INSTITUTO DE PSIQUIATRIA – IPUB

Universidade Federal do Rio de Janeiro

MARINA DYSKANT MOCHCOVITCH

Aspectos translacionais do transtorno de ansiedade generalizada: Modelo fisiopatológico e abordagens terapêuticas.

Rio de Janeiro, 2018.

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Tese de doutorado submetida ao corpo docente do Programa de Pós-Graduação em Psiquiatria e Saúde Mental (PROPSAM) do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para a obtenção do grau de Doutor em Psiquiatria.

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RIO DE JANEIRO
2018

Mochcovitch, Marina Dyskant.

DM688a Aspectos translacionais do transtorno de ansiedade generalizada: Modelo fisiopatológico e abordagens terapêuticas/Marina Dyskant Mochcovitch--Rio de Janeiro: UFRJ, 2018.
80 folhas

Orientador: Antonio Egidio Nardi.
Tese (Doutorado) - Universidade Federal do Rio de Janeiro, Instituto de Psiquiatria, programa de pós-graduação em psiquiatria e saúde mental, 2018
.

1. Transtorno de ansiedade generalizada. 2. Neuroimagem 3. Fisiopatologia 4. Farmacoterapia 5. Enxaqueca. I. Nardi, Antonio Egidio, orient. II. Título

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Antonio Egidio Nardi - Presidente

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Aos meus pais, Bruno e Beni.

AGRADECIMENTOS

Ao professor Antonio Egidio Nardi, a quem sou profundamente grata pelo apoio e incentivo constantes ao longo de toda a minha formação, sendo um grande exemplo de médico e pesquisador que levo para toda a vida.

Aos meus pais, Helio e Miriam, e a meu marido Bruno por todo o amor, acolhimento e paciência nesta e em outras tantas jornadas.

Ao meu filho Beni, por ser a grande motivação para a busca de me tornar sempre melhor.

À minha irmã Nicole, meu cunhado Dan, minha tia Diana e meu primo Marcelo, pelo apoio e carinho de sempre.

À Minnie Klinger, pelo suporte fundamental em toda a minha trajetória.

Aos colegas Rafael Freire e Rafael Garcia pela parceria.

RESUMO

Esta tese visa apresentar quatro estudos realizados pela autora e colaboradores, tendo como objetivo geral o melhor entendimento do modelo fisiopatológico para o transtorno de ansiedade generalizada (TAG) e a busca de orientações para seu manejo terapêutico. A metodologia utilizada nestes quatro trabalhos foi a revisão sistemática da literatura, baseada no método PRISMA. No primeiro artigo, são revisados os estudos de neuroimagem funcional em pacientes com TAG visando encontrar embasamento neurobiológico para os diferentes modelos cognitivos descritos para este transtorno. Nesta revisão, encontramos que estes pacientes apresentam déficit no processo de regulação emocional e na capacidade de seleção de estímulos ameaçadores, assim como de supressão das preocupações induzidas. Em todas estas tarefas, foi encontrado o prejuízo no engajamento dos córtex pré-frontal e córtex cingulado anterior, o que levaria a maior ativação da amídala e outras estruturas límbicas associadas à resposta ao medo condicionado. No segundo artigo, reunimos os estudos que avaliam a eficácia da atividade física na melhora dos sintomas de ansiedade em idosos saudáveis (sem diagnóstico de TAG) e discutimos os mecanismos ansiolíticos desta prática levando em conta as alterações endócrino-metabólicas associadas a estes sintomas. Concluímos que a atividade física regular é eficaz na melhora dos sintomas de ansiedade nesta população. Sugere-se que os benefícios da atividade física nestes sintomas se devam à melhora na regulação hormonal e do sistema nervoso autônomo, levando à redução do estado pró-inflamatório e do estresse oxidativo, com aumento de produção de fatores neurotróficos. Esta prática também funcionaria como exposição interoceptiva, útil para a aprendizagem do entendimento e manejo as ansiedade pelo paciente. No terceiro artigo, são analisados ensaios clínicos que avaliam a eficácia do tratamento farmacológico na prevenção de recaídas em pacientes com TAG, discutindo-se o tempo de manutenção deste tratamento. Esta revisão sistemática mostrou que a continuidade do tratamento por ao menos 6 meses é eficaz na prevenção de recaídas, sendo este o tempo mínimo de manutenção do tratamento. No quarto artigo, revisamos estudos de prevalência da comorbidade entre TAG e enxaqueca, analisando os possíveis mecanismos fisiopatológicos comuns às duas patologias e sugerindo condutas terapêuticas para este quadro comórbido. Os estudos encontrados confirmam a maior prevalência de enxaqueca em pacientes com TAG e vice-versa. Esta sobreposição pode ser explicada por ambas as

patologias serem associadas a hipoativação do córtex pré-frontal e córtex cingulado anterior, ao estado pró-inflamatório e de maior estresse oxidativo e à desregulação dos sistemas serotoninérgico e noradrenérgico. O tratamento com antidepressivos, psicoterapia e atividade física é proposto baseado nas evidências de eficácia para esta comorbidade. Ao final, os dados dos quatro artigos são reunidos com enfoque no objetivo geral da tese de entendimento do modelo fisiopatológico do TAG, trazendo orientações para o manejo clínico deste transtorno.

ABSTRACT

This thesis aims to present four studies carried out by the author and collaborators, with the overall aim of better understanding the pathophysiological model for generalized anxiety disorder (GAD) and bringing orientations for its therapeutic management. The methodology applied for these four studies was the systematic review of the literature, based on the PRISMA method. In the first article, functional neuroimaging studies are reviewed in patients with GAD to find a neurobiological basis for the different cognitive models described for this disorder. In this review, we found that these patients present deficits in the emotional regulation process and in the ability to select threatening stimuli, as well as in the suppression of the induced worries. In all these tasks, the impairment in the engagement of the prefrontal cortex and anterior cingulate cortex was found, which would lead to greater activation of the amygdala and other limbic structures associated with conditioned fear response. In the second article, we have reviewed the studies that evaluate the efficacy of physical activity in improving anxiety symptoms in healthy elderly (without diagnosis of GAD). We also discuss the anxiolytic mechanisms of this practice taking into account the endocrine-metabolic changes associated with these symptoms. We conclude that regular physical activity is effective in improving anxiety symptoms in this population. It was suggested that the benefits of physical activity in these symptoms are due to the improvement in hormonal and autonomic nervous system regulation, leading to the reduction of the pro-inflammatory state and oxidative stress, with an increase in the production of neurotrophic factors. This practice would also work as an interoceptive exposure, useful for patient's understanding and managing of anxiety.

In third article, clinical trials evaluating the efficacy of pharmacological treatment in the prevention of relapses in patients with GAD are analyzed, and the ideal duration for this treatment is discussed. This systematic review showed that treatment continuation for at least 6 months is effective in preventing relapses, thus it would be the minimum period for treatment maintenance. In the fourth article, we reviewed studies evaluating the prevalence of the comorbidity between GAD and migraine, analyzing the possible common pathophysiological mechanisms and suggesting therapeutic conducts for this comorbid condition. The studies found confirm the higher prevalence of migraine in patients with GAD and vice versa. This overlapping can be explained by both pathologies being

associated with hypoactivation of the prefrontal cortex and anterior cingulate cortex, the pro-inflammatory state and the higher oxidative stress and the dysregulation of the serotonergic and noradrenergic systems. Treatment with antidepressants, psychotherapy and physical activity is proposed based on the evidence of efficacy for this comorbidity. Finally, the data of the four articles are gathered with focus on the overall objective of the thesis of elaboration of a model for understanding the pathophysiology of GAD and providing orientations for the clinical management of this disorder.

LISTA DE SIGLAS

TAG - transtorno de ansiedade generalizada

LabPR - laboratório de pânico e respiração

DSM - Manual diagnóstico e estatístico de transtornos mentais

ECA - epidemiological catchment area study

NCS - National Comorbidity Survey

WMHS - World Mental Health Surveys

ESEMeD - European Study of the Epidemiology of Mental Disorders

RMa- ressonância magnética anatômica

RMf – ressonância magnética funcional

BOLD - Blood oxygenation level-dependent

DTI - tensor de difusão

RMfrs - ressonância magnética funcional de repouso

ISRS - antidepressivos inibidores de recaptação de serotonina

IRSN – antidepressivos inibidores de recaptação de serotonina e noradrenalina

DPOC – Doença Pulmonar obstrutiva crônica

PFC - prefrontal cortex

ACC - anterior cingulate cortex

PSWQ - Penn State Worry Questionnaire

ASL – Arterial Spin Labeling

CS- Conditioned stimulus

SAD – Social Anxiety Disorder

PD – Panic disorder

PA – Physical activity

BDNF – Brain-derived Neurotrophic Factor

UNCP2 - mitochondrial uncoupling protein 2

IGF -1 - insulin-like growth factor-1

BAI - Beck Anxiety Inventory

BDI - Beck Depression Inventory

CAMCOG - The Cambridge Cognitive Examination for Mental Disorders of the Elderly

CES-D - Center for Epidemiologic Studies Depression Scale

HADS-A - Hospital Anxiety and Depression Scale - Anxiety Subscale

BSI-53 - Brief Symptom Inventory-53.

GDS - Geriatric Depression Scale

RM - repetition maximum

POMS - Profile and Mood States

VAMS - Visual Analogue Mood Scale

HRR – heart rate reserve

SECF - Scale of Elderly Cognitive Function

HAM-D - Hamilton Depression Rating Scale

HAM-A – Hamilton Anxiety rating scale

SCID -I - Structured Clinical Interview for DSM-IV Axis I Disorders

ICHD-II - Second Edition of International Classification of Headache Disorders

MINI - Mini International Neuropsychiatric Interview

WHO-CIDI - World Health Organization Composite International Diagnostic Interview

MDD - major depressive disorder

A-LIFE - Longitudinal Interval Follow-up Evaluation for Adolescents

PAG - periaquedutal gray

CGRP - Calcitonin-gene related peptide

SP - substance P

VIP- vasoactive intestinal peptide

HPA - hypothalamic–pituitary–adrenal axis

CRP - -reactive protein

NADPH - nicotinamide adenine dinucleotide phosphate

NOS - oxidase activation and modulation of nitric oxide synthase

SUMÁRIO

1. APRESENTAÇÃO

"Tive uma vida horrível. Só que ela nunca aconteceu."
M.L., Paciente com transtorno de ansiedade generalizada.

A frase acima, dita por uma paciente com TAG, simboliza bem o que me motivou a estudar este transtorno. A partir de relatos como este, entendi que o TAG é um transtorno que traz enorme sofrimento e leva, muitas vezes, ao desperdício de uma vida que poderia ter muito mais qualidade, mas que acaba por ser vivida de forma sofrida desnecessariamente.

Sempre fiquei muito intrigada com este transtorno, que tende a ser tratado como de menor gravidade do que outros transtornos mentais, sendo, por muitos, até questionado se seria mesmo um transtorno ou uma variação da normalidade, mas que, ao mesmo tempo, gera relatos de tanto sofrimento.

Além disso, o TAG é um transtorno muito frequente, pouco estudado e com fisiopatologia ainda pouco conhecida (1). Seu melhor entendimento se faz importante não apenas para o conhecimento do transtorno em si, mas também por ser a patologia de base que, muitas vezes, propicia o terreno fértil para o surgimento de outros transtornos como depressão e uso de álcool e drogas, assim como comorbidades clínicas como enxaqueca, síndrome do intestino irritável, fibromialgia, doença coronariana, entre outras (1).

Este relato de sofrimento subjetivo dos pacientes é confirmado por dados epidemiológicos quanto ao prejuízo funcional e social provocado por este transtorno. Segundo a organização mundial se saúde, 56.3% dos pacientes com TAG apresentam incapacidade grave e recebem auxílio do Estado em algum momento da vida (2). Adultos jovens portadores de TAG, apresentam, inclusive, maior risco de suicídio, após controle para comorbidades e eventos estressores externos (3).

Assim, apesar de ter estudado transtorno de pânico durante o mestrado e fazer parte do laboratório de pânico e respiração (LabPR) desde 2008, optei por estudar TAG no meu doutorado. Para isso tive o apoio incondicional do professor Antonio Egidio Nardi, que pode entender a minha opção e se manteve como meu orientador, e do professor Rafael Freire, que iniciou a linha de pesquisa em TAG, dentro do LabPR.

Publicamos, então, em 2014, o artigo 1 desta tese, que aborda os estudos de ressonância magnética funcional que testam os diferentes modelos cognitivos descritos para o TAG.

Optei por este tema em específico com o objetivo de estabelecer uma ponte entre o entendimento dos mecanismos cognitivos do TAG e suas bases neurobiológicas, através dos achados de neuroimagem funcional.

Ainda no final de 2014, cursei a disciplina no doutorado sobre exercício físico e envelhecimento da professora Andrea Deslandes. Nesta disciplina, muito se falou sobre as alterações inflamatórias dos transtornos psiquiátricos e como a atividade física poderia modificar este processo. Fiquei, então, interessada em estudar mais a fundo os mecanismos pelos quais a atividade física promove melhora de sintomas de ansiedade. Considerei que esta também seria, em última análise, uma forma de entender os mecanismos fisiopatológicos de transtornos de ansiedade como o TAG, no que tange às alterações endócrino-metabólicas e inflamatórias. E, inspirada pela disciplina da professora Andrea e por observar esta lacuna na literatura, foquei este estudo na população idosa. Assim, em conjunto com os coautores, escrevi o artigo 2, publicado em 2015.

Ao longo de 2015 e 2016, também realizei, paralelamente, uma revisão sistemática da literatura visando responder uma pergunta que muitas vezes surgia na minha prática clínica: A manutenção do tratamento farmacológico para o TAG é válida? E por quanto tempo?

Para tentar responder à estas questões, escrevemos o artigo 3, analisando os ensaios clínicos que avaliam a eficácia da manutenção do tratamento farmacológico do TAG na prevenção de recaídas.

Já em 2017, resolvi estudar a comorbidade entre TAG e enxaqueca, uma questão cujo interesse também foi despertado por situações da prática clínica, mas que seguia o principal eixo norteador do doutorado de entendimento das bases fisiopatológicas do TAG. Além de haver uma implicação clínica importante, busquei encontrar mecanismos fisiopatológicos comuns entre estas duas doenças que, comumente, se apresentam associadas. Escrevemos, assim, o artigo 4, que ainda não foi publicado.

Esta tese consiste, então, da compilação destes 4 artigos e ao escrevê-la, em sua introdução e conclusão, busquei costurar os achados destes artigos e montar este "quebra-cabeça", visando construir um modelo fisiopatológico unificado para o TAG que nos ajudasse também a trazer orientações terapêuticas.

2. INTRODUÇÃO

2.1 Ansiedade e TAG: Breve histórico e definições

A ansiedade é definida como uma sensação vaga e difusa, desagradável, de apreensão expectante que pode ser acompanhada de diversas manifestações físicas (4). Deve ser diferenciada do medo, uma emoção básica e primitiva, que ocorre como uma resposta adaptativa saudável a uma ameaça ou perigo percebido. A ansiedade, por sua vez, é uma resposta emocional orientada pelo medo, que resulta da ativação de um complexo sistema cognitivo, afetivo, fisiológico e comportamental (4). Tal ativação se dá em resposta a situações percebidas como imprevisíveis ou incontroláveis e interpretadas como uma ameaça pelo indivíduo ou pela antecipação de uma ameaça em potencial (5,6). Sensações de ansiedade são uma parte normal da experiência humana, mas a ansiedade excessiva ou inadequada pode se tornar um transtorno (5).

Desde a antiguidade, a ansiedade vem sendo descrita como uma emoção negativa e há relatos de médicos e filósofos gregos contemporâneos de Hipócrates de quadros semelhantes aos atuais transtornos de ansiedade (7). No entanto, até o século XIX, a ansiedade não era classificada como uma doença em separado. Pacientes que apresentassem estes sintomas eram classificados como sendo portadores de outros transtornos, como na descrição de Robert Burton em seu livro “The anatomy of Melancholy”. Boissier de Sauvages, no século XVIII, descreveu quadros semelhantes ao transtorno de ansiedade generalizada e ao transtorno de pânico dentro da denominação de “panophobias” (do adjetivo grego panophobos, “medo de tudo”) (7).

Ao final do século XIX, a ansiedade passou a ser característica central de novas categorias diagnósticas como a neurastenia de Beard que incluía sintomas de depressão e ansiedade, fadiga crônica e hipocondria (7). Freud e Kraepelin foram contemporâneos de Beard. Freud trata ansiedade no contexto das neuroses, que classifica em neurose de ansiedade ou angústia (ansiedade livremente flutuante ou expectante), neurose fóbica, neurose histérica e neurose obsessiva. Kraepelin, por sua vez, deu menos importância aos quadros de ansiedade do que aos afetivos e psicóticos como transtornos isolados, mas considerava a ansiedade ("Angst") um afeto negativo anormal muito comum e chegou a admitir uma categoria nosológica para fobias (7).

Já no século XX, surgiram os manuais de classificação diagnostica dos transtornos mentais como o Manual diagnóstico e estatístico de transtornos mentais (DSM) e nas suas primeiras versões (DSM-I e DSM-II), os transtornos de ansiedade eram definidos como transtornos neuróticos seguindo a teoria freudiana. Em 1980, foi publicada a terceira edição do DSM (DSM-III) que marcou uma nova classificação diagnostica para os transtornos de ansiedade não mais embasados na teoria psicanalítica. Foi quando se deu a primeira descrição do TAG entre outros transtornos de ansiedade como transtorno de pânico, fobias, transtorno obsessivo-compulsivo e transtorno de estresse pós-traumático. O TAG era caracterizado por ansiedade e preocupação incontroláveis e difusas, acompanhadas de diversos sintomas psicofisiológicos, com duração mínima de 1 mês (7,8). Já no DSM-III-R, houve uma mudança do tempo de duração exigida dos sintomas de 1 para 6 meses (8). Esta classificação foi mantida e aprimorada no DSM –IV, no qual a preocupação excessiva e incontrolável passou a ser considerada o principal sintoma no TAG. A lista de sintomas físicos de ansiedade associados foi reduzida de 18 para 6 sintomas, detalhados a seguir (8,9).

Em 2013, foi publicada a quinta edição do DSM (DSM –5) (10), atualmente em voga, na qual o TAG é definido por ansiedade e preocupação excessivas e incontroláveis, ocorrendo na maioria dos dias por pelo menos 6 meses e relacionada a inúmeros eventos ou atividades (p.ex. trabalho e desempenho escolar). A ansiedade e a preocupação estão associadas a 3 (ou mais) dos seguintes sintomas (com pelo menos alguns sintomas estando presente na maioria dos dias nos últimos seis meses): inquietação ou sensação de estar no limite, cansar-se facilmente, dificuldade de concentração, irritabilidade, tensão muscular, distúrbios do sono (dificuldade de iniciar ou manter o sono e sensação sono não satisfatório).

