INSTITUTO DE PSIQUIATRIA-IPUB

Universidade Federal do Rio de Janeiro

Programa de Pós -Graduação em Psiquiatria e Saúde Mental

**TESE DE DOUTORADO**

# *"Aspectos Clínicos, Cognitivos e Terapêuticos dos Transtornos de Ansiedade"*

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**Orientador**

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Instituto de Psiquiatria/UFRJ
RIO DE JANEIRO
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# DEDICATÓRIA

Aos meus pais, Jaime e Florinha, pelos exemplos de perseverança, dignidade e carinho.

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**LISTA DE SIGLAS**

ABP- Associação Brasileira de Psiquiatria

AMB- Associação Médica Brasileira

DSM- Manual diagnóstico e estatístico dos transtornos mentais

GABA- Ácido gama-aminobutírico

HS- Habilidades sociais

IRSN- Inibidores de recaptação de serotonina e noradrenalina

IRSS- Inibidores seletivos de recaptação de serotonina

LABPR- Laboratório de pânico e respiração

TAG- Transtorno da ansiedade generalizada

TAS- Transtorno de ansiedade social

TCC- Terapia cognitivo-comportamental

TP- Transtorno de pânico

UFRGS- Universidade Federal do Rio Grande do Sul

UFRJ- Universidade Federal do Rio de Janeiro

USP-RP- Universidade de São Paulo/ Ribeirão Preto

## RESUMO

Esta tese visa apresentar os trabalhos publicados pela autora a respeito de aspectos clínicos dos transtornos de ansiedade. Os primeiros trabalhos consistiram em duas diretrizes, a primeira relacionada ao tratamento do transtorno de ansiedade social (TAS) e a segunda ao diagnóstico e diagnóstico diferencial do transtorno de pânico (TP), ambas realizadas para a Associação Médica Brasileira da Associação Brasileira de Psiquiatria e coordenadas pela autora. Dentre várias informações homogêneas sobre os transtornos, ressaltou-se a importância da combinação de terapia com fármacos no tratamento do TAS e da diferenciação do TP para outros diagnósticos, tanto clínicos quanto psiquiátricos. O terceiro artigo teve como objetivo avaliar habilidades sociais (HS) em pacientes com TAS e controles quando expostos a uma tarefa de falar em público. Ambos os grupos apresentaram déficit em HS, porém o grupo clínico apresentou maior déficit e menor discrepância de avaliação em relação aos controles. O quarto e quinto artigo consistiram em revisões da literatura sobre o tratamento psiquiátrico com a agomelatina, o primeiro no tratamento dos transtornos de ansiedade, e o segundo, no transtorno de ansiedade generalizada (TAG). Este último, que tratou exclusivamente do tratamento do TAG foi realizado à convite da revista. Nos dois artigos, ressaltou-se a eficácia da agomelatina no tratamento do TAG, além de resultados promissores em estudos de menor porte com outros transtornos de ansiedade. No sexto artigo, avaliamos a assertividade em paciente com TP e controles e não encontramos uma diferença significativa entre os grupos, apenas quando separamos o grupo com TP por gravidade. Desta forma, pacientes com TP mais graves poderiam beneficiar-se de um treino em assertividade.

## ABSTRACT

This thesis aims to present the works published by the author regarding clinical aspects of anxiety disorders. The first studies consisted of two guidelines, the first related to the treatment of social anxiety disorder (SAD) and the second to the diagnosis and differential diagnosis of panic disorder (PD) for the Brazilian Medical Association and the Brazilian Psychiatric Association and they were coordinated by the author. Among several information about the disorders, the importance of therapy and pharmacology in SAD was emphasized. Besides, the differences between PD and other clinical as well psychiatric disorders were provided . The third paper was designed to assess social skills (SS) in patients with SAD and controls when exposed to a task of public speaking. Both groups showed a deficit in SS, but the clinical group had a higher deficit and lower discrepancy evaluation in relation to the control group. The fourth and fifth article were literature reviews on the use of antidepressant agomelatine, in which the first approached the treatment of anxiety disorders, and the second, the generalized anxiety disorder (GAD) treatment. This last article that was exclusively on the treatment of GAD was developed by invitation from the journal. Both articles demonstrated the effectiveness of agomelatine in the treatment of GAD, and promising results in smaller studies with other anxiety disorders. Finally, in the sixth article, we evaluated assertiveness in patients with PD and controls and did not find a significant difference between the groups, except when the PD group was separated by severity. In this way, severe PD patients could benefit from a assertiveness training.

# APRESENTAÇÃO

*Desenvolvimento acadêmico*

Minha formação acadêmica se iniciou no Instituto de Psicologia da UFRJ em 1999, onde fui bolsista de iniciação cientifica. Porém o maior interesse em pesquisa desenvolveu-se em 2003 quando atuei como estagiária da equipe de terapia cognitivo-comportamental do Prof. Bernard Rangé, onde discutíamos artigos sobre o tratamento e diagnóstico dos transtornos psiquiátricos, além de apresentações em congressos. Neste mesmo período, também fui estagiária do Instituto Estadual de Diabetes e Endocrinologia (IEDE) com a Prof. Monica Duchesne em um estudo para transtorno da compulsão alimentar periódica, onde auxiliei na preparação do protocolo de tratamento psicológico e como terapeuta.

Ao me graduar em 2005, iniciei minha atuação clínica profissional, mas não me encontrava satisfeita somente com o consultório. Sentia falta do intercâmbio acadêmico, de produzir textos e ser orientada. Desta forma, em 2006, ingressei no Programa de Pós-Graduação em Psiquiatria e Saúde Mental do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (PROPSAM), onde fui incentivada pelo Prof. Antonio Egidio Nardi, a trabalhar nas minhas áreas de interesse, e assim, tive o primeiro contato com um grupo de pesquisa e um ambulatório voltado para este propósito.

Meu objetivo inicial era estudar habilidades sociais (HS) nos pacientes com transtorno de pânico (TP), mas ao longo do envolvimento em outras pesquisas no Mestrado, acabei por desenvolver pesquisas focadas no transtorno de ansiedade social

(TAS). Isso ocorreu, pois fomos convidados a desenvolver um capítulo de livro sobre o tema e uma diretriz de diagnóstico e tratamento do mesmo. Além da pesquisa no Laboratório de Pânico & Respiração (LABPR), fui desenvolver juntamente com estudantes de medicina bolsistas de pesquisa, um estudo sobre postura corporal em pacientes com TAS na Universidade de São Paulo em Ribeirão Preto (USP-RP), onde tive minha primeira experiência de cooperação com grupos de pesquisa de outra instituição.

Quando ingressei no Curso de Doutorado, além de pesquisas com TAS em andamento, fui convidada para uma nova diretriz, desta vez para o TP, que me fez retornar ao tema de maior envolvimento do nosso grupo. A seguir encontram-se as referências dos artigos produzidos no Mestrado.

a) Levitan MN, Nardi AE. Social Skill Deficits in Socially Anxious Subjects. *The World Journal of Biological Psychiatry*, 10: 702-9, 2008.

b) Levitan MN, Nascimento I, Freire RC, Mezzasalma MA, Nardi AE. Equivalência semântica da versão brasileira da Social Avoidance and Distress Scale. *Revista de Psiquiatria do Rio Grande do Sul,* 30 (1): 49-58, 2008.

c) Levitan MN, Nardi AE. Nocturnal Panic Attacks: Clinical Features and Respiratory Connections. *Expert Review of Neurotherapeutics,* 9(2):245-54, 2009.

d) Levitan MN, Crippa JA, Bruno LM, Pastore DL, Freire RC, Arrais KC, Hallak JE, Nardi AE. Postural balance in patients with social anxiety disorder. *Brazilian Journal of Medical and Biological Research*, 45(1): 38-42, 2012.

*Produção acadêmica do Doutorado*

O TP é um dos transtornos psiquiátricos que conta com maior produção acadêmica atual, e não à toa, deu nome ao nosso Laboratório. O TP vem abrindo espaço para muitos temas de estudo, e como integrante do grupo, me interessei por alguns aspectos que desenvolvia concomitantemente. No LABPR também provemos assistência e pesquisamos outros transtornos de ansiedade conforme o interesse do aluno. Assim, artigos produzidos sobre outros transtornos psiquiátricos foram incluídos nesta tese.

Dois artigos com o mesmo objetivo foram produzidos por convite da Associação Médica Brasileira (AMB) juntamente com a Associação Brasileira de Psiquiatria (ABP) aos grupos de pesquisa Universitários com vasta produção acadêmica nos temas. Foram estas, diretrizes estruturadas para o diagnóstico e diagnóstico diferencial do TP e de tratamento do TAS. Tendo em vista que nem sempre os profissionais de saúde conseguem ter acesso às pesquisas mais relevantes sobre os transtornos psiquiátricos, ou encontram muita dificuldade em reconhecer, tratar ou encaminhar os pacientes, diretrizes vêm sendo desenvolvidas, visando oferecer orientações atuais que poderão ajudá-los. As informações foram oferecidas através de um método de busca estruturada sobre os temas, especialmente para o Psiquiatra e Médico generalista em sua prática clínica.

Um grande interesse do nosso grupo é de delinear aspectos clínicos e investigar os possíveis subtipos de TP. Além do subtipo respiratório, no qual artigos do grupo são amplamente citados pela produtividade no tema, os ataques de pânico noturnos também começaram a ser pesquisados no LABPR. Por convite de uma revista, publicamos uma revisão da literatura dirigida por especialistas, sobre aspectos clínicos dos ataques de pânico

noturnos e suas conexões respiratórias. Em função desta revisão, a qual identificou um padrão de sono prejudicado em pacientes com TP, despertei o interesse em avaliar a qualidade do sono nestes pacientes. A partir deste objetivo acrescentamos o estudo de uma medicação que ainda estivesse sendo testada para transtornos de ansiedade e que apresentasse melhora na sincronização de ritmos circadianos. A agomelatina foi escolhida por ter apresentado resultados satisfatórios no tratamento de sintomas ansiosos de pacientes com transtorno de ansiedade generalizada (TAG), sendo uma alternativa medicamentosa na ausência de resultados favoráveis ou na intolerância a efeitos colaterais com medicações já amplamente utilizadas. Desta forma, foram produzidas duas revisões da literatura. A primeira sobre estudos que avaliaram a eficácia da agomelatina nos transtornos de ansiedade, e a segunda, através do convite de uma revista, um artigo sobre o perfil da agomelatina e eficácia no tratamento do TAG.

Os artigos sobre o TAS abordaram uma diretriz sobre seu tratamento, como já citado, e um estudo sobre a avaliação das habilidades sociais (HS) dos pacientes quando expostos à tarefa de fazer um discurso em público. Acredito que os resultados obtidos possam auxiliar na compreensão dos mecanismos psicológicos subjacentes ao transtorno e o refinamento de técnicas da TCC.

O último artigo, como mencionado, um dos meus primeiros interesses como pesquisadora, ainda em submissão, teve como objetivo avaliar assertividade, um tipo de HS, em pacientes com TP comparados a um grupo controle. Alguns estudos enfatizam esta característica como preditora de depressão e recaída e pacientes com TP.

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# INTRODUÇÃO

*Transtorno de Ansiedade Social*

O TAS é o transtorno de ansiedade mais comum e o terceiro transtorno psiquiátrico mais frequente, com início geralmente na infância e adolescência (Kessler et al., 2005). Caracteriza-se por um medo intenso de ser avaliado negativamente em interações sociais, frequentemente levando à esquiva de várias situações em que a humilhação e o embaraço possam surgir (APA, 1994).

Algumas situações comumente evitadas são: falar, comer e urinar em público; iniciar conversas; assinar documentos diante de outros e fazer provas. Esta ansiedade é frequentemente acompanhada por sintomas somáticos como palpitações, sudorese, tensão muscular, boca seca, náusea e cefaléia. Outros sintomas mais específicos são o rubor, o tremor e a urgência urinária (Nardi, 2003). A esquiva social é um sinal importante para o diagnóstico e, em casos extremos, pode resultar em um total isolamento social. Considera-se que o indivíduo com o subtipo generalizado seja um tímido patológico (Nardi, 2003; APA, 1994).

Vários fatores podem contribuir para a etiologia da ansiedade social. Há fortes evidências quanto a existência de componente genético (Fyer et al., 1993), de envolvimento de neurotransmissores como a dopamina, serotonina, noradrenalina e ácido gama-aminobutirico (GABA) (Figueira, 2001) e fatores cognitivos associados ao desejo de causar impressão favorável (Clark et al., 1995).

*Transtorno de Pânico*

O TP apresenta prevalência ao longo da vida estimada entre 1,5 e 5% (Kessler et al., 2005) e é caracterizado por ataques súbitos de ansiedade, onde sintomas se desenvolvem abruptamente e há um preocupação permanente com sua recorrência (APA, 1994). Os sintomas somáticos mais frequentes são falta de ar, taquicardia, sudorese e tremores, e os psicológicos são despersonalização, desrealização, medo de morrer, perder o controle e enlouquecer.

É uma condição incapacitante, associada a consequências negativas a longo prazo como perda de produtividade, bem-estar, contato social e auto-realização, além de levar a um grande consumo de recursos médicos (Marciniak et al., 2005). Muitos pacientes passam a evitar situações ou lugares em que já tiveram um ataque de pânico ou que consideram possível sua ocorrência, desenvolvendo a *agorafobia*, associada à pior gravidade do TP, maior duração do quadro e maior número de ataques de pânico (Uhlenhuth et al., 2006).

Fatores de base genética parecem ser determinantes para o surgimento dos sintomas do TP. O modelo do falso alarme de sufocação (Klein, 1993), modelos neuroquímicos: noradrenérgico, serototinérgico e gabaérgico e a hipótese cognitivo-comportamental, puramente cognitiva (Clark, 1986) ou baseada no modelo do alarme falso (Barlow, 1998) estão entre as hipóteses etiológicas mais difundidas.

*Transtorno de Ansiedade Generalizada*

O TAG é um transtorno crônico e incapacitante, caracterizado pela presença de preocupações recorrentes sobre temas da vida cotidiana, como segurança, finanças, saúde, entre outros. Os pacientes encontram dificuldade em controlá-las, apresentando frequentemente sintomas como: irritabilidade, tensão muscular e fadiga. Sua prevalência ao longo da vida é de 4.3-5.9% (Wittchen & Jacobi , 2005 ).

Estima-se que sem tratamento, a doença não remita (Noyes et al., 1996). A sua prevenção e identificação precoce pode ser determinante no curso da doença, visto que o desenvolvimento de depressão, ataques de pânico e abuso de substâncias ocorrem com frequencia nestes pacientes. (Nutt et al., 2006)

Estudos familiares demonstram que em uma família sem transtorno de ansiedade, a chance de um dos membros ter TAG é de apenas 2%. Estudos com gêmeos também sugerem a participação do fator hereditário. Possíveis anormalidades no receptor benzodiazepínico central e seu sítio asssociado para ligação do neurotransmissor inibitório GABA estão entre os principais modelos biológicos (Schinohara & Nardi, 2001). O modelo cognitivo-comportamental ressalta um exagero relacionado à periculosidade na percepção do paciente, além de uma intolerância à incerteza, predispõe o paciente à vulnerabilidade cognitiva.

***Estudos realizados***

*Transtorno de ansiedade social e habilidades sociais*

No Curso de Mestrado, as HS em pacientes com TAS foram estudadas através de uma revisão da literatura sobre experimentos comportamentais onde ao pacientes participavam de uma exposição social espontânea ou estruturada. No Curso de Doutorado, realizamos uma pesquisa na qual pacientes com TAS e controles foram solicitamos a falar para público de pesquisadores sobre um assunto de seu interesse, onde posteriormente, as gravações individuais eram avaliadas por alunas do Instituto de Psicologia da Universidade do Estado do Rio de Janeiro (UERJ). Este estudo também contou com a colaboração do grupo de Neurociências e Comportamento da Universidade de São Paulo/ Ribeirão Preto.

As HS são definidas como diferentes classes de comportamentos sociais presentes no repertório do indivíduo para lidar de maneira adequada com as demandas das situações interpessoais (Del Prette & Del Prette, 2002). É a habilidade de comunicar-se e interagir com outros de uma maneira eficaz e apropriada, considerando-se o contexto sócio-cultural vivido (Caballo, 2003). Desta forma, o indivíduo que não possui repertório de comportamentos socialmente eficazes, acaba por comportar-se de maneira inadequada na exposição social ou esquivando-se.

O TAS é comumente associado ao déficit em HS em função das dificuldades relacionadas às interações sociais, levando autores a aventarem a hipótese de pessoas socialmente ansiosas não possuírem um repertório adequado de HS. Ainda não há consenso sobre esta explicação, principalmente devido a resultados positivos (Monti et al., 1980) e negativos (Heimberg et al., 1990) advindos do treinamento em assertividade para estes

pacientes. Assim, pesquisas experimentais que investigam a hipótese do desempenho social do indivíduo ser afetado pelo déficit em HS vêm sendo conduzidas, onde o pior desempenho é encontrado em grande parte de interações, com ênfase em situações não estruturadas, onde os participantes não sabem que estão sendo avaliados.

Em nosso estudo, avaliamos a exposição social destes pacientes e de um grupo controle sem TAS na tarefa de fazer um discurso para o público de pesquisadores. Após avaliação de vídeos com as interações, três pesquisadores diferentes identificaram uma pior performance no grupo clinico, além de HS menos eficazes. No entanto, as cognições do grupo clínico foram compatíveis com seu desempenho, diferentemente do grupo controle, que se avaliou pior do que foi avaliado. No artigo, as hipóteses para estes resultados são discutidas.

*Diretrizes da AMB e ABP para o transtorno de ansiedade social e pânico*

O *Projeto Diretrizes* caracteriza-se pelo levantamento de dados e consenso sobre orientações aos profissionais de saúde por diversos grupos de referência no atendimento e tratamento de transtornos psiquiátricos no Brasil. O LABPR foi convidado a desenvolvê-lo para o TP e TAS. Para tal, os pesquisadores foram solicitados a utilizar a estratégia de busca sistemática na literatura, a estratégia PICO (paciente-intervenção-comparação-desfecho). Nesta busca-se a melhor evidência científica disponível, levando-se em consideração: o desenho da pesquisa, a consistência das medidas e a validade dos resultados dos trabalhos levantados, contemplando os desfechos clínicos de natureza diagnóstica, terapêutica, preventiva e prognóstica.

Nas duas diretrizes, disponíveis no site da ABP, o grupo de pesquisa foi formado por Rio de Janeiro (UFRJ), Rio Grande do Sul (UFRGS), e Ribeirão Preto (USP-RP). Os resultados desta busca também estão sob a forma de dois artigos, incluídos nesta tese, que estruturam as orientações e dados obtidos de forma que possa ser facilmente utilizado pelos profissionais de saúde. As diretrizes também serão disponibilizadas pela Associação Médica Brasileira e pelo Conselho Federal de Medicina.

*Agomelatina e transtornos de ansiedade*

A busca por novos fármacos que possam ser usados com eficácia para os transtornos psiquiátricos é bastante desejável pelos pacientes, pelos médicos e pela indústria farmacêutica. Quando estas medicações são testadas em estudos bem estruturados com alto grau de evidência, além de serem aprovados para tal condição, passam a despertar interesse sobre seu uso para outros quadros com características comuns. É o caso da agomelatina, um antidepressivo agonista dos receptores da melatonina MT1 e MT2 e que apresenta efeito antagonista dos receptores serotoninérgicos 5-$HT_{2C.}$ Estudos identificaram que além de agir em sintomas depressivos, a agomelatina também resultou em melhora nos sintomas ansiosos nestes pacientes, possivelmente pelo bloqueio de receptores $5HT_{2C}$ ou por seu efeito hipnótico. Assim alguns estudos com agomelatina e transtornos de ansiedade começaram a ser conduzidos (Levitan et al., 2012).

Os estudos mais consistentes, compostos por ensaios clínicos randomizados, foram conduzidos com o TAG. No primeiro estudo, foi encontrada uma melhora mais significativa nos sintomas ansiosos no grupo clínico, principalmente em queixas somáticas a partir da 6ª semana de tratamento, quando comparado ao grupo placebo (Stein et al.,

2008). No segundo estudo, onde avaliou-se a eficácia a longo prazo e prevenção de recaídas após 6 meses de tratamento, além de uma melhora significativa nos sintomas ansiosos, encontrou-se uma menor taxa de recaída (Stein et al., 2009). O terceiro estudo utilizou além do placebo, um comparador medicamentoso (escitalopram) no tratamento do TAG como exigido por agências reguladoras (Stein et al., 2012). Ao final da 12ª semana, as taxas de remissão com agomelatina correspondiam a quase o dobro de taxa de resposta ao escitalopram, além de melhora significativa do sono.

A agomelatina também vem sendo testada para outros transtornos de ansiedade, porém com estudos de pequeno porte e relatos de caso com casos refratários, obtendo resultados satisfatórios. Os estudos foram descritos no artigo 4, ressaltando que em função da existência de tratamentos eficazes para alguns transtornos de ansiedade, a agomelatina seria uma alternativa possível na ausência de resultados positivos, ou no caso de efeitos colaterais não tolerados (Fornaro, 2011).

*Transtorno de Pânico e Assertividade*

O último estudo, ainda em submissão, visou avaliar a assertividade em pacientes com TP e controles através de uma escala. Apesar dos grupos não apresentarem diferença significativa na assertividade, quando o grupo clínico foi separado por gravidade, o grupo mais afetado mostrou-se mais inassertivo. Além disso, a agorafobia foi associada ao déficit de assertividade. A partir destes resultados, aventamos a hipótese desta HS ser incluída em atendimentos de pacientes com TP com psicopatologia mais grave.

