. In the multivariate model, obese patients were nearly twice (OR = 1.97, 95% CI: 1.06 – 3.69, p = 0.03) as likely to have a history of suicide attempt(s).

CONCLUSION: Our results emphasize the relevance of obesity as an associated factor of suicide attempts in bipolar disorder. Obesity may be seen as correlate of severity and as such, must be considered in the comprehensive management of bipolar patients.

KEYWORDS

Bipolar disorder; suicide; obesity.

INTRODUCTION

Bipolar disorder is a major public health concern worldwide, and is associated with significant morbidity and mortality [1]. In addition to an increased rate of death by suicide, community and clinical studies indicate that bipolar patients usually present a broad range of comorbid general medical conditions, which contribute to overall mortality rates [2,3].

Of significant interest is the co-occurrence of metabolic disturbances in bipolar disorder, particularly obesity. In addition to the burden related to the expanding obesity epidemic in both developed and developing countries such as Brazil, in which prevalence rates have reached up to 11% of the population [4], bipolar disorder and comorbid obesity are associated with increased medical morbidity and worse psychiatric outcome [5]. Data from clinical samples have shown that the prevalence of obesity in bipolar disorder patients is exceedingly high, ranging from 20-35%, when compared to controls [6-8], even in those not exposed to the weight gaining effects of pharmacological treatments [9,10]. Furthermore, obese patients usually have more markers of illness severity, such as more previous affective episodes [11] and suicide attempts [12-14].

Recent studies have addressed the relationship between obesity and psychiatric morbidity [15]. Data from community surveys from the USA [16] and Canada [17] have indicated that obesity has been associated with suicidal behavior, particularly suicidal ideation and previous attempts. This is of particular concern since both obesity and suicidal behavior is a common feature of bipolar disorder [18]. A recent meta-analysis of 36 suicide studies in this patient population identified several risk factors for suicide, including early onset of mood episodes, longer duration of depressive symptoms, rapid cycling, family

history of suicide, previous suicide attempts and co-morbid psychiatric conditions such as substance use disorders [19].

Only a couple of studies have investigated the association of obesity and suicidal behavior in this group of patients. Fagiolini et al [12] found a positive association between a higher BMI and previous suicide attempts at baseline, in a sample of 175 patients with bipolar I disorder participating in a clinical trial. Similarly, a second cross-sectional study of 171 patients by the same research group [13] reported an association between both a diagnosis of the metabolic syndrome and the presence of abdominal obesity, and a lifetime history of suicidal behavior.

There remains a paucity of data regarding this association, with no studies from outside the USA and a relatively low number of patients in previous reports. This study, therefore, aimed to further examine an independent relationship of obesity and suicide attempts in a larger sample of patients with bipolar disorder.

MATERIALS AND METHODS

Subjects

Subjects were recruited from the Bipolar Disorder Program at the Hospital de Clínicas de Porto Alegre and the University Hospital at the Universidade Federal de Santa Maria. Two hundred fifty-five patients, aged 18 years or older, with a diagnosis of bipolar disorder type I or II were consecutively evaluated from January 2004 to December 2007. Written informed consent was obtained from all patients before study entry. This research project received approval from local ethics committees.

Methods

Psychiatric diagnosis of bipolar disorder and psychiatric comorbidities were confirmed with the Structured Clinical Interview for DSM-IV-axis I (SCID I). Socio-demographic and clinical variables were collected as part of a structured standard protocol [20]. Depressive and manic symptoms were assessed with validated Portuguese versions of the 17-item Hamilton Rating Scale for Depression [21] and the Young Mania Rating Scale [22], respectively. A lifetime history of suicide attempt was defined as at least one conscious intent to end his/her life, even if ambivalent, through means that the patient believed could result in death [23]. This definition does not include minor self harm but potentially lethal acts. Data regarding suicide attempts was obtained from best available information including interviews with patients, relatives and review of medical records.

