INSTITUTO DE PSIQUIATRIA - IPUB

Centro de Ciências da Saúde - CCS

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Paula Vigne Pires Ferreira

O Insight no Transtorno de Ansiedade Social

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Dissertação de Mestrado submetida ao Corpo Docente do Programa de Pós-graduação em Psiquiatria e Saúde Mental -PROPSAM- do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para a obtenção do Grau de Mestre em Psiquiatria.

Orientadores:

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Gabriela Martins Bezerra de Menezes
Doutorado em Psiquiatria pelo IPUB/UFRJ

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Rio de Janeiro
____ de 2015

À Maria Luiza, minha mãe,

exemplo de perseverança notável.

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À Oftalmologia, pois sem ela talvez eu não estivesse aqui hoje.

Resumo

O Transtorno de Ansiedade Social (TAS) caracteriza-se por medo intenso de ser avaliado negativamente em situações sociais diversas e de desempenho, causando sintomas ansiosos e prejuízo funcional na vida do indivíduo. Tal medo deveria ser considerado irracional ou exagerado pelo próprio paciente, segundo a terceira versão do Manual Diagnóstico Estatístico de Transtornos Mentais (DSM – III), o que nem sempre era observado na prática clínica. Tal critério foi modificado no DSM – 5 para a não obrigatoriedade de o indivíduo reconhecer tal medo como irracional ou exagerado. Os objetivos deste estudo foram avaliar o reconhecimento pelo indivíduo da irracionalidade desse medo exagerado ou o nível de *insight* do paciente com TAS, compará-lo com o nível (ou grau) de *insight* no Transtorno Obsessivo Compulsivo (TOC) e avaliar se há relação entre nível de *insight* e características sócio-demográficas ou clínicas no próprio TAS. O estudo será apresentado na forma de dois artigos já publicados. No primeiro artigo "Can Hoarding be a symptom of Social Anxiety Disorder? A case study" relatou-se o caso de um paciente com fobia social grave que apresentou colecionismo como conseqüência direta de crenças relacionadas com a ansiedade social e comportamentos de segurança atípicos. O segundo artigo,"A study of poor *insight* in Social Anxiety Disorder", avaliou o grau de *insight* , características sócio-demográficas e clinicas em 37 pacientes com TAS, comparou com o grau de *insight* em 51 pacientes com TOC e investigou se havia relações possíveis entre nível de *insight* com características sócio-demográficas ou clínicas no TAS. Os pacientes com TAS apresentaram níveis de *insight* que eram tão baixos quanto os observados nos pacientes com TOC , com 29.7 % deles sendo caracterizados como *insight* pobre. Foi encontrado que esses pacientes com *insight* pobre são mais frequentemente casados, menos deprimidos e mostram uma tendência estatística a maiores taxas de abandono precoce da terapia cognitivo-comportamental.

Abstract

The Social Anxiety Disorder (SAD) is characterized by intense fear of being negatively evaluated in various social and performance situations, and this is cause of anxiety symptoms and functional impairment. This fear should be considered irrational or exaggerated by the patient according to the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM - III), which was not always observed in clinical practice. This criterion was modified in the DSM - 5 for non obligation of the individual to recognize such fear as irrational or exaggerated. The objectives of this study were to evaluate the recognition by the individual of the irrationality of this exaggerated fear or the patient's level of insight in SAD, compare it with the level (or degree) of insight in Obsessive Compulsive Disorder (OCD) and assess whether there is a relationship between level insight with socio-demographic or clinical features inside the TAS. The study will be presented in the form of two articles already published. In the first article "Can Hoarding be a symptom of Social Anxiety Disorder? A case study "it was reported the case of a patient with severe social phobia who displayed hoarding as a direct consequence of social anxiety-related beliefs and atypical safety behaviors. The second article, "A study of poor insight in Social Anxiety Disorder", assessed the degree of insight, socio-demographic and clinical features in 37 patients with SAD, compared with the degree of insight in 51 patients with OCD and investigated whether there were possible relationships between insight level with socio-demographic and clinical characteristics in TAS. Patients with SAD had insight levels that were as low as those observed in patients with OCD, with 29.7% of them being characterized as poor insight. It was found that these patients with poor insight are more often married, less depressed and show a statistical trend to higher early withdrawal rates of cognitive-behavioral therapy.

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Introdução

O Transtorno de Ansiedade Social (TAS) caracteriza-se por medo ou ansiedade excessiva em uma ou mais situações em que o indivíduo se sinta exposto ao possível escrutínio alheio, de acordo com a última versão do Manual Diagnóstico Estatístico de Transtornos Mentais, (DSM-5 - APA, 2013). Essa ansiedade, ou medo, causa sintomas ansiosos e prejuízos funcionais importantes, atingindo as esferas das relações interpessoais, acadêmicas e laborais na vida do indivíduo (Ballenger, 1998; Katzelnick and Greist, 2001). É um transtorno que se inicia precocemente, ainda na infância ou adolescência (Kessler *et al.*, 2005) sendo bastante prevalente. Segundo o *National Comorbidity Survey replication*, sua taxa de prevalência é de 12,1% durante a vida e de 6,8% em doze meses (Kessler *et al.*, 2005) .