## OBJETIVOS ESPECÍFICOS

1. Desenvolver diretrizes Brasileiras para dois importantes transtornos de ansiedade
2. Avaliar as habilidades sociais de pacientes com TAS
3. Estudar as evidências disponíveis acerca da eficácia da agomelatina nos transtornos de ansiedade
4. Avaliar a assertividade em pacientes com TP

## RELEVÂNCIA

A partir da avaliação e tratamento de pacientes atendidos no ambulatório do LABPR, questões associadas ao melhor entendimento dos transtornos de ansiedade vem sendo estudadas ao longo do Curso de Doutorado. Aspectos clínicos do TP, TAS e TAG foram discutidos em revisões da literatura, com o objetivo de prover informações padronizadas e atualizadas para profissionais de saúde. Embora a informação hoje possa ser mais facilmente obtida, levando em conta a extensão do nosso país, nem sempre periódicos internacionais e pesquisas relevantes podem ser acessados por qualquer médico. O resultado costuma ser a dificuldade em prover o diagnóstico correto e na escolha medicamentosa menos respaldada cientificamente.

O estudo sobre avaliação de HS em pacientes com TAS busca prover mais orientações sobre como o paciente se comporta em ambientes ansiogênicos, especialmente para terapeutas cognitivo-comportamentais, que utilizarão estas ferramentas, e os processos psicológicos envolvidos nesta exposição. Já na pesquisa sobre assertividade no TP, visou-se identificar fatores psicológicos que diferenciam estes pacientes de pessoas sem este transtorno para que os mesmos possam ser trabalhados em terapia e possivelmente diminuir o impacto no prognóstico e prevenção de recaída do TP.

No âmbito do tratamento, novas alternativas medicamentosas são necessárias para perfis diferentes de pacientes e à baixa tolerância a algumas medicações. Visamos contribuir para pesquisa de novos agentes farmacológicos a partir do uso de agomelatina nos transtornos de ansiedade  e formular novos direcionamentos terapêuticos.

## ARTIGOS PUBLICADOS NO DOUTORADO

a) Levitan MN, Chagas MH, Crippa JA, Manfro GG, Hetem LA, Andrada NC, Salum GA, Isolan L, Ferrari MC, Nardi AE. Diretrizes da Associação Médica Brasileira para o Tratamento do Transtorno da Ansiedade Social. *Revista Brasileira de Psiquiatria,* 33(3):292-302, 2011.

b) Levitan MN, Chagas MH, Linares IM, Crippa JA, Terra MB, Giglio AT, Cordeiro JL, Garcia GJ, Hasan R, Andrada NC, Nardi AE. Brazilian Medical Association guidelines for the diagnosis and differential diagnosis of panic disorder. *Revista Brasileira de Psiquiatria*, 35(4):406-15, 2013.

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**Artigo 1: Diretrizes da Associação Médica Brasileira para o Tratamento do Transtorno da Ansiedade Social.** ***Revista Brasileira de Psiquiatria.*** **33(3):292-302, 2011.**

# Diretrizes da Associação Médica Brasileira para o tratamento do transtorno de ansiedade social

## *Guidelines of the Brazilian Medical Association for the treatment of social anxiety disorder*

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**Resumo**

**Introdução:** O transtorno de ansiedade social (TAS) é o transtorno de ansiedade mais comum, freqüentemente sem remissões, sendo comumente associado com importante prejuízo funcional e psicossocial. A Associação Médica Brasileira (AMB), através do "Projeto Diretrizes", busca desenvolver consensos de diagnóstico e tratamento para as doenças mais comuns. O objetivo deste trabalho é apresentar os achados mais relevantes das diretrizes relativas ao tratamento do TAS, servindo de referência para o médico generalista e especialista. **Método:** O método utilizado foi o proposto pela AMB. A busca foi realizada nas bases de dados do MEDLINE (PubMed), Scopus, Web of Science e Lilacs, entre 1980 e 2010. A estratégia utilizada baseou-se em perguntas estruturadas na forma P.I.C.O (acrônimo das iniciais "paciente ou população"; "intervenção, indicador ou exposição"; "controle ou comparação" e; "*outcome* ou desfecho"). **Resultados:** Estudos evidenciam que o tratamento farmacológico de primeira linha para adultos e crianças são os inibidores seletivos de recaptação de serotonina e os inibidores de recaptação de serotonina e noradrenalina, enquanto que a terapia cognitivo-comportamental é apontada como melhor tratamento psicoterápico. Além disso, algumas comorbidades psiquiátricas foram associadas a uma pior evolução do TAS. **Conclusões:** Apesar da alta prevalência, o TAS acaba por não receber a devida atenção e tratamento. A melhor escolha para o tratamento de adultos é a associação psicoterapia cognitivo-comportamental com inibidores seletivos de recaptação de serotonina e os inibidores de recaptação de serotonina e noradrenalina. Outras opções como benzodiazepínicos ou inibidores da monoamino-oxidase devem ser usados como segunda e terceira opção respectivamente.

**Descritores:** Transtornos fóbicos; Adesão a medicação; Psicoterapia; Diretrizes; Ensaios clínicos controlados aleatórios como assunto

***Abstract***

***Introduction****: Social anxiety disorder (SAD) is the most common anxiety disorder, usually with no remission, and is commonly associated with significant functional and psychosocial impairment. The Brazilian Medical Association (BMA), with the project named Diretrizes (Guidelines, in English), seeks to develop consensus for the diagnosis and treatment of common diseases. The aim of this article is to present the most important findings of the guidelines on the treatment of SAD, serving as a reference for the general practitioner and specialist.* ***Method:*** *The method used was proposed by the BMA. The search was conducted in the databases of MEDLINE (PubMed), Scopus, Web of Science and LILACS, between 1980 and 2010. The strategy used was based on structured questions as PICO (acronym formed by the initials of "patient or population", "intervention, display or exhibition", "control or comparison" and "outcome").* ***Results:*** *Studies show that the first-line pharmacological treatment for adults and children are serotonin selective reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors, whereas cognitive-behavioral therapy is considered the best psychotherapeutic treatment. Moreover, some psychiatric comorbidities were associated with a worse outcome of SAD.* ***Conclusions:*** *Despite its high prevalence, SAD does not receive adequate attention and treatment. The best choice for the treatment of adults is a combination of cognitive-behavioral psychotherapy with serotonin selective reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors. Other options as benzodiazepines or monoamine oxidase inhibitors must be used as second and third choices, respectively.*

***Descriptors:*** *Phobic disorders; Medication adherence; Psychotherapy; Guidelines; Randomized controlled trials as topic*

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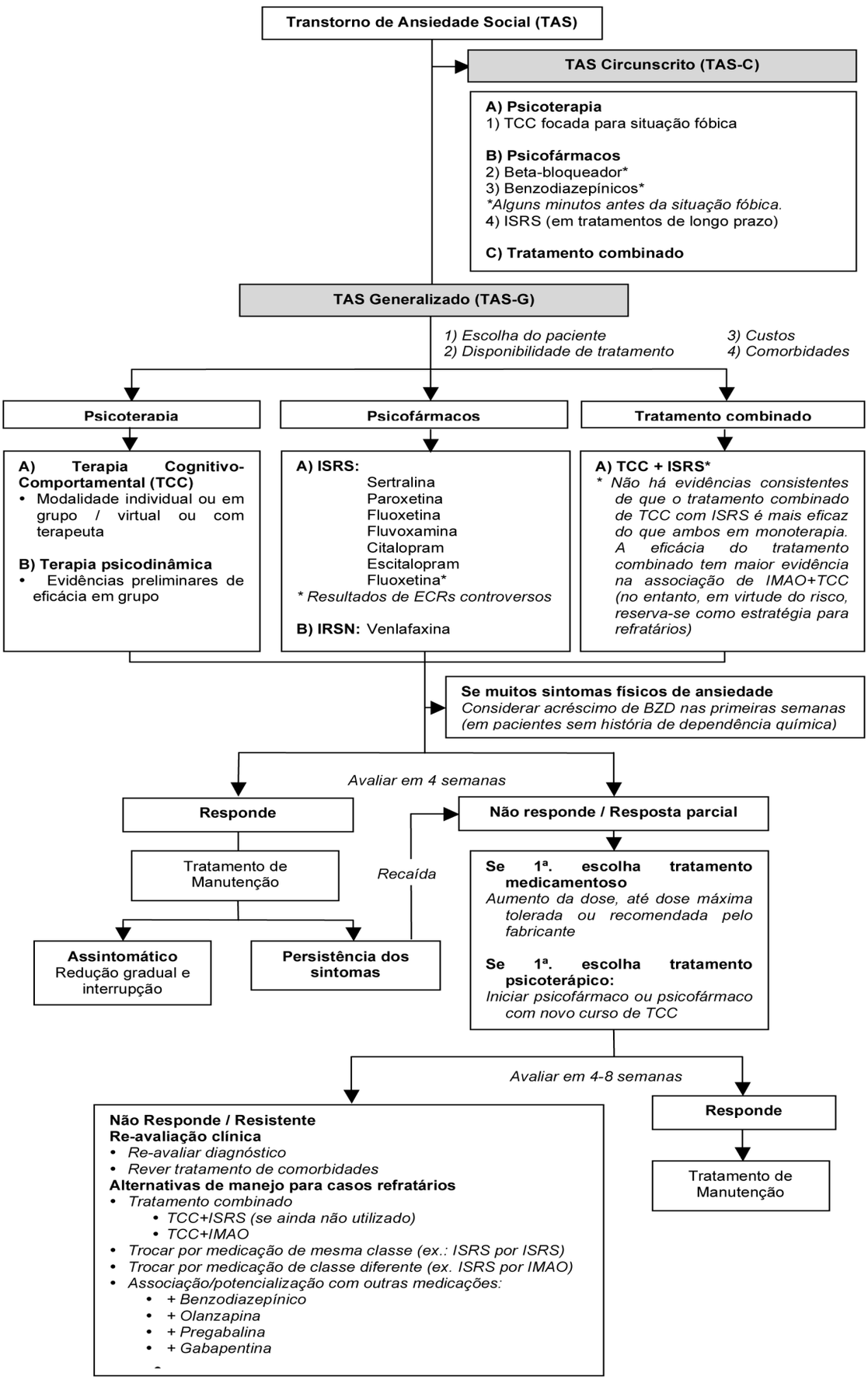
Transtorno de Ansiedade Social (TAS)
TAS Circunscrito (TAS-C)
A) Psicoterapia
1) TCC focada para situação fóbica
B) Psicofármacos
2) Beta-bloqueador*
3) Benzodiazepínicos*
*Alguns minutos antes da situação fóbica.
4) ISRS (em tratamentos de longo prazo)
C) Tratamento combinado
TAS Generalizado (TAS-G)
1) Escolha do paciente
2) Disponibilidade de tratamento
3) Custos
4) Comorbidades
Psicoterapia
Psicofármacos
Tratamento combinado
A) Terapia Cognitivo-Comportamental (TCC)
• Modalidade individual ou em grupo / virtual ou com terapeuta
B) Terapia psicodinâmica
• Evidências preliminares de eficácia em grupo
A) ISRS:
Sertralina
Paroxetina
Fluoxetina
Fluvoxamina
Citalopram
Escitalopram
Fluoxetina*
* Resultados de ECRs controversos
B) IRSN: Venlafaxina
A) TCC + ISRS*
* Não há evidências consistentes de que o tratamento combinado de TCC com ISRS é mais eficaz do que ambos em monoterapia. A eficácia do tratamento combinado tem maior evidência na associação de IMAO+TCC (no entanto, em virtude do risco, reserva-se como estratégia para refratários)
Se muitos sintomas físicos de ansiedade
Considerar acréscimo de BZD nas primeiras semanas (em pacientes sem história de dependência química)
Avaliar em 4 semanas
Responde
Não responde / Resposta parcial
Tratamento de Manutenção
Recaída
Assintomático
Redução gradual e interrupção
Persistência dos sintomas
Se 1ª. escolha tratamento medicamentoso
Aumento da dose, até dose máxima tolerada ou recomendada pelo fabricante
Se 1ª. escolha tratamento psicoterápico:
Iniciar psicofármaco ou psicofármaco com novo curso de TCC
Avaliar em 4-8 semanas
Não Responde / Resistente
Re-avaliação clínica
• Re-avaliar diagnóstico
• Rever tratamento de comorbidades
Alternativas de manejo para casos refratários
• Tratamento combinado
• TCC+ISRS (se ainda não utilizado)
• TCC+IMAO
• Trocar por medicação de mesma classe (ex.: ISRS por ISRS)
• Trocar por medicação de classe diferente (ex. ISRS por IMAO)
• Associação/potencialização com outras medicações:
• + Benzodiazepínico
• + Olanzapina
• + Pregabalina
• + Gabapentina
Responde
Tratamento de Manutenção

## Introdução

Apesar da alta prevalência e da morbidade significativa do transtorno de ansiedade social (TAS), apenas metade dos pacientes ao longo da vida irão procurar tratamento, com tempo mediano de procura de 16 anos. Além disso, as estimativas americanas apontam para uma adequação mínima de tratamento para essas condições de cerca de 40%[1]. O tratamento adequado do TAS se inicia com o seu reconhecimento e diferenciação de quadros de timidez (ausência de sofrimento e prejuízo). Posteriormente, é realizada a avaliação das comorbidades comumente associadas ao transtorno, com ênfase em outros transtornos de ansiedade, depressão, abuso de álcool e de outras substâncias psicoativas.

Após o diagnóstico, deve-se proceder para a adequada escolha terapêutica. Nas duas últimas décadas, o crescente reconhecimento do TAS tem sido acompanhado por um maior número de opções de tratamento farmacológico e psicoterápico. A terapia cognitivo-comportamental (TCC) e os psicofármacos parecem ter eficácia semelhante em curto prazo[2,3]. A escolha do tratamento deve considerar a disponibilidade do local determinado, a preferência e motivação dos pacientes e os custos associados.

De modo geral, a meta do tratamento do TAS deve ser a remissão total dos sintomas. Apesar das freqüentes dificuldades relacionadas à remissão completa, estudos evidenciam que os sintomas residuais são um dos principais fatores associados à recaída dos quadros de TAS em médio e longo prazo[4].

Em função da baixa procura por tratamento, pacientes com TAS freqüentemente perdem oportunidades de crescimento pessoal e profissional, desenvolvendo auto-avaliação negativa e isolando-se ainda mais na participação na sociedade. Desta forma, é de extrema importância que profissionais de saúde possam encaminhar ou orientar os pacientes ao melhor tratamento disponível.

A Associação Médica Brasileira (AMB), conjuntamente com o Conselho Federal de Medicina, iniciou no ano de 2000 a elaboração do projeto Diretrizes, com a finalidade de conciliar informações da área médica e padronizar condutas que auxiliem o raciocínio e a tomada de decisão do médico. Em 2009, a AMB convidou a Associação Brasileira de Psiquiatria (ABP) para colaborar com as normas de procedimentos sobre transtornos mentais, baseada em um método que está fundamentado nos conhecimentos da medicina baseada em evidências, através de perguntas com cenário clínico bem definido, estruturadas no acrônimo P.I.C.O. (descrito na seção Método). Assim, os objetivos das presentes diretrizes são: orientar e discutir o tratamento farmacológico e psicoterápico do TAS.

## Método

Estiveram envolvidos neste projeto 10 profissionais de saúde, médicos e psicólogos, membros de grupos de pesquisa produtivos no Brasil e coordenados por uma profissional experiente no método e na realização do projeto. Para desenvolvimento destas diretrizes, foram revisados 80 artigos nas bases de dados do MEDLINE (PubMed), Scopus, Web of Science e Lilacs, entre 1980 e 2010. Além disso, artigos que apresentam relevância na literatura e eram de conhecimento dos autores e manuais diagnósticos (DSM-IV e CID-10) também foram utilizados na elaboração das diretrizes. A estratégia de busca utilizada baseou-se em perguntas estruturadas segundo o acrônimo P.I.C.O., formado pelas iniciais de "paciente ou população", "intervenção ou exposição", "controle ou comparação" e "*outcome* ou desfecho", conforme preconizado pela AMB nesta fase do projeto Diretrizes. A utilização de questões clínicas estruturadas objetivou facilitar a elaboração de estratégias de busca de evidências. Por exemplo, a estratégia de busca para a pergunta "Qual o impacto da depressão no tratamento do TAS?" foi estruturada da seguinte forma: P – paciente com TAS e depressão como comorbidade, I – tratamento farmacológico e psicoterapêutico, C – não há, e O – impacto da associação. Desta forma, o cruzamento dos seguintes descritores [("phobic disorders" OR "social phobia") AND "depression" AND ("psychotherapy" OR "drug therapy")] levou aos artigos que passaram pelas seguintes etapas: (I) seleção da evidência; (II) crítica da evidência; (III) extração de resultados; (IV) tradução das pesquisas em grau de recomendação e (V) força da evidência. Estas foram dispostas da seguinte maneira: *A*: Estudos experimentais ou observacionais de melhor consistência; *B*: Estudos experimentais ou observacionais de menor consistência; *C*: Relatos de casos e; *D*: Opinião desprovida de avaliação crítica, baseada em consensos, estudos fisiológicos ou modelos animais.

Para cruzamentos de acordo com o tema proposto em cada tópico das perguntas P.I.C.O., foram utilizados os descritores: *phobic disorders*, *social phobia*, *social behavior disorders*, *mutism*, *anxiety disorders treatment outcome*, *behavior therapy*, *cognitive therapy*, *psychologic/methods*, *group psychotherapy*, *individual psychotherapy*, *child*, *adolescent*, *drug therapy*, *antidepressive agents*, *comorbidity*, *psychotherapy*, *depression*, *alcohol drinking*, *alcohol-related disorders*, *substance-related disorders*, *severity of illness index*, *recurrence/prevention*, *control*, e *age of onset*. Após a cuidadosa análise deste material, foram selecionados os artigos relativos às perguntas que apresentavam melhor grau de recomendação e força de evidência, os quais originaram e fundamentaram estas diretrizes. Abaixo, estão descritos os achados mais relevantes das diretrizes da AMB e ABP relativas ao tratamento medicamentoso e psicoterápico do TAS.

## 1. O tratamento psicoterápico é eficaz para o TAS? Quais as técnicas mais recomendadas?

Estudos mostram que a farmacoterapia tende a provocar resultados um pouco melhores do que a TCC, porém o tratamento combinado se mostra superior às monoterapias. Em um estudo

controlado randomizado (ECR), o percentual de pacientes com TAS em remissão foi de 46,9% no tratamento combinado e 7,4% para o placebo (OR= 11,03, IC 95%; 2,23-54,57). Na monoterapia, as taxas de remissão foram de 22.1% no grupo com fenelzina (OR= 3.70; IC 95%; 0,82-19,14) e 8.8% no grupo de TCC (1.21; 0,19-7,81)[5] **(A)**.

As técnicas utilizadas na psicoterapia cognitivo-comportamental incluem psicoeducação, relaxamento muscular progressivo, treinamento de habilidades sociais, exposição imaginária e ao vivo, vídeo *feedback* e reestruturação cognitiva[6] **(D)**. Embora haja controvérsia a respeito de qual elemento da psicoterapia cognitivo-comportamental é mais eficaz, sabe-se que trabalhar o componente cognitivo é essencial, com 84% dos pacientes apresentando melhora dos sintomas e persistência dos resultados no seguimento de um ano[7] **(A)**. Quando confrontados com uma situação social, pacientes com TAS superestimam as conseqüências negativas do contato social e desvalorizam suas habilidades sociais a serem utilizadas na situação exposta. Intervenções psicoterapêuticas buscam a identificação e reestruturação das cognições distorcidas, além de utilizarem técnicas comportamentais de exposição gradativa às situações sociais e treinamento de habilidades sociais para melhora do desempenho social[8] **(D)**.

Há preditores de abandono do tratamento com TCC antes do início da mesma, que devem ser reconhecidos para indicação mais precisa do tratamento: nível mais alto de sintomas do TAS, associação com comorbidades como transtornos de depressão e personalidade esquiva e abandono escolar[9] (**A**).

## 2. A terapia em grupo mostra-se mais adequada no tratamento do TAS do que a terapia individual?

A TCC em grupo para o TAS é uma escolha bastante utilizada, embora poucos estudos comparativos com a terapia individual tenham sido conduzidos. Na TCC em grupo, há a facilidade do uso da exposição às situações temidas, uma vez que o grupo é utilizado como rede de suporte para os desafios terapêuticos. Existe a possibilidade de se desenvolver habilidades e comportamentos por observação dos outros participantes[10] **(B).**

O uso da terapia em grupo apresenta algumas limitações, como o longo período de espera para a formação do grupo e uma menor flexibilidade de agendamento de sessões, o que pode levar a uma maior taxa de abandono em comparação à terapia individual[11] **(B)**. Além disso, é possível que questões individuais deixem de ser trabalhadas ou que o grupo faça uma esquiva generalizada a algumas situações[12] **(B)**. Dois estudos apontam para uma baixa taxa de melhora do TAS com a TCC em grupo, variando de 38[13] **(B)** a 60%[14] **(A)**.

Ao contrário do que vem sendo apontado como o melhor preditor de resultados no TAS, um estudo randomizado com duração de quatro meses evidenciou que metade dos participantes com TAS tratados com TCC em grupo ainda apresentavam diagnóstico de TAS, contra 13,6% da terapia individual. Além disso, a TCC individual produziu melhora dos sintomas avaliados por meio de escalas referentes à gravidade do TAS de 84% versus 44% do grupo[10] **(B).** A TCC individual parece facilitar o acesso às crenças disfuncionais e comportamentos de segurança, além de fornecer um ambiente menos amedrontador para o paciente. Porém, apesar da sua maior eficácia, deve-se considerar o contexto de aplicação, no qual realizar uma terapia em grupo pode significar um custo mais baixo e maior número de pacientes atendidos.

## 3. Qual o tratamento psicoterápico do TAS em crianças e adolescentes?

Estudos evidenciam que o tratamento psicoterápico mais eficaz com crianças e adolescentes com TAS é o cognitivo-comportamental. Ao comparar vários tipos de TCC para o tratamento de crianças com TAS, não houve diferenças significativas entre tratamento individual ou em grupo, e o envolvimento dos pais foi eficaz nas duas formas de terapia[15] **(B)**.

Em uma metanálise[16] **(A)** que avaliou oito tratamentos cognitivo-comportamentais em crianças, todos encontraram uma diminuição significativa no nível de prejuízo associado ao TAS nos participantes ao final do tratamento, com tamanhos de efeito variando entre 4,06 ± 1,31[17] **(B)** e 1,25 ± 0,24[18] **(B)**. Além disso, três relataram tamanhos do efeito moderados a grandes no aumento da competência social, variando entre 0,91 ± 0,22[19] **(B)** até 0,59 ± 0,10[18] **(B)**. Os sintomas do TAS também foram reduzidos nestes tratamentos.