Anthropometrical variables included height, weight and BMI which was calculated as [weight in kilograms/(height in meters)^2]. Patients were classified

as normal weight (BMI < 25.0), overweight (BMI ranging 25.0-29.9) or obese (BMI ≥ 30) [24].

Statistical Analysis

A multilevel logistic regression analysis to check the association between obesity and suicidality controlling for factors previously associated with suicide or suicide attempts[19]. These included age and sex (first level), illness characteristics such as bipolar subtype, rapid cycling, anxiety and substance use disorders (second level) and HAM-D score and obesity (third level). As such, obesity is controlled for all the above-established risk factors. All tests were two-tailed.

RESULTS

The sample consisted of 255 bipolar patients. A history of suicide attempts was present in 133 subjects (52.2%) and 80 patients (31.4%) were classified as obese. Table 1 shows socio-demographic and clinical variables of the sample. The majority of patients (87.8%) were taking mood stabilizers (lithium, valproate or carbamazepine) alone or in combination, 20.4% were on atypical antipsychotics and 23.5% were receiving antidepressants.

Obese patients were twice as likely to have a history of suicide attempts (OR = 2.00, 95% CI: 1.16 – 3.44, *p*= 0.02). Furthermore, obesity was not associated with depressive symptoms (*p*=0.77), rapid cycling (*p*=0.068) or anxiety (*p*=0.67), alcohol (*p*=0.87) and drug use disorders (*p*=0.24). Data regarding treatment regimens are presented in table 2.

Obesity remained associated with suicide attempts in the regression model (OR = 1.97, 95% CI: 1.06 – 3.69, *p* = 0.03). Also associated with suicide attempts in the final model were lifetime anxiety (OR =2.15, 95% CI: 1.22 – 3.78, *p* = 0.008) and substance use disorders (OR = 2.36, 95% CI: 1.29 – 4.30, *p* = 0.005), rapid cycling (OR = 2.09, 95% CI: 1.09 – 4.00, *p* = 0.027) and current depressive symptoms (OR = 1.06, 95% CI: 1.02 – 1.10, *p* = 0.005). Age (OR = 0.99, 95% CI: 0.97 – 1.01, *p* = 0.403) and sex (OR = 1.47, 95% CI: 0.83 – 2.60, *p* = 0.191) were dropped from the final model.

DISCUSSION

The main finding of this study is that obesity was associated with a history of suicide attempts in a sample of outpatients with bipolar disorder, even after controlling for well-established risk factors such as lifetime co-morbid anxiety and alcohol use disorders and depressive symptoms.

Our finding adds to the notion that obesity is a correlate of severity in patients with bipolar disorder, and replicates earlier findings from Fagiolini et al [12,13]. In recent years there has been an increasing interest in the relationship of obesity and psychiatric disorders [25], particularly bipolar disorder [5], because weight gain and obesity frequently complicate treatment of mood disorders [15]. Furthermore, obese patients with bipolar disorder usually have more markers of adverse outcome, such as greater number of comorbid general medical conditions, increased number of previous mood episodes and more depressive features [7,8,13].

We also found a significant association between suicide attempts and co-morbid anxiety and alcohol use disorders and depressive symptoms. This is in line with previous findings from our group [26,27]. Bipolar patients with a history of suicide attempts have been shown to have more markers of severity such as greater suicidal ideation, increased number of hospitalizations, aggressive traits, earlier age at onset [28], a family history of suicide [29] and of psychiatric and mood disorders [30], as well as a higher frequency of comorbid anxiety, substance use and cluster B personality disorders [29-32].

One possible link between obesity and suicide in bipolar disorder may be related to depression. Major depression and residual depressive symptoms

are the most common phases of bipolar disorder and both are associated with substantial work, social and family functional impairment [33]. Depressive episodes are related to changes in appetite, eating behavior and physical activity that contribute to obesity [5]. Bipolar depression differs from unipolar depression in key symptom patterns, with atypical features, particularly hypersomnia and hyperphagia being prominent [34]. In addition to the fact that bipolar disorder with predominant depressive polarity is strongly related to suicidal behavior [27,35], a recent report has shown that depression with atypical features is also associated with suicide in this population [29]. We also found a positive association of both depressive symptoms and obesity with suicide attempts.