Apesar de ser um diagnóstico conhecido formalmente há cerca de 35 anos (DSM-III - APA, 1980) durante muito tempo foi um transtorno pouco estudado, subdiagnosticado e pouco tratado (Westenberg, 1998; Katzelnick and Greist, 2001; Kessler *et al.*, 2005). Estima-se que uma baixa proporção dos indivíduos que sofrem do TAS procura o tratamento (Magee *et al.*, 1996; Schneier *et al.*, 1992) e muitos dos que chegam ao tratamento o fazem tardiamente (Westenberg, 1998), motivados, na sua maioria, por comorbidades diversas ao TAS (Davidson *et al.*,1993), e geralmente secundárias ao mesmo (McEvoy *et al.*, 2011).

A falta ou a baixa procura pelo tratamento pode ser explicada pelo comportamento evitativo relacionado com a preocupação de ser humilhado, envergonhado e demonstrar ansiedade diante de outras pessoas (Heckelman *et al.*,1995; Ashbaugh *et al.*, 2007). Uma explicação adicional possível para o indivíduo fóbico social não procurar o tratamento seria a crença de que seu problema seria uma característica de sua personalidade ou timidez,

justificando dessa forma seu conformismo com o sofrimento causado pelo transtorno e prejuízos diversos. Sendo assim, o paciente não reconheceria o sintoma central do TAS - medo intenso de ser avaliado negativamente, em situações sociais diversas e de desempenho - como irracional ou exagerado. Assim como em outros transtornos, o paciente fóbico social poderia ter uma percepção da realidade distorcida de acordo com o grau de comprometimento do seu *insight*.

O *insight* se expressa sob diferentes formas nas diversas patologias, não somente devido às manifestações clínicas de cada doença, mas também às características individuais de cada sujeito (Marková e Berrios, 1995a e 1995b). No contexto do TAS onde a ideia principal baseia-se no medo ou ansiedade da avaliação negativa do outro, a falta de *insight* implicaria no não reconhecimento deste medo ou ansiedade como excessivos ou exagerados.

No surgimento do TAS como categoria diagnóstica na terceira edição do Manual Diagnóstico Estatístico de Transtornos Mentais em 1980 (DSM-III, APA), a presença de *insight* por parte do paciente era condição obrigatória para o diagnóstico ("reconhecimento que seu medo é excessivo ou não razoável"). Tal obrigatoriedade não perdura na quarta edição, uma vez que em crianças esse reconhecimento poderia não estar presente. E, finalmente, esse critério foi abolido no DSM – 5, deixando de ser condição *sine qua non* para o diagnóstico, inclusive em adultos. Esta é uma mudança crucial na compreensão do TAS: enquanto os critérios anteriores indicavam que o indivíduo seria capaz de fazer uma distinção entre pensamentos impulsionados pelo medo e realidade objetiva, o novo critério reconhece a não obrigatoriedade desta distinção e vai ao encontro da proposta deste estudo.

O estudo do *insight* é de extrema relevância, uma vez que a presença ou ausência da crítica em relação aos sintomas possui clara interferência sobre diferentes transtornos

psiquiátricos. No Transtorno Obsessivo- compulsivo (TOC), por exemplo, um *insight* pior tem sido relacionado a pior qualidade de vida (Eisen *et al.*, 2006), pior resposta ao tratamento (Hantouche *et al.*, 2000; Catapano *et al.*, 2001; Erzegovesi *et al.*, 2001; RaviKishore *et al.*, 2004; Himle *et al.*, 2006), e a um pior funcionamento global do indivíduo (Storch *et al.*, 2008). No transtorno bipolar do humor, a falta de *insight* acarreta menor adesão ao tratamento (Cely *et al.*, 2011; Sajatovic *et al.*, 2009; Copeland *et al.*, 2008) e pior qualidade de vida (Yen *et al.*, 2005).

O estudo do *insight* Também é crucial na abordagem diagnóstica e terapêutica, uma vez que o reconhecimento de um possível *insight* pobre em uma patologia primariamente não psicótica evitaria diagnósticos equivocados e uso de antipsicóticos de forma incorreta. No DSM – V já identificamos o especificador "com *insight* pobre" em algumas categorias diagnósticas como o TOC, o Transtorno de Colecionamento e o Transtorno Dismórfico Corporal.