Devido ao importante papel que os pais de crianças com TAS exercem sobre o quadro, como solucionar os problemas pelos filhos e reforçar a esquiva social, alguns estudos demonstraram que o envolvimento dos familiares no tratamento produz melhores resultados[15, 18] **(A)**.

Em estudos somente com adolescentes, a TCC mostrou-se mais eficaz no tratamento dos sintomas do TAS e de comorbidades freqüentes como a depressão quando comparada à terapia de suporte educacional-familiar[20] **(B)**. O tratamento psicológico que combina treinamento em habilidades sociais, reestruturação cognitiva e exposição gradativa é apontado como o mais eficaz para crianças, adolescentes e adultos.

## 4. Qual o tratamento medicamentoso indicado para o TAS em adultos?

Duas classes de psicofármacos são consideradas de primeira linha no tratamento farmacológico do TAS, tanto pelo fato de terem se mostrados eficazes em vários ECRs com placebo, quanto pela segurança de seus efeitos adversos. Essas drogas de escolha são os inibidores seletivos de recaptação de serotonina (ISRS) e os inibidores de recaptação de serotonina e noradrenalina (IRSN)[21] **(A)**. Apesar dos benzodiazepínicos (BZD) também apresentarem forte evidência de eficácia, não são considerados medicações de primeira linha em função do perfil pouco favorável de efeitos adversos e risco de abuso e dependência[22] **(D)**, assim como

os antidepressivos inibidores da monoaminoxidade (IMAO), devido ao aumento do risco de crise hipertensiva e acidente vascular encefálico quando as recomendações dietéticas não são estritamente cumpridas pelo paciente. Os antidepressivos tricíclicos, além de não demonstrarem tanta eficácia, podem agravar os sintomas fóbicos ansiosos, principalmente devido aos efeitos colaterais como tremores finos e sudorese[23,24] **(B)** (Figura 1).

### Inibidores seletivos de recaptação de serotonina (ISRS)

Entre os ISRS, o escitalopram, a fluvoxamina, a sertralina e a paroxetina são consideradas medicações de primeira linha para o tratamento do TAS[21] **(A)**. Embora seja muito utilizada na prática clínica, apenas um estudo mostrou maior eficácia da fluoxetina em relação ao placebo na população adulta[3] **(A)**. Outros dois estudos falharam em demonstrar essa superioridade[25,26] **(A)**. Apesar da eficácia do citalopram só ter sido testada em um ECR[27] **(A)**, parece não haver diferenças em relação à eficácia entre as medicações consideradas de primeira linha[21] **(A)**.

O uso de sertralina com doses flexíveis entre 50 e 200mg/dia mostrou-se eficaz em reduzir os sintomas fóbicos ansiosos após 12 semanas, com taxa de resposta de 55,6% *versus* 29% de resposta com o uso de placebo[28] **(A)**, com número necessário para tratar (NNT) de 3. Um estudo prévio de 20 semanas apontou para os mesmos resultados, com taxa de resposta de 53% *versus* 29% do grupo placebo, com NNT de 4[29] **(A)**.

Da mesma forma, o escitalopram mostrou-se superior ao placebo em doses de 5 a 20mg/dia em um seguimento de 12 e 24 semanas[30] **(A)**. A resposta à dosagem do escitalopram entre 10 e 20mg também foi superior ao placebo, com taxas de 54% contra 39% e NNT de 7[31] **(A)**.

Em um estudo duplo cego randomizado de 12 semanas, a paroxetina com dosagem máxima de 50mg/dia melhorou sintomas fóbico-sociais (65,7% vs. 32,4%, NNT=3) em relação ao placebo[32] **(A)**. Em outro estudo com o mesmo desenho experimental, 55% dos pacientes que usaram paroxetina e 23,9% dos pacientes em uso de placebo apresentaram resposta ao tratamento de acordo com a escala *Clinical Global Impression* (CGI), com NNT de 3[33] **(A)**. Estes resultados foram replicados por outros estudos[32,34,35] **(A)**.

De forma semelhante, em um estudo duplo-cego controlado por placebo com a fluvoxamina (dose média de 202 mg/dia), 42,9% do grupo com TAS que recebia medicação e 22,7% do grupo placebo apresentaram melhora significativa dos sintomas do TAS com NNT de 5[36] **(A)**. Outros estudos ratificam estes achados, nos quais a fluvoxamina demonstrou-se eficaz no tratamento do TAS em doses entre 150 e 300mg/dia[36-38] **(A)**.

### Inibidores de recaptação de serotonina e noradrenalina (IRSN)

A venlafaxina de liberação estendida foi avaliada no tratamento do TAS em um estudo de 28 semanas. Quando comparada ao placebo, o grupo com a droga ativa apresentou taxas de resposta (58% vs. 33%, NNT=4) e remissão (31% vs. 16%, NNT=7) superiores, tanto em baixas doses (75mg/dia) como em altas doses (150mg e 225mg/dia)[39] **(A)**. Outros estudos encontraram resultados similiares[40-42] **(A)**, apontando que a venfalaxina é uma medicação eficaz, segura e bem tolerada no tratamento do TAS.

### Inibidores de monoamino-oxidase (IMAO)

Apesar de eficazes, os IMAO impõem restrições alimentares importantes em virtude do risco de interação com a tiramina presente em certos alimentos, podendo provocar aumento repentino na pressão sanguínea e reações hipertensivas[43] **(B)**. Desta forma, deve haver cautela em seu uso, além de medidas informativas a serem adotadas pelo médico, como o fornecimento de uma lista de alimentos e medicações que devem ser evitados.

Em particular, a fenelzina, um IMAO irreversível, demonstrou-se bastante eficaz no tratamento do TAS[44] **(B).** Em ensaios clínicos, os IMAO, juntamente com BZD e ISRS, se mostraram superiores no tratamento do TAS, porém a maior evidência de tolerabilidade e eficácia foi associada aos ISRS[45] **(A).**

### Benzodiazepínicos (BZD)

Os BZD (clonazepam, bromazepam, alprazolam) são usados freqüentemente no tratamento dos transtornos ansiosos. O clonazepam, em doses entre 0,5 e 3mg/dia, mostrou-se efetivo no tratamento do TAS com taxas de resposta de 78,3% contra 20% no grupo placebo. Em geral, o clonazepam foi bem tolerado, porém o grupo em uso do mesmo apresentou mais tonturas e instabilidade postural que o grupo placebo[46] **(A)**.

Da mesma forma, o bromazepam mostrou-se efetivo em um estudo de 12 semanas[47] **(A)**. O único ensaio clínico que avaliou o alprazolam falhou em mostrar eficácia desta medicação[2] **(A)**. O risco de abuso e dependência contra-indica o uso de BZD em pacientes com história de dependência e coloca esse tipo de medicação como uma opção de segunda linha no tratamento do TAS.

### Beta-bloqueadores

Embora muito utilizados na prática clínica, os beta-bloqueadores (atenolol, pindolol, propranolol) não apresentam evidência de superioridade no tratamento do TAS em relação ao placebo. A recomendação de seu uso limita-se a situações de desempenho que não fazem parte da rotina do indivíduo, visando reduzir sintomas somáticos associados à ansiedade de desempenho[48] **(A).**

## 5. Qual o tratamento medicamentoso do TAS em crianças e adolescentes?

Infelizmente, pouca atenção tem sido dada ao uso de medicações para o TAS em crianças e adolescentes. Alguns estudos abertos com ISRS têm mostrado resultados promissores, apontando-os como medicações de primeira linha para o tratamento do TAS nesta população.

Em um estudo de 16 semanas com crianças e adolescentes de 8 a 17 anos com dosagem média de paroxetina de 25mg/dia, 77,6

% do grupo com TAS respondeu à medicação, com NNT de 3, contra 38,3% do grupo placebo [49] **(A)**.

A fluoxetina (20mg/dia) utilizada por pacientes entre 7 e 17 anos mostrou-se superior ao placebo no tratamento dos sintomas do TAS em um ensaio clínico de 12 semanas, com melhora de 61% vs. 35% dos casos, respectivamente, fornecendo um NNT de 4[50] **(A)**.

Em um estudo aberto de 8 semanas com sertralina (dose média de 123mg/dia), 36% das crianças com TAS foram classificadas como responsivas ao tratamento e 29% como parcialmente responsivas. Além disso, houve uma diminuição do desconforto em tarefas sociais e nos escores das escalas associadas à timidez e ansiedade[51] **(B)**.

O escitalopram, utilizado por 12 semanas (10-20 mg/dia), provocou melhora dos sintomas do TAS e na qualidade de vida em 65% dos participantes, com tamanhos de efeito variando de 0,9 a 1,9[52] **(B).**

Em outro estudo, adolescentes com TAS apresentaram remissão de sintomas em 52,9% com a TCC, 48,6% com fenelzina e 78,1% com tratamento combinado (psicoterapia e farmacoterapia) em comparação com adultos com TAS, os quais obtiveram melhora de 23,5% com TCC, 25,7% para fenelzina e 53,1% para o tratamento combinado, com diferença significativa para o tratamento combinado[5] (**A**).

## 6. Qual o período mínimo de manutenção do tratamento medicamentoso em pacientes com TAS?

Após a remissão dos sintomas do TAS, a manutenção do tratamento medicamentoso diminui a possibilidade de recaídas[53,54] **(A)**. Um estudo com a paroxetina em dosagem média de 36,67mg/dia demonstrou que o tratamento de manutenção por um período de 24 semanas diminui a taxa de recaídas significativamente, de forma que apenas 14% dos pacientes que mantinham o uso da paroxetina apresentaram recaídas, contra 39% do grupo em uso de placebo, com OR=0,24 (IC 95%; 0,14-0,43; p<0,001)[54] **(A).**

Um estudo semelhante com o escitalopram em dosagens flexíveis de 10-20 mg/dia apresentou resultados similares. Os pacientes que continuaram o uso do antidepressivo por um período de manutenção de 24 semanas apresentaram uma taxa de recaídas significativamente menor do que o grupo controle em uso de placebo, o qual apresentou um risco de recaída 2,8 vezes mais alto do que o grupo tratado com escitalopram[53] **(A)**.

Um período mínimo de 24 semanas após remissão dos sintomas fóbico-sociais tem sido considerado adequado para evitar possíveis recaídas[53,54] **(A)**, porém períodos mais prolongados podem ser necessários.

## 7. Há diferenças no tratamento do TAS circunscrito e generalizado?

Das poucas pesquisas que avaliaram as diferenças nos resultados do tratamento psicoterápico em pacientes com os subtipos de TAS, todos foram realizados com TCC em grupo. Em um estudo, o subtipo circunscrito respondeu significativamente melhor a TCC do que o subtipo generalizado (79% vs. 47%), embora os dois grupos tenham apresentado melhora[55] **(B)**. Já em outra investigação os subtipos não diferiram quanto à melhora geral, porém o subtipo circunscrito terminou a terapia com um melhor índice de funcionamento (grau de comprometimento pelo TAS)[56] **(B)**.

Os estudos farmacológicos são em sua grande maioria conduzidos com pacientes com o TAS de subtipo generalizado, uma vez que selecionar pacientes com apenas uma limitação social que procurem os serviços de saúde não é comum. Em uma revisão da literatura, a partir da avaliação de três ensaios duplo-cegos de 12 semanas controlados com paroxetina (20-50 mg/dia), não foram encontradas diferenças nas respostas ao tratamento entre o grupo circunscrito e generalizado[57] **(A)**. A fluvoxamina também se mostrou eficaz para os dois tipos de TAS com dosagem média de 150 mg/dia em um estudo duplo cego de 12 semanas[37] **(A)**.

No TAS circunscrito, para o tratamento da ansiedade de desempenho, freqüentemente são recomendados os beta-bloqueadores e BZD, que melhoram a sintomatologia fisiológica do TAS no momento da exposição, mas não em longo prazo. Faz-se importante, porém, lembrar que estas medicações não tratam as comorbidades freqüentemente associadas ao TAS e devem ser usadas com cautela pelo risco de dependência[58] **(A).**

## 8. Há diferenças entre a resposta terapêutica do TAS de início precoce e de início tardio?

Poucos estudos abordam a influência da idade de início do TAS na resposta terapêutica. Um estudo brasileiro tratou pacientes com TAS de início precoce (<18 anos) e de início tardio (≥18 anos) com ISRS, tricíclicos e BZD por 10 semanas, e não encontrou diferenças na melhora de sintomas do TAS entre os grupos[59]. De acordo com outros estudos realizados, a idade de início do TAS não parece ser um preditor de resposta ao tratamento.

## 9. O que é o mutismo seletivo?

O mutismo seletivo caracteriza-se por uma falha da criança em falar quando seria esperado que ela se comunicasse, a qual não é explicada por desentendimento do idioma ou não-compreensão do que está sendo falado. Geralmente a recusa não ocorre em toda exposição social, mas com relação a algumas situações ou pessoas[60] **(C)**. Apesar de ainda não haver consenso sobre sua classificação, é considerado por grande parte dos autores como uma forma mais grave e precoce do TAS, ocorrendo normalmente entre os 5 e 11 anos de idade, com uma distribuição entre 0,8 e 1,9%[61] **(B)**.

Observações clínicas indicam que pais de crianças com mutismo seletivo reforçam o comportamento da criança ao apoiarem quando os filhos não respondem aos outros. Além disso, alguns estudos evidenciam que parte das crianças com este quadro apresentam comportamentos desafiadores e agressivos[62] **(C)**. As crianças são frequentemente definidas pelos pais como tímidas e socialmente evitativas[63] **(C)**.

Para inclusão de pacientes com mutismo seletivo, os estudos utilizam os critérios do DSM-IV (APA), avaliados por professores e pais, com duração de pelo menos um mês e interferência no

desempenho social e escolar da criança[64] **(B)**. Uma boa avaliação para mutismo seletivo é feita através de entrevistas com pessoas do convívio da criança, como professores, babá e familiares.

### 10. Qual o tratamento do mutismo seletivo?

Em função da baixa prevalência do mutismo seletivo, poucos estudos abordaram seu tratamento. No maior estudo aberto realizado com fluoxetina, durante 9 semanas com 21 crianças com mutismo seletivo, utilizou-se uma dosagem média de 28,1mg/dia e máxima de 60mg/dia nas últimas semanas do tratamento, onde nenhuma criança obteve melhora com dosagem inferior a 20 mg/dia. Ao final do tratamento, 76% preencheram critérios de melhora do quadro, com uma modificação da média de interferência dos sintomas de 47,1 (moderada interferência) para 67,5 (pouca interferência; p<0,001), sendo inversamente proporcional à resposta ao tratamento[65] **(C)**.

Em um estudo recente, 17 crianças com mutismo seletivo participaram de um programa para melhora dos sintomas em um hospital infantil[66] **(C)**. Oito crianças tomaram uma solução líquida de fluoxetina e duas de sertralina com dosagem máxima de 10 a 25mg/dia e de 25 a 50mg/dia, respectivamente. Sete crianças não obtiveram autorização para a administração de medicação e não participaram do restante do estudo. Após seis meses, as crianças medicadas mostraram melhora em escalas referentes ao mutismo seletivo superior àquelas sem medicação, embora ainda com diagnóstico.

No âmbito psicológico, um estudo de pequeno porte envolvendo cinco crianças e pais durante oito semanas foi realizado no formato de TCC em grupo. Os pais receberam sessões com informações psicoeducativas e intervenções necessárias para aumentar a confiança do filho em se expor. O objetivo era a diminuição da ansiedade nas exposições e o aumento do repertório de comunicação. Todas as crianças obtiveram melhora no grau de confiança ao falar na escola e diminuição da ansiedade. Duas crianças não preencheram mais o diagnóstico de mutismo seletivo[67] **(C).**

### 11. Qual o impacto da comorbidade com depressão no tratamento de pacientes com TAS?

Embora esteja bem estabelecido que as comorbidades aumentam a gravidade e prejuízo associado do TAS, o impacto da depressão no tratamento dos pacientes com TAS é pouco explorado na literatura. Em um estudo que avaliou a eficácia da fluoxetina e TCC no tratamento do TAS, evidenciou-se que a presença de sintomas depressivos em pacientes com TAS foi associada a um quadro mais grave de TAS e pior evolução do tratamento ao longo do tempo. Além disso, pacientes que abandonaram o tratamento apresentavam uma maior taxa de sintomas depressivos[68] **(A).**

Estudos que investigaram o papel da depressão na resposta dos pacientes com TAS a TCC demonstram que esta comorbidade parece não afetar a resposta terapêutica em curto prazo[69,70] **(B)**. Em um desses estudos, no entanto, pacientes com depressão demonstraram ser mais propensos a recair dos sintomas de TAS no seguimento, sugerindo a necessidade de uma intervenção adicional para manutenção dos ganhos da TCC em pacientes com depressão[69] **(B)**. A TCC para depressão em pacientes com comorbidade com TAS parece apresentar resultados satisfatórios para ambas as condições[71] **(A)**.

### 12. Qual o impacto da comorbidade com abuso e dependência de álcool e drogas ilícitas no tratamento de pacientes com TAS?

Pacientes com TAS apresentam aumentado risco de comorbidade com dependência de álcool[72] **(A)**, assim como uma alta prevalência de uso de álcool e drogas ilícitas[73] **(D)**. O uso de álcool é associado à maior freqüência de comorbidades como transtornos de humor e de personalidade, enquanto que o uso concomitante de álcool e drogas ilícitas aumenta ainda mais a probabilidade de incidência de outras comorbidades psiquiátricas e está associado a pensamentos de morte e tentativas de suicídio[73] **(D)**. Pacientes com TAS são mais propensos a usar álcool em situações de desafeto, pressão ou censura social[74] (**A**), com prevalência estimada deste uso em 3,3%[73] (**D**).

Pacientes com TAS e dependência de álcool apresentam prejuízos funcionais em diversos domínios, incluindo perda do suporte social, menor satisfação nas relações interpessoais e maior tendência à manifestação de doenças físicas. No TAS comórbido com álcool e drogas, há uma maior busca por profissionais de saúde e a uma maior utilização de medicação para controle dos sintomas. Assim, a necessidade de uma maior assistência mental e física em pacientes com TAS e dependência de álcool resulta em grandes custos pessoais e sociais[74] **(A)**. A presença de TAS não aumentou o risco de abuso de álcool (OR=1,23, IC 95%, 0,97-1,57, p=0,09), mas aumentou significativamente a chance de dependência (OR=2,26, IC 95%, 1,88-2,70, p<0,001)[74] **(A)**.

### 13. Qual o impacto da comorbidade com outros transtornos de ansiedade no tratamento de pacientes com TAS?

Estudos mostram que o tratamento psicoterápico do TAS comórbido a outros transtornos de ansiedade apresenta uma taxa similar de sucesso quando comparado ao TAS puro, todavia, poucos estudos farmacológicos avaliaram esta associação. Em um estudo com TCC de 12 semanas com adultos, grupos com TAS puro e TAS associado com transtorno de ansiedade generalizada exibiram uma percentagem de melhora dos sintomas de ansiedade similar, inclusive durante o seguimento[75] **(B)**.

Em um estudo com TCC em crianças, os transtornos de ansiedade comórbidos não foram associados com o desfecho da terapia, onde 68,4% dos pacientes sem comorbidades e 70,6% dos pacientes com comorbidades tiveram remissão do TAS. Os pacientes que permaneceram com as comorbidades após o tratamento apresentavam menor susceptibilidade a remissão dos sintomas do TAS[76] **(B).**

Em um estudo farmacológico, pacientes com TAS e transtorno de pânico (TP) comórbido receberam tranilcipromina, um IMAO, durante 12 semanas, com doses de 30mg/dia ou 60mg/dia. Não foram encontradas diferenças significativas na redução de ataques de pânico. O grupo que recebeu 30mg/dia teve os ataques de pânico reduzidos em 69,6%, enquanto o grupo de 60mg/dia teve redução de 74,8%, porém, a dose maior mostrou-se mais eficaz na diminuição de sintomas de ansiedade social (30mg/dia=–17,9 ± 14,7 e 60mg/dia= –35,0 ± 14,8). Desta forma, apesar da dosagem maior ter sido necessária para a melhora do TAS, o TP comórbido não pareceu afetar o desfecho do tratamento farmacológico do TAS[77] **(A)**.

## Conclusões

A partir da extensa revisão da literatura realizada, os tratamentos que mais se destacaram para o TAS foram os ISRS, IRSN e a TCC. Além da eficácia dos ISRS encontrada nos ECR, o menor número de efeitos colaterais e a melhor tolerância dos pacientes colocam-nos como opção medicamentosa de primeira linha no tratamento do TAS. A TCC também foi associada à boa adesão dos pacientes com TAS, além de alcançar resultados semelhantes ou superiores aos dos fármacos.

O projeto Diretrizes, da AMB em parceria com a ABP, visa facilitar e auxiliar nas decisões dos médicos em geral, devendo apresentar clareza, aplicabilidade clínica e relevância prática. Apesar da alta prevalência, o TAS é freqüentemente associado à personalidade, e acaba por não receber a devida atenção e tratamento.

As diretrizes sobre diagnóstico e diagnóstico diferencial do TAS já foram realizadas[78], disponibilizando um guia para avaliação correta do transtorno, que agora é complementado pelos algoritmos de tratamento. As vantagens e desvantagens dos tratamentos são expostas, de forma que o profissional possa discutir com seu paciente sobre a melhor escolha de tratamento. Percebe-se, no entanto, que a maior parte dos estudos medicamentosos foi realizada há mais de duas décadas e há a necessidade de novas pesquisas. Além disso, estudos com crianças ainda são escassos, inviabilizando o tratamento precoce e um melhor prognóstico na idade adulta.

Conclui-se que a apresentação destas diretrizes permitirá que profissionais de saúde possam facilmente identificar as opções terapêuticas disponíveis para crianças e adultos com TAS e selecionar o tratamento mais adequado ao seu paciente, provendo informações envolvidas nesta escolha e manejando com segurança os resultados.