Recent data have stressed common features in the underlying pathophysiology of obesity and bipolar disorder which may also be another possible explanation for our findings. Leptin, a key hormone in regulation of adiposity has been shown to be positively associated with risk for depression in a prospective study [36]. Disturbances in metabolic pathways such as insulin-mediated glucose homeostasis, overactivation of the hypothalamic–pituitary–adrenal axis, dysregulated immune and inflammatory processes and adipocytokines profiles are present in both conditions [37]. Such deleterious alterations in key adaptive mechanisms are a component of allostastic load [38] and may explain some of the complex interactions between bipolar disorder, common general medical conditions and resilience to mood episodes and life events [39]. This framework provides another standpoint from which obesity may be seen as a correlate of allostatic load in bipolar disorder and its relationship with suicide attempts a marker of illness severity.

This report described a cross-sectional study in a tertiary treatment setting. Most of our sample consists of difficult-to-treat patients referred to the Bipolar Disorder Program, which may limit the ability to generalize our results to the whole spectrum of bipolar disorder. The retrospective assessment of some variables may be influenced by recall bias; because of the complex nature of obesity and suicidal behavior, prospective studies are needed to further clarify the causal nature of this association.

In addition to well-established risk factors such as previous suicide attempts, depressive symptoms and co-morbid psychiatric conditions, clinicians must be aware that obesity may be a severity feature relevant not only to pharmacological treatment decisions but also to the comprehensive management of bipolar disorder. It is plausible to speculate that therapeutic interventions targeted to obesity may be of potential benefit in the course of bipolar disorder.

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DISCLOSURE

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Dr. Cunha declares no financial ties.

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Table 1. Clinical and demographic variables of the sample.

Variable	Total sample (n=255) (% / mean ± SD
Age	41.51 ± 11.78
Gender	
Female	72.5
Ethnicity	
Caucasian	85.4
Marital status	
Married/living with partner	40.0
Education, years	9.45 ± 4.08
Age at onset	25.93 ± 11.54
Years of illness length	15.92 ± 11.17
No. hospitalizations	3.67 ± 5.08
Current mood symptoms	
HAM-D score	10.15 ± 8.01
YMRS score	7.86 ± 9.70
Diagnosis	
Bipolar disorder type I	88.9
Bipolar disorder type II	
Rapid cycling	27.1
Smoking	31.0
Lifetime psychiatric comorbidities	
Anxiety disorders	57.4
Alcohol abuse/dependence	27.9
Drug abuse/dependence	21.7
Eating disorders	7.8
Family history	
Mood disorders	31.4
Completed suicide	18.5
BMI classification	
Normal weight	34.9
Overweight	33.7
Obesity	31.4

Table 2. Treatment regimens according to patient groups.

Medication	Obese (n=80) N (%)	Non-obese (n=175) N (%)	*p*-value	Suicide attempters (n=133) N (%)	Non-attempters (n=122) N (%)	*p*-value
Mood stabilizers	73 (91.2)	151 (86.3)	0.307	120 (90.2)	104 (85.2)	0.253
Typical antipsychotics	30 (37.5)	63 (36.0)	0.889	51 (38.3)	42 (34.4)	0.603
Atypical antipsychotics	20 (25.0)	32 (18.3)	0.242	33 (24.8)	19 (15.6)	0.087
Antidepressants	17 (21.2)	43 (24.6)	0.635	39 (29.3)	21 (17.2)	0.027

6.3. Artigo 3

Clinical correlates of general medical comorbidities

In bipolar disorder

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TITLE PAGE

Title: Clinical correlates of general medical comorbidities in bipolar disorder.

Running Title: Correlates of medical comorbidities in BD.

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ABSTRACT

OBJECTIVE: The study was aimed to evaluate clinical correlates of general medical comorbidities in outpatients with bipolar disorder (BD).