A preocupação persistente e excessiva é a característica principal do TAG. Embora o conteúdo das preocupações possa variar, ela tende a ser ampla e penetrante e pode incluir uma gama de domínios, tais como as relações interpessoais, saúde física, escola/ trabalho, finanças e até mesmo a preocupação por estar preocupado (11). Para o diagnóstico, é importante, também, que estes sintomas causem sofrimento clinicamente significativo, com prejuízo para o desempenho em atividades sociais, ocupacionais, entre outras (10).

2.2 Da nosologia à epidemiologia: Inter-relação entre critérios diagnósticos e dados epidemiológicos no TAG

Os avanços na operacionalização de critérios diagnósticos para os transtornos psiquiátricos permitiram a realização de pesquisas epidemiológicas de mais larga escala como a epidemiological catchment area study (ECA) (12), a National Comorbidity Survey (NCS) (13) e a World Mental Health Surveys (WMHS) (14). Estas, por sua vez, auxiliam na avaliação do impacto da aplicação de diferentes critérios diagnósticos e contribuem para o aprimoramento destes critérios (15).

Os transtornos de ansiedade são os mais prevalentes dentre os transtornos mentais em diversos estudos epidemiológicos ao redor do mundo. A prevalência ao longo da vida do TAG, assim como dos demais transtornos de ansiedade, varia muito de país para país. A mais baixa foi encontrada na Nigéria - 0,1% e a mais alta no Canadá - 8,7% (15, 16, 17). No Estados Unidos, um estudo de 2012 encontrou prevalência ao longo da vida de 4,3% e na Nova Zelândia de 6,2% (15,18). Estudos de países europeus também demostram variação de 0,8% (Alemanha) a 6,4% (Itália) (16). No Brasil, o "São Paulo Megacity Mental Health Survey" encontrou prevalência para o TAG de 3,7% (18). Estas diferenças podem ser explicadas por diferenças de fatores de risco e resiliência de cada região e por questões culturais que influenciam no limite entre normal e patológico e na possibilidade de reconhecer e assumir um transtorno mental, além de vieses introduzidos pela tradução de escalas diagnósticas (15).

A média de prevalência em 12 meses do TAG de 2% é, possivelmente, subestimada já que o TAG é um distúrbio de curso oscilante ao longo da vida, com fases de melhora e piora (19). O início do quadro é frequente na adolescência ou início da idade adulta, mas pode se iniciar de forma dispersa nas diferentes faixas etárias (15,16). O estudo americano de Kessler et al (19) e o brasileiro "São Paulo Megacity Mental Health Survey" (18) avaliaram o risco de desenvolver TAG caso o indivíduo chegasse a 75 anos de idade e encontraram taxas, respectivamente, de 9% e 8,5%. A ampla diferença entre prevalência em 12 meses e estimativa de risco de TAG aos 75 anos mostra que a instalação do TAG pode se dar em idade mais avançada (18,19).

Com o aumento do tempo de manifestação dos sintomas de 1 para 6 meses implementada a partir do DSM-III-R, houve redução significativa da prevalência encontrada (que chegava a 21% em estudos utilizando critérios do DSM-III). A exigência da preocupação excessiva como critério central para o TAG a partir do DSM-IV também levou a redução da prevalência encontrada para o transtorno (16). A partir destas mudanças dos critérios

diagnósticos, a confiabilidade inter-avaliador do TAG melhorou muito em relação aos estudos anteriores (chegando a k = .67) (20).

Os estudos epidemiológicos também ajudam na distinção entre TAG e outros transtornos de ansiedade e depressão, já que estes comumente se apresentam em comorbidade. Até 93% dos casos em amostras clínicas de TAG apresentam comorbidades e três quartos dos pacientes com TAG desenvolvem depressão e algum momento da vida (16, 21,22). Bases genéticas e neurobiológicas comuns são propostas para estes transtornos chamados do espectro internalizante. No entanto, estudos epidemiológicos mostram que o TAG apresenta um "cluster" de sintomas que se diferencia da depressão, com diferentes curso e evolução, sendo um constructo de boa validade (23). Segundo estudo canadense, pacientes com TAG isolado relataram taxas de sofrimento psicológico moderado a grave e de incapacidade moderada a grave comparáveis (ou mesmo um pouco mais altas) do que aqueles com depressão isolada (17). Estes achados foram equivalentes aos encontrados no estudo europeu “European Study of the Epidemiology of Mental Disorders” (ESEMeD), em que os níveis de sofrimento e prejuízos percebidos para o TAG e para a depressão foram semelhantes, porém distinguíveis (24). Outro dado importante é que muitos pacientes com TAG só procuram tratamento quando desenvolvem depressão ou transtorno de pânico comórbidos, consistindo em um viés para amostras clínicas em relação às amostras de população geral (17,21).

2.3 Entendendo e diferenciando o TAG: da nosologia a neurobiologia

A validação do diagnóstico do TAG esbarra na questão essencial que desafia toda a classificação diagnóstica categorial dos transtornos psiquiátricos que é o fato de se basear em dados fenomenológicos e não empíricos (25). A falta de biomarcadores e medidas objetivas da psicopatologia dificultam a diferenciação entre normal e patológico e entre as diversas patologias (26). O conhecimento a respeito dos mecanismos neurais da cognição, comportamento e emoções e suas possíveis patologias ainda é rudimentar (26).

Apesar do refinamento dos critérios diagnósticos do TAG ao longo dos últimos anos e dos estudos epidemiológicos corroborarem com sua diferenciação de outros transtornos de ansiedade e afetivos, a integridade nosológica do TAG ainda tem sido questionada, em grande parte pelo ainda incipiente embasamento neurobiológico (21,22,26). Tal embasamento vem sendo cada vez mais estudado, objetivando-se tornar possível a validação desta classificação diagnóstica e otimizar o arsenal terapêutico para o tratamento do TAG e outros transtornos psiquiátricos.

2.3.1 Achados de neuroimagem: investigando alterações do funcionamento cerebral no TAG

Nos últimos anos, métodos de imagem não-invasivos como a ressonância magnética anatômica (RMa) e funcional (RMf) vem sendo utilizados na busca de maior compreensão dos mecanismos neurobiológicos do TAG.

A RMf é uma técnica que utiliza mudanças de intensidade de sinal da ressonância magnética para rastrear alterações hemodinâmicas no cérebro. Estas alterações hemodinâmicas, conhecidas como resposta BOLD (do inglês "blood oxygenation level-dependent") podem ser utilizadas como medida aproximada para a função neuronal local, permitindo a inferência de quais regiões do cérebro são ativadas durante uma determinada tarefa ou situação e do grau de anormalidade destas ativações comparadas a controles (27).

Para entendermos os estudos com RMf realizados para investigação do TAG, precisamos falar, inicialmente, sobre os modelos cognitivos formulados para a compreensão deste transtorno, já que as tarefas realizadas durante a execução do exame de RMf se baseiam nestes modelos. O primeiro artigo que compõe esta tese (artigo 1) consiste em uma revisão sistemática que avalia justamente a correlação entre os modelos cognitivos para o TAG e os achados em estudos de RMf que os testam.

O mais estudado deles é o modelo da "desregulação emocional", que afirma que pacientes com TAG apresentam hiperresponsividade a estímulos afetivos positivos e negativos, especialmente negativos, e um déficit na capacidade de entender e lidar com estas emoções. A associação destes dois fatores leva ao aumento da ansiedade e desconforto quando estes pacientes se deparam com situações que despertam emoções mais intensas (28,29). É descrita ainda a dificuldade em regular e minimizar cognitivamente esta emoção sentida (28). A preocupação excessiva surgiria então como o principal mecanismo de evitação do enfrentamento das emoções negativas mais intensas, tão difíceis de serem administradas pelos pacientes com TAG.

O modelo da desregulação emocional vem sendo testado por diversos estudos de RMf através da tarefa de enfrentamento de faces de expressões emocionais durante a realização do exame avaliando áreas hipo ou hiperativadas no processo de reação às faces e, em alguns dos estudos, no processo de regulação cognitiva desta reação (27). Como será descrito no primeiro artigo desta tese, disfunções nos circuitos relacionados aos processos de reação e regulação emocionais são encontradas nos estudos de RMf em pacientes com TAG, fortalecendo esta

teoria cognitiva. A principal delas a ser destacada seria o prejuízo da função inibitória do córtex pré-frontal e córtex cingulado anterior no processo de regulação emocional (27).

Técnicas de neuroimagem de tensor de difusão (DTI) e de ressonância magnética funcional de repouso (RMfrs) também vem sendo utilizadas para a identificação das interconexões anatômicas e funcionais in vivo e, potencialmente, das anormalidades encontradas nestas redes neuronais em diversas patologias (30). A presença de anormalidades nos circuitos relacionados a estados de ansiedade e o déficit na capacidade de regulação da atividade amigdaliana pelas estruturas corticais superiores como o córtex pré-frontal e córtex cingulado anterior também já foram relatados por estudos que avaliaram a conectividade estrutural (DTI) (31) e funcional (RMfrs) (32) entre estas áreas.

Outro modelo interessante para o entendimento da fisiopatologia do TAG é o da chamada "hipergeneralização do medo condicionado". Liessek propõe que pacientes com diversos transtornos de ansiedade, entre eles o TAG, apresentam prejuízo na capacidade de diferenciar estímulos condicionados dos não condicionados a estímulos aversivos. Com isso, estímulos de alguma forma semelhantes aos condicionados aos aversivos (chamados de estímulos de generalização) disparam respostas psicofisiológicas semelhantes às disparadas pelos estímulos condicionados aos aversivos, levando ao aumento de situações consideradas ameaçadoras capazes de disparar tais respostas (33). Estudos de RMf e RMfrs também já demonstraram prejuízo no recrutamento do córtex pré-frontal ventromedial durante a inibição da resposta ao estímulo não condicionado (estímulo de generalização) (34,35).

2.3.2 Alterações neuroendocrinológicas: a importância do processo inflamatório, estresse oxidativo e sistemas monoaminérgicos na etiopatogenia do TAG

Como sugerido pelos modelos descritos na seção acima, o TAG caracteriza-se pelo prejuízo na regulação emocional e no processo de resposta ao medo condicionado (36). Na última década, diversos estudos vêm sendo realizados visando entender os mecanismos envolvidos nesta desregulação da resposta ao medo e ao estresse no TAG e em outros transtornos de ansiedade.

Para além das alterações dos sistemas monoaminérgicos e gabaérgico que de início erma o foco dos estudos relacionados ao mecanismo fisiopatológico dos transtornos afetivos e de ansiedade, a importância das alterações nos sistemas inflamatório e imunológico vem sendo cada vez mais estudada e compreendida (36, 37). Devido ao estresse crônico e hiperativação da amigdala e outras estruturas límbicas envolvidas no circuito do medo condicionado, ocorre

a ativação do eixo hipotálamo-hipófise-adrenal e alterações inflamatórias e imunológicas (36, 38), que serão descritas nos artigos 2 e 4 desta tese.

No artigo 2 esta abordagem é feita no contexto do entendimento da importância da atividade física em sintomas de ansiedade em idosos. Já no artigo 4, o processo inflamatório em pacientes com TAG é analisado para a compreensão da frequente comorbidade entre TAG e enxaqueca, onde o estado inflamatório crônico pode ser visto como possível mecanismo fisiopatológico comum.

O papel dos sistemas serotoninérgico e noradrenérgico no TAG ainda é bastante controvertido apesar da comprovada eficácia dos antidepressivos inibidores de recaptação de serotonina (ISRS) e inibidores de recaptação de serotonina e noradrenalina (IRSN), primeira linha para o tratamento farmacológico deste transtorno. Estes neurotransmissores apresentam papel modulatório no processo de resposta ao medo e de regulação emocional (39).

Os neurônios serotoninérgicos do núcleo da rafe apresentam terminações dendríticas na amígdala e córtex pré-frontal, onde, através de receptores 5HT2c, principalmente, facilitam a resposta ao medo condicionado, enquanto, através dos receptores 5HT1a, podem inibir esta mesma resposta na substância cinzenta periaquedutal (40).

A ativação dos neurônios noradrenérgicos originados no locus ceruleus e outros núcleos do tronco cerebral modula a resposta ao estresse agudo e crônico em diversas áreas do sistema límbico como a região central da amígdala e o núcleo do leito lateral da estria terminal (39).

Em pacientes com TAG, foi sugerido haver um estado disfuncional com redução crônica da transmissão serotoninérgica e esgotamento por ativação tônica do sistema noradrenérgico (39). Foi demonstrado que o cortisol aumenta a recaptação de serotonina na fenda sináptica em controles, mas não em pacientes com TAG, supondo-se que os níveis cronicamente elevados de cortisol nestes pacientes levaram ao estado máximo de recaptação de serotonina (41).

2.4 Abordagens terapêuticas para o TAG

2.4.1 Tratamento farmacológico

Os antidepressivos ISRS e IRSN são o tratamento farmacológico considerado de primeira linha para o tratamento do TAG (42). Estes antidepressivos demonstram eficácia em diversos ensaios clínicos de curto e longo prazo e apresentam perfil relativamente favorável de efeitos colaterais[6]. A paroxetina, a sertralina e o escitalopram são os ISRS mais estudados e a venlafaxina foi mais amplamente estudada dentre os IRSN, mas a duloxetina também já apresenta eficácia comprovada (42,43).

No entanto, em torno de 30% dos pacientes com TAG são refratários a estas medicações de primeira linha ou não toleram efeitos adversos a longo prazo como a disfunção sexual e o embotamento afetivo (44). Além disso, casos de comorbidade com transtorno bipolar do humor são comuns (em torno de 15%) (43) quando o uso de antidepressivos pode ser temerário. Com isso, apesar dos ISRS e ISRN permanecerem como primeira linha para o tratamento do TAG de acordo com consensos internacionais, outras opções de medicamentos vêm sendo estudadas.

A pregabalina é uma medicação anticonvulsivante já está aprovada para o tratamento do TAG em países europeus (45,46). Atua como ligante da unidade α2δ dos canais de cálcio em neurônios pré-sinápticos hiperexcitados, reduzindo, assim, a liberação de neurotransmissores excitatórios como o glutamato (45,46).

A quetiapina de liberação prolongada, um antipsicótico atípico, também vem sendo estudada (oito ensaios clínicos) como alternativa para o tratamento medicamentoso do TAG, mas ainda não foi aprovado para o tratamento deste transtorno (47). A principal limitação ao uso desta medicação é o risco elevado de ganho de peso e desenvolvimento de síndrome metabólica (43,47). As dosagens utilizadas para o TAG são inferiores àquelas utilizadas para efeito antipsicótico (100-200 mg/dia) (47).

A agomelatina e a vortioxetina são novos antidepressivos que também vem sendo testados para utilização no TAG, mas ainda são poucos os estudos disponíveis (48,49,50).

Comumente, uma única medicação não é suficiente para a remissão dos sintomas do TAG, ou para abarcar todas as diferentes manifestações sintomáticas de um determinado paciente. Nestes casos, faz-se necessária a associação de uma segunda droga ao esquema terapêutico (42,43). As medicações mais utilizadas em associação aos antidepressivos são os benzodiazepínicos, como o clonazepam, o diazepam e o alprazolam. São interessantes por

serem eficazes nos sintomas físicos de ansiedade e para o tratamento da insônia, muito comumente presente nestes pacientes e apresentarem ação imediata (42,43).

Há, no entanto, limitações importantes ao uso dos benzodiazepínicos, como a possibilidade de desenvolvimento de tolerância e o risco de abuso e dependência. Além disso, pacientes idosos ou com doenças pulmonares como doença pulmonar obstrutiva crônica (DPOC) apresentam contraindicação relativa ao uso de benzodiazepínicos. Nestes casos, pregabalina (51), a buspirona e a quetiapina de liberação prolongada (44, 47) podem ser alternativas. A risperidona e a olanzapina também já demonstraram eficácia no tratamento adjuvante do TAG, porém o perfil de efeitos colaterais tende a ser ainda mais desfavorável do que o da quetiapina de liberação prolongada (47).

Por ser um transtorno crônico, mas sofrer flutuações ao longo da vida, uma importante pergunta que surge no manejo clínico do TAG é quanto à duração do tratamento medicamentoso. O artigo 3 desta tese visa responder esta pergunta através da revisão sistemática de ensaios clínicos que avaliam a prevenção de recaídas com a manutenção da droga ativa versus manutenção com placebo.

2.4.2 Tratamento não-farmacológico

A psicoterapia é considerada fundamental para o tratamento bem-sucedido do TAG. A terapia cognitivo-comportamental é o método psicoterápico mais estudado e com mais evidências na literatura (52).

Estudos controlados concluíram que as diversas abordagens cognitivo-comportamentais produzem mudanças significativas (com grandes tamanhos de efeito) que são mantidas no longo prazo (52).

As técnicas utilizadas incluem os seguintes componentes: psicoeducação, auto monitoramento dos sinais de ansiedade, relaxamento, exposição imaginária, dessensibilização e habilidades de enfrentamento e reestruturação cognitiva (53).

Como descrito pelo modelo de desregulação emocional do TAG, a preocupação é vista como uma atividade mental consciente e elaborada que tenta reavaliar estímulos potencialmente negativos de maneira menos ameaçadora. Ela funciona como uma esquiva cognitiva que visa inibir a excitação emocional (54). Ocorre ainda subestimação da capacidade interna de lidar com eventos externos, o que acarreta em tentativas frustradas de controlar ou extinguir a preocupação. Essas tentativas em longo prazo acabam por aumentar o nível de

ansiedade e vigilância do indivíduo. Sendo assim, a base cognitiva do TAG é vista como um ciclo vicioso e auto perpetuador e a terapia visa intervir neste processo elaborativo (55).