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| Membro do grupo de autores | Local de trabalho | Verba de pesquisa | Outro apoio à pesquisa ou educação médica continuada | Honorários de palestrante | Participação acionária | Consultor/Conselho consultivo | Outro[3] |
|---|---|---|---|---|---|---|---|
| Levitan MN | UFRJ | CNPq | - | - | - | - | - |
| Chagas MHN | USP-RP | - | - | - | - | - | - |
| Crippa JAS | USP-RP | CNPq** | - | - | - | - | Czec Neurological Foundation<br>Aché<br>Elly Lilly<br>Roche |
| Manfro GG | UFRGS | CNPq*<br>FIPE-HCPA* | - | - | - | - | Roche* |
| Hetem LAB | USP-RP | - | - | - | - | - | - |
| Andrada NC | AMB | - | - | - | - | - | - |
| Salum GA | UFRGS | CAPES | - | - | - | - | - |
| Isolan L | UFRGS | - | - | - | - | - | - |
| Ferrari MCF | USP-RP | FAPESP | - | - | - | - | - |
| Nardi AE | UFRJ | CNPq** | - | Glaxo-SmithKline*<br>Roche* | - | Aché*<br>CNPq* | Editora Artmed* |

** Modesto*
*** Significativa*
**** Significativa. Montantes fornecidos à instituição do autor ou a colega para pesquisa onde o autor tem participação, não diretamente ao autor.*

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# Brazilian Medical Association guidelines for the diagnosis and differential diagnosis of panic disorder

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**Objective:** To present the most relevant findings regarding the Brazilian Medical Association guidelines for the diagnosis and differential diagnosis of panic disorder.
**Methods:** We used the methodology proposed by the Brazilian Medical Association for the Diretrizes Project. The MEDLINE (PubMed), Scopus, Web of Science, and LILACS online databases were queried for articles published from 1980 to 2012. Searchable questions were structured using the PICO format (acronym for ''patient'' [or population], ''intervention'' [or exposure], ''comparison'' [or control], and ''outcome'').
**Results:** We present data on clinical manifestations and implications of panic disorder and its association with depression, drug abuse, dependence and anxiety disorders. In addition, discussions were held on the main psychiatric and clinical differential diagnoses.
**Conclusions:** The guidelines are proposed to serve as a reference for the general practitioner and specialist to assist in and facilitate the diagnosis of panic disorder.

**Keywords:** Panic disorder; anxiety; guidelines; diagnosis; differential diagnosis

## Introduction

Panic disorder (PD) is characterized by the presence of sudden anxiety attacks accompanied by somatic symptoms (panic attacks) and development of a persistent concern about their recurrence and possible implications.[1] PD a disabling condition associated with long-term negative consequences such as decreases in productivity, welfare, social relations and self-realization, and may lead to high utilization of medical resources.[2] The lifetime prevalence of PD is estimated to range from 1.5 to 5%.[3]

Many patients begin to avoid situations or places where they previously experienced a panic attack or believe one may occur, developing an avoidance known as agoraphobia. People with PD are often not recognized as having the disorder. It is common for patients to seek several experts depending on their predominant somatic complaints (e.g., heart, stomach, respiratory symptoms) and undergo a variety of tests before being diagnosed with PD. Without a correct diagnosis, the appropriate treatment cannot be provided and the disorder tends to become chronic.[4] PD often occurs alongside other psychiatric comorbidities. Community surveys have showed a high frequency of substance abuse, depression, and suicide attempts in these patients.[5] The difficulty in establishing the diagnosis of PD or the distinction between PD and other diseases prevents early treatment and a better quality of life for these patients.

Based on this evidence, the Brazilian Medical Association (BMA) and the Brazilian Psychiatric Association (BPA) have developed guidelines to help medical professionals through the general diagnosis and differential diagnosis of PD.

## Methods

We reviewed articles written between 1980 and 2012 and indexed in the following databases: MEDLINE (PubMed), Scopus, Web of Science, and LILACS. Relevant publications and diagnostic manuals, such as the DSM-IV and the ICD-10, were also included. The search strategy was based on structured questions formulated according to the PICO format, which stands for ''patient'' (or population''), ''intervention'' (or exposure), ''comparison'' (or control), and ''outcome,'' as recommended by the BMA. The use of objective and structured clinical questions enables the development of strategies for finding the best

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evidence. For example, the search strategy we used for the question: "Is there current evidence of the role of genetic factors in the etiology of PD?" was as follows: P - patients with PD (panic disorder OR panic agoraphobia), I - indicators of genetic influence (genetic predisposition to disease genetics OR* models, genetic linkage OR chromosome mapping genetic markers, OR family twin studies OR dizygotic twins, monozygotic twins), C - no control group, O - no outcome. This strategy led to articles that were chosen according to the following steps: selection of evidence, critical evidence, extraction, and translation of the results according to the grade of recommendation and strength of evidence. These criteria were arranged as follows: a) experimental or observational studies with better consistency; b) less consistent experimental and observational studies; c) case reports; and d) opinions devoid of critical evaluation, based on physiological studies or animal models.

For intersections in accordance with the proposed question, we used the following keywords: panic disorder, agoraphobia, diagnosis, questionnaires, sensitivity and specificity, classification, epidemiology, prevalence, prevention and control, life change events, severity of Illness Index, prognosis, recurrence, age factors, age distribution, risk factors, comorbidity, phobic disorders, generalized anxiety disorder, depression, post-traumatic, sleep, sleep disorders, polysomnography, genetic predisposition to disease, genetics, genetic markers, social environment , phenotype, differential, lactates/diagnostic use, carbon dioxide/diagnostic use, respiration/drug effects, heart/physiopathology, heart diseases, cardiovascular diseases, arrhythmias, hypertension, blood pressure, heart rate, electrocardiography, thyroiditis, autoimmune, cerebral cortex/abnormalities, image processing, magnetic resonance imaging, antidepressive agents, cognitive therapy, and combined modality therapy.

After analyzing this material, we selected articles that had higher recommendation grades and greater strength of evidence to support these guidelines. The following sections list the most important findings of the BMA and BPA guidelines that relate to both the diagnosis and differential diagnosis of PD.

## Results and discussion

*What is the significance of scales in the identification and evaluation of patients with PD?*

Scales for assessment of panic attacks are widely used in clinical trials, ensuring that information collected regarding specific symptoms is standardized and compared with other studies for later application in clinical practice. The goal of initial evaluation is to characterize the clinical picture systematically and quickly and cover a wide range of symptoms. The collected data are transformed into a numerical score that reflects the total frequency and severity of symptoms. Assessment may be repeated throughout treatment to investigate the clinical improvement and therapeutic effects of the administered treatment and to provide objective data on the clinical progress of the patient[6] (D).

Diagnostic identification has been determined through semi-structured clinical interviews, such as the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[7] (D) and the Mini International Neuropsychiatry Interview (MINI) - Brazilian version[8] (B), which are both based on the DSM-IV (American Psychiatric Association, 1994) (D). Administered to a Brazilian population suspected of suffering from PD with agoraphobia, MINI showed a sensitivity of 44% and specificity of 97%, yielding a likelihood of disease (LR+) of 14.67 (95%CI 4.71-45.69), increasing the LR+ from 5 to 44%[8] (B).

Scales that assess symptoms of PD may be divided into global scales of anxiety, scales of the frequency and intensity of panic attacks, scales of phobic avoidance, and scales of distorted cognition regarding physical reactions of anxiety[6] (D). Several scales have been translated into Portuguese, but no specific scale for clinical features or identification of patients with PD has been validated in a Brazilian sample. The scales most commonly used in Brazilian practice are described below.

The Clinical Global Impression (CGI), which provides an overall assessment of the severity of PD on a scale of 1 to 7 according to the frequency and intensity of panic attacks, anticipatory anxiety levels, levels of phobic avoidance, and family/occupational dysfunction, has been used to evaluate the severity of panic after pharmacological treatment[9] (D). The Hamilton Anxiety Scale (HAM-A) measures overall anxiety and consists of 14 items divided into two groups: seven mood symptoms related to anxiety and seven physical symptoms of anxiety. This scale exhibits better diagnostic capacity when studying depression in relation to anxiety[10] (B).

The Panic Disorder Severity Scale (PDSS) measures the severity of core symptoms of PD. The PDSS is a five-point Likert scale that includes the frequency of panic attacks and limited symptom episodes, the anguish caused by these attacks, anticipatory anxiety, fear, agoraphobic avoidance, social impairment, and loss of productivity in work activities caused by panic attacks[11] (A). This scale has better diagnostic capacity for patients with agoraphobia, a sensitivity of 99%, and a specificity of 98%, yielding a LR+ of 49.50 (95%CI 12.55-195.2), increasing the diagnostic certainty from 5% (prevalence/pretest probability) to 72%.[12] For patients without agoraphobia, the PDSS has low diagnostic power, with a sensitivity of 83.3% and a specificity of 64%, yielding a LR+ of 2.31 (95%CI 1.75-3.04) and increasing the diagnostic probability to only 11%[13] (A).

The Panic Associated Symptoms Scale (PASS) measures the severity of the following core symptoms of PD: panic attacks, anticipatory anxiety, and agoraphobia. Using a cutoff point of 7.6, it has a sensitivity of 99% and specificity of 98%, providing a LR+ of 49.50 (95%CI 12.55-195.22), increasing the diagnostic certainty from 5% (prevalence) to 72%[14] (B). The Hamilton Anxiety Scale (HAM-A) shows good correlation with the PASS[14] (B), with $r = 0.78$.

Patients seen in primary care and at risk of psychiatric disorders may be evaluated using the Patient Health Questionnaire (PHQ-PD)[15] (B). The PHQ-PD found that

4.8% of patients suffer from PD, with a higher rate of 7.6% in patients who already had psychiatric comorbidities and 9.8% of patients before they presented inexplicable physical complaints. This questionnaire has a sensitivity of 71% and a specificity of 83%, providing a LR+ of 4.18 (95%CI 2.66-6.56), which increases the pretest probability (prevalence of disease) from 5 to 18% for the general population and 10 to 32% for patients with inexplicable somatic complaints[15] (B).

For screening, the Panic Disorder Self-Report (PSR) is a self-enforcement questionnaire, based on the DSM-IV[1] (D), which showed 100% specificity and 89% sensitivity as compared with a structured diagnostic interview. This instrument also features test-retest reliability, discriminant validity, and clinical validity, but has not yet been validated in Portuguese[16] (B). The PSR provides a LR+ of 89 (95%CI 12.64-626.42), which increases the pretest probability of disease from 5 to 82%.

*What are the clinical manifestations of PD in adults?*

Individuals with PD have recurrent, unexpected anxiety attacks. A panic attack is defined as a brief period of intense fear or discomfort, during which somatic symptoms develop abruptly[1] (D). For the diagnosis of PD, the patient must present spontaneous panic attacks which occur ''out of the blue.'' Often, the attacks become situational, associated to previous places or situations where the patient had a spontaneous panic attack, such as crowds or traffic[1] (D).

The other feature of PD is anticipatory anxiety. The patient develops a concern about the recurrence of panic attacks, maintaining heightened awareness of bodily sensations. Once the anxiogenic situations associated with panic attacks are avoided, agoraphobia soon develops[17] (D). In this phase, there is avoidance of places or situations in which it is difficult or embarrassing to obtain help in the case of a panic attack. In general, the agoraphobic patient tends to avoid being alone and in crowded places. Thus, safety behaviors are developed, such as the use of anxiolytic drugs and ensuring that one is in the company of others, which greatly restrict functionality[17] (D).

According to the DSM-IV[1] (D), panic disorder is a period of intense fear and discomfort in which four or more of the following symptoms are present: 1) shortness of breath (dyspnea) or feeling of choking; 2) dizziness, unsteadiness, lightheadedness, or feeling faint; 3) palpitations or accelerated heart rate (tachycardia); 4) trembling or shaking; 5) sweating; 6) smothering; 7) nausea or abdominal distress; 8) depersonalization or derealization; 9) paresthesias (numbness or tingling); 10) chills or hot flushes; 11) chest pain; 12) fear of dying; and 13) fear of going crazy or losing control. Furthermore, there must be at least 1 month of persistent concern about having another panic attack, worry about possible implications or consequences of panic attacks, or a significant behavioral change related to the attacks.

The ICD-10 criteria for the diagnosis of PD[18] (D) include: 1) recurrent attacks of severe anxiety (panic attacks) that are not consistently associated with a certain situation or circumstance, i.e., are unpredictable; 2) symptoms include sudden onset of palpitations, chest pain, choking sensations, dizziness, and feelings of unreality (depersonalization or derealization). Moreover, there is often a secondary fear of dying, losing control, or going mad.

*What are the clinical manifestations of PD in children and adolescents?*

Symptoms of PD in children and adolescents are similar to those experienced by adults, such as palpitations, tremors, restlessness, dizziness, shortness of breath, weakness, sweating, chest pain, abdominal discomfort, nausea, numbness, and fear of losing control[19-21] (B). Although PD is considered rare in young individuals, the frequency of the disorder may range from 0.5[22] (B) to 2%[21] (B); rates as high as 6% have been reported. No epidemiological data are available for agoraphobia, except from patients referred to pediatric clinical services, with rates between 15[23] (B) and 18%[22] (B).

As has been reported in several studies and is often noted in clinical practice, many adults with PD report that their symptoms began in childhood or adolescence. When comparing demographic and clinical characteristics of children and adolescents with and without PD, there were no gender differences in expressing symptoms of the disorder; however, there was a higher occurrence of PD in girls.

Regarding differences in the manifestations of PD in each age group, several authors argue that cognitive symptoms (e.g., fear of losing control) would be more present during adolescence and adulthood than in childhood[23] (B). Contrary to this finding, other studies argue that there are no differences in the symptoms presented by children and adults or children and adolescents[19,21] (B).

*Is there evidence of the role of genetic factors in the etiology of PD?*

Among biological factors, the role of genetics in the onset and maintenance of PD has been investigated[24] (D). Family studies show a higher incidence of PD among first-degree relatives of patients[25] (D), with heritability being estimated at 43-48% for PD and 61% for agoraphobia[26] (B).

A number of chromosomal regions have been associated with susceptibility to PD, specifically 2q[27] and 15q[27] (B), chromosome 7[28] (B), chromosome 1q[29] (B), chromosome 9q[30] (B), 12q[31] (D), 22q,[32] and 13q[32] (B). Several studies also suggest that anxiety disorders, including phobias and PD, are complex traits that share at least one susceptibility locus in relation to chromosome 4q[33] (B).

It is important to note that, despite genetic factors, phenotypic expression is established through the interaction between genes and the environment[34] (D). Twin studies have indicated moderate heritability in PD and

suggest that environmental and genetic contributions are equally important[24,35] (B).

*Is there evidence of the role of environmental stressors in the etiology of PD?*

A number of studies note the high prevalence of stressful life events, such as serious illness or an accident involving a family member or close friend, personal physical illness, worsening relations with one's spouse, trouble with one's boss, and worsening conditions in the workplace, prior to development of PD[36,37] (B).

In a study of 187 patients with PD, the average number of significant life events was 7.8, with a mean value of 3.6 for positive events and 5.3 for negative events. Twenty-five percent of events were considered highly undesirable, while 22% were considered very desirable. In addition, adverse life events were associated with worse psychopathology[38] (B).

A 5-year longitudinal study assessed the factors involved in the onset of panic attacks in 2,000 office workers in a factory. Recent stressful events had a direct effect on the first episode of panic (standardized path coefficient of 0.06), with the strongest predictive value among other variables that were evaluated[39] (A).

*What is the importance of agoraphobia in the diagnosis of PD?*

In recent years, agoraphobia has been viewed as directly related to recurrent panic attacks, and in most cases, it appears as a consequence or complication of PD[40] (D). Other authors believe agoraphobia may be conceptualized as an independent disorder, with more specific criteria that are residual and subordinate to PD[41] (D).

In patients with different subtypes of PD, it was observed that situational panic attacks were more related to the presence of agoraphobia and anticipatory anxiety was higher when agoraphobia was accompanied by PD[42] (B). Results from the National Comorbidity Survey Replication found that lifetime prevalences of 22.7% for panic attack as an isolated event, 3.7% for PD without agoraphobia, and 1.1% for PD with agoraphobia, the latter being associated with a greater number of panic attacks and a greater persistence of the disorder. The presence of agoraphobia was associated with increased severity and a greater number of comorbidities[3] (A). Despite the high prevalence of agoraphobia in PD, this condition is often underdiagnosed and undertreated[40] (D).

PD patients with agoraphobia tend to have a more chronic disorder than do those without agoraphobia. In a 3-year cohort study of PD patients with and without agoraphobia, those who had only PD recovered more often than did patients with PD with agoraphobia. Nevertheless, there were no between-group differences in disease recurrence rates at the end of the follow-up period[43] (A). Recovery rates tended to be lower, estimated at 18-64%, in individuals diagnosed with PD and agoraphobia[44] (D).

Likewise, a longitudinal study and a naturalistic observation, the Harvard/Brown Anxiety Research Project, found that the probability of remission for patients with PD at 1-year follow-up was 39%. When agoraphobia was present, this rate fell to 17%[45] (A). In patients who were studied for 8 years, the percentage of remission was higher (38%) among those initially diagnosed as having PD without agoraphobia than for those diagnosed with agoraphobia (20.6%)[46] (B).

*Are there differences between PD patients with or without agoraphobia?*

PD may exist either with or without agoraphobia, but cases of agoraphobia without a history of PD are more uncommon[47] (B) and this diagnostic categorization is still controversial.

Comparisons between outcomes in PD with agoraphobia and in PD without agoraphobia are inconclusive. People with PD and agoraphobia interpret stimuli with a catastrophic way of thinking; yet, research has suggested that the consequences of catastrophizing events were not sufficient to differentiate between the two groups[48] (B). Moreover, it has been observed that, in patients with PD and agoraphobia who were treated with exposure to panicogenic situations, the presence of residual agoraphobia was a strong predictor of relapse[49] (B).

Comparison of the treatments administered to patients with PD with or without agoraphobia showed that, in both groups, a combination of psychotherapy and drug therapy was more effective than monotherapy during the acute phase (first 8-12 weeks of treatment), while patients in the chronic phase (after 12 weeks) should be treated with combined therapy or psychotherapy alone[50] (A). In the acute phase, there is a relative risk reduction associated with combination therapy vs. pharmacotherapy alone, with RR = 1.24 (95%CI 1.02-1.52), and combination therapy vs. psychotherapy alone, with RR = 1.16 (95%CI 1.03-1.30). For treatment during the chronic phase, combination therapy is more effective than pharmacotherapy alone, which reduces the relative risk to RR = 1.61 (95%CI 1.23-2.11), whereas no significant differences between combination therapy and psychotherapy were found (RR = 0.96, 95%CI 0.79-1.16)[50] (A). Additionally, there were no significant differences between the types of pharmacological treatment for PD with and without agoraphobia[51] (B).

*What is the impact of depression on the diagnosis and prognosis of patients with PD?*

Anxiety disorders and depression co-occur with great frequency, and most cases of depression are secondary to an anxiety disorder (67.9%)[52] (A). Studies show that, because depression is the most common mood found in PD, it must be addressed during PD treatment, especially due to its association with worse severity of PD[53] (A). In a WHO study involving 25,916 patients who were treated in the primary health care setting, the likelihood of

depressed patients presenting comorbid PD were 12 times greater than expected[54] (A).

In a population survey, the lifelong prevalence of depression in patients with PD was significantly higher (55.6%, OR = 6.8) than that of PD in people with depression (11.2%, OR = 6.2). In addition, people with PD and depression reported significant more physiological symptoms during attacks (9.1%) than those without depression ($p \leqslant 0.001$). Patients were also more likely to use psychiatric services when suffering comorbid conditions as opposed to one condition[53] (A).

In general, studies have shown that depression in PD is associated with a more severe psychopathology[54] (A), worse prognosis[55] (B), poor response to treatment[56] (B), an increased number of suicide attempts[57] (B), and limited functioning[58] (B) than PD or depression alone. Patients should also be evaluated for presence of the demoralization syndrome, which is characterized by low self-esteem and feelings of inadequacy and guilt arising from the limitations of PD[59] (D) and is sometimes confused with depression. In this syndrome, symptoms improve after successful treatment of PD, often with no need for specific mood-directed treatments. Early diagnosis of PD can reduce the risk of developing depression[52] (A).

*What is the impact of alcohol and illicit drug abuse and dependence on the diagnosis and prognosis of patients with PD?*

Patients with PD may engage in alcohol abuse. There are several explanations for this co-occurrence: a) PD leads to alcohol abuse, which is often used as self- medication for the improvement of anxiety symptoms; b) chronic alcohol use and withdrawal induce neurochemical changes that lead to panic attacks; and c) a third factor, such as familial transmission, leads to the development of the two conditions[60] (D). In a 3-year prospective epidemiological study of women, occasional intake of large amounts of alcohol (binge drinking) was associated with an increased risk of PD, with OR = 2.23 (95%CI 1.01-4.91)[61] (A).

In 73.1% of PD patients, the onset of alcohol use preceded the onset of PD. It has been observed that patients with PD and alcoholism may experience a more severe disorder, with an increased number of panic attacks and increased anticipatory anxiety[62] (B). Other psychoactive substances, such as cocaine, cannabis, and nicotine, also appear to be able to trigger panic attacks or increase the frequency and intensity of these attacks[63] (D).

Moreover, patients with both PD and alcohol abuse or dependence tend to frequently report a history of depression and use of other psychoactive substances. Alcoholic patients with comorbid PD often have other comorbidities as well, such as depression, dysthymia, and a history of more suicide attempts[64] (B). Individuals who experience panic attacks attempt suicide more often, especially if they abuse alcohol[57] (B).

*What are nocturnal panic attacks? What is the significance of nocturnal panic attacks in the diagnosis of PD?*

Nocturnal panic attacks are characterized by a sudden awakening from sleep in a state of panic, which is defined as an abrupt and rapid period of intense fear or discomfort, accompanied by physical or cognitive symptoms. These panic attacks occur without an obvious trigger[65] (B). They are distinguished from night terrors, sleep apnea, and nightmares[66] (D), and their prevalence ranges from 44 to 71% of patients with PD[66] (D). On the other hand, diurnal panic attacks occur when the subject is awake and can be spontaneous or situational.