METHODS: We performed a cross-sectional study of 203 patients with DSM-IV BD, 18 years or older, consecutively recruited from the Bipolar Research Program (PROTAHBI) in Porto Alegre. Clinical, demographic and anthropometrical variables were systematically assessed and General medical comorbidity was measured by means of the Cummulative Illness Rating Scale (CIRS).

RESULTS: The prevalence of at least one medical comorbidity was 90.1% and the most common comorbidities were from endocrine-metabolic-breast, neurologic and vascular categories. The mean number of CIRS categories endorsed by BD patients (CIRS count) was 2.18 ± 1.27 [0 - 6] and the mean CIRS total score of the sample was 4.02 ± 2.54 [0 - 10]. A high burden of general medical comorbidities (CIRS total score ≥ 4) was related to increasing age and body mass index and longer duration of illness after controlling for confounding factors.

CONCLUSION: BD is associated with a high burden of general medical conditions related to age, obesity and longer duration of illness. Medical comorbidity must be incorporated as a core feature in the development of effective treatment strategies for bipolar disorder.

KEYWORDS: bipolar disorder; general medical comorbidity; CIRS

1. INTRODUCTION

Bipolar disorder (BD) is a chronic and complex clinical entity associated with significant illness burden and deleterious effects in general functioning (Belmaker, 2004). In addition to mood and cognitive symptoms– which are highly relapsing and dominate the clinical picture – patients with BD usually present a wide range of psychiatric and medical comorbidities that are associated with poor prognosis (Soreca et al, 2009).

Several studies have highlighted the increased prevalence of general medical conditions associated with BD and its relationships with premature death, morbidity, treatment costs and functional impairment (McIntyre et al, 2007). Although most clinical conditions are overrepresented in BD populations, cardiovascular and metabolic problems are of particular concern since they are usually related to unhealthy lifestyles and psychotropic treatment (Morriss & Mohammed, 2005). Recently, there has been an increased interest in which factors – particularly those related to BD itself – may be associated to a common underlying pathophysiology.

1.1 Aims of the study

The present study was aimed to evaluate the prevalence and clinical correlates of general medical comorbidities in a sample of Brazilian outpatients with bipolar disorder. We hypothesized that patients with a high burden of medical comorbidities would present with more severe BD clinical features.

2. MATERIALS AND METHODS

2.1. Subjects

Two hundred three patients, aged 18 years or older, with a diagnosis of bipolar disorder type I or II were consecutively evaluated from January 2004 to December 2007 from the Bipolar Disorder Program at the Hospital de Clínicas de Porto Alegre. Written informed consent was obtained from all patients before study entry. This research project received approval from local ethics committee.

2.2. Methods

Psychiatric diagnosis of bipolar disorder and psychiatric comorbidities were confirmed with the Structured Clinical Interview for DSM-IV-axis I (SCID I). Socio-demographic and clinical variables were collected as part of a structured standard protocol (Gazalle et al, 2005). Anthropometrical variables included height, weight and body mass index (BMI) which was calculated as [weight in kilograms/(height in meters)^2]. Patients were classified as normal weight (BMI < 25.0), overweight (BMI ranging 25.0-29.9) or obese (BMI ≥ 30) (WHO, 1997).

Data regarding medical comorbidities was obtained from best available information including interviews with patients, relatives and review of medical records. For each patient, the first author (FAG) generated a score on the Cumulative Illness Rating Scale (CIRS) which was used as an index for the burden of general medical conditions. The CIRS is a valid and reliable instrument developed to assess chronic medical burden (Linn et al, 1968) and

has been used in studies with psychiatric populations (Miller et al, 1992; Mistry et al, 2004), including bipolar disorder (Soreca et al, 2008; Kemp et al, 2009).