Uma prática que também vem sendo muito estudada para o tratamento do TAG é o Mindfulness, que tem origem em práticas orientais de meditação. É descrita como uma forma de manter a atenção no momento presente, sem qualquer tipo de julgamento, elaboração ou tentativas de alterar a experiência (56). A partir disso, desenvolveu-se o modelo comportamental baseado em aceitação e Mindfullness para tratamento do TAG (53). Sua eficácia poderia ser explicada pelo fato de pacientes com TAG terem como característica focar a atenção sobre potenciais catástrofes, levando à diminuição da consciência no momento presente (57). Além disso, esses indivíduos tendem a julgar ou avaliar suas experiências internas de forma negativa, criando dificuldades de regulação emocional (53). Redução da consciência do momento presente e uma postura julgadora para experiências internas podem interferir na aprendizagem adaptativa e ampliar as respostas emocionais distorcidas, perpetuando, assim, a evitação comportamental comum nestes pacientes (56). No entanto, ainda é um modelo de tratamento recente, com eficácia menos comprovada do que a de outros modelos de terapia cognitivo-comportamental para o tratamento deste quadro,

A prática de atividade física regular também vem sendo cada vez mais reconhecida como forma de tratamento auxiliar no TAG e outros transtornos de ansiedade (58,59). A atividade física auxilia na regulação do eixo hipotálamo-hipófise-adrenal, a reduzir a hiperatividade simpática, a aumentar a atividade de citocinas anti-inflamatórias e de enzimas antioxidantes melhorando o estado pró-inflamatório destes pacientes. Tais efeitos auxiliam no aumento da produção de neurotrofinas como o BDNF e melhora da neurogênese e neuroplasticidade (60,61). No artigo 2 desta tese foi explorada a importância da atividade física para o tratamento dos sintomas de ansiedade em idosos (ainda que sem diagnóstico de TAG), já que nesta população muitas vezes a farmacoterapia pode ser dificultada por maior intolerância e mais interações medicamentosas.

Técnicas de neuromodulação não-invasivas como a estimulação magnética transcraniana vem sendo estudadas como novas alternativas ao tratamento farmacológico para o TAG, em quadros de intolerância ou refratariedade. Dois ensaios clínicos randomizados placebo-controlados e um outro ensaio clínico piloto mostraram eficácia da estimulação do córtex pré-frontal dorsolateral direito na melhora dos sintomas referidos em pacientes com TAG (62,63,64). O protocolo exato de estimulação para o tratamento deste quadro (se alta ou baixa frequência de estimulação, por exemplo), ainda não é bem determinado devido a escassez de estudos.

3. OBJETIVO GERAL

Reunir dados da literatura visando o melhor entendimento da fisiopatologia do TAG e fornecer orientações para o tratamento deste transtorno.

4. OBJETIVOS ESPECÍFICOS

- Investigar as bases fisiopatológicas para os diferentes modelos cognitivos propostos para o TAG através da revisão de estudos de ressonância magnética funcional com estes pacientes (artigo 1).
- Avaliar a eficácia da atividade física em sintomas de ansiedade em idosos e discutir os mecanismos de ação desta prática nas alterações neuroendócrinas provocadas pela ansiedade (artigo 2).
- Avaliar a eficácia da farmacoterapia na prevenção de recaídas no TAG visando responder à pergunta sobre o tempo de manutenção do tratamento medicamentoso neste quadro (artigo 3).
- Investigar a prevalência da comorbidade entre TAG e enxaqueca e a partir destes achados discutir mecanismos fisiopatológicos comuns a estas duas condições clínicas (artigo 4).

5. METODOLOGIA

A metodologia utilizada nos quatro artigos apresentados nesta tese foi a revisão sistemática da literatura com base no método "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) (62). O PRISMA consiste em recomendações baseadas em evidências para a realização de revisões sistemáticas e metanálises, utilizando-se de uma lista de checagem ("PRISMA checklist") e de um fluxograma a serem seguidos.

6. DESENVOLVIMENTO

1) Mochcovitch MD, da Rocha Freire RC, Garcia RF, Nardi AE. A systematic review of fMRI studies in generalized anxiety disorder: evaluating its neural and cognitive basis. J Affect Disord. 2014; 167:336-42.

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ARTIGO 1

Mochcovitch MD, da Rocha Freire RC, Garcia RF, Nardi AE. A systematic review of fMRI studies in generalized anxiety disorder: evaluating its neural and cognitive basis. J Affect Disord. 2014; 167:336-42.

Journal of Affective Disorders 167 (2014) 336–342

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review

A systematic review of fMRI studies in generalized anxiety disorder: Evaluating its neural and cognitive basis

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ARTICLE INFO

Article history:
Received 8 June 2014
Accepted 24 June 2014
Available online 2 July 2014

Keywords:
Generalized anxiety disorder
fMRI

ABSTRACT

Background: Generalized anxiety disorder (GAD) is a prevalent anxiety disorder, but its neurobiological basis has been poorly studied. A few cognitive models have been proposed for understanding GAD development and maintenance. The aim of this study is to review functional Magnetic Resonance Image (fMRI) studies conducted with GAD patients and evaluate if they support and underpin the theoretical cognitive models proposed for this anxiety disorder.

Methods: A literature systematic review was undertaken in PubMed and ISI databases with no time limits.

Results: From the studies included in this review, 10 explored the "emotional dysregulation model", showing, prefrontal cortex (PFC) and anterior cingulate cortex (ACC) hypofunction and deficient top-down control system during emotion regulation tasks, despite conflicting techniques and results. Only one study explored the "conditioned fear overgeneralization theory", other the "intolerance of uncertainty model" and two studies were unspecific (worry induction tasks). Between those, there were 4 studies evaluating pre- and post-treatment with antidepressants or "mindfulness".

Limitations: The studies' methodologies differ between one another making it difficult to identify a common finding.

Conclusion: Emotion dysregulation seems to be an important cognitive dysfunction in GAD patients and fMRI studies suggest that it is related to PFC and ACC hypofunction as well as a deficient cortex–amygdala functional connectivity.

Contents

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http://dx.doi.org/10.1016/j.jad.2014.06.041
0165-0327/

1. Introduction

Generalized anxiety disorder (GAD) is a common anxiety disorder, with estimated lifetime prevalence around 5%, with significant impacts on healthcare systems (Kessler et al., 2001; Hoffman et al., 2008). GAD is characterized by chronic, excessive and uncontrollable worry about a variety of topics. The worry causes distress and/or functional impairment, and is associated with restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or having one's mind go blank, irritability, muscle tension, and sleep disturbance (APA, 2013). It causes important loss of productivity and reduces patient's quality of life (Kessler et al., 2001; Hoffman et al., 2008)

Different cognitive models have been proposed for understanding development and maintenance of GAD (Behar et al., 2009). One that is widely known is the "emotion dysregulation model" (Behar et al., 2009) It asserts that individuals with GAD experience emotional hyperarousal, which applies to both positive and negative, but particularly to negative, emotional states (Mennin et al., 2005). Besides that, individuals with GAD have a poorer understanding of their emotions and have more negative attitudes about them (e.g., the perception that emotions are threatening) than other individuals. Finally, they evidence maladaptive emotion regulation and management, making unsuccessful attempts to either minimize or over-control emotions. As such, worry plays a fundamental role in this model as an ineffective strategy to cope with emotions (Behar et al., 2009).

Another model that shares some of its concepts with the previous one is the "Avoidance model of worry" that asserts that worry is a verbal linguistic, thought based activity (Behar et al., 2005) that inhibits vivid mental imagery and associated somatic and emotional activation. This model also advocates that GAD patients show dysfunctional emotion regulation, but it is centered in the role of worry as a cognitive attempt to remove a perceived threat, while simultaneously avoiding the aversive somatic and emotional experiences that would naturally occur during the process of fear confrontation (Behar et al., 2009).

Yet, a third theoretical model for GAD that also shows similarities with the other two described above assumes that individuals with GAD do not tolerate uncertain or ambiguous situations and experience chronic worry in response to them. Ambiguous stimulus is interpreted as threatening, and worry would serve to either help them cope with feared events more effectively or to prevent those events from occurring at all (Borkovec and Roemer, 1995; Davey et al., 1996). This cognitive model is called the "intolerance of uncertainty model".

Despite its clinical and epidemiological importance and the effort for understanding its cognitive and emotional basis, GAD has been considerably less studied than other anxiety disorders from the neurobiological point of view (Etkin and Wager, 2007).

In this paper, we systematically reviewed functional Magnetic Resonance Image (fMRI) studies conducted with GAD patients aiming to discuss what these studies present about GAD neurobiology and if they support and underpin the theoretical cognitive models proposed for this prevalent and clinically challenging anxiety disorder.

2. Methodology

A literature systematic review was performed in PubMed and ISI (Web of Science – Thomson Reuters) scientific databases by two different investigators, using the following keywords: "generalized anxiety disorder" and "fMRI". No time limits were set for any database. The last search was conducted on May 31, 2014. The inclusion criteria were original research studies that evaluated adult GAD patients with fMRI. Studies with different fMRI methods or cognition tasks during the exam as well as resting-state exams were included, but studies presenting data about other imaging techniques as structural MRI, diffusion tensor imaging and spectroscopy were excluded. Studies that were not in English language or not original were also excluded from this review.

We found 97 articles on total, from which 23 were duplicated and two were not in English language. From those who left, 42 were excluded for not being original articles or not evaluating GAD patients in their samples. From the 30 remaining articles, 11 were excluded for showing data about other imaging techniques as structural MRI (two articles), diffusion tensor imaging (six articles), spectroscopy (three articles) and other eight articles were excluded for presenting data about children or adolescent samples (Fig. 1). On total, 14 studies were included in this review.

3. Results

The studies included in this section are divided in five different groups. The first one encompasses the studies evaluating the "emotional dysregulation model". The second one consists of studies not grounded by an specific cognitive model, wherein worry was tested generically. The third is formed by studies testing the "conditioned fear overgeneralization theory" and the fourth group by that testing the specific role of amygdala in this disorder. The fifth group consists of studies including treatment evaluation and treatment response prediction. All studies evaluated in this review are summarized in Table 1.

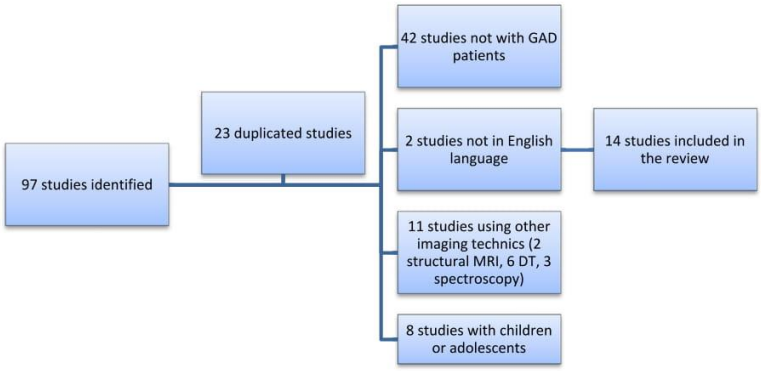

Fig. 1. Studies' selection flow for the systematic review. GAD=generalized anxiety disorder; DT=diffusion tensor.

Table 1
Studies included in the systematic review. GAD=generalized anxiety disorder; SAD=social anxiety disorder; HC=healthy controls; PFC=prefrontal cortex; ACC=anterior cingulate cortex; MBSR=mindfulness based stress reduction; SME=stress management education.

Study	Underlying cognitive theory	Sample (*N*)	Task during fMRI	Main results
Blair et al., 2008	Emotional dysregulation	17 GAD+SAD patients	Emotional faces confrontation	SAD presented increased amygdalar response to fearful faces.
		17 SAD patients		GAD presented increased responses to angry expressions in the lateral PFC.
		17 HC		
Ball et al., 2013	Emotional dysregulation	28 GAD patients	Emotional pictures reappraisal	GAD and PD showed less dorsolateral and dorsomedial PFC activation than HC.
		18 PD patients		
		23 HC		
Palm et al., 2011	Emotional dysregulation	15 female GAD patients	Implicit face emotion task (gender recognition during facing emotions)	Female GAD showed attenuated PFC activation to fearful, sad, angry and happy facial expressions.
		16 HC		Attenuated signal in the ACC to happy and fearful facial expressions.
Etkin et al., 2010	Emotional dysregulation		Trial to trail "emotional conflict adaptation" (using face expressions overlapped by matched/conflicted emotion words)	GAD patients failed in activating ACC (negative top-down ACC–amygdala connectivity during the regulation of emotional conflict). No difference in amygdala activation between GAD and HC.
Etkin et al., 2009	Emotional dysregulation		Resting-state fMRI	GAD: disrupted connectivity patterns of the amygdala subregions and a reduced PFC–amygdala connectivity.
Blair et al., 2012	Emotional dysregulation	34 GAD patients	Emotional pictures reappraisal	All patient groups showed reduced dorsal ACC activity compared to HC.
		37 SAD patients		
		34 SAD+GAD patients	Emotional Stroop task	Intact lateral PFC function.
		36 HC		
Paulesu et al., 2010	Not a specific one (worry induction)	8 GAD patients	Sentences to induce worry	GAD patients showed hyper-activation in medial PFC and ACC during both worry induction and posterior resting state phases while HC showed this response just during worrying phase.
		12 HC	Sad and neutral faces to induce mood states	
Andreescu et al., 2011	Not an specific one (worry induction)	7 elderly GAD patients	Individualized stimulus to induce worry and posterior worry suppression	GAD patients failed in activating PFC during worry-suppression task.
Greenberg et al., 2013b	Conditioned fear overgeneraliza-tion	32 female GAD	A range of rectangles in the screen paired with electric shocks	GAD patients showed a deficient ventromedial PFC recruitment during fear inhibition of "Generalization stimuli". The anterior insula area facilitates fear response to CS.
		25 female HC		
Yassa et al., 2012	Intolerance to uncertanty		Non-contingent monetary loss task (Gambling)	Decreased activity in the amygdala and increased activity in the BNST in GAD patients comparing to controls.
Hoehn-Saric et al., 2004	Emotional dysregulation	6 GAD patients		Treatment with citalopram reduced activation in PFC, the striatum, insula and paralimbic regions. Treatment with citalopram reduced the differences in responses to worry and neutral stimuli.
Whalen et al., 2008	Emotional dysregulation	15 GAD patients	Emotional faces confrontation	Pretreatment greater reactivity in ACC and lesser in the amygdala predicted the magnitude of treatment response. No difference in ACC and amygdala activation between GAD and HC. No difference before and after treatment in GAD patients
Nitschke et al., 2009	Emotional dysregulation	14 GAD patients	Affective pictures confrontation (evaluating emotion anticipation with cues)	GAD patients showed greater anticipatory activity in the amygdala for all stimuli. Higher levels of pretreatment anterior cingulate cortex activity in anticipation were associated with greater clinical outcome in GAD patients.
		12 HC		
Hölzel et al., 2013	Emotional dysregulation	15 GAD patients (MBSR)	Faces labeling task	GAD patients presented higher amygdala activation than HC in response to neutral, but not angry faces.
		11 GAD patients (SME)		The response in ventrolateral PFC showed greater increase in MBSR than SME participants. Functional connectivity between amygdala and PFC regions increased significantly pre- to post-intervention within the MBSR, but not SME group.

3.1. *Studies analyzing the "emotional dysregulation model"*

Six studies analyzed the neurocircuitry involved in emotional regulation process in GAD patients. These studies are based on the assumption that patients with this disorder resort to worry because of an underlying abnormality in regulating emotional processing. Two competing hypotheses may be elaborated for the neural bases of this deregulation. The first, based on the conceptualization that GAD involves an overactive top-down control system, posits that individuals with GAD exhibit prefrontal cortex

(PFC) and anterior cingulate cortex (ACC) hyper-activation during emotion regulation. A second hypothesis posits that GAD patients show attenuated PFC and ACC response (reflecting inadequate top-down control) during emotional regulation process.

In favor to the first hypothesis, there is one study by Blair et al. (2008) using a face emotion task during fMRI. The study compared 17 patients with social anxiety disorder (SAD) without GAD, 17 patients with SAD with GAD and 17 healthy controls. In this study, authors were tracking to compare SAD and GAD neural substrates, concluding that they seem to show different dysfunctional regions. While SAD patients without GAD showed increased amygdala response to fearful faces, patients with GAD were marked by increased responses to angry expressions in the frontal cortex, particularly a lateral region of the middle frontal gyrus and reduced amygdala response to fearful faces.

Besides that, most evidences have been favoring the second hypothesis. In a recent study by Ball et al. (2013) 28 GAD patients, 18 panic disorder (PD) patients and 23 controls were asked to reappraise or maintain emotional responses to negative images selected from the International Affective Picture System (Lang et al., 2008). Reappraisal or "changing how we think about a situation in order to decrease its emotional impact" (Gross, 2002) is one of the most studied forms of emotion regulation (Ball et al., 2013). Two processes were examined with the emotional regulation task: in each trial, individuals either maintained or reappraised their emotional responses to negative images. For the maintain condition participants were instructed to "maintain your emotional reaction until the picture disappears". For the reappraise condition, participants were asked to "change the way that you think about the picture in order to decrease your negative emotions". Suggested reappraisal strategies included generating a positive interpretation or taking a more detached perspective (Ball et al., 2013). As results, patients with GAD and PD demonstrated less dorsolateral and dorsomedial PFC activation than healthy controls during cognitive modulation of emotion (for both maintenance and reappraisal processes) and those with the least PFC activation reported the greatest anxiety severity and impairment.

Another study analyzing patients' reaction to emotional face expressions that also favored the second hypothesis was the one by Palm et al. (2011).They compared 15 female patients with GAD to 16 healthy controls for an implicit face emotion task during fMRI scanning. Patients were presented to expressions of anger, disgust, fear, happiness, sadness and neutrality (Ekman and Friesen faces) (Ekman and Friesen, 1976) and were asked to judge whether the faces were male or female by pressing a button on a hand-held button box. In this study, GAD female patients showed an attenuated BOLD signal in the PFC to fearful, sad, angry and happy facial expressions and an attenuated signal in the ACC to happy and fearful facial expressions to evaluate emotion regulation, Etkin et al. (2010) compared the trial to trial "emotional conflict adaptation" between GAD patients and controls. For this task the authors used face expressions overlapped by emotion words (as "fear" or "happy") that either matched or conflicted with the face expression. They hypothesized that GAD patients would show abnormalities in adapting to emotional conflict in this task. As results, this hypothesis was confirmed and it was observed that patients failed to activate the ACC and demonstrated negative top-down ACC - amygdala connectivity during the regulation of emotional conflict.

Before that study, Etkin et al. (2009) had also showed findings from resting state fMRI where compared to controls, GAD patients showed disrupted connectivity patterns of the amygdala subregions (basolateral and centromedial nuclear groups) and a reduced PFC–amygdala connectivity.

Aiming to compare GAD and social anxiety disorder (SAD) again (as did in the study from 2008 (Blair et al., 2008)) and explore different cognitive tasks involved in emotion regulation, Blair et al. (2012) evaluated explicit emotion regulation and top-down attentional control in these two groups of patients. These two cognitive functions are components of the emotional regulation process which are usually attributed to dorsal ACC. The sample was composed by 37 SAD patients, 34 GAD patients, 32 comorbid SAD/GAD and 36 controls. Explicit emotion regulation was tested trough emotional pictures reappraisal (individuals alternatively viewed and upregulated or downregulated responses to emotional pictures) and for attentional control task they performed an emotional Stroop task. All patients groups showed reduced dorsal ACC activity compared to controls and were not different from each other. Lateral PFC function was considered intact in these patients.