A polysomnographic study of PD patients showed respiratory irregularities in the subgroup of patients with panic attacks, which suggests that nocturnal panic attacks could be a variant of PD[67] (C). Similarly, another study indicated that patients with prominent respiratory symptoms are more sensitive to $CO_2$ inhalation and have higher rates of nocturnal panic attacks, which is related to a more severe subtype of panic, a longer duration of the disease, and more intense phobic symptoms[68] (B). Patients with nocturnal panic attacks are more often depressed or have other psychiatric symptoms[69] (B) and tend to be more prone to developing anorexia nervosa and somatization disorder[70] (B).

Thus, diurnal and nocturnal panic attacks seem to develop in different ways. In nocturnal panic attacks, biological factors such as dysfunction of the autonomic nervous system can be a crucial aspect, whereas cognitive and psychological factors may act as an initial stimulus for diurnal panic attacks[71] (D).

Several pharmacological agents are more effective in patients with nocturnal panic attacks, while cognitive and behavioral strategies may be more suitable for daytime panic attacks[72] (D). It is also possible that patients with diurnal and nocturnal panic attacks are similar with respect to comorbidities, symptoms of negative affect, and impact in interpersonal functioning. Patients with nocturnal attacks tend to have more sleep disturbances and less agoraphobic avoidance, because the association between panic situational factors is less frequent,[73] (B) but do not differ from patients with diurnal panic attacks in sleep architecture, sleep physiology, sleep quality, or self-reported severity of PD[66] (D). Likewise, in a short-term prospective study of 57 patients taking nortriptyline, both groups showed similar features in terms of phenomenological results[65] (B).

*Should psychiatrists screen PD patients for sleep disorders?*

Subjective reports have shown high rates of sleep complaints in PD patients as compared with control groups[74] (A). Although the findings of polysomnographic studies of PD patients are still inconsistent[75] (B), decreases in the efficiency and duration of sleep have been reported[76,77] (B). In general, lack of sleep has been

strongly associated with comorbid depression, with a prevalence rate of 30-40%[78] (A).

Chronic complaints about sleep occur in up to 53% of PD patients without comorbidities. When there is a comorbid mood disorder, this rate reaches 86%[79] (B). The most common complaints are often confused with depression and are related to initiating and maintaining sleep, early awakening, difficulty awaking, oversleeping, lethargy, and daytime sleepiness[79] (B).

In general, a high percentage of patients (77%) with nocturnal panic attacks reported sleeping problems[79] (B). Nocturnal panic attacks may disturb sleep, buth by interrupting it and because of subsequent anticipatory anxiety, which is characterized by fear of sleeping and having a panic attack. This fear leads to the avoidance of sleep and then to sleep deprivation, which further aggravates anxiety. Polysomnography is of particular importance in the clinical diagnosis because it allows for the differential diagnosis of panic attack, night terrors, nightmares, and sleep apnea[66] (D).

*In the case of panic attacks in a social situation, how does one make the differential diagnosis between social anxiety disorder (SAD) and PD?*

Symptoms related to social anxiety and PD may be confused, especially when the patient's only avoidance is social situations[80] (A). Identifying the focus of fear is essential to establishing a diagnosis. In cases of social anxiety, fear and somatic symptoms are triggered by situational activators, such as exposure and social performance. In PD, these symptoms are sudden and often do not result from a trigger.

Beliefs related to fear are also different. In the context of SAD, fears are related to the fear of being humiliated in a social situation or displaying excessive anxiety. In PD, beliefs are associated with fear of having a panic attack in public and the inability to receive help in a social environment.

*What are the differences between the most common concerns of patients with generalized anxiety disorder (GAD) and patients with PD?*

In GAD, patient concerns are focused on situations of everyday life, and are accompanied by stress, worry, and fear of the worst, e.g., family violence or health problems. There is no focus on bodily sensations or fear of having a panic attack, but rather an excess of continued anxiety symptoms[1] (D).

*In the event of an extremely anxiogenic situation, how does one differentiate between PD and post-traumatic stress disorder (PTSD)?*

In PTSD, the patient must have experienced or witnessed a situation posing real danger to their life or to others. After the traumatic experience, a person with PTSD usually has distressing memories of the event and intrusive dreams. Because the memories are painful, the person tends to avoid thoughts, activities, and places related to the trauma. Other symptoms such as insomnia, irritability, and difficulty concentrating tend to occur[1] (D).

Conversely, in PD, there is no history of direct or indirect exposure to the types of situations that typically cause PTSD. Instead, the panic attack is spontaneous, sudden, with no apparent cause, and may even occur during sleep.

*Which clinical diseases should be considered in the differential diagnosis of PD?*

The set of symptoms that characterize panic attacks or PD may be confused with a series of clinical medical conditions[81] (D). In the differential diagnosis of PD and clinical entities of an organic nature, late onset (after the age of 45 years) and the presence of atypical symptoms, such as dizziness, unconsciousness, and loss of sphincter control, suggest that an organic cause may be associated with the attacks[82] (D). It is also important to note that clinical diseases may co-occur with PD, in which case both conditions must be treated.

The differential diagnosis should include the following clinical diseases, stratified by organ system involved: 1) cardiovascular system – acute myocardial infarction may be the clinical situation that most often resembles PD, because its symptoms – such as chest tightness, shortness of breath, palpitations, sweating, and feeling of impending death – may also occur in anxiety attacks and coexist in both situations. Thus, the patient should undergo tests such as ECG and serum cardiac markers to rule out an organic etiology. Normal ECG and cardiac markers confirm the diagnosis of PD[82] (D). Other cardiovascular diseases from which PD must be differentiated include congestive heart failure, hypertension, mitral valve prolapse, angina pectoris, and atrial tachycardia[83] (B); 2) neurological system – neurological conditions such as temporal lobe epilepsy, space-occupying lesions, multiple sclerosis[82] (D), and Parkinson disease[84] (C) can mimic a panic attack; 3) endocrine system – Addison's disease, Cushing's syndrome, diabetes, hypoglycemia, hyperthyroidism, hypoparathyroidism, self-immune thyroiditis[85] (C), and pheochromocytoma can mimic a panic attack[82] (D). In addition to these conditions, premenstrual syndrome and menopausal disorders can also exhibit characteristics that may warrant inclusion into the differential diagnosis of PD[82] (D); 4) acute lung diseases – asthma, pulmonary embolism, and chronic obstructive pulmonary disease or acute anxiety can trigger situations with clinical manifestations similar to those found in PD[87] (D); 5) other medical conditions – drug use (hallucinogens, marijuana, cocaine, amphetamines, and nicotine) and withdrawal syndromes (alcohol, benzodiazepines, opiates, and cocaine) can also mimic the symptomatology of PD[82] (D).

*What are the results of laboratory studies of PD?*

Pharmacological induction of panic attacks in the laboratory has been one of the strategies used in PD

research. This technique enables study of panic attacks under controlled conditions and evaluation of the efficacy of pharmacotherapy for PD.

In one study, unmedicated patients with PD (n=31) were subjected to inhalation of 35% $CO_2$ and compressed atmospheric air. Overall, 71% of the patients (n=22) had panic attacks with $CO_2$, whereas none of the subjects reacted to the compressed air[86] (B). In another study by the same group, panic attacks were blocked by clonazepam (2 mg/day) but not by placebo, and patients who took clonazepam did not present any panic attacks at the end of the study ($p \leqslant 0.001$)[87] (B).

In a trial of antidepressant treatment of PD, after the 7th day, responses to $CO_2$ diminished significantly in groups receiving imipramine (20 mg/day, $p = 0.004$), paroxetine (10 mg/day, $p = 0.001$), and sertraline (25 mg/day, $p = 0.004$),[88] (A).

In general, hyperventilation or breath-holding maneuvers, despite inducing respiratory alkalosis with transient breathlessness, dizziness, and anxiety, have not been proven to cause panic attacks in most patients who undergo this experiment, except in patients who are more susceptible[89] (D).

*What are the results of neuroimaging studies in PD?*

With the advent of functional imaging studies, cerebral regions are being mapped and correlated with behavioral disorders, including anxiety disorders[90] (B).

In a study with 12 PD patients and 12 controls, the volume of the right and left amygdala was decreased in PD patients, while controls showed no change in their sizes[91] (B). Following this line of research, other authors found that the left temporal lobe of 11 PD patients exhibited a reduction in volume compared to 11 healthy controls[92] (B).

The hippocampal region of the septum seems to play an important role in controlling anxiety[93] (D). Thus, there is suspicion that the septo-hippocampal system plays a role in the occurrence of PD. In one study, researchers detected a high frequency of cavum septi pellucidi with electroencephalographic abnormalities in patients with PD[94] (B). Another study, however, did not confirm the previous observations in 21 patients with PD compared with 21 controls[95] (B).

When comparing the gray matter of 19 PD patients to 20 healthy volunteers, researchers found an increase in the left insula of this area in PD patients compared to healthy controls and an increase in the superior temporal gyrus, midbrain and bridge. Relative gray matter deficits were observed in the right anterior cingulate cortex. The authors concluded that abnormalities in the brain stem are involved in the generation of panic attacks[96] (B).

*Is there any benefit to performing heart tests after a diagnosis of PD has been established?*

A study of 5,187 patients showed that the presence of any anxiety disorder diagnosis was significantly associated with the presence of various diseases. PD was associated with vascular conditions (OR = 2.28), bone or joint diseases (OR = 2), and neurological conditions (OR = 1.75). Other anxiety disorders such as GAD, SAD, and simple phobias had less of an association with physical illness than did PD[97] (A). A population-based study in Norway evaluated 64,871 patients to explore the correlation between PD and systolic blood pressure. GAD was associated with the presence of low systolic blood pressure, while patients with PD had a mean systolic blood pressure of 140 mmHg[98] (A).

Decreased heart rate variability was identified as a potential risk factor for sudden death in patients recovering from myocardial infarction[99,100] (B). Evidence suggests that patients diagnosed with PD exhibit reduced heart rate variability compared with controls. These findings suggest that individuals with PD show changes in cardiac autonomic control, and these changes could place them at an increased risk of ventricular arrhythmia and sudden cardiac death[101] (B)[102] (C).

A study of 3,369 postmenopausal women showed that those who experienced at least one full-blown panic attack in the preceding 6-month period were more likely to have the cardiovascular risk factors smoking, hypertension, and diabetes mellitus, as well as a history of cardiovascular morbidity (A).[103]

A 32-year study of 402 cases of coronary heart disease (137 cases of nonfatal myocardial infarction, 134 cases of angina, 131 cases of fatal coronary heart disease, 26 cases of sudden cardiac death, and 105 cases of non-sudden death) and 1,869 individuals without coronary artery disease showed that subjects with coronary disease who reported symptoms of anxiety had a higher risk of fatal outcome, with an OR of 3.20 (95%CI 1.27-8.09) for fatal coronary disease and an OR of 5.73 for sudden death (95%CI 1.26-26.1). An increased risk of myocardial infarction or nonfatal angina was not found[104] (A) These data suggest an association between anxiety and fatal coronary heart disease, particularly sudden cardiac death, in patients with coronary heart disease and symptoms of anxiety, which indicates the need for careful study of this population.

## Conclusions

These guidelines, which were designed by the BMA in partnership with the BPA, serve to facilitate and assist in the decisions of physicians and to provide clarity, clinical applicability, and practical relevance for the diagnosis and differential diagnosis of PD.

Due to the close association between PD and autonomic activation, PD is often mistaken for clinical conditions such as stroke and high blood pressure, which can delay treatment. This confusion can also occur with other psychiatric disorders that have symptoms similar to those of PD. In addition to prolonging patient suffering, unsuitable treatment of the patients leads to unnecessary financial costs.

Research on PD has intensified during the last decade, particularly regarding neuroimaging, which reflects the interest of the scientific community in gaining a better

understanding of this disorder. Laboratory studies using panicogenic agents are also important for exploring the mechanisms underlying the development of PD.

## Disclosure

The authors report no conflicts of interest.

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**Artigo 3: Public speaking in social phobia: a pilot study of self-ratings and observers' ratings of social skills. *Journal of Clinical Psychology*, 68(4): 397-402, 2012.**

# Public Speaking in Social Phobia: A Pilot Study of Self-Ratings and Observers' Ratings of Social Skills

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**Objectives:** The aim of this pilot study was to investigate whether patients with social anxiety disorder (SAD) differ from controls in the quality of skill-related behaviors displayed during a speech and in overall behavioral adequacy as perceived by observers and by the patients themselves. **Design:** A total of 18 SAD patients and 18 controls were screened by a diagnostic interview and took part in a 3-minute speech of their own choosing. For each videotaped speech, observers rated the adequacy of the skill-related behaviors and overall performance adequacy. After the experiment, participants were asked to rate their own overall performance adequacy. **Results:** The results showed that SAD patients exhibited significantly worse voice intonation and fluency of the speech, however no differences were found in global self-ratings. Moreover, the performance evaluations of the SAD group were consistent with the observers, while the controls evaluated their performance lower than the observers. **Conclusions:** The results are inconsistent with the cognitive model, because patients with SAD did not underestimate their performance. Compared with spontaneous interactions, the clear rules established for such social situations as speeches may result in less cognitive distortion for SAD patients.  J. Clin. Psychol. 68:397–402, 2012.

Keywords: social anxiety; performance; social skills; social exposure

Social anxiety can affect social functioning as well as vocational performance. The inability to make effective oral presentations can predict mediocre advances in school and career (Beidel, Turner, & Dancu, 1985). Previous studies indicate that socially anxious subjects tend to have fewer years of study and more days off from school and work than subjects who suffer from other anxiety disorders (Whittchen et al., 2000). Behavioral studies have addressed whether socially anxious individuals differ from adults who do not have social anxiety disorder (SAD) regarding social performance adequacy.

One possible explanation for SAD relates to the social skills (SS) deficit. Although varying definitions of SS have been offered, the term generally implies the ability to interact with other people in a way that is both appropriate and effective (Spitzberg & Cupach, 1989). Some authors suggest that socially anxious people would have failed to learn effective social behavior and that their anxiety and avoidance is partially a reaction to those deficits and to the resulting negative responses by others (Segrin, 2001; Segrin & Flora, 2000). The above hypothesis relies on studies that indicate a decrease in social anxiety among SAD patients who receive SS training (Turner, Beidel, Cooley, Woody, & Messer, 1994; Wlazlo, Schroeder-Hartwig, Hand, Kaiser, & Munchau, 1990).

Cognitive models predict that SAD patients fear negative evaluation by others and that they tend to underestimate the quality of their own social behavior. From this perspective, patients with SAD possess adequate SS but their anxiety caused by erroneous beliefs prevents their ability to focus on social interactions and thus use skills (Clark & Arkowitz, 1975; Clark & Wells, 1995).

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The literature indicates that patients with SAD perform worse on social tasks compared with control participants. Beidel et al. (1985) evaluated 13 males and females with SAD and considered the SAD participants less socially skilled than controls. Baker and Edelman (1985) evaluated 18 social phobics, 18 clinically anxious, and 18 controls and observed that SAD patients were rated as significantly less adequate regarding gesture, speech fluency, and overall performance than the other groups. In a large behavioral assessment of SS, Beidel Rao, Scharfstein, Wong, and Alfano (2010) found that generalized SAD patients ($n = 119$) and nongeneralized SAD patients ($n = 60$) reported equal stress to an impromptu speech task, when compared with nonpsychiatric group ($n = 200$), suggesting that this type of exposure is not well tolerated by SAD patients in general. In contrast, other studies could not find differences between SAD patients and other groups in this type of situation (Rapee & Lim, 1992; Pilkonis, 1977; Voncken & Bogels, 2008).

The assessment of SS is usually made at micro-level or midi-level (Baker & Edelman, 2002). Micro-level analysis consists of frequency counts and/or duration of specified behaviors (objective evaluation), whereas midi-level analysis utilizes a rating scale (subjective evaluation; Monti et al., 1984). Studies using a midi-level analysis suggest that judges rate socially anxious individuals as less socially skilled and more anxious than those who are low in social anxiety (Arkowitz, Lichtenstein, McGovern, & Hines, 1975; Farrell, Mariotto, Conger, Curran, & Wallander, 1979; Halford & Foddy, 1982; Twentyman & McFall, 1975).

To investigate whether SAD patients differ from controls in behavioral adequacy as perceived by themselves and others, we invited adults with SAD and a nonpsychiatric group to take part in a public speaking task. The current experiment comprises a pilot study that is designed to evaluate the suitability of specific hypotheses and observations for a larger future study. We intend to delineate differences on both groups regarding observation of public speaking. The current study's hypotheses are based upon previous findings in the literature. It is hypothesized that SAD patients will be rated by observers as exhibiting less adequate behaviors than controls and that SAD patients' evaluation of their own overall performance will be worse global than observers´ evaluation. Moreover, we believe that the observers will rate SAD patients performance lower than the controls performance.

## Method

### *Participants*

Participants comprised 36 total people, of whom 18 were nonclinical control participants selected from the staff. The other 18 participants were individuals who had generalized SAD and who were referred to the Psychiatry Institute of the Federal University of Rio de Janeiro and the Department of Psychiatry of the University of Sao Paulo, Brazil. The patients were not receiving psychotherapy at the time of the study, and both groups received a diagnostic assessment that entailed the administration of the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinical Version (First, Spitzer, Gibbon, & Williams, 1997) by trained psychiatrists who were not involved on the next steps of the study. Evaluated individuals were invited to participate in a psychological experiment. None of the 18 controls, but all of the 18 social phobics, met the DSM-IV criteria (American Psychiatric Association, 1994) for SAD.

### *Test Procedure*

The experiment consisted of a speaking for 3 minutes in front of an audience about a chosen topic. The audience comprised the researcher and two assistants (medical students), none of whom had met the participants prior to the experiment. The speech was recorded with the consent of the participants. Subjects were allowed to make notes during the preparation period, but had to discard them before speaking. Subjects who indicated a desire to end the task or who showed extreme difficulty in continuing the speech (e.g., remaining completely silent for an entire minute) were encouraged to continue (e.g., "you are doing fine, keep going").

### *Ratings of Adequacy of Behavior*

Observers viewed the videotapes of participants' speeches and were instructed to complete a series of rating scales for each individual observed. The scales were derived from qualitative scales developed by Trower, Bryant, and Argyle (1978) and included subjective evaluation of the following social skills: visual contact (i.e., use of mutual and direct eye contact in accordance with expressive and regulatory norms of conversation and context), voice intonation (i.e., adjustment of tone according communication of feelings), gestures (i.e., demonstration of hand, arm, and head movements to compliment and/or elaborate on utterances), fluency on the speech (i.e., demonstration of speech disturbances such as stutters, omissions, or repetitions), and facial expression (i.e., demonstration of emotion appropriate to the content of the speech).

The scales were anchored with a rating of 1 (*not at all adequate*) to 3 (*highly adequate*). Using this 3-point rating scale, each observer rated the adequacy of participants' behaviors. The overall adequacy of performance for each individual observed was rated using a 7-point scale, with higher ratings indicating greater degrees of the behavior. Observers analyzed the participants' recorded behavior and were not present during the experiment. Observers did not know what groups there were or which participants belonged to which group. All observers had prior training in evaluation through an SS course. When the scores did not match across observers, an experienced SS researcher, otherwise independent of the current study, conducted a discussion to resolve the final score by unanimous decision.

## Results

### *Descriptive Data/Independent Variables*

There were no statistical differences in demographic data between the groups. Mean sample age was 36 years (68.6% women). Additionally, 54.3% of the participants were single and 60% had at least a college education.

### *Experimental Data*

Of the five behavioral qualities analyzed by observers, the only significant differences between the two groups were for the voice intonation (P = .001) and fluency of the speech ($P = .001$), where the scores of the experimental group were lower than the control group (Table 1).

The overall performance mean evaluated by the raters was 5.90 for controls and 4.06 for SAD subjects (P = .000). However, there was no significant difference between the two groups in mean performance self-evaluations (4.88 for controls vs. 4.39 for SAD).

A paired *t* test was performed to compare the overall performance means by evaluators with the self-evaluated overall performance means for each group. There was a significant difference between the evaluator means and the self-evaluated means for the control group ($P \leq .0008$),

Table 1
*Mean Scores And Standard Deviation for Subjective Ratings by Diagnostic Group*

| | Controls | | | Patients | | | |
|---|---|---|---|---|---|---|---|
| Ratings | *M* | *SD* | CI 95% | *M* | *SD* | CI 95% | *p* |
| Visual contact | 1.33 | 0.77 | 0.95–1.71 | 1.00 | 0.69 | 0.65–1.34 | 0.178 |
| Voice intonation | 1.72 | 0.47 | 1.49–1.95 | 0.94 | 0.73 | 0.58–1.30 | 0.001 *** |
| Gestures | 1.44 | 0.70 | 1.09–1.79 | 0.94 | 0.80 | 0.54–1.34 | 0.055 |
| Fluency | 1.61 | 0.61 | 1.30–1.91 | 0.89 | 0.59 | 0.59–1.17 | 0.001*** |
| Facial expression | 1.78 | 0.43 | 1.56–1.99 | 1.39 | 0.78 | 1.00–1.77 | 0.072 |

*Note.* SD = standard deviation; M = mean; CI = confidence interval.
*** $P \leq .001$.

Table 2
*Mean Scores for Discrepancy in Performances Scores by Diagnostic Group*

| Controls | *M* | *SD* | CI 95% | *p* |
|---|---|---|---|---|
| Raters' evaluation | 5.90 | 0.99 | 5.39–6.41 | 0.008** |
| Self-evaluation | 4.88 | 1.36 | 4.18–5.58 | |
| Patients | *M* | *SD* | CI 95% | *p* |
| Raters' evaluation | 4.05 | 1.16 | 3.47–4.63 | 0.582 |
| Self-evaluation | 4.38 | 2.00 | 3.39–5.38 | |

*Note.* SD = standard deviation; M = mean; CI = confidence interval.
** $P \leq .01$.

in which the control group gave lower grades for their performance than the evaluators. For the SAD group, there was no significant difference between the evaluator means and the self-evaluated means (Table 2).