A diminuição de *insight* é bem documentada nos transtornos psicóticos, como esquizofrenia e transtorno bipolar (Amador *et al.*,1994; David,1990; Peralta *et al.*,1998; Ghaemi *et al.*,1997; Pini *et al.*, 2001), e vem sendo progressivamente mais estudada em outras categorias diagnósticas, como nos transtornos alimentares (Konstantakopoulos *et al.*, 2012), transtorno de colecionamento (Dimauro *et al.*., 2013), transtorno dismórfico corporal (Phillips *et al.*., 2012) e transtorno obsessivo compulsivo (Fontenelle *et al.*., 2010). Ainda identificamos necessidade de estudos avaliando o *insight* nos diferentes transtornos de ansiedade.

Em estudo conduzido por Zimmerman e colaboradores (Zimmerman *et al.*, 2010) em que se investigou o *insight* no TAS, foi descrito que menos de 1 % da amostra se caracterizava por não apresentar *insight* sobre sua patologia. Nesse estudo, no entanto, o

insight era avaliado de forma categorial. A caracterização do *insight* como presente ou ausente nos dá pouca informação de como ele se comporta dentro de um determinado transtorno e mesmo de como ele varia ao longo do tempo em um mesmo indivíduo. A avaliação de forma dimensional permitiria diferenciar indivíduos que possuam desde *insight* bom e razoável até ideias sobrevaloradas e ideações delirantes.

Anteriormente a este estudo ainda não se havia mensurado o *insight* no TAS de forma dimensional. Também não se têm notícias de estudos que estabeleçam correlações possíveis entre *insight* e variáveis sócio-demográficas, adesão ao tratamento, gravidade e aspectos clínicos no TAS. Desta forma, aponta-se para a importância de se acessar de forma mais profunda e detalhada o *insight* no TAS.

No presente estudo procura-se investigar a variabilidade do grau de *insight* no TAS e as correlações entre o grau de *insight* e características clínicas do transtorno, objetivando:

1) avaliar o nível de *insight* do paciente com TAS investigando reconhecimento pelo indivíduo da irracionalidade do medo ou ansiedade exagerados;

2) comparar o nível de *insight* no TAS com o nível (ou grau) de *insight* no Transtorno Obsessivo Compulsivo (TOC);

3) avaliar a possível relação entre o nível de *insight* e as características sócio-demográficas e clínicas dos pacientes com TAS.

O estudo será apresentado em seguida na forma de dois artigos já publicados.

No primeiro artigo" **Can Hoarding be a symptom of Social Anxiety Disorder? A case study"** relata-se o caso de um paciente com fobia social grave que desenvolveu um quadro de colecionismo patológico secundário às crenças relacionadas à fobia e aos comportamentos de segurança atípicos. Apresentava sintomas depressivos moderados, também secundário ao TAS, e que determinaram a busca tardia ao tratamento, uma vez

que seus sintomas depressivos estariam prejudicando sua vida acadêmica ao ponto de interromper o andamento de seu Mestrado (um dos muitos casos da prática clínica da autora que a levou a pensar sobre o *insight* no TAS).

No segundo artigo, **"A study of poor insight in Social Anxiety Disorder"** avaliou-se o grau de *insight* em 37 pacientes com TAS, comparou-se com o grau de *insight* em 51 pacientes com TOC e investigaram-se possíveis relações entre nível de *insight* e características sócio-demográficas e clínicas do TAS. Os pacientes com TAS apresentaram níveis de *insight* tão baixos quanto os observados nos pacientes com TOC, com 29.7 % deles sendo caracterizados como tendo *insight* pobre. Concluiu-se que os pacientes com *insight* pobre são mais frequentemente casados, menos deprimidos e mostram uma tendência estatística a maiores taxas de abandono precoce da terapia cognitivo-comportamental.

Primeiro artigo:

Can Hoarding be a symptom of Social Anxiety Disorder? A case study"

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CAN HOARDING BE A SYMPTOM OF SOCIAL ANXIETY DISORDER? A CASE STUDY*

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ABSTRACT

Background: Hoarding is defined as the excessive collection and failure to discard possessions of apparently little value, leading to clutter, distress, and disability. Although patients with hoarding typically may feel ludicrous for not discarding useless, and sometimes bizarre, possessions, we are not aware of any previous description of patients displaying hoarding as a result

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of social anxiety. *Method:* Single case report. *Results:* In this article, we describe a patient with severe social anxiety disorder who displayed hoarding as a direct consequence of social anxiety-related beliefs and atypical safety behaviors. *Conclusions:* This case is of particular interest to current debates concerning the status of hoarding in new versions of classificatory systems. It also indicates that social anxiety disorder should be included in the list of conditions that needs to be excluded in order to diagnose "primary" hoarding disorder.