3.2. Studies using worry-induction tasks

Instead of analyzing the dysfunction in emotional regulation, some investigators have opted to study the neural correlates of pathological worry, since it is a central symptom in GAD psychopathology. The focus here is in excessive worry, this fallacious strategy that GAD patients tend to use to solve objective and subjective difficulties.

Paulesu et al. analyzed 8 GAD patients and 12 healthy controls inducing worry with specific sentences and using sad or neutral faces to induce mood states during fMRI scans. Medial PFC and ACC were activated during worry-induction in both subjects with GAD and normal controls. However, GAD subjects showed a persistent activation of these areas even during resting state scans that followed the worrying phase. This activation was correlated with scores on the Penn State Worry Questionnaire (PSWQ) (Paulesu et al., 2010).

Elderly GAD patients were evaluated in a recent study where authors induced worry with individualized stimulus and then asked patients to suppress these induced worries. Seven elderly GAD patients were compared to controls using arterial spin labeling (ASL) perfusion fMRI. It was found that patients failed in activating PFC during worry suppress task, similarly to what happened to GAD younger patients with emotional regulation tasks (Andreescu et al., 2011).

3.3. Studies analyzing the "conditioned fear overgeneralization theory"

Conditioned fear overgeneralization has gained interest in recent years due to its proposed role in the pathophysiology of the anxiety disorders (Lissek, 2012). This process is characterized by the transfer of conditioned fear to perceptually similar stimuli in which learned fear responses are extended from threat-related stimuli to nonthreatening cues, called generalization stimuli (GS) (Lissek, 2012).

As observed in the study with healthy volunteers by Greenberg et al. (2013a), the brain regions engaged by the generalization task included the insula, ACC, supplementary motor area (SMA), caudate, amygdala, ventromedial PFC, and the somatosensory cortex. Neural reactivity in the insula, ACC, supplementary motor area (SMA), and caudate follows a generalization gradient with a peak response to a conditioned stimulus (CS) that declines with greater perceptual dissimilarity of GS to the CS. In contrast, reactivity in the ventromedial PFC, a region linked to fear inhibition, showed an opposite response pattern (Greenberg et al., 2013b).

In GAD, overgeneralization may contribute to an increase in the number of events capable of triggering worry, since they act as GS (Greenberg et al., 2013b).

As far as we know, just one study was published testing this theory for GAD patients using the fMRI technique, also by Greenberg et al. (2013b). In this study, 32 women presenting GAD were compared to 25 female healthy controls. The generalization task consisted of 120 trials (15 trials × 8 conditions). Stimuli were seven red rectangles with identical height and varying width. A middle-sized rectangle was the CS; half of the time the CS co-terminated with an electric shock (CSpaired), whereas half of the time it did not (CSunpaired). The six remaining rectangles differed by ±20%, ±40%, or ±60% in width from the CS, and served as the GS. As results, GAD patients showed a deficient ventromedial PFC recruitment during fear inhibition of GS and connectivity analyses across participants implicated the anterior insula in facilitating the fear response to the CS, consistent with a modulatory roll for this area in the execution of fear responses. The authors concluded, then, that GAD patients present deficits in fear regulation (rather than in the excitatory response itself) (Greenberg et al., 2013b).

3.4. Evaluation of the amygdala's role

Studies of other anxiety disorders predict that the amygdala in patients with GAD would be hyperactive to negative emotional or anxiety-provoking stimuli (4). Two studies with adolescents support this prediction (McClure et al., 2007; Monk et al., 2008). Studies in GAD adults, however, have provided conflicting results.

While some have reported a heightened amygdala response to all stimuli, including non-aversive ones (Hoehn-Saric et al., 2004; Nitschke et al., 2009), Blair's study reported a reduced amygdala response to fearful faces in GAD patients (Blair et al., 2008). On the other hand, Whalen et al. (2008) and Etkin et al. (2010) have found no group differences in amygdala activation between GAD patients and controls during processing of emotional stimuli.

A study published by Yassa et al. (2012) evaluated the roles of amygdala and bed nucleus of stria terminalis (BNST) in GAD neurobiology. The authors relied on the theory that these two regions play different roles in stress and anxiety: the amygdala is considered to regulate responses to brief emotional stimuli (phasic fear) while the BNST is involved in chronic regulation of sustained anxiety (Davis et al., 2010). Using a non-contingent monetary loss task which involves high uncertainty on a trial-by-trial basis to attempt to induce a state of sustained anxiety, they predicted that GAD patients would show an increased BNST activation compared to controls and no difference in amygdala activation between groups (Yassa et al., 2012). Actually, a decreased activity in the amygdala and increased activity in the BNST in GAD patients comparing to controls were found. The authors hypothesized, then, that in GAD patients the amygdala might be engaged early in the course of a stressful or threatening event, but after that disengages to allow the BNST to maintain an a continuous anxious state and that this process may be more exaggerated compared to nonanxious individuals (Yassa et al., 2012).

3.5. Studies evaluating treatment effects and response prediction

Some studies have also proposed to evaluate if a specific neurocircuit activity could predict treatment response or may show changes after treatment. The first of them was the one by Hoehn-Saric et al., wherein fMRI images of six GAD patients were compared before and after 7 week-treatment with citalopram. Reduced activity in the right medial frontal gyrus, right precentral gyrus, left insula, right anterior and middle cingulate, right parahippocampal gyrus, left middle temporal gyrus, right lingual gyrus and left pons during worry stimulus after treatment was observed. In addition, contrasts before and after treatment revealed reductions in the differential response that existed between worry and neutral statements, but reduction of anxiety attenuates the response to both types of cues (Hoehn-Saric et al., 2004).

The magnitude of treatment response to venlafaxine could be predicted by greater pretreatment reactivity to fearful faces in rACC and lesser reactivity in the amygdala (Whalen et al., 2008) as well as higher levels of pretreatment ACC activity in anticipation of both aversive and neutral pictures (Nitschke et al., 2009).

A recent study evaluated the effect of a Mindfulness Based Stress Reduction program (MBSR) on brain activity measured by fMRI in GAD patients during faces labeling activity (Hölzel et al., 2013). This program consisted in an eight-week, manualized program (Kabat-Zinn, 1990) wherein mindfulness is trained via sitting and walking meditation, yoga exercises, and the "body scan", in which attention is sequentially directed through the whole body. Participants also receive stress education. In addition to the group sessions, participants are instructed to practice mindfulness exercises at home (with the help of an audio recording). They are taught to practice mindfulness also in their daily activities, such as eating, washing the dishes, taking a shower, etc., as a way to facilitate the transfer of mindfulness into daily life. This group (15 GAD patients) was compared before and after treatment with 11 patients that have got just stress management education (SME) (Hölzel et al., 2013).

The authors observed a greater increase in ventrolateral PFC activity after treatment in MBSR than SME group. Functional connectivity between amygdala and PFC regions increased significantly pre- to post-intervention within the MBSR, but not SME group.

This study reproduced the finding that treatment enhanced ventrolateral PFC activity found in a smaller study by Maslowsky et al. (2010).

4. Discussion

In this review we described studies that aimed to investigate the neurobiological basis of GAD through fMRI experiments (Table 1). One can easily observe that the major problem for drawing any conclusion is complete lack of uniformity of the studies' methodologies. Most of them have used face emotion tasks to evaluate emotion regulation while less have used affective pictures, but the specific task that can be involved in the complex emotional regulation process varied between the studies. This variation in the specific task used in each study makes a generalization impossible when we analyze the results all together.

Despite the difficulty for generalization, we can observe that the most consistent finding is that GAD patients fail to activate PFC and ACC during emotional regulation tasks. Thus, considering the two hypotheses elaborated for the neural basis of emotional dysregulation in GAD, the one that defends that a deficient top-down control system during the emotional regulation task is more consistent with the studies' results.

These findings are compatible with what Ball et al. (2013) have suggested about GAD dysfunction in emotional regulation process: the inability to sufficiently engage PFC in the service of emotion regulation could be a consequence of a chronic over-responsiveness of limbic circuitry that would, in turn, fatigue the top-down system, rendering it unable to effectively exert control when needed (Ball et al., 2013). Thus, the more chronic and severe the pathology, the less the PFC would be activated. In Ball's study, worry severity was inversely associated with PFC activation (Ball et al., 2013) (Fig. 2).

It is possible to suppose that Blair's study with GAD and SAD patients from 2008 (Blair et al., 2008) may had showed different

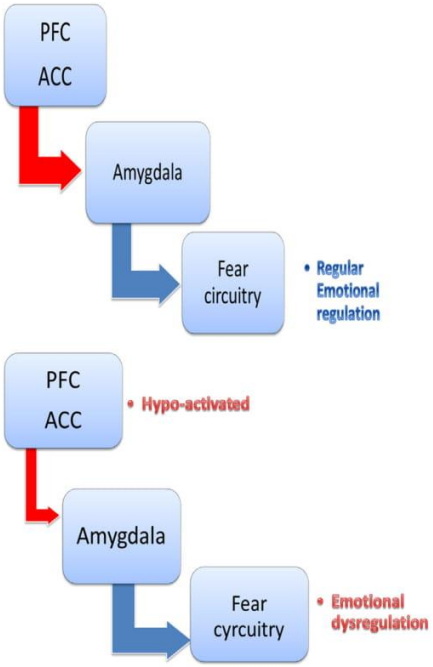

Fig. 2. Findings with fMRI on emotional dysregulation in GAD. (a) In normal subjects (healthy controls), PFC and ACC inhibits the amygdala's activation, acting as a top-down regulation of the fear circuitry during an emotion regulation task. Inhibition is symbolized in the figure by the red color and activation by the blue color. (b) In GAD patients, there is a hypo-activation of the cortical areas, leading to a deficit in the top-down control system during emotional regulation tasks. GAD=generalized anxiety disorder; PFC=pre-frontal cortex; ACC=anterior cingulate cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

results because they had subjects with GAD and SAD comorbidity instead of GAD patients without any comorbidity.

Studies analyzing worry induction and suppression are fewer and also present controversial results. The most reliable finding seems to be that medial PFC and ACC are hyper-activated during worry induction tasks and this activation reduces with effective treatment (Hoehn-Saric et al., 2004; Nitschke et al., 2009; Paulesu et al., 2010; Andreescu et al., 2011). During worry suppression task, studies show conflicting results. One of them presents a PFC failure in top-down control (similarly to emotion regulation tasks) while the other shows maintenance of PFC hyper-activation (Paulesu et al., 2010; Andreescu et al., 2011).

As seen, the amygdala response to emotional faces or pictures in GAD patients is controversial. However, after analyzing the results of this literature review, we can suggest that amygdala response must be interpreted under the light of the frontal response at the very same moment and also considering the frontal–amygdala connectivity. If frontal response is considered the main dysfunction in GAD pathophysiology, there is no mean in analyzing the amygdala response as itself.

When the "conditioned fear overgeneralization theory" was evaluated with the fMRI technique in GAD patients, despite the fact that the study was developed on different premises, the findings were similar to those from other studies. One of the most important findings was the deficit in recruiting ventromedial during fear inhibition (Greenberg et al., 2013b).

Studies showing treatment effect on fMRI findings and evaluating their roles as possible predictive factors to treatment response are also very important for the analysis of GAD pathophysiology and management. It is so, not only to endorse previous suppositions on important areas for GAD neural basis, but also to help understanding the mechanism of action of the therapeutic method or medication and evaluate its objective effectiveness (which is different from the objective one, identified by the clinical scales).

To conclude, we undertook a systematic review of the studies describing fMRI findings in adult GAD patients. According to the studies included in this review, one may say that GAD is, above all, a frontal pathology including also a deficit in the functional connectivity between cortical areas (PFC and ACC) and the amygdala. Emotional dysregulation and excessive worry as an avoidance strategy seem to be important cognitive dysfunctions in these patients, although there may be others. Nevertheless, the emotion regulation process still needs to be better understood. Effective treatment with antidepressants or "mindfulness" reduced the difference between GAD patients and controls for fMRI findings, leading to significant changes in fronto-limbic areas.

Role of funding source

This study is supported by the National Council for Scientific and Technological Development (CNPq), a agency of Brazilian Ministry of Science, Technology and Innovation (MCTI).

Conflict of interest

The authors have no financial relationship or special conflict of interest to disclose.

Acknowledgments

We would like to thank the Institute of Psychiatry of the Federal University of Rio de Janeiro for hosting our team studies.

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ARTIGO 2

Mochcovitch MD1, Deslandes AC, Freire RC, Garcia RF, Nardi AE.The effects of regular physical activity on anxiety symptoms in healthy older adults: a systematic review. Rev Bras Psiquiatr. 2016;38(3):255-61.

Revista Brasileira de Psiquiatria. 2016;38:255–261
Associação Brasileira de Psiquiatria
doi:10.1590/1516-4446-2015-1893

REVIEW ARTICLE

The effects of regular physical activity on anxiety symptoms in healthy older adults: a systematic review

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Objective: Anxiety symptoms are common in older adults with or without anxiety disorders. Pharmacological options may be limited for these patients. Alternative treatments, such as physical activity (PA), are often indicated, although few trials have evaluated their efficacy. The aim of this review was to evaluate the efficacy of regular PA on improving anxiety symptoms in older adults without anxiety disorders. Potential neuroendocrine, inflammatory, and oxidative mechanisms, as well as cognitive factors to explain these effects are also discussed.
Methods: A systematic literature review was performed to identify randomized controlled trials, cross-sectional, cohort, and case-control studies, as well as case series including healthy previously sedentary older adults. We searched the PubMed and Web of Science databases for articles published in English, with no set time limits.
Results: Eight studies evaluating the effect of PA on anxiety symptoms in healthy older adults were included in this review. In all studies, regular and supervised PA was directly related to decreased anxiety symptoms in older individuals.
Conclusion: Regular PA may be effective for improving anxiety symptoms in older adults. More studies are needed to identify the ideal PA modality, frequency, duration, and intensity for optimizing the positive effects of exercise on anxiety in this population.

Keywords: Physical exercise; anxiety; aged

Introduction

Anxiety can be defined as a set of physiological and behavioral responses that protect individuals from danger.[1] Nonetheless, anxiety is also clinically defined as an unpleasant, subjective state of vague and diffuse apprehension that is often accompanied by physical sensations, such as sweating, muscle tension, tremors, and tachycardia, among others.[2] Thus, although anxiety may be a valuable mechanism of protection, an anxiety response that is disproportionate to the threat or stimulus may lead to functional impairment, with impact on the personal and professional lives of those affected.[1] According to the DSM-5,[3] anxiety disorders can be categorized into generalized anxiety disorder (GAD), panic disorder (PD), agoraphobia, specific phobia, social anxiety disorder, separation anxiety disorder, and selective mutism. Anxiety scales may be used to assess sub-threshold anxiety symptoms (i.e., excessive worry and fear, chronic apprehension, or somatic anxiety symptoms, such as dyspnea, chest pain, and tachycardia) in individuals who are not diagnosed with a specific anxiety disorder. The Hamilton Anxiety Rating Scale (HAM-A) and the State-Trait Anxiety Inventory (STAI) are the two most commonly used scales to assess anxiety symptoms.[4,5] Although having a better prognosis than threshold anxiety disorders, sub-threshold anxiety has also been linked to impairment in psychosocial and work functioning as well as increases in benzodiazepine and primary health care use.[6,7] These sub-clinical conditions may also increase the risk of onset of a range of comorbid mental health, pain, and somatic disorders, or worsen the course of these conditions.[7]

There are several difficulties in diagnosing anxiety disorders in the elderly, which ultimately delay or prevent recognition of this disorder. Primary challenges include the fact that anxiety, fear, and concerns are often normal in this age group, that older individuals frequently have difficulty completing questionnaires, and that the prevalence of subclinical symptoms is high in this population.[8] Even though the prevalence of anxiety disorders in older adults is lower as compared to younger adults, many older adults report anxiety symptoms.[8,9] Thus, it is possible that the presence of sub-threshold anxiety disorders among older adults is not fully recognized.[9]

In addition to the barriers to diagnosing anxiety disorders and sub-threshold anxiety symptoms in the elderly, pharmacological treatment for older adults may be hampered by several factors, including clinical comorbidities, slower drug metabolism, and drug interactions due to polypharmacy, which is commonly seen in these patients.[8] Thus, non-pharmacological treatments are often employed, such as psychotherapy, relaxation techniques, and physical activity (PA).

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Submitted Dec 15 2015, accepted Mar 29 2016.

Several meta-analyses and systematic reviews have shown the benefits of different modalities of PA for younger adults with both anxiety disorders and anxiety symptoms.[10-13] A recent review of randomized controlled trials (RCTs) evaluating the effect of PA as a treatment for patients with either a diagnosis of anxiety disorder or elevated anxiety symptoms concluded that PA is effective compared to placebo and similar to other treatment modalities, even though most studies had significant methodological limitations.[10] The study also included previous meta-analyses focusing on anxious patients and subjects without a diagnosis of anxiety disorder. Of the five meta-analyses included, four concluded that exercise is an effective treatment for anxiety, with effect sizes ranging from 0.22 (small) to 0.56 (moderate).[10] The meta-analysis by Conn et al.,[11] which was the only one including participants without anxiety disorders, found a small, but significant benefit (effect size = 0.22) of exercise to reduce anxiety symptoms in healthy adults. It also concluded that the results are superior for moderate to high-intensity PA than for low-intensity exercise (an effect size of 0.11 for low intensity vs. 0.45 for moderate to high intensity). The studies included in that meta-analysis did not specify what constituted low, moderate, and high PA intensities or how they were measured. Furthermore, supervised PA had better effects than unsupervised PA (effect sizes 0.47 vs. -0.93). There was no difference between studies that applied only aerobic PA compared to aerobic or flexibility PAs.[11]

A meta-analysis by Bartley et al.[12] did not find significant differences between the exercise and control conditions for anxiety outcomes (effect size = 0.02). Those authors evaluated the effect of aerobic exercise in patients with various anxiety disorders (i.e., PD with or without agoraphobia, GAD, and social phobia). However, when the analyses were restricted to studies comparing exercise to placebo or waitlist controls, exercise had a significant effect (standardized mean difference [SMD] = 1.42, 95% confidence interval [95%CI] 0.80-2.04). The effects of aerobic PA were compared to the effect of other therapeutic interventions and non-aerobic PA as secondary outcomes. The effect of PA effect was also examined in different anxiety disorders. There was no significant difference between aerobic and non-aerobic PA (SMD = -0.28, 95%CI -0.76-0.20), which included strength training, flexibility, or relaxation exercises and varied between studies. The effect of PA was similar for the different anxiety disorders assessed.[12]

Jayakody et al.[13] also carried out a systematic review to evaluate the effect of PA on anxiety disorders, and found that PA was effective as an adjunctive therapy (associated with pharmacotherapy and cognitive-behavioral therapy). No difference was detected between aerobic and non-aerobic PAs. There are no standards regarding the most effective intensity of exercise to reduce symptoms in anxiety disorders. According to Sexton et al.,[14] high-intensity exercise, such as jogging, was superior to light or moderate exercise, such as walking, but this result was not statistically significant.