## Discussion

The current pilot study was designed to determine whether patients with SAD present discrepancies between expected and actual performance ratings and whether the quality of their behavior, as observed by raters, also differs from the behavior of controls. The results indicate that SAD patients (a) were rated by observers as less socially adequate than controls, (b) did not differ in self-evaluation from the controls, and (c), did not differ from observers in evaluating their own performances.

In this study, SAD patients were rated as less adequate on all behavioural indices, especially voice intonation and fluency of speech. In accordance, the overall performance, considered a product of many variables of behavior, was also rated as worse for SAD patients. The results are consistent with Beidel et al. (1985), who found that social phobia patients were rated as less socially skilled, and are partly consistent with Rapee and Lim (1992), who showed that SAD patients were rated as worse than controls in the global rating of behavior, but not in the specific sub-behaviors.

Previous research (Norton & Hope, 2001; Rapee & Lim, 1992; Stopa & Clark, 1993) indicates that socially anxious adults underestimated their own SS to a greater degree than nonanxious adults. In contrast, the current study showed no difference in self-evaluation between the two groups. This inconsistency may be because of developmental differences in the populations studied, which could have a lower severity degree of impairment caused by the disorder (Inderbitzen-Nolan, Anderson, & Johnson, 2007).

Interestingly, although other studies indicate that socially anxious adults engage in a higher degree of negative self-referent thoughts (Lucock & Salkovskis, 1988; Rapee & Lim, 1992; Stopa & Clark, 1993), in our study, SAD patients were consistent with observers in overall performance evaluation, indicating fewer negative thoughts about their performance than would be expected. In contrast with the SAD patients, controls evaluated themselves more poorly in overall performance than raters rated them. The same result was also found in a childhood study (Alfano, Beidel, & Turner, 2006), in which SAD children lacked negative performance thoughts relating to social tasks. The results of this current study raise conceptual questions regarding how negative self evaluation relates to the etiology of this disorder. Perhaps for this type of exposure, in which expected behavior is known and rules are clear, SAD individuals understand their actual deficits and do not underestimate their performance, based on previous feedback and habituation.

We are unable to draw conclusions from the current study; rather we formulated hypotheses that will be tested in a primary study with a larger sample and using more instruments. For example, we intend to assess anxiety related to the task and the effects of a larger audience size.

To better understand the details of the cognitive factors involved in SAD, participants' negative thoughts will also be assessed.

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**Artigo 4: A review of preliminary observations on agomelatine in the treatment of anxiety disorders.** ***Experimental and Clinical Psychopharmacology.*** **20(6): 504-9, 2012.**

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# A Review of Preliminary Observations on Agomelatine in the Treatment of Anxiety Disorders

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Agomelatine is an antidepressant with a novel mechanism of being a selective melatonergic $MT_1/MT_2$ receptor agonist with serotonin 5-$HT_{2c}$ receptor antagonist activities. Although the vast majority of the clinical data concerning the effectiveness of agomelatine concern its antidepressant properties, there is also preliminary evidence of anxiolytic effects. The purpose of the study was to perform a review of studies that investigated the efficacy of agomelatine in the treatment of anxiety disorders (ADs) and a discussion of the clinical utility of agomelatine in this clinical population. Previous clinical data indicated that agomelatine was more efficacious than both placebo and comparator drugs in reducing anxiety symptoms in depressed patients. Moreover, agomelatine effectiveness in the treatment of AD patients was observed in 2 double-blind, randomized trials, in a case series and in 3 case reports. Greater clinical evidence was observed with generalized AD patients. Agomelatine was efficacious both in reducing anxiety symptoms and in preventing relapses after a 6-month follow-up. However, concerning other ADs, evidence of agomelatine's effects on anxiety was found only in isolated case descriptions. Nevertheless, those case reports emphasized the drug's favorable side effect profile (in comparison to serotonin reuptake inhibitors) and its effectiveness in treatment-refractory patients. Considering the high incidence of poor efficacy and tolerability of the first-line agents in the treatment of ADs, agomelatine seems to be a promising option in cases of treatment failure, and it could be used as a second or third option, as monotherapy or as augmentation treatment.

*Keywords:* agomelatine, anxiety disorder, melatonin

Melatonin is a ubiquitous molecule that is widely distributed in nature. In vertebrates, including humans, melatonin is primarily synthesized by the pineal gland (having serotonin as one of its precursors), and its secretion is synchronized with the light/dark cycle with a nocturnal maximum (Pandi-Perumal, et al., 2006). Some of the physiological functions in which melatonin participates include hypnotic and chronobiotic actions and helping in the control of sleep, body temperature, and cortisol (Arendt & Skene, 2005).

Sleep abnormalities, which are common in patients with depression, have stimulated investigation into the relationship between melatonin and depression. Low levels of melatonin evidenced in depressed patients (Srinivasan et al., 2006) and the observation that melatonergic $MT_1$ knockout enhanced depression-like behavior in mice (Weil, Hotchkiss, Gatien, Pieke-Dahl, & Nelson, 2006) contributed to the hypothesis that melatonin is linked to behavior function. In addition, antidepressant treatment of major depressive disorder has led to increases in plasma levels of melatonin with improvements in depressive psychopathology (Thompson, Mezey, Corn, Franey, English, Arendt, & Checkley, 1985).

Agomelatine is an antidepressant with the novel mechanism of being a selective melatonergic $MT_1/MT_2$ receptor agonist with serotonin 5-$HT_{2c}$ and 5-$HT_{2b}$ receptor antagonist activities (McAllister-Williams, Baldwin, Haddad, & Bazire, 2010), while most antidepressants act via the inhibition of the neuronal reuptake of monoamines (mainly serotonin and noradrenaline), with resultant increases in monoamine neurotransmission in the central nervous system (see Figure 1). Although the role of these different receptor activities of agomelatine in relation to its antidepressant action has not been fully elucidated, it seems that its melatonergic agonism and its 5-$HT_{2c}$ antagonism could act synergistically in the restoration of disrupted circadian rhythms, as 5-$HT_{2b}$ receptors are poorly represented in the central nervous system, wherein their functional significance remains obscure (Milan et al., 2003). The evidence corroborating this hypothesis is based on 5-$HT_{2c}$ receptors being the only

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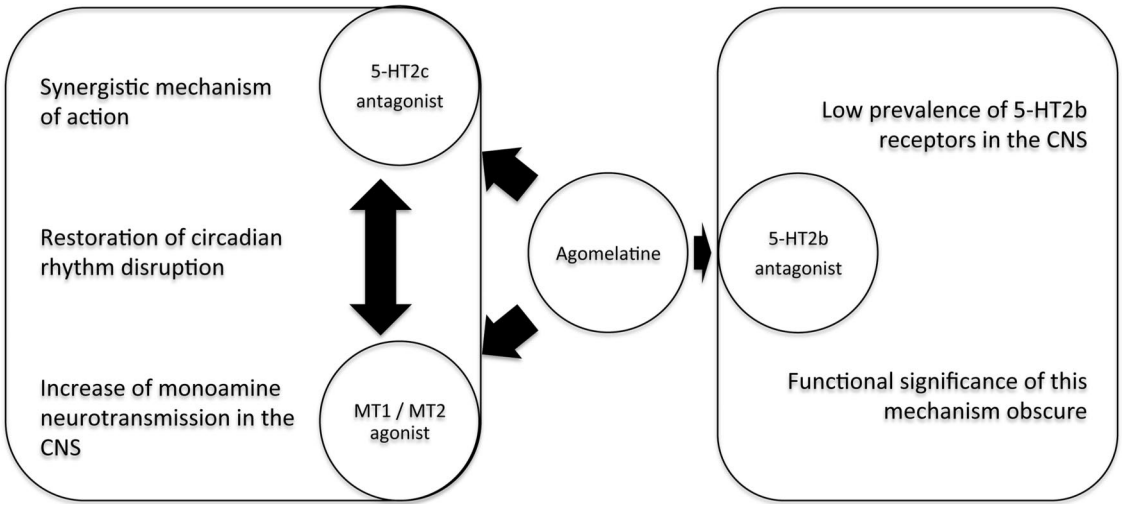


*Figure 1.* Mechanisms of action and antidepressant property of agomelatine. CNS = central nervous system; $MT_1$ = melatonin receptor 1; $MT_2$ = melatonin receptor 2; $5\text{-}HT_{2b}$ = serotonin 2b receptor; $5\text{-}HT_{2c}$= seratonin 2c receptor.

5-HT receptors exhibiting a circadian rhythm of expression (San & Arranz, 2008).

Although agomelatine has a potential hypnotic effect, it should not be regarded simply as a sleep-promoting compound. Indeed, because of its antidepressant properties, agomelatine was approved in 2009 by the European Medicines Agency (EMEA) for the treatment of major depressive episodes in adults (25–50 mg once daily) but not generally as a hypnotic agent (Servier Pharma, 2009). Although it demonstrated a good safety and tolerability profile, isolated and reversible increases in liver transaminases were observed in 1.1% of patients (compared to 0.7% in placebo-treated patients), leading to a recommendation of liver monitoring (EMEA, 2009). A recent meta-analysis reviewed the effectiveness of agomelatine for depression in nine published trials. Five placebo-controlled and four head-to-head comparison trials with fluoxetine, paroxetine, sertraline, and venlafaxine demonstrated the efficacy of agomelatine in the treatment of depression (Singh, Singh, & Kar, 2011).

Although the vast majority of the clinical data concerning the effectiveness of agomelatine are related to its antidepressant properties, there is also evidence of its anxiolytic effects. The blockade of $5\text{-}HT_{2c}$ receptors might be associated with reductions in anxiety (Milan, Brocco, Gobert, & Dekeyne, 2005). This effect can also be observed with agents such as mianserin and mirtazapine, which are potent antagonists of $5\text{-}HT_{2c}$ receptors and which display anxiolytic properties in animals and humans (Casacalenda & Boulenger, 1998). However, the clinical reduction of anxiety could simply be due to the hypnotic and sedative effects of agomelatine rather than its anxiolytic properties.

The first clinical evidence of agomelatine's efficacy in anxiety symptoms was observed in major depression clinical trials as a secondary outcome that was evaluated. In a randomized, double-blind comparison study with sertraline, agomelatine demonstrated improvement in anxiety symptoms among depressed patients, measured with the Hamilton Anxiety Rating Scale (HAM-A). Additionally, this result was maintained even after the exclusion of the item on the HAM-A related to sleep (Kasper et al., 2010).

Recently, data from six multicenter, double-blind, short-term, randomized trials of agomelatine for depression were pooled to evaluate the drug's efficacy in anxiety symptoms within depression versus placebo and versus fluoxetine, sertraline, or venlafaxine (Stein & Kennedy, 2011). Agomelatine was more effective than both placebo and comparator drugs in reducing anxiety symptoms in depressed patients. Specifically, the decrease in HAM-A symptoms was greater with agomelatine when compared to active comparators in the highly anxious population (1.72 [0.8] $p$ = .032).

On the basis of data from major depression trials and from animal models for anxiety, which suggest an anxiolytic effect of agomelatine, few published reports have investigated agomelatine as a possible treatment for anxiety disorders. The aims of this research were to perform a review of these studies and to discuss the clinical profile of agomelatine in the treatment of anxiety.

## Methods

The MEDLINE electronic database was used to search studies, including the keywords *agomelatine*, *anxiety disorders*, and *treatment*. Additionally, the reference lists of the original studies were searched manually. All types of studies were included.

## Results

Only a few publications have investigated the efficacy of agomelatine in patients exhibiting an anxiety disorder (AD) as a primary condition. Table 1 presents these studies according to the publication type and anxiety disorder category investigated.

The first clinical evidence that agomelatine might exert anxiolytic effects in nondepressed patients was observed in a

Table 1
*Description of Agomelatine Studies for the Treatment of Anxiety Disorders*

| Authors (year) | Publication type | Condition | Outcome measure | Main results | Comments |
|---|---|---|---|---|---|
| Stein (2008) | 12-week double-blind placebo-controlled trial | GAD | HAM-A scores | AGO > PLB decrease HAM-A scores (−3.28 [1.58], $p = .04$) | AGO ($n = 63$); PLB ($n = 58$); 12-week trial |
| | | | | Responders (12 weeks): AGO (66.7%) vs. PLB (46.6%) ($p = .026$) | AGO was used in flexible-dosage design (25–50 mg/d) |
| | | | | | AGO ≠ PLB from 6th wk onward |
| Stein (2011) | 16-week open-label trial; remitters randomized to 26-week double-blind placebo-controlled trial | GAD | HAM-A scores | Relapse after 26 weeks: AGO (19.7%) vs. PLB (31.7%) ($p = .046$) | Patients with remission in an open-label trial were randomized for AGO/PLB (26 weeks) |
| | | | | Risk of relapse reduced by 42% compared to PLB ($p = .045$) | AGO was used in a flexible-dosage design (25–50 mg/d) |
| | | | | | AGO: absence of discontinuation symptoms |
| Fornaro (2011b) | Case series | OCD | Y-BOCS scores | 3 of 6 patients with reduction ≥35% (Y-BOCS) during at least a 12-week trial | AGO was used in SSRI-refractory patients |
| | | | | | Presence of psychiatric comorbidities |
| Da Rocha & Correa (2011) | Case report | OCD | Y-BOCS and BDI scores | BDI: from 25 to 8 (2 weeks) | AGO was used as augmentation treatment of CLO 225 mg/d (3-month follow-up) |
| | | | | Y-BOCS: from 36 to 11 (5 weeks) | Previous trials with SERT, RISP, and ARIP |
| De Berardis et al. (2012) | Case report | OCD | Y-BOCS and MADRS scores | Y-BOCS: from 30 to 6 (6 weeks) and to 3 (follow-up) | Lack of efficacy and poor tolerability with previous SSRI and SNRI trials |
| | | | | MADRS: from 18 to 8 (2 weeks) | AGO was used at 50 mg/d as monotherapy |
| | | | | | Absence of other psychiatric comorbidities |
| Crippa et al. (2010) | Case report | SAD | BSPS and SPIN scores | BSPS: from 58 to 16 (10 weeks) | Lack of efficacy and poor tolerability with previous SSRI and SNRI trials |
| | | | | SPIN: from 52 to 14 (10 weeks) | |
| Fornaro (2011a) | Case report | PD | Clinical observation | Sustained remission of panic attacks with AGO (25 mg/d) over 5-month trial | Previous adequate efficacy with low-dose paroxetine but with a high incidence of AEs |

*Note.* GAD = generalized anxiety disorder; HAM-A = Hamilton Anxiety Rating Scale; AGO = agomelatine; PLB = ; OCD = obsessive-compulsive disorder; Y-BOCS = Yale–Brown Obsessive–Compulsive Scale; SSRI = selective serotonin reuptake inhibitors; BDI = Beck Depression Inventory; CLO= clomipramine; SERT = sertraline; RISP = risperidone; ARIP = aripiprazole; MADRS = Montgomery–Âsberg Depression Rating Scale; SNRI = serotonin and noradrenaline reuptake inhibitors; SAD = social anxiety disorder; BSPS = Brief Social Phobia Scale; SPIN = Social Phobia Inventory; PD = panic disorder; AE = adverse effect.

12-week, multicenter, randomized, placebo-controlled trial that examined the efficacy of agomelatine in 121 patients with generalized anxiety disorder (GAD), diagnosed according to *DSM–IV–TR* criteria (Stein, Ahokas, & de Bodinat, 2008). Subjects with other psychiatric disorders were excluded. Agomelatine was increased from 25 to 50 mg daily in a blinded fashion. The agomelatine group was associated with a significantly larger decrease in HAM-A symptoms at the end point (−3.28 [1.58]; 95% confidence interval [CI] = − 6.41 to −0.15), especially on the subscale of somatic symptoms (similar to those symptoms one might expect regarding agomelatine's effects on sleep). However, the difference compared to the placebo group only became statistically significant from Week 6 onward. The authors commented that this observation could have been biased by the small sample size of each group. Nevertheless, by Week 12, agomelatine demonstrated higher rates of response ($p < .001$) and anxiety remission ($p < .001$) than placebo. Finally, preliminary validation of the *DSM–IV* GAD Severity Scale (DGSS) was undertaken using data from this study (Stein et al., 2009). In addition to the positive correlation with the HAM-A ($p < .01$), the agomelatine group showed a significant reduction in DGSS scores at 12 weeks compared to Week 0 (12.33 [9.57] vs. 28.98 [4.46], $p < .01$).

A second trial evaluated the efficacy of agomelatine in preventing relapses in patients with GAD over 6 months (Stein & Kennedy, 2011). The patients received open-label agomelatine for 16 weeks using a flexible-dosage design. Only those patients who exhibited remission that maintained stabilized during Weeks 12 and 16 were randomized to continue agomelatine or to receive placebo. The agomelatine group showed a lower incidence of relapse at the endpoint when compared to the placebo group (19.7% vs. 31.7%, $p = .046$), which translated into a reduction of relapse risk of 42% ($p = .045$).

The potential biochemical mechanism of agomelatine in reducing anxiety, related to 5-$HT_{2c}$ receptor antagonism, and the preliminary clinical evidence of its anxiolytic effects have stimulated other clinical studies that have investigating this compound in the treatment of anxiety disorders.

Obsessive–compulsive disorder (OCD) is a common condition that is potentially disabling and has a high percentage of serious cases (50.6%) (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Although selective serotonin reuptake inhibitors (SSRIs) are considered the first-line treatment option, at least 40% of the patients do not achieve a satisfactory clinical response (Pallanti et al., 2002). Therefore, several strategies have been investigated to help increase responses in these treatment-refractory cases (Dell'Oso, Mundo, Marazziti, & Altamura, 2008; Fornaro, Gabrielli, Albano, Fornaro, Rizzato, et al., 2009). Considering some evidence of delayed slow wave sleep (Mukhopadhyay et al., 2008), as well increased nocturnal secretion of Adrenocorticotropic hormone and cortisol, a melatonin-related "stress hormone" (Catapano, Monteleone, Fuschino, Maj, & Kemali, 1992), a case series was published of six SSRI-refractory patients with OCD who were switched from the SSRI to agomelatine (50 mg/day) and were followed for at least 3 months (Fornaro, 2011b). Three of the 6 patients exhibited a reduction in obsessive–compulsive symptoms of 35% or more. Notably, all of the patients presented other current or psychiatric comorbidities—such as substance abuse, mood disorders, bipolar spectrum soft signs, and bulimia nervosa—and they all had received high doses of more than one class of antidepressant before beginning agomelatine. In the same way, Da Rocha and Correa (2011) described a case of successful augmentation with agomelatine in a male patient with a 3-year history of a treatment-resistant OCD (contamination type), who had a poor response to previous treatment with sertraline (200 mg/day), to current augmentation with risperidone (2 mg/day) for 6 months and subsequently to aripiprazole (10 mg/day) for 35 days. The authors hypothesized that, in addition to the role of 5-HT2c receptor antagonism, the resynchronization of the serotoninergic system (De Botinat et al., 2010; Wulff, Gatti, Wettstein, & Foster, 2010), through modulation of the circadian rhythms (influenced by agomelatine use), might have helped regulate the serotoninergic dysfunction present in patients with OCD. Finally, De Berardis et al. (2012) described another case of OCD symptom remission with agomelatine 50 mg/day in young woman with a treatment-refractory disorder. In addition to the patient's history of previous pharmacologic attempts (fluvoxamine 300 mg/day, venlafaxine 225 mg/day, clomipramine 225 mg/day) and the emergence of numerous adverse effects, it should be noted that unlike findings in previous articles, OCD was the only psychiatric disorder observed in this patient, and agomelatine was used as monotherapy.

A single case report described effective treatment with agomelatine, up to 50 mg/day, in an adult young patient with severe generalized social anxiety disorder (SAD) that was resistant to adequate previous trials with sertraline, citalopram, duloxetine, and venlafaxine, with or without clonazepam. In addition to the major improvement perceived in social anxiety symptoms and the lack of relapse during the 6-month follow-up, the authors emphasized the absence of initial worsening of anxiety or sexual dysfunction with agomelatine use, which are common side effects observed with SSRIs (Crippa et al., 2010). Actually, the side effect profile is also a major factor influencing treatment adherence (Masand, 2003), especially in the management of chronic, disabling and recurrent disorders such as SAD (Filho et al., 2010).

Another case report emphasized the importance of tolerability in achieving continuous pharmacological treatment (Fornaro, 2011a). The author described a patient exhibiting panic disorder (PD) with relevant neurovegetative symptoms. In that case, the patient presented reduction of panic attacks with the use of low doses of paroxetine (10 to 20 mg/day) associated with clonazepam or propranolol. However, medication was discontinued twice because of adverse effects, including iatrogenic sexual dysfunction. After another recurrence of PD symptoms, the patient agreed to a trial with agomelatine (25 mg/day), which was well tolerated and led to remission of the panic attacks during the 5-month follow-up.

## Discussion

Although there is some evidence of the benefit of agomelatine in the relief of anxiety symptoms from preclinical and clinical studies in patients with depression, so far only two controlled trials have investigated its clinical utility in a sample consisting exclusively of anxiety disorder patients. Additionally, GAD was the only anxiety disorder category evaluated in these interventional studies. Nevertheless, the scarce literature reporting agomelatine's properties in reducing anxiety in OCD, generalized SAD, and PD patients cannot be overlooked.

Although the lifetime prevalence of GAD is estimated to be in the range of 2.8% to6.6% among adults, and the evidence base for pharmacotherapy is growing, current guidelines do not offer detailed strategies or recommendations beyond the first level of treatment, which could include the use of an SSRI or SNRI (serotonin and noradrenaline reuptake inhibitor) (Davidson et al., 2010). Moreover, some drugs suggested as second-line treatments have shown little evidence of benefit in the treatment of GAD patients in clinical studies. For instance, the International Psychopharmacology Algorithm Project (IPAP) recommends the use of sedative antidepressants, such as mirtazapine or trazodone, as augmentation therapy in cases of partial response with persistent insomnia. Additionally, IPAP suggests switching to mirtazapine as a third option after inadequate response to two trials of different classes (SSRI and SNRI) or augmentation with bupropion (Davidson et al., 2010). However, only one open-label trial of fixed-dose mirtazapine and one controlled pilot trial of bupropion versus escitalopram have been conducted so far (Bystritsky, Kerwin, Feusner, & Vapnik, 2008; Gambi et al., 2005). Thus, more investigational trials with alternative drugs for the treatment of GAD are needed.