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Key Words: hoarding, social phobia, obsessive-compulsive disorder, psychopathology, and diagnosis

INTRODUCTION

Hoarding is characterized by the excessive acquisition of and the difficulties experienced in discarding objects of apparently little value, leading to clutter, distress, or impairment [1]. It has been argued that hoarding has many potential underpinnings. For example, hoarding is postulated to be driven by: (i) obsessions in obsessive-compulsive disorder (OCD); (ii) decreased energy in major depressive disorder; (iii) delusions in psychotic disorders; (iv) cognitive deficits in dementia; and (v), restricted interest in autism spectrum disorders [2, 3]. As such, hoarding is frequently conceptualized as a "final common pathway" of many different conditions. However, in some cases, hoarding may also represent a primary and standalone problem [4]. In theory, it is important to disentangle these forms of hoarding because treatment type and course may also differ between them.

Perhaps because hoarding has been traditionally viewed as an obsessive-compulsive symptom [5], there has been a particular interest in disentangling it from "true" OCD. Indeed, a number of features are said to differentiate these two conditions [4]. For instance, some have argued that hoarding-related thoughts and emotions are similar to delusions (or overvalued ideas) and cravings, and that they are unrelated to traditional OCD themes [2]. In addition, while hoarding is a clinically significant problem in a minority of patients with OCD [6], most individuals with severe hoarding do not display other OCD symptoms [7]. Finally, in contrast to typical OCD, hoarding worsens over each decade of life [8], is associated with differentiated neuroimaging findings [4], and predicts poor adherence [9] and response to anti-OCD treatment [10]. As such, there are converging lines of evidence to suggest that these conditions are mostly independent.

In the context of OCD, increased severity of hoarding symptoms has been linked to lower scores on the social aspects of ones quality of life as indexed

according to the Short Form Survey-36 [11]. Similarly, in a study with 815 OCD patients [12], hoarding, along with sexual/aggressive obsessions, was associated with worse social adjustment, as shown by Social Adjustment Scale scores. In contrast, Saxena et al. [13] reported that "compulsive hoarders" did not differ from non-hoarding OCD patients in terms of their social and family contacts and/or relations according to the Lehman Quality of Life Interview.

One key issue to consider in this association between hoarding and social functioning is the presence of/absence of a comorbid social anxiety disorder. For instance, in a study of 217 patients fulfilling criteria for hoarding disorder, 23.5% were found to exhibit comorbid social anxiety disorder, but only 18% had comorbid OCD [7]. In the same vein, in a study assessing the severity of hoarding symptoms in treatment-seeking patients with different anxiety disorders, the prevalence of clinically significant hoarding among patients with social anxiety disorder and OCD was almost the same (i.e., 14.8% and 16.7%, respectively) [14]. Clearly, hoarding and social anxiety disorder appear to co-occur, at least to the same degree as hoarding and OCD. On this basis, further investigations of this association are warranted.

Patients with hoarding may feel ludicrous for not discarding useless, sometimes bizarre, objects. While it is intuitive to consider social anxiety as a complication of hoarding, we are not aware of any previous description of hoarding as a symptom of social anxiety disorder. In this article, we describe a patient with severe social anxiety disorder who displays hoarding as direct consequences of social anxiety-related cognitions and "safety behaviors" (i.e., strategies employed prior to or during social situations to reduce the likelihood of negative evaluation by others) [15].

CASE REPORT

Mr. A, a 35-year-old single white administrative manager, sought treatment for not being able to speak to other people at the anxiety disorders clinic located within the Institute of Psychiatry in Rio de Janeiro. He described being in a "limit situation" and argued that, lately, he only does what is "strictly necessary" in his work and personal life. On his first examination, Mr. A greeted the examiner looking downwards, avoiding eye contact, and displaying sweaty hands. He had a low tone, slow and a trembling voice, which was at times difficult to comprehend. Mr. A continually rubbed his hands under the table and remained restless and fidgety for the entire interview, showing few variations in his facial expressions.

Seven years prior to this presentation, while at University, Mr. A exhibited persistent panic attacks during academic presentations. Specifically, he stated that he "feared performing badly and looking stupid." At that time, he described being unable to speak to anyone for the entire week, both while at work and at University. He also reported having insomnia and diarrhea the days prior to such

presentations. Despite these difficulties, he was able to complete his undergraduate course and was accepted into a Masters course. Currently, however, he is unable to attend classes, nor perform his academic tasks due to his social limitations. He also feels ashamed of sending e-mails to his mentor. Mr. A says this is quite frustrating, as he wants to become a professor.

In relation to his developmental history, Mr. A described being shy since the age of 8 years. He gave an example wherein he would "freeze" and be unable to speak in church when requested to preach in front of everyone. Moreover, he assumed that he was not capable of making friends because he was unable to converse in an "intelligent" or "interesting" manner. He also feared being called names or mistreated. As an adolescent, Mr. A felt terrible for not being able to flirt with girls and experienced great anxiety during normal everyday situations, such as ordering a drink in a cafeteria or signaling a bus to stop. Over time, Mr. A stopped attending church, as well as other social activities such as cocktail parties, the movies, and visiting his grandparents. Mr. A's mother, sister, and grandfather were all described as "extremely shy." However, only his sister sought help, was diagnosed with SAD, and is currently under treatment.