The CIRS includes 13 organs systems plus a psychiatric illness category that was excluded for the purpose of this analysis. For each organ system, a score ranging from 0 to 4 is graded. A score of 0 represents “no problem”; a score of 1 is a “current mild or past significant problem”; a score of 2 is “moderate disability requiring first line treatment”, a score of 3 is “uncontrollable chronic problems or significant disability” and a score of 4 is “end organ failure requiring immediate treatment”. No patient received a score of 4 since all study subjects were outpatients. Two indices were obtained: the CIRS count which is the number of categories endorsed by the patient and the CIRS total score which is the sum of each of the 13 individual system scores. Patients were divided according to the magnitude of general medical comorbidities burden into two groups (Kemp et al, 2009): low to moderate (CIRS total score ≤ 3) and high burden (CIRS total score ≥ 4).

2.3. Statistical analysis

Bivariate analyses were performed for differences in demographic and clinical variables associated with each medical comorbidity group using chi-squared tests for dichotomous variables and Student t tests or Mann-Whitney tests for parametric and non-parametric continuous data, respectively. Multilevel logistic regression analysis was used in order to control for confounding factors associated with high burden of general medical comorbidity. Age, gender, marital and education status were included in the first level and other variables

associated with medical comorbidity were included in the second level. All tests were two-tailed.

3. RESULTS

A total of 203 bipolar patients were included in the study. Table 1 shows socio-demographic and clinical variables of the sample. The prevalence of at least one medical comorbidity was 90.1% and the most common comorbidities were from endocrine-metabolic-breast, neurologic and vascular categories (table 2). The mean number of CIRS categories endorsed by BD patients (CIRS count) was 2.18 ± 1.27 [0 - 6] and the mean CIRS total score of the sample was 4.02 ± 2.54 [0 - 10].

Age, female gender, education, duration of illness and BMI were associated with a CIRS total score ≥ 4 in the bivariate analyses. After controlling for potential confounders, age, illness duration and BMI remained associated with a high burden of general medical comorbidities in the regression analysis (table 3).

4. DISCUSSION

Our sample of BD outpatients presented with a high level of general medical comorbidities with approximately 90% of the sample presenting at least one comorbid condition. These results are in line with previous reports indicating a high level of medical comorbidity in BD, usually greater than patients with unipolar depression (Iosifescu et al, 2004; Gildengers et al, 2008) and at a similar level of geriatric patients (Miller et al, 1992). Endocrine/metabolic, neurologic and vascular diseases are also common reported comorbidities associated with BD. (McIntyre et al, 2007).

There is now an increasing body of evidence that medical disease is correlated with several indicators of poorer prognosis in BD (Kupfer, 2005). The relationships among the burden of general medical conditions, BD chronicity and worse outcomes are probably mediated by significant factors not only related to demographic variables such as age, gender and ethnic background, but particularly to illness-related factors (Grande et al, 2011). Previous studies have shown that high levels of medical comorbidity are associated with treatment response and clinical correlates of severity such as BD subtype, obesity, suicidality, history of physical abuse, early onset and longer duration of illness (Thompson et al, 2006; Soreca et al, 2008; Kemp et al, 2009; Kemp et al, 2010, Magalhães et al, 2011). In our sample, age, illness duration and BMI were independently associated with a high burden of medical disease, supporting the hypothesis of a process of accelerated aging in BD related to the cumulative incidence of mood episodes and disease progression (Kapczinski, et al, 2008).

The changing view that BD is a chronic and disabling condition rather than a benign episodic illness is endorsed by data regarding the interplay between psychiatric symptoms and medical comorbidities (Soreca et al, 2009). Illness severity is crucially bonded with medical problems in terms of reciprocal interactions. Notwithstanding potentially shared genetic diathesis, overload of regulatory systems such as endocrine, immunologic and inflammatory networks associated with mood symptomatology have a definite impact on health status and medical disease incidence and progression (Berk et al, 2011). On the other hand, despite direct influences on the underlying pathophysiology of BD, general health status is an important variable concerning quality of life and functioning.

Our findings must be interpreted in the light of some limitations. Due to the cross-sectional nature of the study design and tertiary setting, prospective studies with both clinical and community samples are mandatory in order to elucidate the relationships and cause-effect interactions between BD and general medical conditions. Inclusion of neurobiological data such as biomarkers and measures of physiological mediators are also important to clarify the causal nature of this association.