The two double-blind, placebo-controlled trials investigating the use of agomelatine in the treatment of GAD patients showed evidence of the efficacy of this drug, both in the acute and relapse-prevention phases of treatment. Although the reduction of anxiety symptoms over placebo was only achieved by Week 6 in the first study, the latter study showed that patients achieving remission had a diminishing risk to relapse, which is important considering the need to prevent relapse in chronic disorders such as GAD.

The case series and single case report that evaluated the use of agomelatine in the treatment of nonresponsive OCD patients pro-

vide a portrait of the challenge in treating this condition with the conventional pharmacological strategies. The use of SSRIs is considered the first-line option in the treatment of OCD (Fineberg, Brown, Reghunandanan, & Pampaloni, 2012). Nevertheless, the needs for higher doses of antidepressants than those used to treat depression and the usual delay in the response to treatment of up to 8–12 weeks are common obstacles for clinicians (Math & Janardhan Reddy, 2007).

In addition to switching to different SSRIs or even to an SNRI, augmentation therapies with antipsychotics are considered second-line strategies in cases of treatment failure. In the case series described by Fornaro (2011b), all 6 refractory OCD patients described had been submitted to the recommended pharmacological guidelines. Nevertheless, agomelatine monotherapy was able to reduce obsessive–compulsive symptoms in 3 of them. Although the presence of multiple psychiatric comorbidities could have strengthened this finding, it could also have biased the clinical interpretation, as the amelioration of the OCD symptoms could have been an indirect result of the reduction by agomelatine of other types of psychopathology. In addition, as sleep disturbances were observed in those patients, the restoration of an optimal pattern of sleep (with a reduction in daytime inner tension and hyperarousal) could also have accounted for the efficacy of agomelatine, arguing against its intrinsic anxiolytic properties.

Although the clinical cases described an anxiolytic effect of agomelatine in the treatment of patients in different anxiety disorder categories (OCD, SAD, and PD), one common observation between the two cases might be of note. In the 2 patients with SAD and PD, problems related to potential SSRI adverse effects (AEs) were reported. Actually, their clinical descriptions did not resemble serious cases but rather emphasized the difficulty in achieving remission due to iatrogenic SSRI side effect profiles, leading to poor adherence and the interruption of treatment (Fornaro, 2011b). In this way, the low frequency of sexual dysfunction and the absence of agitation, both of which are common features of SSRI treatment (Anderson, Pace, Libby, West, & Valuck, 2012), could have been important factors in better adherence to treatment (Gartlehner et al., 2005). Finally, Crippa et al. (2010) discussed a possible benefit of agomelatine in diminishing the need for benzodiazepines (BDZ), which are highly prescribed in patients with SAD and PD (Petitjean, Ladewig, Meier, Amrein, & Wiesbeck, 2007), and this effect of agomelatine could be a protective factor in reducing the risk of BDZ abuse or dependence. Moreover, considering that more than 40% of PD patients exhibit at least one nocturnal panic (NP) attack (Craske & Tsao, 2005), which can increase the use of BDZ as a sleep-aid medication, and considering the lack of adequate trials on pharmacological agents in the treatment of this condition (Craske & Tsao, 2005; Levitan & Nardi, 2009), the potential of agomelatine in this subtype of PD might be of investigational interest.

Although this article presented some data corroborating the possibility of the clinical utility of agomelatine in the treatment of AD, some important limitations must be noted. First, this was a descriptive review that included a broad spectrum of studies (double-blind randomized trials, case series, case reports), thus limiting a comparison of the findings. Additionally, as noted before, the presence of patients with multiple psychiatric comorbidities could have biased the interpretation of the anxiolytic effects of agomelatine. Nevertheless, the findings discussed in this review support the possible clinical utility of agomelatine as an anxiolytic drug. Future research should undertake more controlled investigational trials in samples with specific categories of ADs.

## Conclusion

Agomelatine is a novel antidepressant with a $MT_1/MT_2$ melatonergic receptor agonist mechanism of action. Preclinical and clinical studies have shown its efficacy in the treatment of depression with a good profile of safety and tolerability. Other pharmacological properties of agomelatine and the clinical evidence of its efficacy in reducing anxiety symptoms in patients with depression have been corroborated by the observation of agomelatine's effectiveness in the treatment of anxiety disorders in nondepressed patients in two double-blind, randomized trials, in a case series and in three case reports. Considering the high incidence of poor efficacy and tolerability of first-line agents in the treatment of anxiety disorders, agomelatine seems to be a promising option in cases of treatment failure and could be used as a second or third option, as monotherapy or as an augmentation treatment. However, the lack of an adequate number of controlled trials, thus limiting potential confounding factors (such as the presence of multiple diagnoses), prevents a firm conclusion about the role of agomelatine in the treatment of anxiety.

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REVIEW

# Profile of agomelatine and its potential in the treatment of generalized anxiety disorder

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**Background:** Although many generalized anxiety disorder (GAD) patients respond to the available pharmacological treatments, nearly half of them do not present the expected results. Besides, the side effects associated to some drugs have a negative impact on treatment adherence. Therefore, the aim of this review was to report the clinical profile of agomelatine, a selective melatonergic $MT_1/MT_2$ receptor agonist with serotonin $5\text{-}HT_{2c}$ receptor antagonist activities, as a potential pharmacological option in the treatment of GAD.

**Methods:** We performed a literature review regarding studies that evaluated the use of agomelatine in GAD treatment.

**Results:** Two short-term, double-blinded studies and one prevention-treatment trial evaluated the efficacy of agomelatine in the treatment of GAD. Agomelatine was associated with higher rates of clinical response and remission, when compared to placebo. In addition, the long-term use of agomelatine decreased the risk of relapse of anxiety symptoms, even for the severely ill patients. Besides, the tolerability was satisfactory with the absence of discontinuation symptoms, as observed in previous studies.

**Conclusion:** The efficacy and tolerability profiles of agomelatine in the treatment of GAD were good. However, the scarce number of trials, the small sample sizes, and the use of patients without any comorbid conditions were some limitations that impaired the generalization of the results in the general population. Nevertheless, agomelatine is an attractive off-label option in the treatment of GAD that needs more conclusive evidences to establish its role in future guidelines.

**Keywords:** agomelatine, generalized anxiety disorder, pharmacological treatment

## Introduction

Generalized anxiety disorder (GAD) is a chronic illness, characterized by excessive worry about daily life domains, such as finances, responsibilities, and health of family members.[1] Patients with GAD tend to report feelings of exhaustion and irritability associated to ruminative thoughts and often seek medical assistance.

Pharmacological treatment has the objective to reduce acute symptoms, and to prevent relapses in the long term. Therefore, it should be effective and well tolerated. Although selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and pregabalin are first-line options for GAD treatment, nearly 50% of patients do not respond to them.[2] Also, side effects such as nausea and sexual dysfunction for the antidepressant,[3] and sedation and dizziness for pregabalin, can impact on treatment adherence.

Benzodiazepines represent a second-line option in the treatment of GAD because of their particular clinical efficacy and tolerability profile. They appear to have a greater impact on somatic symptoms of anxiety, mainly in the first 2 weeks of treatment. This feature could be interesting, especially considering the latency of efficacy for the

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antidepressants and their potential of worsening symptoms in the acute use.[4] However, continuous use of benzodiazepines can lead to abuse and dependence.[5] In addition, cognitive problems on the long-term use can impact on treatment compliance.

The unsatisfactory efficacy of treatment, especially when considering remission rates and long-term tolerability of drugs, stimulated new pharmacological approaches, as for example the use of atypical antipsychotics,[6] mood stabilizers, and combination treatment of antidepressants (SSRI/SNRI). Among them, agomelatine has shown evidence of anxiolytic effects. It is approved as an antidepressant; however, its mechanism of action is different from that of the currently approved drugs used to treat depression and anxiety.

# Profile of agomelatine

## Pharmacodynamics of agomelatine

Agomelatine is a synthetic naphthalene analog of melatonin and agonist of melatonergic MT1 and MT2 receptors with a longer half-life (mean terminal half-life of 140 minutes) and affinity for these receptors than melatonin.[7,8] In animal studies, both substances show antidepressant-like activity, but only agomelatine exhibits this property when administered to rats in the morning.[9] One of the most important pharmacological properties of agomelatine is its prochronobiological effect.[10] Agomelatine accelerates the resynchronization of circadian rhythms of locomotor activity and relevant biological parameters that are compromised in depression.[11,12] The serotonin 5-$HT_{2c}$ receptor antagonist activity of agomelatine seems to play a role, along with its melatonergic property, in the antidepressive efficacy.[13,14] Indeed, other clinically active antidepressant agents such as mirtazapine and amitriptyline exert 5-$HT_{2c}$ antagonist receptors. Evidence suggests that in contrast to other 5-HT receptors, 5-$HT_{2c}$ receptors influence the frontocortical dopaminergic and adrenergic pathway functions, which are compromised in depressive states.[7]

Besides the antidepressant action of agomelatine, animal models have also demonstrated its anxiolytic properties. Indeed, it has been demonstrated that mice genetically lacking 5-$HT_{2c}$ receptors showed reduced anxiety.[15] By this way, the antagonism of 5-$HT_{2c}$ receptors induced by agomelatine, especially in the frontal cortex, may be associated with anxiolytic properties, and through the blockade of 5-$HT_{2c}$ receptors, agomelatine may also enhance extracellular levels of noradrenaline, therefore increasing anxiolytic response.[15] Another possibility is that the anxiolytic effect may be due to the activation of melatonergic receptors in response to anxious states. Therefore, anxiogenic stimuli may enhance pineal release of melatonin.[15,16] Indeed, the synergistic effect of 5-$HT_{2c}$ antagonism and melatonergic agonism, rather isolated actions of both mechanisms, may explain both the anxiolytic and antidepressive effects of agomelatine. Nevertheless, it is possible that, in some extent, the hypnotic and sedative effects of agomelatine may be responsible for its anxiolytic property.[13]

## Pharmacokinetics of agomelatine

After oral administration, agomelatine is rapidly (0.5–4 hours) and well absorbed (80%) and the time at which maximum blood concentration was achieved was between 45 minutes and 90 minutes after a single oral dose of 25–50 mg.[17] However, its bioavailability is $<5\%$ at the therapeutic oral dose due to the high first-pass metabolism,[18] which may be of concern especially in elderly patients or in subjects with liver disorders.[10]

It presents a moderate volume of distribution of approximately 35 L, a plasma protein binding of 95%, and the peak plasma concentration is achieved within 1–2 hours.[18] At the therapeutic levels, agomelatine blood concentration increases proportionally with dose; at higher doses, a saturation of the first-pass effect may occur. About 80% of the drug is eliminated through urinary excretion of the metabolites, whereas a small amount of the metabolites undergoes fecal excretion.[3,10] The major enzymes involved in the biotransformation of agomelatine are CYPl A2 (90%), and to a lesser extent, CYP2C9/CYP2C19.[19]

## Safety of agomelatine

The safety of agomelatine was observed in 7,900 subjects treated for major depression.[18] Severe adverse reactions were seen, more frequently, with a higher dose of agomelatine. Specifically, clinical studies have documented threefold elevations of transaminases enzymes, particularly in patients taking 50 mg/daily (2.5%), when compared to those taking 25 mg/daily (1.4%). Also, rare cases of hepatic failure were observed.[18] Therefore, agomelatine requires monitoring of liver function, and is contraindicated in patients with impaired liver function,[20] and should be avoided in people over 75 years (although no significant effect has been documented in this group). Others minor adverse drug reactions observed with agomelatine use (seen in between one and ten patients in 100) are related to somnolence, dizziness, headache, fatigue, and gastrointestinal symptoms.[18] One particularity of agomelatine is the different profile of adverse effects compared to SSRIs and SNRIs, commonly associated to weight gain, sexual dysfunction, and psychomotor

agitation.[5] In addition, agomelatine use was not associated with discontinuation symptoms after abrupt treatment cessation.[15,19]

## Clinical profile

Animal models for depression have shown agomelatine antidepressant-like activity.[21] In clinical trials for major depression, agomelatine has proven superior efficacy compared to placebos, and has shown equivalent results when compared to conventional antidepressants such as SSRIs.[22–24] In a meta-analysis of agomelatine trials for major depressive disorders, there was a marginal superiority of agomelatine over the group of antidepressants (fluoxetine, paroxetine, sertraline, and venlafaxine), but it lacks clinical relevance.[24,25] This result could be influenced by the use of scales that rely more on rating sleep problems. Agomelatine's favorable profile on sleep could have influenced its superior reduction in the rating scores compared to the others antidepressants. Lastly, eight of nine trials seemed to have pharmaceutical sponsorship, and publication bias cannot be ruled out. Agomelatine proved to be effective in the treatment of the acute phase of depression and its discontinuation increased relapse probability in the maintenance phase.[26]

The first clinical evidence of agomelatine as an anxiolytic medication was observed as a secondary outcome in major depression clinical trials. Specifically, data from six short-term randomized trials for depression were reviewed to evaluate the efficacy of agomelatine on anxiety in depressed patients.[27–31] Agomelatine showed increased efficacy over both placebo and active drugs (fluoxetine, sertraline, and venlafaxine) in reducing anxiety symptoms in depression, using the Hamilton Anxiety Rating Scale (HAM-A).[26] Since then, there is a continuous interest regarding the properties of agomelatine and its anxiolytic function as an optional treatment for anxiety disorders, specially GAD. Therefore, the aim of this literature review was to expose the studies conducted regarding GAD treatment with agomelatine and discuss their results, limitations, and future implications.

## Drug interactions

Concomitant treatment with medications that interact with isoenzymes CYPl A2 and CYP2C9/CYP2C19 may decrease or increase plasma concentrations of agomelatine.[27] Fluvoxamine, a potent CYP1 A2 and moderate CYP2C9 inhibitor, markedly inhibits the metabolism of agomelatine resulting in a 60-fold (range 12–412-fold) increase of agomelatine exposure. Also, drugs that are potent inhibitors of CYPl A2, such as ciprofloxacin, amiodarone, mexiletine, or zileuton, should be avoided, as well as moderate CYPl A2 inhibitors – including estrogens – that may also increase the exposure of agomelatine.[32]

# Methods

First, we conducted a literature search to identify randomized controlled trials evaluating the efficacy of agomelatine in GAD treatment. Keywords were *agomelatine, generalized anxiety disorder, and anxiety disorders and treatment*. To complement our data, we also included references from selected papers. Electronic research-literature databases included PubMed/Medline. We included papers with no limit of time, and excluded papers that were not written in English. All the authors were involved in the process of selecting the studies and agreed with their inclusion. Some papers that presented redundant data, or did not seem to add information relevant to the purpose of the article were also excluded.

# Results

We found three studies, all performed by the same group of researchers, with the criteria above.

## First study

The first study, conducted by Stein et al (2008),[33] was a 12-week randomized placebo-controlled trial, with 121 GAD patients diagnosed through a semi-structured clinical interview and scales related to anxiety. Only GAD patients with no psychiatric comorbidities were included, and patients receiving psychiatric medication or on psychotherapy were excluded.

The active drug group ($n$=63) could have agomelatine increased from 25 to 50 mg daily in a blinded fashion if sufficient improvement of GAD symptoms was not achieved from 2 weeks onward. A majority of the patients (92.6%) completed the study, and both groups presented a decrease in anxiety as measured by the HAM-A at the end of the 12th week; however, the agomelatine group had a higher decrease (–3.28 [1.58]; 95% CI =–6.41 to –0.15; $P$=0.040). When the comparison was made independently for the subscale scores of HAM-A, the improvement with agomelatine over placebo reached statistical significance only for the somatic symptoms of anxiety ($P$=0.0015).

In a comparison between groups, agomelatine use was statistically superior from 6th week onward ($P$=0.040). However, in the secondary efficacy analysis, a higher rate of responders on agomelatine than on placebo was observed

from 2nd week through 12 week, with the rates at the last value also favorable to agomelatine (66.7% vs 46.6%; E [SE] =20.1 [8.8]; 95% CI =2.8–37.4; *P*=0.026). In addition, as observed in major depression trials,[27–32] agomelatine use was associated with markedly improvement on sleep symptoms, including the items for getting off sleep, quality of sleep, and sleep awakening.

Patients from both groups did not differ in percentage related to adverse effects. The most common adverse events reported in the agomelatine group were dizziness (7.9%) and nausea (4.8%). Finally, discontinuation emergent signs and symptoms were lower on agomelatine than on placebo.

## Second study

This second multicenter trial aimed to evaluate the long-term efficacy and tolerability of agomelatine (25–50 mg) in a 6-month period in preventing relapse in nondepressed patients with GAD.[34] The first stage of the trial consisted of a 16-week open-label treatment period with a flexible dosage of agomelatine (*n*=477). Patients who met the criteria for clinical response (using HAM-A) were randomized to a 26-week, randomized, double-blind, placebo-controlled maintenance treatment period. Finally, at the end of the 26th week, patients were randomized to receive either placebo or agomelatine (same dose) for 1 week to assess potential discontinuation symptoms.

During the open-label treatment with agomelatine, the HAM-A score decreased from 28.0±3.8 at baseline to 9.7±5.9 at week 16. The rate of responders for the patients with at least one post-baseline assessment was 68.1%. In the double-blind 26-week period, when compared to the placebo group (*n*=114), the agomelatine group (*n*=113) evidenced a lower risk of relapse over 6 months (19.5% vs 30.7%; *P*=0.046), with an estimated risk of relapse at 6 months of 19.7% (3.8) versus 31.7% (4.5) in the placebo group. Also, the risk for relapse over time was reduced by 41.8% for agomelatine-treated patients (OR =0.546, *P*=0.005). Similar results were observed with the severely ill patients, and the risk of relapse was reduced by 59.3% in patients treated with agomelatine versus placebo (OR =0.351, *P*=0.006).

Unlike in the previous short-term study, the tolerability profile was measured for the entire 6-month period. When compared to the placebo group, the agomelatine group presented a higher percentage of, at least, one emergent adverse event (40.7% vs 27.2%; *P*=0.032). The most frequent emergent adverse events with agomelatine were similar to those reported during the first study. Seventeen patients (3.6%) had evidenced abnormal liver enzyme value, without clinical relevance. In addition, there were no discontinuation symptoms in patients switched to placebo, compared to those who remained with agomelatine after the end of the 26-week period.

## Third study

The third published study was conducted to confirm the efficacy of agomelatine in GAD treatment, as required by regulatory agencies, and assay sensitivity was evaluated by including an escitalopram group.[35] The design of the study was similar to the first study, including the use of similar instruments to measure anxiety and the same exclusion criteria.

Patients were randomized to receive agomelatine (*n*=139), escitalopram (*n*=142), or placebo (*n*=131) in the evening for 12 weeks; the daily dosage of agomelatine or escitalopram could be increased at the 4th week (agomelatine: from 25 mg to 50 mg; escitalopram: from 10 mg to 20 mg) depending on the lack of a patient's improvement. After week 12, a blind tapering period of 1 week was initiated to avoid possible withdrawal reactions, in which escitalopram dosage was diminished, and the dose of agomelatine remained unchanged, based on previous studies that evidenced that this antidepressant is not associated with discontinuation symptoms, according to the authors.

An improvement in symptomatology was reached by the three groups at the end of week 12, as measured by the HAM-A; however, only the agomelatine (difference vs placebo of 4.71 [1.03], 95% CI (2.69–6.73); $P<0.0001$) and escitalopram (difference vs placebo of 4.77 [1.03], 95% CI (2.74–6.79), $P<0.0001$) groups presented a significant decrease. However, in the subgroup of patients with severe anxious symptoms (HAM-A $\geq$25), remission rates (HAM-A $<$7) were 37.7% for agomelatine, 18.9% for escitalopram, and 20.3% for placebo, and statistical significance was reached only for the comparison between agomelatine and placebo groups (SE =7.23; *P*=0.019). In addition, both agomelatine and escitalopram improved psychic and somatic symptoms of GAD, but agomelatine was more effective on improvement of sleep. Tolerability and safety profiles were similar for agomelatine and escitalopram, but treatment discontinuation due to adverse events was less frequent in the agomelatine group (2.2% vs 7.1%).

# Discussion

In our literature review, agomelatine showed efficacy in the treatment of GAD in two short-term studies and in a 2-phase study, with an open-label trial, followed by 26-week

double-blinded study to investigate the prevention of relapse. The reduction of anxiety symptoms was evidenced for all primary and secondary outcomes, including the decrease in the score of HAM-A, and the rates of response and remission. In addition, tolerability and safety were satisfactory, with the majority of adverse events in the mild to moderate range.

One particular feature of agomelatine in the treatment of GAD is worth emphasizing. Whereas most antidepressants act primarily on psychic symptoms of anxiety (measured by HAM-A), agomelatine had shown equal improvements in psychic and somatic symptoms. Although the positive effect on sleep, which is a key feature of GAD, might explain the superior reduction of somatic symptoms, this observation was also evidenced after the exclusion of sleep-related items of HAM-A.

The three studies showed interest in evaluating the clinical efficacy of agomelatine in severely anxious patients. Agomelatine had positive effects in the treatment of severely ill patients when compared to placebo. Indeed, the risk for relapse in those patients was even lower for agomelatine, than for the nonsevere GAD sample. Particularly, the third study – that used escitalopram as an active comparator – showed that only agomelatine differentiated from placebo in the remission rate for patients with severe anxiety symptoms.

The majority of clinical trials of agomelatine have shown similar results on the tolerability and safety profile, with equivalent rates of emergent adverse events. They were mild or moderate, and in some comparisons, similar to the placebo group. An exception was the higher rate for agomelatine emergent adverse events, when compared to placebo, in the 6-month maintenance period. In the only comparison of tolerability with escitalopram, a different distribution of adverse events was evidenced, with the SSRI presenting with a decreased libido and anxiety. Also, a higher number of patients in the escitalopram group ($n$=11) were withdrawn due to adverse events, compared to placebo group ($n$=4) and the agomelatine group ($n$=3). Finally, all studies repeated the investigation for possible discontinuation symptoms, and corroborated previous results that showed that agomelatine is not associated with the risk of abrupt withdrawal symptoms, commonly seen with SSRIs and SNRIs.