In addition to anxiety symptoms, Mr. A described being continuously sad and unable to experience interest or pleasure in almost all activities during the last 9 months. He also exhibited decreased appetite to the point of losing up to 10 kg and inability to sleep. Restlessness was marked and observable during the interview. Mr. A also described loss of energy, indecisiveness, and recurrent thoughts about not being able to have a family or to make new friends. He is afraid that he would not be able to finish his Masters without help.

At age 14, Mr. A developed the habit of buying books. Initially, he bought extra-curricular volumes to get better prepared for tests, especially on physics and mathematics, wherein he experienced the greatest difficulties. Gradually, however, Mr. A's habit increased to the point of buying books, chronicles, and magazines on various subjects that had no specific relevance. He believed that, after reading them, he could be "a smarter and a more interesting person" and talk about anything with anyone.

Progressively, the quantity of books and magazines purchased increased so much that even basic volumes (e.g., dictionaries) could not be found at his residence, and Mr. A had to buy them again. His belongings occupied nearly two rooms and a further two book cases in his mother's residence. After much insistence from his mother, some items were discarded as they had become moldy and infested by insects. Mr. A described this event as a moment of "great loss" and mourned the event. Nevertheless, he still maintained another family's apartment full of books and magazines. Although he plans to sell some parts of his collection, he finds no time to organize them because "each item is very important and should be carefully classified." Critically, he reported not discarding the books because they might help him "not looking stupid" sometime

in the future. He also argued that, by not having the books handy, he would feel helpless in the event of some upcoming "external" evaluation.

At times, Mr. A acknowledges acting impulsively. He described an occasion when, soon after a "buying binge," he threw some books through the window of the bus, realizing that he had made a "stupid decision." Nevertheless, he is ambivalent and occasionally reports that his hoarding "isn't a problem at all." For instance, after being questioned about the possibility of someone living, renting, or just accessing the family's additional apartment, Mr. A argues that "this could be easily solved after classifying and selecting the books and magazines" as "they are not cluttered, but piled according to some logic rules."

Mr. A was assessed with Mini-International Neuropsychiatric Interview (MINI), which disclosed diagnoses of social anxiety disorder and major depressive disorder. He also scored 6 (severely ill) on the Clinical Global Impression Scale (CGI), 29 (severe depression) on the Beck Depression Inventory, 123 (very severe social anxiety) on the Liebowitz Social Anxiety Scale (LSAS), and 24 (highly impaired) on the Sheehan Disability Scale (SDS). Due to his hoarding behavior, Mr. A was also evaluated with the Structured Interview for Hoarding Disorder, which could not confirm the presence of a *primary hoarding disorder,* as his hoarding was secondary to another condition (in this case, social anxiety disorder). However, Saving Inventory-Revised (SI-R), indicated the presence of severe hoarding symptoms (score 79), and the Clutter Image Rating Scale (CIRS) showed clinically significant clutter (score 4) in all rooms.

Mr. A was prescribed fluoxetine, up to 60 mg/day, and has now been followed for more than 2 years. Soon after treatment was initiated, his depressive symptoms have almost remitted (BDI = 11; mild depression), and his global functioning improved (CGI = 4; moderately ill). Unfortunately, despite our recommendations, Mr. A was unable to obtain cognitive-behavioral therapy, and so remained significantly affected by his condition. At the end of 2 years, he reported feeling somewhat better in the presence of other people, but that he was still symptomatic (LSAS = 101) and disabled (SDS = 18). Since Mr. A sometimes agrees with his wife's intervention, his house is now less cluttered. Nevertheless, hoarding remains a clinically significant problem (SI-R = 57; CIRS = 2).

DISCUSSION

In this article, we have described a patient who exhibited the three core hoarding symptoms (namely, excessive acquisition, difficult discarding, and clutter) as direct consequences of social anxiety-related cognitions and safety behaviors. Distinctively, severe hoarding of books and magazines was linked to the specific fear of looking uneducated for not being able to lead a conversation with unfamiliar people in different topics. We believe our case is of particular interest to current discussions about the status of hoarding in new

versions of classificatory systems. It indicates that social anxiety disorder should be included in the list of conditions that needs to be excluded in order to diagnose "primary" hoarding disorder.

Impulsive behaviors have been consistently reported among patients with both hoarding (e.g. excessive acquisition [16, 17]) and social anxiety disorder (e.g., substance abuse [18], internet addiction [19], sexual addictions [20], and gambling [21]). Indeed, while compulsive shopping, kleptomania, and excessive acquisition of free items are frequently symptoms of hoarding [22], it has been suggested that some patients with social anxiety disorder may engage in similar risk-taking and disinhibited behaviors to strategically regulate their levels of distress [23]. In fact, although behavioral inhibition (e.g., social avoidance) and disinhibition (e.g., compulsive shopping) differ in form, their function in the context of social anxiety disorder may be the same. In the current case, compulsive shopping may temporarily avoid negative evaluation and unwanted anxious feelings and thoughts [23].