Medical comorbidity may be seen as a correlate of illness severity in BD and must be included in patients' global assessment. The notion of disease staging in which more complex patients (ex. highly relapsing, comorbid and with longer illness duration) are considered in a later stage of progression is already established in general medicine and are gaining popularity in psychiatry (Berk et al, 2007; Kapczinski et al, 2009). Chronic care models of treatment are been tested as a new paradigm in the treatment of mood disorders and include

physical health as a core feature (Kilbourne et al, 2008; Kilbourne et al, 2009) since effectiveness in remission of both psychiatric symptoms and stabilization of medical problems are essential for the successful treatment of bipolar disorder.

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Table 1. Socio-demographic and clinical variables of BD outpatients

Variable	Total Sample (n=203) % / mean ± SD	CIRS total score ≤ 3 (n=88) % / mean ± SD	CIRS total score ≥ 4 (n=115) % / mean ± SD	*P* value
Age	41.95 ± 11.76	36.25 ± 10.64	46.35 ± 10,69	< 0.001
Gender				
Female	70.9	63.6	76.5	0.045
Ethnicity				
Caucasian	83.7	84.1	83.3	0.885
Marital status				
Married/living with partner	39.4	35.2	43.0	0.264
Education, years	9.63 ± 4.16	10.45 ± 3.78	8.98 ± 4.34	0.013
Age at onset	25.43 ± 11.84	24.17 ± 11.43	26.42 ± 12.11	0.183
Duration of illness, years	16.40 ± 11.65	12.13 ± 10.48	19.67 ± 11.48	< 0.001
No. hospitalizations	3.21 ± 4.50	2.53 ± 3.73	3.73 ± 4.97	0.060
Diagnosis				
Bipolar disorder type I	87.6	86.2	88.7	0.595
Rapid cycling	28.7	30.7	27.2	0.587
Smoking	25.9	29.9	22.7	0.255
Lifetime psychiatric comorbidities				
Anxiety disorders	63.2	56.3	68.4	0.078
Alcohol abuse/dependence	28.7	32.2	26.1	0.343
Drug abuse/dependence	21.3	28.7	15.7	0.024
Eating disorders	8.5	8.0	8.8	0.855
Medication				
Mood stabilizers	93.9	92.9	94.7	0.610
Atypical antipsychotics	25.8	25.9	25.7	0.972
Typical antipsychotics	29.8	29.4	30.1	0.918
Antidepressants	24.7	18.8	29.2	0.094
BMI classification				
Normal weight	32.6	48.6	21.9	< 0.001
Overweight	34.9	34.3	35.2	
Obesity	32.6	17.1	42.9	

Table 2. Prevalence rates of comorbidity in each organ systems among BD outpatients

Category	Patients with at least one comorbidity (%)
Endocrine/Metabolic/Breast	50.2
Neurologic	35.5
Vascular	29.1
Musculoskeletal/Integumentary	25.6
Respiratory	21.2
Genitourinary	13.3
Hepatic/Pancreatic	10.8
Cardiac	7.4
Renal	7.4
Head and neck	6.4
Upper gastrointestinal	6.4
Lower gastrointestinal	3.9
Hematological	2.0

Table 3. Regression analysis of the association of clinical variables with high burden of general medical comorbidity in BD patients

Variable	B	Standard Error	Wald χ^2	*P* value	Odds Ratio	CI (95%)
Age	0.053	0.021	6.472	0.011	1.06	1.01 - 1.10
Married/Living with partner	0.026	0.405	0.004	0.949	1.03	0.46 - 2.27
Female gender	-0.741	0.449	2.729	0.099	0.48	0.20 - 1.15
Education, years	-0.017	0.051	0.107	0.744	0.98	0.89 - 1.09
Duration of illness, years	0.047	0.021	4.773	0.029	1.05	1.01 - 1.09
Number of hospitalizations	0.001	0.047	0.000	0.986	1.00	0.91 - 1.10
Smoking	0.295	0.441	0.446	0.504	1.34	0.57 - 3.19
Alcohol use disorders	-0.077	0.457	0.029	0.866	0.91	0.38 - 2.27
Substance use disorders	-0.683	0.495	1.909	0.167	0.51	0.19- 1.33
Anxiety disorders	0.215	0.417	0.266	0.606	1.24	0.55 - 2.81
BMI	0.122	0.040	9.168	0.002	1.13	1.04 - 1.22