The anxiolytic mechanisms of PA are not entirely clear. However, several hypotheses have been postulated to explain the observed effects. Abnormalities in conditioned fear processing are central to the pathophysiology of several anxiety disorders.[15] Exaggerated activation of the neurocircuitry of fear engenders a state of chronic stress that may produce several harmful effects, which, in turn, lead to anxiety disorder perpetuation. These effects include: hypothalamic, pituitary, adrenal (HPA) axis activation and consequent cortisol production, increased levels of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, tumor necrosis factor-alpha and interferon-gamma, and reactive oxygen and nitrogen species production.[16] This chronic pro-inflammatory state causes a reduction in the levels of neurotrophins, including brain-derived neurotrophic factor (BDNF), which negatively affects brain neurogenesis and neuroplasticity.[16]

PA may regulate the HPA axis, reduce the sympathetic nervous system hyperactivity that is seen in patients with anxiety disorders, and increase parasympathetic function.[17] Research has demonstrated that regular PA enhances anti-inflammatory mechanisms, with increases in the levels of anti-inflammatory cytokines, such as IL-10 and IL-1 receptor antagonist.[9] Several studies have reported that regular, moderate PA reduces markers of oxidative stress, potentially through an increase in antioxidant enzyme activity.[9] PA has been shown to induce increases in mitochondrial uncoupling protein 2 (UNCP2), which has been demonstrated to increase the production of adenosine triphosphate and decrease superoxide production.[9] The effects on energy metabolism appear to underpin the many positive PA-induced effects on neurogenesis and brain plasticity.[16] Thus, PA appears to exert anxiolytic effects by providing protection from toxic inflammation and oxidative stress, potentially by promoting neurotrophins and anti-inflammatory and antioxidant activity in key brain regions. Therefore, PA may help regulate normal processes of neurogenesis, neuroplasticity, and apoptosis.[16] The protective effects of PA on neurogenesis have been demonstrated through increases in neurotrophic factors, including BDNF and insulin-like growth factor-1 (IGF-1) levels.[16-18]

Alternative hypotheses have also been proposed for the anxiolytic effects of PA on activating the endocannabinoid system[19,20] and modulating adenosine receptors.[21] PA increases circulating levels of endocannabinoids, including anandamide.[19,20] In turn, these neuromodulators induce antianxiety and antidepressive effects by regulating the signaling of other neurotransmitters (i.e., dopaminergic and glutamatergic signaling) and reducing metabolism in the pre-frontal cortex.[19,20] Cannabinoids may also have anxiolytic effects by regulating the HPA axis and enhancing BDNF expression.[19] The intense psychological experiences that are elicited by activating endocannabinoid receptors are strikingly similar to the "runner's high," - including analgesia, sedation, reduced anxiety, euphoria, and difficulty estimating the passage of time.[20] It is also known that this nucleotide plays an important role in regulating blood flow, synaptic transmission, and neuronal excitability in the adenosine system.[21] Studies with rats[21,22] show increased adenosine concentrations in the entire brain as well as increased hippocampal adenosine receptors (A2A) after aerobic exercise

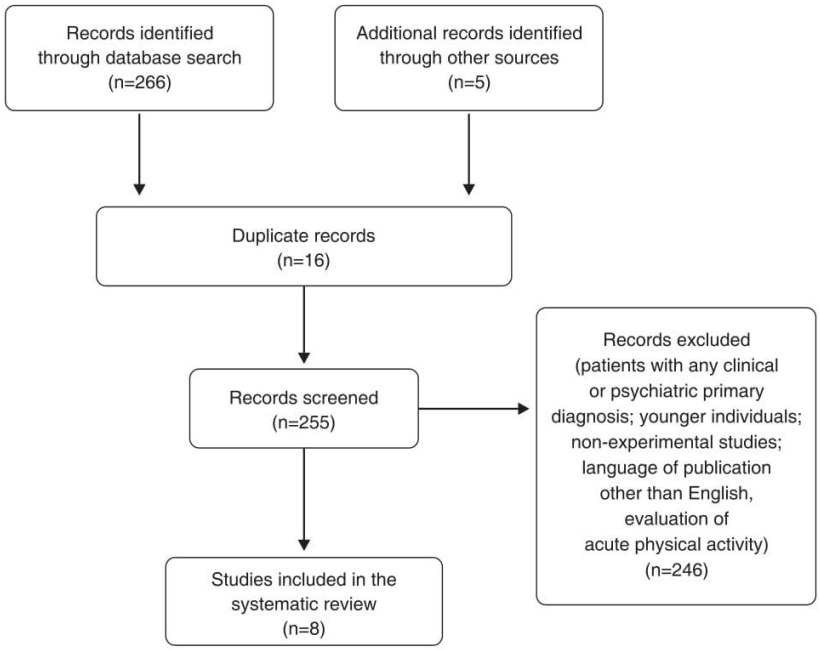

Figure 1 Flowchart of search and selection of articles.

with a simultaneous decrease in anxiety-related behavior and sleep pattern improvements.[21,22]

Finally, several studies have demonstrated that aerobic exercise is effective in reducing high sensitivity to anxiety (i.e., the propensity to fear anxiety sensations based on appraisals that they will lead to catastrophic consequences), a trait that is characteristic of most anxiety disorders. This result may reflect a type of interoceptive exposure, because it evokes physiological changes, such as elevated heart rate, muscle tension, shortness of breath, and sweating, which mimic anxiety responses. Like other interoceptive exposure strategies, PA may facilitate habituation to bodily sensations that normally trigger anxiety and panic symptoms in a controlled and safe manner, dissociating them from the subjective experience of anxiety and consequent catastrophic interpretations.[17]

Physical exercise appears to be an effective alternative treatment for anxiety symptoms in younger patients with or without diagnosed anxiety disorders. However, only limited data are available for older populations, and no systematic reviews focusing on this group have been conducted so far. Thus, we performed a systematic review of the literature evaluating the efficacy of PA for improving anxiety symptoms in older adults, hypothesizing that it would be similar to the efficacy reported for younger individuals.

Methods

In this systematic literature review, PubMed and Web of Science databases were searched for RCTs, cross-sectional, cohort, and case-control studies, and case series evaluating the effect of PA programs on anxiety symptoms in healthy previously sedentary older adults (without a diagnosed anxiety disorder). The keywords (medical subject headings) utilized for the search were anxiety, physical exercise, and aged. Only studies published in English were considered, but no time limits were set. Studies evaluating patients with any primary medical or psychiatric disorder were excluded. Studies with other designs, e.g. review articles and meta-analyses, as well as those evaluating the effect of acute PA rather than regular PA during the follow-up were also excluded. The references of selected studies were manually searched for additional articles.

Results

The search of databases yielded 265 articles, and five additional articles were identified in the manual reference check. Of these 271 studies, we excluded 16 duplicate records, 19 articles written in languages other than English, 192 articles evaluating patients with a primary psychiatric or medical condition or focusing on younger adults, and 18 papers not reporting experimental studies (i.e., review articles or meta-analyses). An additional 18 articles were excluded for evaluating the effect of acute PA rather than regular PA. Thus, eight studies were included in this review (Figure 1).

The quality of the studies included was assessed during the selection process considering risk of bias (selection, performance, detection, and attrition bias). However, because very few studies met the inclusion criteria, all were included, despite their bias potential. Of eight studies, five were RCTs, two were cross-sectional studies, and one was a cohort study. Table 1 shows the quality

Table 1 Quality assessment of the randomized controlled trials included

Study	Sample size (n)	Randomization method	Comparable groups	Double-blinding	Dropouts (absolute number)
Antunes et al.[23]	46	Unclear	Yes	No	0
Tsutsumi et al.[24]	42	Unclear	Yes	No	1
Cassilhas et al.[25]	43	Unclear	Yes	No	0
Katula et al.[26]	80	Unclear	Yes	No	1
Zhang et al.[27]	150	Unclear	Yes	No	6*

*2, 3, 1, 0, 0, respectively for each group.

analysis of the five RCTs considering sample size, randomization method, comparability between groups, double-blinding, and dropout rate. Neither subjects nor investigators were blinded in any of the RCTs, which can be explained by the nature of the intervention (PA).

Cross-sectional studies

One cross-sectional study by Cassidy et al.,[28] focusing on community-based women aged 70 years and over (n=278; mean age = 74.6 years), evaluated the association between modifiable lifestyle variables (i.e., smoking, alcohol consumption, PA, nutrition, and education) and mental health (i.e., depression, anxiety, quality of life, and cognitive function). Anxiety and depression symptoms were evaluated by the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI). The Cambridge Cognitive Examination for Mental Disorders of the Elderly (CAMCOG) evaluated cognitive functioning, and the Short Form 36 Health Survey (SF-36) assessed health-related quality of life. Patients were categorized as physically active if they reported three or more cumulative hours of PA per week (ranging from light exercise, such as walking the dog to vigorous exercise, such as aerobics). Otherwise, participants were considered to be physically inactive. The study showed that physically active women were half as likely to present anxiety (defined by BAI $\geqslant$ 8) and depression symptoms (defined by BDI $\geqslant$ 10) compared to the physically inactive group (both odds ratio = 0.5, 95%CI 0.3-0.8). Participants who had ever smoked more than 20 cigarettes per day were at increased risk for depression and moderate alcohol consumption, while participants who had higher education levels had higher CAMCOG scores. There was no relationship between vitamin B12/folate deficiencies or obesity and the outcome measures.[28]

A second inventory was conducted by McHugh & Lawlor,[29] who interviewed 583 community-based adults aged 60 years or more. The aim of that study was to evaluate the correlation between hours of PA per week, social support, and psychological distress (i.e., depression symptoms, anxiety symptoms, and perceptions of stress). The Center for Epidemiologic Studies Depression Scale (CESD-8) was used to assess depressive symptoms, the Hospital Anxiety and Depression Scale - Anxiety Subscale (HADS-A) was used to assess anxiety symptoms, and the Perceived Stress Scale was used to assess stress experienced in the previous month. These scores were correlated to the number of hours per week spent exercising (i.e., walking, jogging, cycling, swimming, aerobics, tennis, dancing, golf, yoga, bowling, judo, Gaelic football, horse riding, rugby, badminton, tai chi, and sailing). Social support was evaluated with the Lubben Social Network Scale and was also correlated with the number of hours of PA per week as well as psychological distress. Thus, the authors investigated the extent to which exercise and social support independently predicted cross-sectional psychological outcomes. Both PA and social support from friends were independently related to lower anxiety, depression, and perceived stress scores ($p < 0.001$). PA appeared to protect against the effect of low social support on depression. Potential confounders, including age, gender, pain, activities of daily living, instrumental activities of daily living, the Age-Adjusted Charlson comorbidity index, and neuroticism were controlled for in the analyses.

Cohort studies

In a prospective study by Bäckman et al.,[30] a cohort of former Finnish male athletes (n=504) and referent subjects (n=349) were followed up to investigate the relationship between changes in PA and subsequent self-reported mood and daily living functioning in 1985, 1995, and 2001. The cohort included 2,448 male athletes who represented Finland at least once in international or inter-country events between 1920 and 1965; the cohort's mean age was 68.6 years in 2001. Mood and anxiety symptoms were evaluated with two Brief Symptom Inventory-53 (BSI-53) subscales. PA levels in 1985 were associated with mood, anxiety symptoms, and daily living functioning in 1995 and 2001. Additionally, an increase in PA between 1985 and 1995 protected against the onset of anxiety between 1995 and 2001. In contrast, low levels of PA at baseline predicted poor physical functioning at the end of the study.

Randomized controlled trials

Several RCTs have been developed to analyze the effects of PA on anxiety symptoms in healthy but sedentary older adults. These studies explore different types of PA, including aerobic exercise, strength exercise, or mixed activities.

Antunes et al.[23] evaluated 46 sedentary seniors aged between 60 and 75 years who were randomly assigned to an experimental group and a control group. Experimental group members participated in an aerobic fitness program that consisted of ergometer cycle sessions three times a week on alternate days for 6 months, working at a heart rate corresponding to the ventilatory threshold-1 intensity. Subjects were evaluated for anxiety symptoms with the

STAI, for depressive symptoms with the Geriatric Depression Scale (GDS), and for quality of life with the SF-36. A significant decrease in depressive and anxiety scores and improvements in quality of life were found in the experimental group ,with no significant changes in the control group.

Two studies analyzed the effect of strength (or resistance) exercise on anxiety symptoms in older patients. The first was published in 1997 by Tsutsumi et al.[24] and evaluated the effects of high and low-intensity strength exercises on muscular fitness, psychological effect, and neurocognitive function in 42 older adults (mean age = 68 years). Patients were randomly assigned to a high-intensity/low-volume 12 week-program (2 sets of 8-10 repetitions at 75 to 85% of 1 repetition maximum [RM]), a low-intensity/high-volume 12 week-program (2 sets of 14-16 repetitions for 55 to 65% of 1 RM), or no exercise control program. The Profile and Mood States (POMS) and the STAI trait/state inventory were used to evaluate changes in mood and anxiety states. Strength-trained subjects had improvements in mood and trait anxiety compared to those who did not participate in the PA program. There were no significant differences between the low and high-intensity subgroups on anxiety scores.

A second study by Cassilhas et al.[25] was conducted in 2010 and included 43 elderly men aged between 65 and 75 years who were randomly assigned to con-trol or high resistance exercise groups. The exercise program consisted of three, 1 hour sessions per week, on alternating days for 24 weeks, in which patients completed two sets of eight repetitions each for 80% of 1 RM. During the intervention, three 1 RM tests were conducted to adjust for training overload at weeks 15, 18, and 21. This study also evaluated IGF-1 serum levels before and after the PA program, which were hypothesized to be associated with improvements resulting from PA on mood and anxiety symptoms. The exercise group had lower state and trait anxiety than the control group after the 24 weeks of training (evaluated by the STAI) and showed improvements in mood as shown by lower mean scores on all four Visual Analogue Mood Scale (VAMS) measures (anxiety, physical sedation, mental sedation, and other feelings and attitudes). The experimental group also showed higher IGF-1 levels compared to the control group. Interestingly, in this study, the control group also went to the research center once a week for exercise without over-load, warm-ups, or stretching, following the same schedule as the exer-cise group. Thus, the authors were able to conclude that the observed improvements were not attributable to socializing during exercise sessions.

A study carried out by Katula et al.[26]= in 1999 evaluated the relationship between exercise intensity, anxiety, and self-efficacy in healthy older adults. Eighty subjects aged between 60 and 75 years were recruited from another RCT and completed measures of self-efficacy and the STAI (state anxiety inventory [SAI]) before and after light, moderate, and high-intensity PA. Participants had been previously randomized into aerobic outdoor walking or stretching and toning programs. Both groups met three times per week for six months and session times increased gradually from 15 to 40 minutes along the study. The light-intensity sub-group used a standard exercise protocol throughout the six-month time period. Participants self-selected their actual intensity within the prescribed range for heart rate and perceived exertion. The mean age-predicted percentage of heart rate reserve (HRR) in this group was 29%. The moderate-intensity condition included timed completion of the one mile Rockport Fitness Walking Test[31] in the last week of the six-month trial (i.e., participants were instructed to walk one mile on an indoor track as fast as possible). The mean percentage HRR in the moderate-intensity condition was 49%. Finally, the maximal-intensity condition included completing a maximal graded exercise test at the end of the six-month trial (i.e., participants walked at three miles per hour with grade increases of 2% every two minutes on a treadmill). The mean percentage HRR for this group was 96%. State anxiety was significantly reduced by light-intensity PA, not-significantly reduced by moderate-intensity PA, and was significantly increased by maximal-intensity PA. These results contradicted other research on younger adults and were explained by several factors. First, anxiety and arousal were confounded for the impact of the arousal component on the SAI, which increased after maximal-intensity PA. In addition, the researchers noted that the environment may have influenced the anxiety responses because of the moderate and maximal-intensity PAs were completed in an unfamiliar environment that minimized social interaction as compared to the light-intensity condition.

One study by Zhang et al.[27] compared different PA modalities for treating anxiety symptoms in older adults. In this study, 150 older adults (aged between 60 and 70) were divided into five groups, which included swimming, running, square dancing, tai chi, and a control group. Subjects in each group engaged in a moderate-intensity exercise program (i.e., equivalent to 65 and 75% of the maximum HRR], four times per week for 18 months. Participants completed the P300 test, Scale of Elderly Cognitive Function (SECF), Hamilton Depression Rating Scale (HAM-D), and HAM-A scale at baseline 6, 12, and 18 months after the intervention. All intervention groups had significant decreases in HAM-A scores compared to the control group after 12 months of PA. There were no significant differences between the different PA modalities for reducing anxiety symptoms.

The results from this review are summarized in Table 2.

Discussion

Sub-threshold anxiety symptoms are prevalent and commonly unrecognized in older adults. Pharmacotherapy for this age group may have limitations; thus, practicing regular and supervised PA may be an alternative treatment.

As shown in this review, most of the published studies evaluating the effect of PA on anxiety disorders or symptoms have been conducted with young adults. The studies here analyzed showed that PA is effective for improving anxiety symptoms also in older populations. Several plausible physiological mechanisms may explain these results, including neuroendocrine, anti-inflammatory, and

Table 2 Summary of the studies included in the systematic review

Studies	Study design	Assessment scale	Main results
Cassidy et al.[28]	Cross-sectional	BAI	PA was associated with lower BAIscores (OR = 0.5, 95%CI 0.3-0.8).
Bäckman et al.[30]	Cohort	BSI-53	PA protected against future onset of anxiety (OR = 0.9, 95%CI 0.8-1.0).
Antunes et al.[23]	RCT	STAI GDS	Aerobic-trained group showedreduction in anxiety ($p < 0.001$) and depression scores ($p < 0.05$) comparedto controls.
Tsutsumi et al.[24]	RCT	STAI POMS	Strength-trained group presented more improvement in mood and trait anxiety than control group ($p < 0.001$).
Cassilhas et al.[25]	RCT	STAI VAMS	The strength exercise group showed reduction in state and trait anxiety ($p < 0.05$) while control group did notchange significantly; strength-exercise group presented mood improvement ($p < 0.05$) and higher levels of IGF-1($p < 0.05$).
Katula et al.[26]	RCT	STAI	State anxiety was significantly reduced by light-intensity PA, not-significantly reduced by moderate-intensity PA, and was significantly increased by maximal-intensity PA.
Zhang et al.[27]	RCT	HAM-D HAM-A	No differences were found between the different PA modalities for reducing anxiety symptoms.