The inability to discard, another key dimension of hoarding, has been linked to sensitivity to punishment, at least in OCD samples [24]. In social anxiety disorder, punishment could correspond, at least in theory, to negative evaluation by others. Sensitivity to punishment has been ascribed to increased activity of the so-called Gray's behavioral inhibition system, a set of independent neural networks which are thought to be involved in different psychiatric conditions [25]. We suggest that sensitivity to punishment may contribute to hoarding behaviors across different diagnostic categories, including not only OCD, but also social anxiety disorder [26] and perhaps other anxiety disorders [14].

Books, journals, and magazines are among the most common collected items by hoarding patients [27]. In the context of OCD, a significant correlation between fantasy thinking (i.e., the tendency that an individual has to identify him or herself with fictitious characters in books, films, or plays) and the severity of hoarding symptoms has been reported [28]. While it remains to be shown that fantasy thinking is also an issue among patients with social anxiety disorder, hoarding of books may also represent a maladaptative attempt to cope with related attentional deficits [29] and/or metacognitive impairments [30].

Some might dispute that hoarding disorder and SAD do coexist in our patient as independent disorders or as a "true" comorbidity. Theoretically, for instance, SAD-related beliefs could represent mere *post hoc* explanations or justifications for the patient's hoarding disorder symptoms. Accordingly, in order to unequivocally demonstrate that hoarding is a symptom of SAD, one could argue that social anxiety-related cognitions had to be identified *at the moment* of *discarding* (something like "others will think that I am weird if they see me discarding things now"). Despite not exhibiting this sort of symptom, we still believe there are reasons to conceptualize hoarding as a consequence of SAD in our particular

case. By describing that he saved books because he might read them in the future *in order not to look stupid*, Mr. A clearly provided SAD related-beliefs at the core of his hoarding behaviors.

Our case report suggests that clinicians should not routinely assume that social anxiety disorder is a mere consequence of hoarding. Instead, it indicates that social anxiety disorder may represent a primary phenomenon. Nevertheless, only future studies comparing the demographics, genetics, neuroimaging, and treatment outcome of patients with hoarding as a symptom of primary social anxiety disorder (like ours) and patients with hoarding disorder plus social anxiety disorder, will be able to clarify whether the primary vs. secondary distinction makes any sense.

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Segundo artigo**:**

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A study of poor insight in social anxiety disorder

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ABSTRACT

We investigated levels of insight among patients with Social Anxiety Disorder (SAD) as compared to patients with Obsessive–Compulsive Disorder (OCD) and evaluated whether levels of insight in SAD were related to specific sociodemographic and/or clinical features. Thirty-seven SAD patients and 51 OCD patients attending a tertiary obsessive–compulsive and anxiety disorders clinic were assessed with a sociodemographic and clinical questionnaire, a structured diagnostic interview, the Brown Assessment of Beliefs Scale (BABS), the Social Phobia Inventory (SPIN), the Beck Depression Inventory (BDI), the Sheehan Disability Scale (SDS), and the Treatment Adherence Survey-patient version (TAS-P). According to the BABS, SAD patients exhibited insight levels that were as low as those exhibited by OCD patients, with up to 29.7% of them being described as "poor insight" SAD. Although poor insight SAD patients were more frequently married, less depressed and displayed a statistical trend towards greater rates of early drop-out from cognitive-behavioral therapy, their insight levels were not associated with other variables of interest, including sex, age, employment, age at onset, duration of illness, associated psychiatric disorders, SPIN and SDS scores. Patients with poor insight SAD might perceive their symptoms as being less distressful and thus report fewer depressive symptoms and high rates of treatment non-adherence.

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1. Introduction

Insight is the human ability to critically appraise one's own mind state "from inside" (Oyebode, 2008). Poor levels of insight have been well documented in psychotic disorders (e.g. schizophrenia) and severe mood disorders (e.g. bipolar disorder), but have also been identified in patients with obsessive-compulsive disorder (OCD) (Fontenelle et al., 2010), body dysmorphic disorder (BDD) (Phillips et al., 2012), hoarding disorder (HD) (Dimauro et al., 2013), as well as other neuropsychiatric conditions (Konstantakopoulos et al., 2012; Hartmann et al., 2013). Regardless of the primary syndrome, poor insight is generally associated with a more severe clinical presentation. In OCD, for instance, poor insight has been associated with an earlier age of onset (Ravi Kishore et al., 2004; Catapano et al., 2010), higher rates of comorbid mood (Turksoy et al., 2002; Ravi Kishore et al., 2004; Alonso et al., 2008, Catapano et al., 2010), anxiety (Turksoy et al., 2002), and personality disorders (Turksoy et al., 2002; Alonso et al., 2008; Catapano et al., 2010); family history of psychosis (Catapano et al., 2010), poorer quality of life (Eisen et al., 2006) and functioning (Storch et al., 2008), and worse treatment response (Hantouche et al., 2000; Catapano et al., 2001; Erzegovesi et al., 2001; Ravi Kishore et al., 2004; Himle et al., 2006).