7. CONSIDERAÇÕES FINAIS

O avanço da pesquisa em psiquiatria nos últimos anos permitiu grandes avanços em relação ao entendimento da fisiopatologia e o desenvolvimento de tratamentos eficazes para os transtornos mentais. A melhora aguda dos sintomas psiquiátricos, bem como a remissão e recuperação do quadro psicopatológico já são possíveis na prática clínica atual, porém, a recuperação funcional ainda é um desafio significativo (Ostacher, 2004). Os pacientes portadores de transtornos mentais graves, particularmente o transtorno bipolar, apresentam, como características próprias da doença, elevados índices de recaída dos episódios de humor e um grau importante de comprometimento do funcionamento, tanto durante as fases sintomáticas quanto nos períodos de remissão (Müller-Oerlinghausen et al, 2002).

Outra característica marcante do transtorno bipolar é presença simultânea de outras entidades clínicas, ou seja, comorbidades, tanto de natureza psiquiátrica, quanto condições médicas gerais (Soreca et al, 2009). Os estudos apresentados nesta Tese fornecem dados adicionais sobre a prevalência de fatores de risco cardiovasculares e de comorbidades nos diversos sistemas fisiológicos em pacientes bipolares brasileiros. A compreensão do papel das comorbidades clínicas, incluindo as doenças decorrentes das alterações neurofisiológicas das doenças mentais e os efeitos adversos relacionados aos tratamentos farmacológicos, é fundamental para que a abordagem psiquiátrica seja mais efetiva e haja melhora em outros desfechos clínicos relevantes, tais como mortalidade e qualidade de vida.

O estudo dos fatores subjacentes à associação entre condições médicas gerais e doenças psiquiátricas é um foco atual de pesquisa (Fleischhacker et al, 2008). Além de poder ajudar a desvendar a natureza dessa associação, pode oferecer a oportunidade de se conhecer melhor a fisiopatologia das próprias doenças psiquiátricas. Quando se fala em interação entre doenças psiquiátricas e doenças sistêmicas, naturalmente emergem como candidatos a mediadores dessa associação substâncias responsáveis pela comunicação entre diferentes células do organismo, tais como os hormônios e os mediadores imuno-inflamatórios. De fato, existem dados importantes referentes à contribuição dos sistemas endócrino e imunológico e à interação entre o cérebro e os demais órgãos e sistemas do organismo, tanto em indivíduos sadios quanto em pacientes portadores de transtornos mentais (McEwen, 2004; Juster et al, 2010).

A fim de manter o equilíbrio das funções fisiológicas e sobreviver, os organismos necessitam de mecanismos homeostáticos – que se referem à propriedade de um sistema de regular seu meio interno e manter uma condição estável – eficientes. Tais mecanismos usualmente se referem a processos locais e pontuais como, por exemplo, a regulação da glicemia através da ação dos hormônios insulina e glucagon. Um avanço em relação à fisiopatologia das comorbidades clínicas pode ser alcançado valendo-se de outro conceito importante: a alostase. Este conceito se refere aos mecanismos modulatórios mais amplos e complexos, com enfâse no controle cerebral dos processos regulatórios primários e nas mudanças fisiológicas e comportamentais antecipatórias a eventos futuros (Sterling & Eyer, 1988; Schulkin, 2003). Diversos sistemas, como o imunológico e o neuroendócrino, participam dessa

regulação mais ampla. O envolvimento do sistema nervoso central permite que os pontos de estabilidade variem em resposta às demandas ambientais (Sterling & Eyer, 1988). Desta maneira, a exposição a fatores estressores leva a uma série de alterações adaptativas a longo prazo em uma ampla gama de sistemas, de maneira a equiparar o meio interno a uma nova situação ambiental. O acúmulo dessas mudanças ao longo da vida foi conceituado como carga alostática (McEwen & Stellar, 1993).