95%CI = 95% confidence interval; BAI = Beck Anxiety Inventory; BSI-53 = Brief Symptom Inventory-53; GDS = Geriatric Depression Scale; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; IGF-1 = insulin-like growth factor 1; OR = odds ratio; PA= physical activity; POMS = Profile and Mood States; RCT = randomized controlled trial; STAI = State-Trait Anxiety Inventory; VAMS = Visual Analogue Mood Scale.

antioxidant effects of PA. In addition to physiological effects, there are also behavioral, social, and psychological mechanisms involved in symptom amelioration.[16-18]

However, there are insufficient data to determine the best PA modality (i.e., aerobic, resistance, or relaxation and flexibility training) for treating elderly patients, because most studies found no significant differences between modalities.[11-13] Studies with young patients show that moderate to high-intensity PA is superior to low-intensity PA. However, it should be noted that standardized definitions of PA intensity are not available.[12,13] Also, the ideal frequency and duration of PA have not been established.

Two meta-analysis provide interesting information on PA intensity. First, Petruzzello et al.[32] evaluated clinical samples and found that PA duration should be at least 16 weeks. This conclusion is justified by the effect sizes: 0.17 for PA duration of less than 10 weeks, 0.50 for 10 to 15 weeks of PA, and 0.63 for 16 weeks or more of PA. For the frequency of PA, a meta-analysis by Wipfli et al.[33] evaluating clinical samples and healthy adults showed that a PA frequency of three to four times a week was superior to lower or higher PA frequencies.

For older adults, most RCTs have implemented a three times per week program for 12 to 24 weeks,[23-26] but there were no systematic comparisons between different PA frequencies and durations. Two studies compared PA intensities for this age group. Tsutsumi et al.[24] compared low to high intensities for resistance PA and found no significant differences. In contrast, Katula et al.[26] found that light-intensity PA was superior to moderate and intense PA in reducing anxiety symptoms, which contradicted studies with younger patients. However, the authors noted that the lack of a controlled environment for systematically varying PA intensities was a limitation that compromised interpretation of the results (i.e., the environment varied for each of the three intensity conditions). Thus, data are too scarce to draw conclusions on the ideal intensity of resistance and aerobic training for treating anxiety symptoms in older adults.

Although no controlled studies have compared supervised and non-supervised PA for older adults, most authors suggest that PA should be supervised to optimize clinical effects and reduce risks.[11,24,25,28] In contrast to younger adult populations, comparison studies with older patients would be ethically questionable given the higher risks of unsupervised PA in this group.

It is known that meta-analysis studies provide the highest level of scientific evidence. However, a meta-analysis was not possible in the present study due to the methodological heterogeneity among included studies.

In conclusion, although there is insufficient evidence to recommend a detailed PA program as a treatment for anxiety symptoms in older adults, we may infer that PA may be effective to improve anxiety symptoms in this population. This assertion is aligned with the American College of Sports Medicine position stand, which recommends PA for older populations and states that regular PA may minimize the physiological and psychological effects of an otherwise sedentary lifestyle while increasing life expectancies.[34] As people age, they tend to exercise progressively less. Thus, it is important to develop strategies to overcome barriers to PA and stimulate the participation of older individuals in regular PA programs by adapting PA and providing individualized supervision.

Acknowledgements

This study is supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

Disclosure

The authors report no conflicts of interest.

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ARTIGO 3

Mochcovitch MD, da Rocha Freire RC, Garcia RF, Nardi AE. Can Long-Term Pharmacotherapy Prevent Relapses in Generalized Anxiety Disorder? A Systematic Review. Clin Drug Investig. 2017;37(8):737-743.

Clin Drug Investig
DOI 10.1007/s40261-017-0528-x

SYSTEMATIC REVIEW

Can Long-Term Pharmacotherapy Prevent Relapses in Generalized Anxiety Disorder? A Systematic Review

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Abstract

Background and Objectives Generalized anxiety disorder (GAD) is a persistent anxiety disorder with a high rate of relapse. While several trials have demonstrated the efficacy of pharmacotherapy for GAD treatment, fewer studies have investigated its efficacy in preventing symptom relapse in long-term treatment. The aim of this study is to evaluate if long-term pharmacotherapy may prevent relapses in GAD patients.

Methods This is a systematic review of the relapse prevention trials with GAD patients.

Results Eight trials were included in this review with 5304 patients in total. All patients showed a higher risk of relapse if treatment was not maintained for at least 6 months after remission, with hazard ratios ranging from 0.12 to 0.58 and mostly moderate effect sizes (0.19–1.06).

Conclusion Long-term pharmacotherapy may prevent symptom relapse in GAD patients. As the relapse rate is very high, the data support the continuation of pharmacotherapy for as long as possible.

Key Points

GAD is a chronic disorder with high risk of relapse.

Relapse prevention trials showed that continuation pharmacotherapy can prevent symptoms relapse if maintained for at least 6 months after remission.

It is not possible to determine an optimal treatment duration but it is recommended to maintain for it as long as possible while well tolerated.

1 Introduction

Generalized anxiety disorder (GAD) is a chronic anxiety disorder characterized by persistent, excessive and uncontrolled worries and anxiety accompanied by at least three of the following symptoms: fatigue, restlessness, sleep disturbance, muscle tension, irritability or difficulty concentrating for at least 6 months [1]. Symptom severity may fluctuate, but patient impairment tends to be chronic, and spontaneous remission is rare [2].

Current pharmacological treatment options for GAD include selective serotonin reuptake inhibitors (SSRIs), serotonin–noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants and benzodiazepines [3–5]. Due to their proved efficacy and favorable side-effect profile, SSRIs (especially escitalopram, paroxetine and sertraline) and SNRIs are considered the first-line treatment option for GAD [3–5]. Pregabalin has also been studied for the treatment of GAD in adults and although not yet labelled by FDA, is now also included as a first-line treatment option in guidelines from the World Federation of Societies

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Published online: 21 April 2017

of Biological Psychiatry [6]. Its anxiolytic effect is explained by high-affinity binding to the alpha-2-delta subunit of the P/Q type voltage-gated calcium channel in "over-excited" presynaptic neurons, thereby reducing the release of excitatory neurotransmitters such as glutamate [7].

As a second-line treatment option, quetiapine XR has demonstrated efficacy in GAD patients as monotherapy [8] and as adjunctive therapy [9, 10]. Another two drugs that have been recently tested for GAD is agomelatine and vortioxetine. The first is a serotonergic and melatonergic antidepressant. A placebo-controlled trial and two reviews have shown and discussed its efficacy and tolerability in GAD patients [11, 12]. The second is a multimodal antidepressant that acts as a serotonin reuptake inhibitor, 5HT3 and 5HT7 antagonist, 5HT1B partial agonist and 5HT1A agonist. Its efficacy in GAD patients is not well established yet, since the two existing trials show conflicting results [13]. Valproic acid also appears to be effective in GAD patients, especially for those with comorbid bipolar disorder, but the data are preliminary and need to be confirmed by future studies [14].

Although an extensive body of literature demonstrates the efficacy of a range of pharmacotherapies in the acute treatment of GAD, there is a smaller body of studies confirming the benefits of longer-term continuation treatment [15–17]. Because GAD is a chronic disorder, a major clinical issue in the routine care of these patients is how long to continue treatment. Beyond reducing anxiety symptoms and treating possible comorbidities, treatment should aim to prevent anxiety and depression relapse [18].

Thus, it is imperative that long-term trials evaluate the optimal duration of treatment and the degree to which medication discontinuation is associated with symptom and/or anxiety relapse.

The aim of this systematic review is to describe GAD relapse prevention trials that have been published to date and evaluate the ideal maintenance time for pharmacotherapy in the treatment of these patients.

2 Methods

In this systematic review, the authors searched in PubMed and ISI databases for all randomized, placebo-controlled, parallel-group studies on symptom relapse after acute responses to drug therapy for GAD. Keywords used in the search were "relapse", "prevention", "generalized anxiety disorder" and "discontinuation". Articles should be written in English and no limits were set on publication dates. The last search was held in March, 2017. Manual review of reference lists of the articles founded by electronic search was also performed. Only relapse prevention studies that were double-blind, randomized and placebo-controlled with a continuation phase were included. Patients must have been previously diagnosed with GAD according to DSM-IV criteria, and patients who had entered the continuation phase must have been responsive to acute treatment. Studies with any type of drug therapy were included. Exclusion criteria were review articles, studies without a placebo-control arm in the continuation phase, and studies evaluating patients with other primary psychiatric disorders or patients subjected to any type of psychotherapy during follow-up. Definitions of the baseline diagnosis and illness severity as well as criteria for treatment response pre-randomization and for relapse post-randomization are described for each study. Not all the studies reported data on time to relapse. For those that did not, the proportion of relapses for each comparison group is described as the primary outcome.

3 Results

Eight relapse prevention studies were included in this review. Four of them involved the use of SSRIs or SNRIs (escitalopram, paroxetine, venlafaxine and duloxetine); one involved agomelatine; one involved quetiapine XR and one involved pregabalin (Fig. 1).

3.1 Studies with SSRIs and SNRIs

Allgulander et al. [19] evaluated 491 patients with a primary diagnosis of GAD and a Hamilton Anxiety (HAMA) total score $\geq$20, who received 12 weeks of an open-label treatment with escitalopram 20 mg/day. Of these, 375 patients responded to the treatment (HAMA total score $\leq$10) and were randomized in a double-blind trial to either escitalopram 20 mg/day or the placebo for an additional 24–76 weeks. Relapse was defined as either an increase in HAMA total score to $\geq$15 or lack of efficacy, as judged by the investigator. The results showed a beneficial effect of escitalopram relative to the placebo on the time to relapse of GAD (log-rank test, $p < 0.001$). The proportion of patients who relapsed at the end of the study was significantly higher in the placebo group (56%) than in the escitalopram group (19%) ($p < 0.001$, $d = 0.45$). In the secondary analysis of time to relapse, based on the Cox proportional hazards model, the hazard ratio was 4.04 (95% CI 2.75–5.94); that is, the risk of relapse was 4.04 times higher with the placebo than with escitalopram.

A 32-week trial by Stocchi et al. [20] assessed the risk of symptom relapse in GAD patients taking paroxetine or a placebo. Six hundred and fifty-two adults with GAD according to the DSM-IV and a Clinical Global Impressions-Severity of Illness (CGI-S) score of 4 received

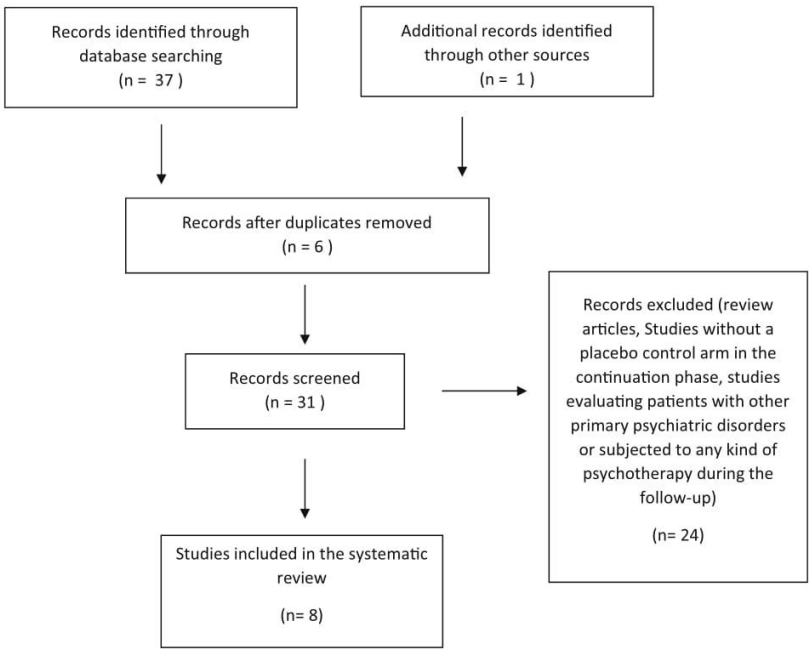

Fig. 1 Flow chart of search and selection of the articles (PRISMA diagram)

paroxetine (20–50 mg/day) for 8 weeks. Patients whose CGI-S score had decreased by at least 2 points to a score of 3 or less at week 8 were randomly assigned in a double-blind trial to either paroxetine or the placebo for an additional 24 weeks. Relapse was defined as an increase in CGI-S score of at least 2 points to a score ≥4 or withdrawal resulting from a lack of efficacy. Significantly fewer patients on paroxetine than on the placebo relapsed during the 24-week double-blind phase (10.9 vs. 39.9%; $p < 0.001$, $d = 0.34$), and patients on the placebo were almost five times more likely to relapse than paroxetine patients [estimated hazard ratio = 0.213 (95% CI 0.1–0.3); $p < 0.001$].

Both venlafaxine and duloxetine have also been evaluated in relapse prevention trials. Rickels et al. [21] conducted an 18-month study with venlafaxine XR consisting of 3 treatment phases: a 6-month, open-label, venlafaxine XR, flexible-dose treatment phase (75–225 mg/day) (phase 1); a 6-month, randomized, double-blind, placebo-controlled relapse phase (phase 2); and a final 6-month, randomized, double-blind, placebo-controlled relapse phase (phase 3). Those who responded to 6 months of open-label venlafaxine XR treatment were randomized to the double-blind trial. Patients who completed 12 months of venlafaxine XR treatment were further randomized for an additional 6-month-period or a total of 18 months. Patients who had already been receiving the placebo since month 6 (still double-blind) continued with the placebo in phase 3. Of 268 patients with a diagnosis of GAD entering the open-label venlafaxine XR treatment phase, 158 completed 6 months of the treatment phase; 136 entered relapse phase 2 (6–12 months); and 59 patients entered relapse phase 3 (12–18 months). Patient relapse was defined as meeting symptom criteria for a Structured Clinical Interview for DSM IV GAD diagnosis and having an HAM-A score of at least 16, having a CGI-S score of at least 4 (moderate or higher), and having a CGI-I score of 6 or 7 (worse or very much worse) compared with baseline of the double-blind relapse phase. After 6 months of open-label venlafaxine XR treatment, significantly more patients who switched to the placebo (53.7%) over the next 6 months relapsed compared with patients who continued on venlafaxine XR (9.8%) ($p < 0.001$, $d = 1.06$). Patients who were treated with venlafaxine XR for 12 months before being shifted to the placebo experienced a lower relapse rate (32.4%) than patients who were shifted to the placebo after being on venlafaxine XR for only 6 months (53.7%); this difference was also statistically significant. The results of Kaplan–Meier analyses separately performed for phases 2 and 3 were highly significant for phase 2 (hazard ratio 9.73) and borderline statistically significant for phase 3 (hazard ratio 6.86). Thus, this study concluded that GAD patients should be treated for 12 months with venlafaxine XR to prevent relapse.

Duloxetine treatment for relapse prevention was assessed in a study by Davidson et al. [22]. Eight hundred and eighty-seven GAD patients were treated with duloxetine 60–120 mg/day for 26 weeks. Patients who completed the

open-label phase and were responsive to treatment (≥50% reduction in HAM-A total score to ≤11 and "much/very much improved" ratings for the last 2 visits of the open-label phase) were randomly assigned to receive duloxetine or the placebo for a 26-week double-blind continuation phase. Relapse was defined as ≥2-point increase in CGI-I or by discontinuation due to a lack of efficacy. Significantly more placebo-treated patients (41.8%) met relapse criteria compared with duloxetine-treated patients (13.7%) ($p \leq 0.001$, $d = 0.38$). Among patients who did relapse, duloxetine-treated patients had a longer time to relapse compared with patients who were switched to the placebo (log-rank test, $p \leq 0.001$).

3.2 Studies with Other Drug Classes

In addition to first-line antidepressants, relapse prevention studies in GAD patients have also been conducted with other drugs.

Feltner et al. [23] evaluated the long-term efficacy of pregabalin in preventing relapse of GAD. Six hundred and twenty-four patients receiving outpatient care were treated with pregabalin 450 mg/day for 8 weeks, and those who responded to treatment were randomized to receive either pregabalin (450 mg/day) or the placebo ($n = 168$ and 170, respectively) for 24 weeks. Relapse was defined by the following scenarios: (1) the patient met study inclusion criteria which were HAM-A ≥20 and met diagnostic criteria for GAD by the MINI (Mini International Neuropsychiatric Interview) at two successive visits 1 week apart; (2) the patient was rated as "much worse" or "very much worse" on CGI–I compared to the endpoint of the open-label phase and met diagnostic criteria for GAD by the MINI at two successive visits 1 week apart; (3) clinician judgment. The log-rank test showed that pregabalin was superior to the placebo in slowing the relapse of anxiety ($p < 0.0001$). At the end of the 6-month double-blind phase, 42.3% of the patients on pregabalin and 65.3% of the placebo-treated patients relapsed ($d = 0.22$).

A study by Katzman et al. [24] tested the efficacy, safety and time to relapse of quetiapine XR monotherapy. After an 18-week open-label phase ($n = 1248$), 432 patients who remained stable for at least 12 weeks were assigned to a double-blind trial for up to 52 additional weeks. Patients either continued with usage of blinded quetiapine XR or switched to a matching placebo at the same dose taken at the last visit of the open-label stabilization period. The permitted doses of quetiapine XR were 50, 150, and 300 mg/day, which could be increased or decreased based on the clinical judgment of the investigator. The primary variable was the time from randomization to an anxiety event (relapse), which was defined as an occurrence of one of the following conditions: a HAM-A total score ≥15 at two consecutive visits, a CGI-S score ≥5 at a study visit, hospitalization because of anxiety symptoms, initiation of prohibited medication to treat anxiety symptoms for 1 week or greater. During the randomized treatment period, quetiapine XR significantly increased the time to relapse of anxiety symptoms (anxiety event) compared with the placebo group, with an estimated HR of 0.19 (95% CI 0.12–0.31; $p < 0.001$). Anxiety events were experienced by 84 patients (38.9%) in the placebo group and 22 patients (10.2%) in the quetiapine XR group ($d = 0.40$).