Some limitations regarding the studies of agomelatine for treatment of GAD deserve mention. First, patients included in the GAD studies may not be representative of those seen in general psychiatric or medical practice. Significant comorbidity with depression is commonly seen in patients with anxiety disorders.[36] Although most trials in GAD exclude primary psychiatric comorbidity, which helps to compare the results of those three studies with previous results in the literature, it impairs the generalization of the results in real clinical settings. Besides depression, subthreshold GAD was cited as the most frequent mental health disorder in primary care.[37] Also, primary care patients with subthreshold GAD had comorbidity rates of 48.5%.[38] Finally, pharmacological treatment of GAD in patients with clinical comorbidities such as diabetes, obesity, and hypertension should be made cautiously. Hence, more naturalistic studies should be conducted to investigate the efficacy of agomelatine in the general population.

The three studies were conducted by the same group of researchers, and sponsorship played a key role in leading the design and conduction of the study, including data collection, management, and analysis. A recent meta-analysis, reviewing the efficacy of agomelatine in the treatment of major depression, reported that for the ten trials included in the review, only one did not disclosure sponsorship.[24] So, publication bias cannot be ruled out.

The sample sizes of the studies are considered small, and larger and longer-lasting trials were required for a full evaluation of the efficacy and safety profile of agomelatine in the treatment of GAD. Although the sample size of the second study had a larger sample, the study evaluated the efficacy of agomelatine in an open-label phase. Besides, the 6-month double-blind period of that trial did not evaluate agomelatine in the acute phase of GAD, but rather observed the risk of relapse. In addition to the comments for the studies design, the lack of more active-drug arms impairs the comparison of agomelatine to standard pharmacological treatments for GAD.

The current algorithms for the treatment of GAD include several pharmacological options. Unfortunately, inadequate clinical response and different profiles of tolerability may have a negative impact on treatment adherence. Therefore, new potential treatments are needed, especially for those refractory patients. Although the number of trials is scarce, agomelatine proved to be useful in the short- and long-term treatment of GAD, with satisfactory tolerability, even for the more severely anxious patients. The antidepressant property of agomelatine strengthens its use in the treatment of anxiety, as depression comorbidity is common. For instance, pregabalin, a first-line agent for GAD treatment, may not be suitable for the treatment of anxiety in the presence of depression as monotherapy. Agomelatine might be chosen as a second-line agent for GAD in patients who have poor tolerability with SSRIs and SNRIs, especially when other off-label drugs need to be avoided. For instance, despite the efficacy of quetiapine in the treatment of anxiety symptoms, its long-term metabolic effects might

compromise treatment continuation. In addition, one might argue if agomelatine treatment could be associated with less benzodiazepine use, considering its improvement in several sleep measurements in patients with depression and anxiety.

Nevertheless, the potential clinical utility of agomelatine in anxiety treatment is dependent upon the development of future research that can evidence its efficacy in more naturalistic scenarios. In addition, agomelatine should be compared with more active-drug comparator studies to test its efficacy directly against standard pharmacological therapy. Specifically, augmentation treatment trials might be interesting, in order to evaluate agomelatine as an adjunctive treatment for GAD. For now, agomelatine is an attractive option in GAD treatment that still awaits a definitive role in future pharmacological algorithms.

## Disclosure

The authors report no conflicts of interest in this work.

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**Artigo 6- em submissão. *Brief report*. Do patients with panic disorder lack assertiveness?**

*DO PATIENTS WITH PANIC DISORDER LACK ASSERTIVENESS?*

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## ABSTRACT

**Background***:* Unassertiveness seems to be associated with the severity of panic disorder (PD) and with the development of other psychiatric disorders. This study aimed to evaluate assertiveness in a sample of patients with PD and discuss the implications of the results for treatment. **Method***:* Forty-six symptomatic PD patients who were screened with a structured clinical interview and 46 college students completed scales related to assertiveness and provided data. **Results:** The clinical group was characterized as non-assertive and slightly less assertive than the controls, and the deficit in assertiveness was correlated with the severity of PD. Moreover, the diagnosis of agoraphobia was correlated with unassertiveness. **Conclusions**: Personality traits and interpersonal difficulties may negatively affect the treatment prognoses of PD patients. These data demonstrate the importance of managing assertiveness in PD patients, particularly agoraphobics, because unassertiveness can be related to treatment failure, as reported in other studies.

**Keywords:** social skills; panic; agoraphobia; personality traits; social competence

# 1. INTRODUCTION

PD treatment is well established in the pharmacological and psychological field [1]. Nevertheless, some authors have noted that for a group of patients, it is also important to focus on the interpersonal difficulties that may have contributed to the development of PD [2]. Some of these observations have been based on therapists' clinical practices and have led to investigations of whether PD patients present with personality traits that could facilitate the development of PD and the identification of prognostic factors that are associated with the success of PD treatment.

Some authors have emphasized the role of social skill (SS) deficits in PD patients. SSs are classes of behaviors that exist in the individual's repertoire and contribute to socially competent performances [3]. Although few studies have evaluated this subject, several studies have related unassertiveness to agoraphobic and PD patients [4-6]. The available studies have investigated assertiveness, which is a type of SS that is defined as the ability to express feelings and desires in an honest and appropriate manner, primarily in agoraphobia, based on the DSM-III criteria [7].

Some association-related SS deficits have been hypothesized to exist in PD patients by various authors. With the increase in feminine studies, the impairments in agoraphobic patients have been attributed to unassertiveness towards a close relative, particularly in marital relationships. Agoraphobic patients have been reported to be unhappier than non-agoraphobics in marital relationships [8,9]. Bandura, Adams, Hardy and Howells [10] proposed the hypothesis that although agoraphobics attribute their fears to the environment,

they may feel that they are not able to cope with themselves, which lowers their self-efficacy. Another influential explanation that is similar to that of Bandura et al. relies on the demoralization syndrome. This syndrome refers to feelings of helplessness and sadness that are based on the loss of opportunities in life and are associated with the development of PD. The low senses of self-efficacy and self-esteem that are associated with PD often lead to isolation and depression, which lead the patient to feel fragile and, consequently, non-assertive about his life.

Assertiveness seems to play an important role in the course of PD. In a 2-year longitudinal study that evaluated the factors associated with the development of episodes of depression in a PD sample, the patients with low assertiveness scores were found to be more likely to experience an episode of depression [6]. Twenty-five percent of the patients experienced a depression episode during the study. The authors suggested that demoralization syndrome, which frequently develops into PD, may predispose an individual to depression and that patients tend to report being uncertain about the future because panic attacks are unexpected and disabling.

Some authors have used the available data to improve treatment protocols. Feldman, Giardino and Lehrer [11] and Lehrer et al. [12] included a module on assertion and communication training for PD patients with asthma due to issues that require a patient to exhibit high levels of social competence. Deficits in SS may interfere with an individual's ability to provide answers to health care providers that are related to ensuring both proper self-treatment and that the individual does not expose him/herself to asthma triggers.

Based on the importance of identifying variables that might influence PD treatment, the aim of this study was to evaluate whether PD patients exhibit scores related to a moderate degree of assertiveness and to determine whether there is a possible correlation between this feature and clinical data relative to a healthy control group.

## 2. **METHODS**

The participants consisted of a total of 92 people, of which 46 (35 women in their first year of college) composed the nonclinical group, and the 46 other participants were PD patients from the Psychiatric Institute of the Federal Univeristy of Rio de Janeiro, Brazil, who agreed to participate in the study. The patients received a diagnostic assessment that entailed the administration of the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinical Version [13] by trained psychiatrists. There were no exclusions for secondary comorbid psychiatric disorders, with the exception of personality and psychotic disorders.

The following scales were used: the *Rathus Assertiveness Schedule (RAS)* [14], which is a 30-item questionnaire that assesses self-reported assertiveness in different types of situations; the *Anxiety Sensitivity Index, Revised* (ASI-R) [15], which is a 36-item scale that measures the fear of anxiety-related symptoms; the *Agoraphobic Cognitions Questionnaire (ACQ*) [16], which assesses thoughts related to panic attacks and consists of 14 items that may be scored as a total scale or according to two subscales (loss of control and physical concerns); and the *Body Sensations Questionnaire (BSQ)* [16], which assesses

the intensity of fear that the patient exhibits while anxious and is scored according to the average of the responses to 17 items.

## 3. RESULTS

### *3.1 Descriptive data*

The descriptive statistics of the clinical sample are displayed in table 1. Most of the participants were women (67% *vs*. 70% of the controls and clinical sample, respectively). The majority of the patients (*f*=71-76%) were taking antidepressants and benzodiazepines, although they still met the criteria for PD (at least 1 panic attack in the last month); on average, 1 panic attack was experienced per week. Additionally, agoraphobia was the most frequent comorbid psychiatric disorder (*f*=65%).

### *3.2 Assertiveness and the scales*

The RAS scores of the PD patients revealed a non-assertive sample (*M*=-0.61; *SD*=24.46) that was slightly less assertive than the controls (*M*=1.57; *SD*=22.02). However, a *t test* that was applied to evaluate the differences was not significant (*p*=0.65). To evaluate the correlations between assertiveness and the scales, *Pearson correlations* were performed. These tests revealed that the RAS scores were significantly correlated with the scores for the following scales: ASI-R ($r=0.33$; $p<0.05$), ACQ ($r=-0.46$; $p<0.05$), and BSQ ($r=0.40$; $p<0.05$). To evaluate the relationship of the diagnosis of agoraphobia with some of

the measures, we used *Spearman correlation tests*. Agoraphobia was negatively correlated with the RAS score ($r=-0.40$; $p<0.05$).

*3.3 Assertiveness and the severities of the scales*

First, we separated the group into two subgroups according to PD severity, as measured with the ACQ and BSQ. A *t test* was used to evaluate the differences in the RAS scores of the subgroups. Although the RAS scores were lower in the more severe sample, the difference was not statistically significant (**BSQ** 5.24 ± 29.5 *vs* -3.42± 21.91, $p=0.20$; **ACQ** 5.60 ± 20.08 *vs* -7.90 ± 28.22, $p=0.08$). The correlations of the scales with these two groups were also not significant (**BSQ** $r= -0.18$, $p=0.23$; **ACQ** $r= -0.26$, $p= 0.08$).

We then separated the groups into four severity groups (i.e., more severe, severe, less severe and not severe) according to the ACQ scores. An *ANOVA* revealed a significant between-group difference in the RAS scores ($p=0.00$). However, no difference in the BSQ scores was found ($p=0.07$, table 2). *Spearman tests* were used to evaluate the correlations between the RAS sores and these severity quartiles, and significant negative correlations were found for both scales (**BSQ** $r=-0.35$, $p<0.05$; **ACQ** $r=-0.37$, $p<0.05$).

# 4. DISCUSSION

Assertiveness in PD is a theme that has scarcely been studied. To our knowledge, few studies [5,6,17] have performed such investigations in agoraphobic and PD individuals. This lack of studies is intriguing because agoraphobia has been identified as a feature that predisposes PD patients to depression [6] and consequently worsens the disorder and its prognosis. Therefore, it is possible that we are not focusing sufficient attention on this feature, which can be crucial to PD treatment in the clinical setting.

Similar to the previously cited studies, our PD sample also proved to be non-assertive and less assertive than the controls, but this difference was not statistically significant. The RAS is an instrument that evaluates more general and strict aspects of SS, and it is possible that the differences between the groups were rather subtle. Additionally, more severe PD manifestations, as measured by the scales related to anxiety, sensitivity, body sensations and agoraphobic cognitions, were associated with less assertiveness. This finding calls attention to the importance of evaluating this type of social skill in PD patients because the severity of PD can impair the patient's life and worsen the psychiatric disorder.

We also found a conclusive difference in assertiveness when the patients were evaluated according to severity quartiles. Therefore, the PD patients with more agoraphobic cognitions proved to be less assertive than the PD patients with fewer agoraphobic cognitions. The difference in the fear of body sensations approached but did not reach significance. It is difficult to understand the reason for this difference because these scales

complement each other. It is likely that the differences in assertiveness according to this measure of severity would have appeared with a larger sample.

Another important finding was that the diagnosis of agoraphobia was correlated with unassertiveness. Indeed, comorbid conditions may predispose patients to refrain from pursuing their rights or expressing their opinions because such actions worsen the severity of the disorder. In this manner, patients isolate themselves and may develop demoralization syndrome. This syndrome is described as the experiences of hopelessness, loss of meaning, and existential distress associated with chronic medical illness and social isolation that are associated with the subjective sense of incompetence, feelings of greater dependency on others or the perception of being a burden [18].

Another of the important identified correlations was that observed between assertiveness and the severity of PD. This correlation seems to confirm the hypothesis that the severity of PD is associated with a deficit in assertiveness. However, it is difficult to determine whether this lack of assertiveness was a condition that arose before or after the development of the disorder. A longitudinal study with a general population that evaluated the occurrence of PD over the lifetime would be necessary to evaluate the effect of the degree of assertiveness on the development of PD.

Based on these data, psychological treatments that address SS training in PD patients might be important. Emmelkamp et al. [5] compared treatments for agoraphobics and found that assertiveness training and exposure therapy are the best choices for unassertive agoraphobic patients. Some authors are already including assertiveness training as one entire session of the protocol for PD patients with asthma because these patients

require a high level of social competence that is often lacking in PD patients [11,12]. It seems that health professionals are not addressing assertiveness in PD patients as a protective factor for the maintenance of results and the prevention of the development of other psychiatric disorders. Studies have indicated the importance of spending more time, specifically during the final of the treatment, working on personality traits or individual characteristics that can lead to a relapse [19].

Our study has several limitations. First, the data regarding assertiveness and panic disorder are outdated because few studies have conducted similar investigations. Unfortunately, there has only been one study longitudinal study in which the relationship between assertiveness and depression in PD has been evaluated [6]. Second, the small size of the sample limits further conclusions. Third, although in PD, medication is not used to improve social interactions, the use of medications such as benzodiazepines might have influenced assertiveness responses because such medications decrease the degree of anxiety in anxyogenic situations.

In the future, observational studies should be developed because such studies tend to more accurately evaluate SS deficits. It is important to propose the hypothesis that PD patients experience relapses due to interpersonal difficulties that need to be addressed. An important issue that we expected will be addressed is that although the pharmacological treatment of PD is successful, in terms of the psychological approach, we are taking SS training and other psychological variables for granted. Data have shown that, for example, the lifelong prevalence of depression in PD patients is significantly elevated (55.6%) [19], and it is possible that social training could contribute to changing this rate.

# 5. CONCLUSION

To conclude, this study confirmed that PD patients are unassertive and that the severity of this psychiatric disorder is associated with the degree of assertiveness. The participants with more agoraphobic cognitions and a greater fear of body sensations were more unassertive than the patients with less severe symptoms. Therefore, SSs should be evaluated in PD patients, and a social skill training module should perhaps be included in conventional PD treatment.

**Table 1- Demographic and clinical features of the panic disorder sample**

| | % | M | SD |
|---|---|---|---|
| Age | | 40.7 | 10.5 |
| Women | 70 | | |
| PD duration | | 6.1 | 6.2 |
| Benzodiazepines | 80 | | |
| Antidepressant | 75 | | |
| Number of PA | | 1.4 | 1.4 |
| Depression | 15 | | |
| Agoraphobia | 65 | | |
| Rathus | | -5.4 | 22.1 |
| ASE | | 112.7 | 28.2 |
| BSS | | 63.7 | 17.3 |
| ACQ | | 42.9 | 12.8 |

* PA=panic attacks in the evaluation month; ASE= anxiety sensitivity scale;

BSS = body sensations scale; ACQ= agoraphobic cognitions questionnaire

**Table 2- Rathus means according to severity quartile**

| **BSQ** | **RAS** | **N** | **SD** |
|---|---|---|---|
| Very severe | 15.30 | 10 | 27.12 |
| Severe | -2.91 | 11 | 25.23 |
| Less severe | 5.50 | 8 | 16.30 |
| No severe | -11.82 | 11 | 23.18 |
| **ACQ** | **RAS** | **N** | **SD** |
| Very severe | 10.30 | 10 | 20.96 |
| Severe | 1.67 | 12 | 21.85 |
| Less severe | 8.50 | 12 | 20.32 |
| No severe | -22.09 | 11 | 24.01 |

* N= number of patients; SD=standard deviation

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# NOTAS FINAIS

Apesar de apresentarem critérios diagnósticos diferenciados, o TP, TAS e TAG possuem o medo e preocupação como características comuns. Isso frequentemente provoca diagnósticos equivocados, especialmente no caso de ataques de pânico durante exposição social ou preocupação/esquiva social secundária ao TP. Os trabalhos foram realizados antes da finalização do DSM-V, desta forma, algumas características mencionadas principalmente nas diretrizes de diagnóstico e tratamento poderiam ser revisitadas. Estão entre elas, a nova subdivisão do TAS em medo de performance e outros medos sociais e a separação diagnóstica do TP da agorafobia.

A importância do diagnóstico correto e tratamento dos pacientes levou a AMB a propor diretrizes para transtornos psiquiátricos, que podem facilitar a rotina dos ambulatórios, principalmente dos que contam mais com médicos generalistas, com equipes reduzidas ou com pouco acesso a informações atualizadas geralmente só disponíveis em base de periódicos não acessíveis.

As diretrizes de tratamento do TAS evidenciaram que os ISRS, IRSN e TCC são considerados os tratamentos de escolha para o mesmo. O tratamento combinado de TCC com estes fármacos se mostra superior à farmacoterapia. Além disso, a comorbidade com outros transtornos psiquiátricos como a depressão, está associada a uma maior gravidade do TAS e pior evolução do tratamento. Um aspecto importante a considerar é o uso de álcool para o enfrentamento de situações sociais, que frequentemente provoca dependência, levando à maior tendência de doenças físicas. Um algoritmo de tratamento foi disponibilizado no artigo para auxiliar na escolha terapêutica.

Nas diretrizes de diagnóstico e diagnóstico diferencial do TP, foram apresentadas as principais escalas de rastreio de sintomas do TP, além de fornecer os critérios diagnósticos para agorafobia em adultos e crianças. Aspectos genéticos como uma alta incidência de TP em parentes de primeiro grau de pacientes com este transtorno e regiões cromossômicas associadas a uma maior suscetibilidade são expostos. A agorafobia, ainda ligada ao TP em função do DSM-IV-TR, foi associada a uma maior cronicidade do TP e menores taxas de remissão. O rastreio da qualidade do sono é aconselhável em função da alta prevalência de transtorno do sono em pacientes com TP, além da possível associação com ataques de pânico noturnos. Estudos de neuroimagem sugerem o envolvimento de algumas áreas cerebrais como o septo hipocampal no desenvolvimento de ataques de pânico. Por último, uma associação entre ansiedade e doenças cardiovasculares é discutida, ressaltando-se a necessidade de investigação de ambas as condições em um paciente com ataques de pânico.

Os experimento comportamental com o TAS avaliou aspectos comuns como ansiedade e medo durante a tarefa da EI e falar em público. O levantamento de características clínicas e psicológicas visam também contribuir para o tratamento psicoterápico de melhor eficácia, baseado em evidências. Através deste estudo empírico esperamos que este estudos possa contribuir com os dados e orientações para protocolos com maior eficácia para o TAS. Diferenças em HS moleculares foram encontradas, e diferentemente do que se esperava os pacientes com TAS avaliaram de forma similar sua performance em relação aos pesquisadores. Discutimos neste artigo que os pacientes com TAS podem não apresentar uma distorção cognitiva acentuada, mas sim um significativo déficit em HS a ser melhorado por técnicas psicoterápicas.

A agomelatina foi o agente farmacológico escolhido para as revisões de literatura acerca do tratamento com transtornos de ansiedade. No primeiro artigo referente aos

transtornos de ansiedade, esta medicação foi selecionada em função da alta prevalência de distúrbios do sono em pacientes com transtornos de ansiedade, especialmente no TP, pela privação de sono exercida pelos pacientes em função dos ataques de pânico noturnos. Apesar de resultados satisfatórios em grande parte dos casos, os estudos ainda são compostos por amostras pequenas ou relatos de caso, exceto no TAG.

Devido a resultados não tão eficazes para o tratamento do TAG, a agomelatina, por sua atuação hipnótica e ansiolítica, foi escolhida para ensaios clínicos randomizados. Nos três estudos realizados pelo mesmo grupo (Stein et al., 2008; Stein et al., 2009; Stein et al., 2012)., os resultados indicaram altas taxas de melhora clínica, remissão dos sintomas do TAG e prevenção de recaídas em seu uso a longo prazo. Ao ser comparada com o escitalopram, ambas apresentaram eficácia na diminuição dos sintomas, porém em paciente com sintomas ansiosos graves, a agomelatina apresentou as maiores taxas de melhora. Um aspecto importante é a boa tolerabilidade à medicação com poucos sintomas colaterais na maioria dos pacientes. Por último, uma vantagem desta medicação quando comparada a outros antidepressivos, foi a melhora significativa tanto nos sintomas psíquicos quanto somáticos.

O último artigo, ainda em fase de submissão, abordou diferenças na assertividade de um grupo com TP e controles. Quando os grupos foram avaliados como um todo, as diferenças entre a assertividade não foram significativas. Este resultado somente se mostrou positivo quando separamos o grupo clínico em quartis de gravidade. Desta forma, é possível que pacientes com TP com pouca gravidade de sintomas não apresentam diferenças nesta HS quando comparados aos controles. Com estes resultados objetivamos melhorar a eficácia de protocolos de tratamento psicoterápico, visto que a assertividade se mostrou em outro estudo, preditor de depressão em pacientes com TP ao longo do tempo.

Desta forma para pacientes com TP grave, trabalhar a assertividade pode prover melhores resultados e prevenir recaídas.

Em suma, este conjunto de artigos visou abordar aspectos clínicos dos transtornos de ansiedade visando prover informações relevantes acerca de seu diagnóstico e tratamento, além de fornecer dados para auxiliar a psicoterapia dos mesmos. Também foram abordadas novas opções farmacológicas para o tratamento destes transtornos, visto que um significativo número de pacientes não de adapta às medicações disponíveis ou não apresentam a melhora esperada.

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