A situação em que as mudanças alostáticas falham, seja devido a exposições crônicas ou a mecanismos regulatórios falhos, foi chamada de sobrecarga alostática, representando uma "exaustão" do sistema e estando diretamente relacionada a condições patológicas. Por exemplo, a liberação de cortisol promove alostase regulando a disponibilidade energética, porém níveis persistentemente elevados, resultados da ativação crônica do eixo HPA, podem induzir resistência a insulina, diabetes, obesidade, aterosclerose e hipertensão. De fato, o acúmulo de carga alostática está relacionado a doenças cardiovasculares, declínio cognitivo e mortalidade em geral (Seeman et al, 2001; Karlamangla et al, 2002).

A importância do papel do cerébro no conceito de carga alostática e sua relação com a exposição ao estresse e à associação com doenças clínicas levaram à aplicação desse paradigma aos transtornos psiquiátricos, como transtorno do estresse pós-traumático (Glover, 2006), depressão (McEwen, 2003a) e transtorno bipolar (Kapczinski et al, 2008). Diversos aspectos da concepção de carga alostática podem ser usados para compreender elementos da fisiopatologia dos transtornos do humor, como os processos que levam às alterações neuroestruturais e déficits cognitivos, além da maior prevalência de

comorbidades clínicas nessa população. A via final de lesão e comprometimento funcional parece ser mediada por mecanismos tradicionais como a inflamação, apoptose e danos associados ao estresse oxidativo. Apesar da evidência empírica ainda ser preliminar e da necessidade de mais estudos explorando essa questão, a sobrecarga alostática surge como uma interessante hipótese para explicar a conexão entre doenças psiquiátricas e clínicas.

Os três estudos apresentados nesta Tese identificaram diversas variáveis associadas a fatores de risco cardiovasculares e comorbidades clínicas em pacientes com TB. Assim como na população geral, o envelhecimento é um fator determinante para o aparecimento de doenças físicas, principalmente de natureza cardiovascular e metabólica (McEwen, 2003b). Nos pacientes bipolares esse efeito é marcante e parece ser potencializado ao se associar a outras variáveis relacionadas à doença. Pacientes com início mais precoce e maior tempo de duração da doença, obesos e com comorbidades psiquiátricas tais como ansiedade e uso de álcool e/ou drogas apresentam maior chance de apresentarem maior risco cardiovascular e doenças físicas. Tal constatação reforça a idéia de os mecanismos fisiopatológicos associados aos episódios de humor tem um efeito de sobrecarga alostática que acelera o processo de envelhecimento em pacientes bipolares (Kapczinski et al, 2008).

Os pacientes portadores de transtornos mentais apresentam um alto índice de comorbidades clínicas, recebem pior atendimento médico e morrem mais cedo quando comparados com a população em geral (McIntyre et al, 2007). Diversos fatores contribuem para esse cenário, estando distribuídos em

três níveis: pacientes, profissionais e sistema de saúde (Viron & Stern, 2010). Além de serem vulneráveis às doenças a partir dos efeitos da própria doença mental e do seu tratamento, muitos pacientes não encontram provedores capacitados a enfrentarem o problema, os quais, por sua vez, estão inseridos em um sistema ineficiente e pouco articulado, que acaba não cumprindo satisfatoriamente os princípios de universalidade e integralidade (Gentil, 2011).

Assim, é necessária uma mudança de paradigma que inclua obrigatoriamente as comorbidades clínicas nas agendas de pesquisa e de manejo dos transtornos mentais. Desta forma, além de propiciar uma maior compreensão do próprio mecanismo fisiopatológico dos transtornos psiquiátricos, a identificação dos mecanismos subjacentes a essa associação pode oferecer novas ferramentas de prevenção e tratamento de ambas as condições.

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