Stein et al. [25] evaluated the efficacy of agomelatine in preventing anxiety relapse in GAD patients. Four hundred and forty-seven patients were treated with agomelatine 25–50 mg/day for 16 weeks. Those who responded to the open-label treatment were randomly assigned to the continuation phase for an additional 26 weeks ($n = 227$). Relapse was defined as either an increase in HAMA total score to ≥15 or a lack of efficacy based on clinical judgment. The proportion of patients who relapsed during the double-blind phase in the agomelatine group was lower than in the placebo group (19.5 vs. 30.7%, respectively, $d = 0.19$). The risk of relapse over 6 months was significantly lower with agomelatine than the placebo ($p = 0.046$), and the risk of relapse over time was reduced by 41.8% for agomelatine-treated patients (HR = 0.5820). The results are summarized in Table 1 and the quality assessment of the studies is exposed in Table 2 [26].

Lastly, a study by Baldwin et al. [26] investigated the efficacy of Lu AA21004 (vortioxetine) at 5 or 10 mg/day in the prevention of relapse in patients with GAD who had responded to acute treatment with this medication. 687 adult patients with a primary diagnosis of GAD received 20-week, open-label treatment with vortioxetine at 5 or 10 mg/day. Four hundred and fifty-nine patients responded to treatment (HAM-A total score ≤10 at both week 16 and week 20) and were randomized to 24–56 weeks of double-blind treatment with vortioxetine ($n = 229$) or placebo ($n = 230$). T Relapse was defined as a HAM-A total score ≥15, or an insufficient therapeutic response, according to the investigator's clinical judgment. Fewer vortioxetine-treated patients relapsed (15%) compared with placebo-treated patients (34%) ($d = 0.69$). The active drug showed a significant effect relative to placebo on the time to relapse of GAD, with a hazard ratio of 2.71 ($p < 0.0001$).

4 Discussion

Generalized anxiety disorder is a long-term illness with a high likelihood of relapses and recurrences. According to the Harvard-Brown Anxiety Research Project (HARP), which was conducted over 12 years, 58% of GAD patients

Table 1 Studies included in the review

Study	Drug tested	Pre-randomization treatment (weeks)	Post-randomization treatment (weeks)	Relapse rates for placebo	Relapse rates for active drug	Effect size (Cohen's d)	Risk to relapse over time
Allgulander et al. [19]	Escitalopram 20 mg/day	12	24–76	56%	19%	0.45	Log rank test $p < 0.001$
Stocchi et al. [20]	Paroxetine 20–50 mg/day	8	24	39.9%	10.9%	0.34	HR 0.23 (drug/placebo)
Rickels et al. [21]	Venlafaxine xr 75–225 mg/day	24	24–52	Phase 2—53.7% Phase 3—32.3%	Phase 2—9.8% Phase 3—6.7%	1.06	Phase 2—HR = 9.73 (placebo/drug) Phase 3—HR = 6.86 (placebo/drug)
Davidson et al. [22]	Duloxetine 60–120 mg/day	26	26	41.8%	13.7%	0.38	Log rank test $p < 0.001$
Katzman et al. [24]	Quetiapine XR 50,150, 300 mg/day	12	52	38.9%	10.2%	0.40	HR = 0.19 (drug/placebo)
Feltner et al. [23]	Pregabalin 450 mg/day	8	24	65.3%	42.3%	0.22	Log rank test $p < 0.0001$
Stein et al. [25]	Agomelatine 25–50 mg/day	16	26	30.7%	19.5%	0.19	HR = 0.582 (drug/placebo-placebo/drug)
Baldwin et al. [26]	Vortioxetine (Lu AA21004) 5–10 mg/day	20	24–56	34%	15%		HR = 2.71 (placebo/drug)

HR hazard ratio

Table 2 Quality assessment of the studies included in the review

Study	Randomization method (selection bias)	Blinding (performance and detection bias)	Data collection (attrition bias)	Reporting bias
Allgulander et al. [19]	Unclear	Unclear	Low risk	Low risk
Stocchi et al. [20]	Low risk	Unclear	Low risk	Low risk
Rickles et al. [21]	Low risk	Unclear	Low risk	Low risk
Davidson et al. [22]	Unclear	Low risk	Low risk	Low risk
Katzman et al. [24]	Unclear	Unclear	Low risk	Low risk
Feltner et al. [23]	Unclear	Unclear	Low risk	Low risk
Stein et al. [25]	Low risk	Unclear	Low risk	Low risk
Baldwin et al. [26]	Low risk	Unclear	Low risk	Low risk

Adapted from Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [27]

recovered, and of those who recovered, 45% relapsed [28]. A more recent study by Rodrigues et al. showed a 39% probability of recovery in primary care patients with GAD over 2 years [29].

Two common questions in the management of stabilized patients with GAD: (1) when to discontinue treatment and (2) what is the risk assumed with this discontinuation? In this review, it was shown that the continuation of treatment had a substantial effect on preventing relapse in GAD patients for all of the different drugs tested.

Treatment duration varied between 8–26 weeks' pre-randomization and 24–76 weeks' post-randomization. Based on the results, we can suggest that the minimum treatment duration should be 6 months, but most studies showed the benefit of treatment continuation for at least 1 year. Only one of the studies [20] that compared 6-month treatment to 12-month treatment concluded that those who maintained venlafaxine for 12 months showed fewer relapses than those treated for 6 months.

In most of the studies included in this review, patients were flexibly dosed pre-randomization, and that dose was maintained during the blinded randomization phase.

The dose during the continuation phase may have influenced relapse or tolerability. However, this effect was not well explored and requires further evaluation.

Response and relapse criteria were also relatively consistent, with HAM-A, CGI-I or -S scales commonly used. The CGI-I has been shown to be a reliable measure of disease severity, to be sensitive to change, and to correlate well with scores from disorder-specific anxiety scales [30]. On the other hand, clinical judgment was also used in some of the studies, which may be less reliable.

It is possible that the higher relapse rate in placebo arms might reflect drug withdrawal rather than recurrence of the underlying anxiety disorder. Not all of the studies reported details about the discontinuation period, but most of them indicated no significant relapses or discontinuation symptoms. Additionally, an inspection of Kaplan–Meier curves in studies that provided this information did not show an obvious increase in patients relapsing early in the post-randomization phase.

Since the majority of the studies evaluated the effect of antidepressants, the evidence for this drug class in preventing symptom relapse in GAD patients is more consistent than the evidence for other medications such as pregabalin and quetiapine. More studies are necessary to confirm these findings regarding drugs other than antidepressants.

When considering the long-term treatment, we need to take into account the possible side effects that may arise. The SSRIs and the SNRIs commonly affect the sexual function and may cause weight gain (3, 4). Quetiapine is associated with development of metabolic syndrome and also weight gain (3, 4, 14). As for pregabalin, there are reports of risk of abuse [31, 32]. Thus, the cost-benefit of the long-term treatment must be evaluated individually.

This review has limitations that must be acknowledged. The number of reviewed studies is small and varied with regard to the drug tested and treatment duration. Since all of the studies showed positive results for the active drugs, it is important to consider the possibility of publication bias.

5 Conclusion

Despite the limitations above, we can conclude that therapy continuation is beneficial for patients' response for at least 6 months, but it is not possible to determine an optimal treatment duration.

The studies included in this review had a maximum follow-up time of 18 months. Although this length of time is long for follow-up, it may still not be enough to most efficiently prevent GAD relapse. This may be evident from the fact that even for the medication groups, the medium relapse rate was approximately 20%. Considering this chronic natural course, the pharmacological treatment of GAD should be maintained for as long as possible. It is common in clinical practice for both the doctor and patient to agree to maintain medication across the lifespan.

Compliance with Ethical Standards

Funding This study is supported by the National Council for Scientific and Technological Development (CNPq), an agency of Brazilian Ministry of Science, Technology and Innovation (MCTI).

Conflict of interest The authors have no financial relationship or special conflict of interest to disclose.

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ARTIGO 4

Mochcovitch MD, Freire RC, Veras AB, Nardi AE. Generalized anxiety disorder and migraine: A systematic review of clinical findings and insights on possible common mechanisms. Manuscrito submetido para publicação.

Generalized anxiety disorder and migraine: A systematic review of clinical findings and insights on possible common mechanisms.

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ABSTRACT

Purpose: Migraine is often comorbid with psychiatric disorders, and this comorbidity may complicate its diagnosis and treatment and worsen the prognosis. The current study aims to review the association between migraine and generalized anxiety disorder and discuss possible mechanisms underlying this comorbidity. Method: A systematic review was conducted using the PRISMA methodology, including studies on the prevalence of migraine and GAD as comorbidities. Results: Six studies were included, showing that GAD patients present increased frequency of migraine headache and that migraineurs show higher frequency of GAD. Common neurolimbic dysfunctions, increased inflammation and oxidative stress, and serotoninergic and

noradrenergic imbalance are potentially common mechanisms in these two disorders. Conclusions: GAD and migraine are often comorbid and share common neurolimbic and aminergic dysfunctions. An integrative treatment for both disorders with pharmacological and non-pharmacological approaches is proposed.

Key words: generalized anxiety disorder; migraine; comorbidity; inflammation; serotonin.

1. Introduction:

Generalized anxiety disorder (GAD) is the most common anxiety disorder in clinical samples. In the general population, GAD prevalence has been estimated at 2%, and lifetime prevalence of GAD is 4.3% [1]. In Brazil, Viana et al estimated a lifetime risk of 8.5% for GAD at age 75 [2]. This anxiety disorder is characterized by persistent and disproportionate worry and tension lasting six months or longer [3]. High levels of disability, low satisfaction with life, and impaired quality of life are often associated with GAD [3].

Migraine is a highly prevalent neurological condition that can decrease overall quality of life and impair the individual's daily activities and productivity [4]. It is typically characterized by moderate to severe attacks of unilateral pulsating headache, aggravated by routine activity and associated with nausea and/or photophobia and phonophobia. Approximately 28 million people experience migraine, and lifetime prevalence rates are 12–22% in women and 4–10% in men [5]. The direct annual clinical costs associated with migraine have been estimated at $4.3 billion in the United States [6]. Additionally, approximately 20 billion dollars per year in the U.S. are lost in productive time and absenteeism due to migraine-related pain [7].

The relationship between psychiatric disorders and migraine is complex and largely unclear. Psychiatric comorbidities may complicate diagnosis, impact quality of life, affect treatment adherence, and alter the course of migraine [8]. Comorbid psychiatric disorders are also associated with increased medical costs, reduced treatment satisfaction, poorer prognosis, and increased disability [9]. Chronic daily headache, and particularly transformed migraine [i.e., episodic migraine that converts to chronic migraine], has been associated with higher rates of depressive and anxiety disorders than episodic headache [10]. In an 8-year longitudinal study, Guidetti et al found that anxiety disorders were the only type of psychiatric disorder that was predictive of persistent headache [11].

Clinical trials have shown that individuals who suffer from migraine have significantly higher rates of depression compared to those without the condition [12,13]. However, the link between migraine and other psychiatric illnesses such as anxiety have received less attention, even though prevalence of anxiety among migraineurs is considerably higher than prevalence of depression [12,13,14].

The aim of this systematic review is to assess studies on prevalence of GAD and migraine as comorbidities on both clinical and population-based samples. Secondly, we aimed to clarify this complex comorbidity, discussing possible common pathophysiological causes and clinical implications.

2. Method:

Research was conducted in September of 2017, and no time limits were set. The following inclusion criteria were used: Original cross-sectional or case-control studies published in English that evaluated either the prevalence of GAD in migraine patients or the prevalence of migraine in GAD patients. Studies evaluating other psychiatric disorders, unspecified anxiety and depression symptoms, or other types of headache as primary outcome were excluded.

A systematic review was performed in ISI and Pubmed databases using the key words (“generalized anxiety disorder” or "GAD") and “migraine” or ("generalized anxiety disorder" or "GAD") and "migraine" and "comorbidity". Manual review of the article references was also performed after the electronic search.

From each study included, the following information was obtained: Number of participants, how the cases and controls were selected and defined (which diagnostic tools were used to identify patients with GAD and migraine) and the chance of having GAD in patients with or without migraine or the chance of having migraine in patients with or without GAD. It was not used a piloted form.

The quality assessment of the studies included was conducted based on the Newcastle-Ottawa scale (NOS), a tool for assessing the quality of non-randomized studies (15).

3. Results:

Sixty-seven abstracts were found in the electronic search. Of these, nineteen were duplicates and three were not written in English. Another forty-one articles were excluded

because they were not original experimental studies or they evaluated other psychiatric disorders or other types of headache as the primary outcome. Two more articles were included trough manual review. Thus, six studies were included in this review (figure 1). According to the NOS, all studies were considered of high quality.

The first two studies assessing the GAD prevalence in patients with migraine were conducted in the early 1990s by Breslau et al and Merikangas et al [16,17]. The first studied a random sample of 1,007 young adults from a health maintenance organization in Detroit, USA. Migraine was ascertained by a structured interview that elicits information needed to diagnose migraine according to the 1988 definition of the Headache Classification Committee of the International Headache Society, and data on psychiatric disorders were elicited by the National Institute of Mental Health's Diagnostic Interview Schedule (DIS), revised according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition revised (DSM-III-R). Compared to persons with no migraine, persons with either migraine subtype (with or without aura) had higher rates of all the psychiatric disorders covered in the study, including GAD (OR =5.5, 95% CI =2.3-13.2, for migraine without aura vs none and OR= 4.1, 95% CI =1.4-11, for migraine with aura vs none). The second paper examines the association between psychiatric disorders and headache syndromes in a longitudinal epidemiological sample of young adults selected from the general population of Zurich, Switzerland. Migraine and psychiatric disorders were diagnosed using the same criteria of the study by Breslau described above. The study showed a strong association between GAD and migraine, especially with aura (18.2% of GAD in migraine with aura versus 2.5% in controls, $p<0.05$).

Not until 2011, another study specifically evaluating a sample of GAD patients was published. Mercante et al [18] assessed the prevalence of primary headaches in GAD patients and controls. Thirty patients diagnosed with GAD according to Diagnostic and Statistical Manual of Mental Disorders, Forth Edition (DSM-IV) and 30 healthy controls were included in the study. All patients were interviewed for psychiatric diagnosis, using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-1), and primary headaches were diagnosed according to the criteria established in the Second Edition of International Classification of Headache Disorders (ICHD-II), using a structured interview. Lifetime prevalence of primary headaches was higher among GAD patients than among controls (86.7 vs. 46.7%; P = 0.001; OR = 7.43; 95% CI = 2.08–26.55). Migraine was also more frequent among GAD patients compared to controls (66.7 vs. 13.3%; P=0.001; OR = 13.00; 95% CI = 3.55–47.6). Frequency of headaches was significantly higher in GAD patients than in controls

(9.3 SD 9.5 vs. 2.0 SD 2.0 days per month; P = 0.001), as was headache duration (20.9 ± 22.3 vs. 4.5 ± 7.6 h; P = 0.004) and headache intensity (5.6 ± 2.2 vs. 3.9 ± 2.4; P = 0.049).

Lucchetti et al [19] interviewed 383 people from a low-income Brazilian community to assess the prevalence of primary headache (migraine and tension-type headache) and GAD, subthreshold anxiety, and anxiety symptoms (meeting at least two GAD criteria, causing clinically significant distress or problems with activities of daily living). Primary headache diagnosis was based on ICHD-II, and anxiety was evaluated using the Mini International Neuropsychiatric Interview (MINI). Individuals with subthreshold anxiety had 2.28-fold higher odds of migraine; 3.83-fold higher odds of chronic migraine, and 5.94-fold higher odds of tension-type headache. Individuals with GAD also showed higher odds of migraine (OR = 5.84, 95% CI =2.94–11.59), chronic migraine (OR = 13.18, 95% CI = 3.74–46.42), and tension-type headache (OR= 7.02, 95% CI=1.92–25.67). Thus, the presence of two or more anxiety criteria (not necessarily meeting all the criteria for GAD) was associated with primary headache disorder.

A recent study by Fuller-Thomson et al [20] used a large population-based sample of Canadian adults to evaluate the prevalence and the unadjusted and adjusted 12-month odds of GAD among adults with migraine (n=2232) compared to those without migraine (n=19.270). The authors also investigated whether debilitating pain and/or limitations in instrumental activities of daily living (IADLs) are potential mediators of the migraine-GAD association, besides the factors potentially associated GAD in the previous year among adults with migraine. GAD was assessed using the World Health Organization Composite International Diagnostic Interview (WHO-CIDI), a diagnostic interview guide based on DSM-IV and ICD-10. The socio-demographically adjusted odds of GAD in the previous year were two and a half times higher among individuals with migraine (OR = 2.46; 95% CI = 2.00, 3.02). Debilitating pain was associated with four-fold odds of GAD among individuals with migraine, and limitations in IADLs were associated with twice the odds of GAD among migraineurs. In the sample limited to migraineurs, the factors associated with higher odds of 12-month GAD included having a university degree, low income, not having a confidant, and male gender. The authors had expected that several other factors would be associated with GAD among migraineurs, but this did not prove to be the case. These were age, race, marital status, religious coping, physical activity, obesity, substance abuse, and adverse childhood experiences.

Another recent study aimed to examine the associations between major depressive disorder (MDD) and generalized anxiety disorder (GAD) in a group of older adolescents and college-age individuals with migraine [21]. 227 patients 15 to 20 years of age underwent a comprehensive psychiatric assessment to establish the presence of MDD and GAD according to the DSM-IV-TR and to rate their symptom severity using the Longitudinal Interval Follow-up Evaluation for Adolescents (A-LIFE), after which they completed the ID Migraine. After adjusting for gender, having a diagnosis of GAD was significantly associated with presence of migraine (OR = 3.0, 95% CI = 1.3, 6.8, p = 0.0101). Having a diagnosis of MDD was also associated with higher prevalence of migraine [OR = 3.4, 95% CI = 1.1, 10.2, p = 0.029]. Twenty-six percent of participants had comorbid MDD and GAD. Prevalence of comorbidity was significantly higher in participants with migraine (55 vs. 22%, $p < 0.0001$). To examine the independent contribution of MDD and GAD to risk of migraine, both were entered concurrently in the logistic regression model. After adjusting for gender, GAD remained significantly associated with migraine (OR = 2.4, 95% CI = 1.1 - 5.3, p = 0.0366), with a statistical trend for MDD to be associated with it (OR = 2.7, 95% CI = 0.9 - 8.4, p = 0.0786).

4. Discussion:

The current review found that GAD patients show increased frequency of migraine headache and that migraineurs show higher frequency of GAD.