As patients with OCD and other OC-related disorders such as BDD and HD differ in their awareness of symptoms, developers of the DSM-5 added specifiers regarding levels of insight for each disorder (APA, 2013). These specifiers are intended to alert clinicians that patients with OC-related disorders should not be classified and treated as patients with other psychotic disorders generally managed with an antipsychotic monotherapy. Although there is evidence that antipsychotic augmentation therapy is beneficial in SRI-resistant OCD cases (Bloch et al., 2006), this strategy has been linked with potentially severe side effects (Meyer, 2007) and may not be effective when employed as a monotherapy in OCD-related disorders (Keuneman et al., 2005). Probably, a similar strategy can be adopted to prevent antipsychotic

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treatments being administered to poor insight patients with other disorders that are frequently comorbid with OCD, such as anxiety disorders.

Social anxiety disorder (SAD) indeed has substantial overlap with several conditions that may present with poor insight, including OC-related disorders and eating disorders. Each of these conditions has an early age of onset, is highly comorbid with each other, and tend to respond to similar pharmacological treatments (e.g. serotonin reuptake inhibitors) (Schneier et al., 2002). In fact, when SAD is comorbid with other disorders, it tends to emerge first (McEvoy et al., 2011). The characteristic feature of SAD (i.e., fear of being negatively evaluated by others) is also evident in the clinical picture of these comorbid disorders – for example, in relation to sexual-religious obsessions in OCD (Assuncao et al., 2012), dysmorphic concerns in BDD (Fang and Hofmann, 2010), bizarre possessions in HD (Frost et al., 2011), and weight and shape in ED (Hinrichsen et al., 2003).

Until DSM-IV-TR, only those patients who displayed insight into their social anxiety symptoms were qualified for a diagnosis of SAD (APA, 2000). However, a relevant change that has taken place with the DSM-5 conceptualization of SAD is that patients no longer need to recognize their symptoms as irrational (Bogels et al., 2010). Although in one study it was reported that less than 1% of patients with SAD failed to recognize that their fears as excessive or unreasonable (Zimmerman et al., 2010), we are not aware of any previous attempts to investigate levels of insight in SAD patients using standardized instruments to measure insight as a dimensional construct. Also, if some patients with poor insight SAD do exist, it is not clear whether they demonstrate specific sociodemographic or clinical features. Based on the findings described in other disorders, we hypothesized that poor insight SAD would likely be associated with an earlier age of onset, more severe SAD and depressive symptoms, greater rates of comorbid major depression, and a poorer adherence to treatment.

In this study, we investigated the levels of insight among patients with SAD compared to OCD patients, and evaluated whether poorer insight was related to distinct sociodemographic features, comorbidity patterns, or clinical characteristics, including treatment adherence with particular focus on pharmacotherapy and cognitive-behavioral therapy.

2. Methods

Thirty-seven SAD patients and 51 OCD patients attending our University (tertiary) Anxiety and Obsessive–Compulsive Disorders Clinic were recruited for this study. To be included, patients had to (i) have a diagnosis of SAD or OCD according to DSM-IV-TR criteria – if other psychiatric disorders were present, they had to be less severe (according to the interviewing psychiatrist's clinical judgment) and associated with a later age of onset than SAD and OCD – (ii) be aged between 18 and 65 years, and (iii) have the ability to read, comprehend and complete written forms. Patients with a comorbid diagnosis of both OCD and SAD, schizophrenia, acute mania or delusional depression were excluded from our sample. All recruited patients signed an informed consent and agreed with the objectives and procedures of this study, which was approved by the local Institutional Review Board and in accordance with the Declaration of Helsinki.

Part of the OCD sample included here was described in a previous paper (Santana et al., 2013). Subjects were assessed with a sociodemographic and clinical questionnaire, scales to measure the severity of SAD or OCD symptoms [Social Phobia Inventory (SPIN) (Vilete et al., 2004), and the Dimensional Yale–Brown Obsessive–Compulsive Scale (DY–BOCS) (Rosario-Campos et al., 2006)], an instrument to evaluate associated depression [Beck Depression Inventory (BDI) (Cunha, 2001)], and a scale focusing on disability levels [Sheehan Disability Scale (SDS)] (Sheehan et al., 1996).