Although this can be considered a bidirectional relationship, Merikangas et al. [17] proposed a progressive disorder model in which anxiety disorders generally precede migraine, which is often followed by depression. The authors postulated that there is ‘‘a syndromic relationship between migraine, anxiety and depression’’, a spectrum of symptoms initiating with anxiety [frequently in early infancy], followed by the occurrence of migraines and subsequent depressive episodes in adulthood.

This putative syndromic relationship between GAD and migraine suggests the existence of an underlying pathophysiological condition in these disorders.

- The neurolimbic model of migraine:

Migraine attacks are a manifestation of central and peripheral sensitization. The central sensitization hypothesis suggests an altered processing sensory signal in the brainstem, where neurons of the trigemino-cervical system become hyperexcitable [22]. Once the attack has begun, central neurons can propagate information about the pain process without the need for further external stimuli [22,23]. Peripheral sensitization depends on the activation of peripheral

nociceptors. The primary afferent nociceptive neurons express increased responsiveness to external thermal or mechanical stimulation in the site of inflammation or injury [22].

However, pain is not the direct expression of a sensory event but rather the product of an elaborate processing by the brain, based on a variety of neural signals. In particular, sensory, affective, cognitive, and environmental components interact in a no hard-shelled pattern. Recently, based on the influence of forebrain and limbic pathways in the brainstem, a "neurolimbic" model of migraine disease has been proposed. This model also accounts for the dynamic bidirectional influence of pain, mood and anxiety on the migraine disease constituting a more comprehensive explanation of the complex migraine constellation [24]. Neuroimaging studies of migraine attack demonstrate activation of the PAG (periaquedutal gray) and limbic system. Further, studies during the interictal period demonstrated abnormal connectivity between the PAG and limbic system, which appears to be progressive with duration and severity of illness. Both brainstem (including PAG and dorsal pons, near the locus ceruleus) and cortical structures (especially anterior cingulate cortex – ACC) activated during the attack, but only the brainstem, specifically the region of the PAG, remained active after sumatriptan injection relieved migraine symptoms. The persistence of brainstem activation was thought to reflect continuing vulnerability to migraine and led to the designation of the PAG as the "migraine generator". The ACC activation may well represent descending modulation of pain, and abnormal connectivity in this pathway may represent migraine vulnerability [25]. High frequency migraineurs displayed prominent reduced functional connectivity between the PAG and PFC (prefrontal cortex), and to a lesser degree with ACC, amygdala, and medial thalamus. Migraineurs with allodynia showed decreased connectivity between the PAG, PFC, ACC, and anterior insula [26].

One could draw parallels to fMRI findings in GAD patients in which a deficit in the functional connectivity between cortical areas (PFC and ACC) and the amygdala was found during emotion regulation processes [27]. This deficient top-down control system during emotion regulation tasks leads to hyperactivity of the amygdala and other limbic areas of the "fear circuitry".

A neurolimbic model may help bridge the gap in understanding migraine attack, interictal dysfunctions in episodic migraine, progression to chronic migraine, and the common comorbidities with mood and anxiety disorders such as GAD, which can also be considered a neurolimbic disorder.

- The role of inflammation and oxidative stress in migraine and GAD:

In addition to these common "generating centers", GAD and migraine appear to share systemic responses involving inflammatory processes and oxidative stress which may in turn be triggers or potentiators of central dysfunctions.

It has become increasingly evident that activation of meningeal afferents, neuropeptide release, and neurogenic inflammation play a pivotal role in the generation of pain in migraine headache [28,29]

Neurogenic inflammation refers to a neurally mediated inflammatory response in meningeal tissue characterized by vasodilatation, leakage of plasma protein from blood vessels, and mast cell degranulation. Activation of primary afferent neurons causes the “retrograde” release of proinflammatory neuropeptides. These neuropeptide mediators, in turn, interact with endothelial cells, mast cells, immune cells, and vascular smooth muscle, thus initiating a cascade of inflammatory responses characterized by erythema and hyperemia, local edema, and hypersensitivity (secondary to alterations in the excitability of certain sensory neurons) [30]. Calcitonin-gene related peptide (CGRP), substance P (SP), and vasoactive intestinal peptide (VIP) are the main neuropeptides released when the trigeminal fibers or trigeminal ganglion are activated [31]. CGRP is a key sensory vasoactive neuropeptide with vasodilatory, immunomodulatory, and inflammatory roles. It is implicated in dilation of cerebral and dural blood vessels, stimulation of nociceptive trigeminovascular pathway, and induction of mast cell degranulation. Elevated concentrations of CGRP, SP, and VIP have been found in plasma samples during migraine attacks [32,33,34, 35].

Continuous exposure to stressful stimuli in GAD patients results in reactivity of the hypothalamic–pituitary–adrenal (HPA) axis, immune system activation, and release of proinflammatory cytokines [36]. Heightened sympathetic tone and reduction in parasympathetic activity as well as the likely dysregulation of the HPA axis in anxiety disorders could lead to increased inflammation [34]. Alterations in C-reactive protein (CRP) levels have also been shown in patients diagnosed with GAD, e.g., a longitudinal study of 146 GAD patients demonstrated increased CRP levels compared to those without GAD [37]. Vieira et al. have found increased circulating concentrations of TNF-α and lower circulating concentrations of anti-inflammatory cytokines such as IL-2 and IL-4 in GAD patients [38]. Also, disruptions in regular sleep patterns that are common in GAD patients can have a highly detrimental effect on the immune system [39]. Severe sleep loss has been shown to increase circulating levels of CRP and IL-6 [40,41].

This increased inflammation and cytokine activity can lead to a variety of other adverse physical conditions frequently comorbid with GAD, including migraine, musculoskeletal disorders, cardiovascular disease, chronic fatigue syndrome, fibromyalgia, and irritable bowel disease [42,43].

Both anxiety and inflammation are associated with increased oxidative stress [42]. Proinflammatory cytokines increase superoxide production through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation and modulation of nitric oxide synthase (NOS) activity [43].

Migraine may be associated with increased vulnerability to oxidative stress. Lower activity of superoxide dismutase [an antioxidant enzyme] has been found in the erythrocytes [44] and platelets [45] in migraine, as have decreased activity of glutathione peroxidase [another antioxidant enzyme] in erythrocytes and lower total antioxidant capacity [44]. TRPA1 ion channel was recently identified in nociceptors and is specifically activated by oxidative and nitrosative stress [46]. In animals, CGRP can be released from dural afferents, promoting neurogenic inflammation, pain sensitivity, and reported symptoms of migraine, by agonists of the TRPA1 channel [47]. The hypothesis is that migraine triggers (including psychological stress and anxiety) might have in common that they induce oxidative stress in the brain [48].

- The role of aminergic neurotransmitters: Migraine and GAD as chronic low serotonergic syndromes and noradrenergic modulation.

Although the exact cascade of events that link abnormal serotonergic neurotransmission to the manifestation of headache and the accompanying symptoms has yet to be fully understood, recent evidence suggests that a low 5-HT state facilitates activation of the trigeminovascular nociceptive pathway [49].

In the migraine brain, changes in modulation of thalamic neurons by various inputs may have significant effects on thalamic functional connectivity during both the interictal and ictal states. The diverse neurochemical pathways that converge on thalamic trigeminovascular neurons and the likelihood that many of them modulate neuronal activity in different directions define a sophisticated neuroanatomical network that may help us conceptualize how sensory, physiological, cognitive, and affective conditions trigger, worsen, or improve migraine headache [50].

A recent neuroimaging study performed interictally in migraineurs, using a highly selective 5-HTT ligand and single photon emission computed tomography, has reported

increased availability of brainstem 5-HTT in these patients, pointing to dysregulation of the brainstem serotonergic system [51]. Such an alteration would be consistent with decreased levels of 5-HT at the synaptic cleft, due to decreased synthesis and/or release, although increased catabolism cannot be excluded. A chronically low serotonergic disposition presumably predisposes the individual to cortical spreading depression, in turn increasing the sensitivity of trigeminovascular pathways that underlie migraine pain. Because anxiety disorders are also associated with reduced serotonergic availability, migraine and GAD may ultimately share a dysfunction in central 5-HT availability. It is hypothesized that chronic increase in cortisol levels in GAD patients leads to an increase in serotonin reuptake [52].

Findings of an increased rate of 5-HT synthesis in several brain regions in migraine patients within six hours of a spontaneous attack—compared with interictal levels—would support increased 5-HT availability early in the attack [53]. These observations lead to the hypothesis that chronically low serotonin disposition may form the biochemical basis of migraine etiology, and that a sudden increase in 5-HT release is part of the triggering events that culminate in migraine attacks.

The efficacy of triptans—selective 5-HT1 receptor agonists—has been attributed to their ability to constrict cerebral blood vessels and modulate trigeminovascular nociception. However, acute administration of sumatriptan or zolmitriptan in rats decreased the 5-HT synthesis rate in dorsal raphe nucleus and in several projection areas including cerebral cortex, hippocampus, and thalamus [54], probably by interaction with somatodendritic 5-HT1A and terminal 5-HT1B/1D autoreceptors. These findings indicate that triptans, acting through different 5-HT1 receptor subtypes located on distinct neuronal pathways or parts of 5-HT neurons, can concurrently but independently modulate 5-HT synthesis and pain pathways [49,54]. Such a decrease in the 5-HT synthesis rate could be an additional effect of triptans in the acute treatment of migraine headache [49].

Noradrenergic fibers project heavily to all thalamic sensory nuclei and act on both α and β adrenergic receptors, which together modulate firing rate, set a pacemaker current, determine membrane resting potential, and synaptic strength [50,55]. In the context of migraine, noradrenaline, which usually prolongs the activation of thalamic neurons,75-78 may be involved in setting abnormal excitability level in trigeminovascular neurons, centrally, and the magnitude of arterial hypertension, peripherally. This view is supported by the finding that β1 adrenergic receptor blockers, which are approved drugs as migraine prophylactics, inhibit the activity of thalamic trigeminovascular neurons [57,58].

The noradrenergic system has also been associated with enhanced arousal and alert waking states [59] as well as to behavioral inhibition [60]. Pathological dysfunctions in this system have been proposed for GAD. Gerra et al. investigated noradrenergic-related plasma hormone levels in a GAD sample by administering various stress tests to adolescents. Plasma norepinephrine levels were comparable before stress in GAD and controls, but increased in GAD after stress, thus providing preliminary evidence of pathological changes in the noradrenergic system in GAD [61].

- Implications for clinical practice:

Comorbidity between primary headaches and GAD increases the severity of both conditions. Research has shown severe functional disability and marked personal burden (anxiety, depressive symptoms, fatigue, and excessive daytime sleepiness), as well as medical and social consequences (functional incapacity, greater use of healthcare services, and lower quality of life) in patients with primary headache and concomitant GAD [19].

Baldacci et al. found that anxiety–depression symptoms are associated with higher susceptibility to migraine triggers, more severe allodynic symptoms, and higher attack frequency. The presence of anxiety–depression symptoms may not only influence the pain perception but also be associated with enhanced general sensation during the migraine attack. The authors suggested that this results from lower pain threshold due to central sensitization and higher cortical hyperactivity in a broader context of a possible neurolimbic dysfunction [62].

Use of analgesics is greater in GAD patients with primary headache than in controls with primary headache [63]. Patients may take analgesics prior to the onset of a headache, due to anxiety and excessive worrying, which are characteristic of GAD. Ferrari [64] analyzed the reasons cited by patients gave for this behavior: 67% reported difficulty in coping with the pain, 62% feared its emergence, and 45% consumed analgesics to reduce anxiety. Meanwhile, many analgesics or antimigraine medications contain caffeine, which is known to exacerbate anxiety symptoms [65,66].

Treatment strategies for patients presenting this comorbidity should include pharmacological and non-pharmacological therapies that are approved for both GAD and migraine. Cognitive behavioral therapy, mindfulness meditation, physical exercise, and sleep hygiene are effective nonpharmacological therapeutic strategies that should be emphasized for these patients [67]. Pharmacological treatment should be considered in patients that are resistant

to these strategies. Venlafaxine and tricyclic antidepressants have proven effective for both GAD and migraine prophylaxis and may thus be considered drugs of first choice [67,68].

5. Conclusions:

This systematic review aimed to encompass all studies that assess a prevalence of GAD in migraineurs and reverse (prevalence of migraine in GAD patients) in order to shed light on this important clinical condition.

All studies included in this review showed that migraine increases the risk of onset of GAD, whereas GAD increases the risk of onset of migraine and other primary headaches.

Patients with this comorbidity should receive comprehensive care, and greater understanding of the shared vulnerabilities and pathological mechanisms that underpin both disorders can lead to unified treatments. Considering their prevalence, treatments that help target both migraine and comorbid GAD will have significant public health implications.

As a limitation, we can point out that in order to avoid missing any study available addressing the subject, we have included methodologically heterogeneous studies, including studies investigating other types of primary headache besides migraine. However, we have analyzed in this review only the results concerning patients with migraine. The same occurred for the studies that included patients with other psychiatric disorders besides GAD.

Funding: This study is supported by the National Council for Scientific and Technological Development (CNPq), an agency of Brazilian Ministry of Science, Technology and Innovation (MCTI).

Conflict of interest: The authors have no financial relationship or special conflict of interest to disclose.

Ethical Approval and Informed Consent: Not applied.

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7. CONCLUSÃO

Após a exposição dos quatro artigos no desenvolvimento desta tese, podemos reunir os dados encontrados para discutir um modelo fisiopatológico para o TAG e reforçar orientações para o tratamento deste transtorno.

Os achados de neuroimagem expostos no artigo 1 mostram que pacientes com TAG apresentam disfunção na capacidade de regulação emocional assim como no processo de aprendizagem afetiva (hipergeneralização do medo condicionado), o que é demostrado pelo déficit de engajamento do córtex pré-frontal ventromedial e córtex cingulado anterior durante a execução destas tarefas em estudos com RMf.

Em revisão recente sobre os estudos com RMf avaliando respostas a tarefas de regulação emocional em pacientes com TAG, Fonzo & Etkin (27) reafirmam que estes pacientes apresentam redução da conectividade entre amígdala e córtex pré-frontal ventromedial e córtex cingulado anterior ventral durante processos de regulação implícita e explícita da reação emocional. Mostram ainda um padrão inflexível de persistência neste aumento de conectividade entre córtex pré-frontal e amígdala durante e após uma preocupação induzida, porém falha de engajamento cortical na tentativa de supressão da preocupação (dados também expostos no artigo 1 desta tese). Porém, estes autores interpretam estes dados à luz de uma teoria parecida, mas não idêntica à teoria da "desregulação emocional", que seria a teoria "do contraste" proposta por Newman & Llera (66). Segundo esta teoria, a preocupação excessiva e persistente no TAG não faz exatamente evitar a vivência da emoção negativa, mas, na verdade, induz um estado permanente de afeto negativo atenuado independente dos estímulos externos que impede a ocorrência de mudanças muito intensas e abruptas (provocadas por estímulos ambientais) no estado emocional do indivíduo, com as quais este paciente tem dificuldade de lidar (66).

Haveria, assim, um déficit cortical na capacidade de adaptar e modular estados cerebrais e fisiológicos em resposta às demandas do ambiente e deficiência na capacidade de distinção entre estímulos ameaçadores dos não ameaçadores (27).

Como discutido nos artigos 2 e 4, este estado de afeto negativo permanente leva à hiperativação crônica de estruturas límbicas como a amígdala, hipotálamo e substância cinzenta periquedutal com desregulação do eixo hipotálamo-hipófise-adrenal e ativação simpática, que resultam em estado pró-inflamatório e pró-oxidativo sistêmico crônico. Estes, por sua vez, levam à redução na produção de neurotrofinas, como o BDNF, importantes no processo de formação e extinção de memórias e cuja deficiência é associada a prejuízo no funcionamento da

resposta ao medo condicionado (60,61). O hipercortisolismo e o aumento de citocinas inflamatórias como IL-6 e IL-1β estão associados à atrofia hipocampal, com inibição de neurogênese e aumento de apoptose no hipocampo (41,67,68). Além disso, o aumento de produção de IL-6 pela vacina contra febre-tifóide foi associado a redução na conectividade funcional entre córtex pré-frontal ventromedial, córtex cingulado anterior e amígdala (67). O estado de estresse crônico pode, portanto, retroalimentar a deficiência na resposta à estímulos afetivos no TAG (36,67,69).

Como já visto, o tratamento farmacológico do TAG baseia-se, principalmente, no uso de ISRSs e ISRNs, medicamentos que atuam nos sistemas serotoninérgico e noradrenérgico, que exercem efeito modulador sobre a resposta ao estresse. No artigo 1, encontramos evidências de que tanto o tratamento farmacológico com antidepressivos quanto o tratamento com Mindfullness podem diminuir diferenças encontradas no funcionamento cortical e na conexão entre córtex e amígdala entre pacientes com TAG e controles.

No artigo 2, apontamos que a atividade física pode ser uma modalidade terapêutica que atua em sintomas de ansiedade através de seu mecanismo anti-inflamatório, antioxidante e propiciador de neurogênese, com aumento de BDNF.

Já no artigo 4, foi analisado o impacto da comorbidade entre TAG e enxaqueca, onde sugerimos que a disfunção cortical, o estado crônico pró-inflamatório e as alterações crônicas nos sistemas serotoninérgico e noradrenérgico podem ser mecanismos comuns às duas patologias e devem ser tratadas de forma global. Nestes casos, a venlafaxina surge como medicamento de escolha e a importância da prática de atividade física e da psicoterapia é aqui reafirmada.

No artigo 3, concluímos que o tratamento medicamentoso do TAG previne recaídas a longo prazo, devendo ser mantido por ao menos 6 meses. Sendo o TAG um transtorno crônico e flutuante, a duração do tratamento deve ser individualizada, podendo ser mantido, até mesmo, por toda a vida.

Em suma, O TAG é um transtorno que leva a grande prejuízo funcional para o paciente, com impacto importante em sua saúde física e mental (1). Resulta de uma complexa interação entre corpo e meio: Genética, temperamento, fatores ambientais durante o desenvolvimento e relações interpessoais, todos contribuem para o surgimento e manutenção do TAG (1). Portanto, sua abordagem precisa ser integral.

Ainda que não se possa reduzir o TAG a um transtorno estritamente orgânico, o melhor entendimento das alterações neurais, endócrinas e inflamatórias encontradas nestes pacientes

pode abrir caminhos para novas possibilidades terapêuticas, farmacológicas e não-farmacológicas.

8. REFERÊNCIAS DA INTRODUÇÃO E DA CONCLUSÃO

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9. APÊNDICE: OUTROS TRABALHOS REALIZADOS

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