Insight was evaluated using the Brown Assessment of Beliefs Scale (BABS), a seven-item semi-structured clinician-administered scale with specific probes and anchors designed to assess insight into a dominant belief that has preoccupied the patient during the past week (Eisen et al., 1998). The dimensions covered by the scale include conviction; perception of others' view of beliefs; explanation of differing views; fixity of ideas; attempt to disprove beliefs; and insight and ideas of reference. For each item, there are specific probes with five anchors ranging from 0 (nondelusional/least pathologic) to 4 (delusional/most pathologic). The seventh item is not included in the total score. Ratings represent an average score for the past week.

The BABS was employed to rate insight into (i) core SAD beliefs, which are generally described as the fear of being criticized or negatively evaluated by others, but expressed in more specific forms and assessed in greater detail in each patient (e.g. fear of looking "silly", "like an idiot", "not intelligent", "crazy", "unprepared", or "disturbing", among others) and (ii) core OCD beliefs in different OCD dimensions, identified as relevant by means of a score ≥ 3 on the Dimensional Yale–Brown Obsessive–Compulsive Scale-Short Version. Given the multisymptomatic nature of OCD, two methods of using BABS in OCD samples were employed, as described previously (Santana et al., 2013): (i) a dimension-specific strategy, which assess insight into all clinically significant OCD symptoms separately, thus allowing the identification of the beliefs associated with lower insight levels and (ii) a traditional approach, recommended by developers of the scale, which rates insight into OCD symptoms as a composite of the general average insight level.

Adherence to CBT and pharmacotherapy was assessed with the Treatment adherence survey-patient version (TAS-P), a rater-administered questionnaire originally developed by Mancebo et al. (2008). We felt the TAS-P would be the most appropriate instrument to assess treatment adherence across SAD and OCD samples due to its simplicity and ease of administration although, to date, its use has been restricted to OCD patients. For instance, the TAS-P assesses if CBT and/or pharmacotherapy were previously recommended, started, interrupted or declined; the approximate number of CBT sessions attended and/or of weeks of medication use; and the reasons, if any, for non-adherence to these forms of treatment. In our study, we investigated lifetime treatment adherence, including adherence to treatment recommendations made while in our clinic.

2.1. Statistical analyses

Categorical variables were summarized in terms of frequencies and percentages and continuous variables were summarized in terms of means ($\pm$ standard deviations). Two types of comparisons were made: (i) SAD patients vs. patients OCD patients and (ii) poor insight SAD patients (BABS ≥ 13) vs. good insight SAD patients (BABS < 13). The cut-off score for BABS was empirically defined through the observation of a zone of rarity in the histogram depicting the distribution of conventional BABS scores over the entire studied sample (data not shown). Chi-square or Fisher's exact test categorical variables and Student's t test or Mann–Whitney test for continuous variables were used.

3. Results

SAD patients were compared to OCD patients in terms of sociodemographic and clinical features (see Table 1). SAD patients were predominantly female, belonged to a higher socioeconomic stratum, displayed increased rates of alcohol dependence, had more unproductive days at school or work, and reported an earlier onset of symptoms. In contrast, OCD patients displayed higher rates of unemployment, greater religiosity, and a trend towards more frequent prescription of drug treatments.

As emphasized in Table 1 and described above, insight levels assessed using the BABS were analyzed according to two approaches. When compared to insight levels in OCD patients rated against their primary symptom domain, SAD patients demonstrated equivalent (low) insight levels. However, when compared to insight levels in OCD patients rated across all symptom domains, SAD patients demonstrated significantly lower insight levels. A comparison between SAD and OCD in terms of treatment adherence is depicted in Table 2.

In relation to SAD, up to 29.7% of the sample (11 patients) exhibited poor insight, defined as a score of 13 or more on the BABS. Poor insight SAD patients were more frequently married and had lower BDI scores than good insight SAD patients (Table 3). There were no other distinct differences between the groups, although poor insight SAD patients displayed a statistical trend towards higher rates of CBT non-adherence (Table 4).

4. Discussion

In this study, patients with SAD were characterized by levels of insight that were as low as those exhibited by OCD patients – a

Table 1
Comparison of sociodemographic and clinical features presented by patients with social anxiety disorder and patients with Obsessive–Compulsive Disorder.

	Patients with SAD	Patients with OCD	Statistics
Socio-demographic features			
Age (in years)	43.7 (13.5)	40.7 (13.7)	$t=1.02$; d.f.=86; $p=0.31$
Sex			$\chi^2=3.65$; d.f.=1; $p=0.05$
Female	12 (32.4%)	27 (52.9%)	
Male	25 (67.6%)	24 (47.1%)	
Marital status			$\chi^2=3.99$; d.f.=1; $p=0.53$
Never married	23 (62.2%)	35 (68.6%)	
Ever married	14 (37.8%)	16 (31.4%)	
Religiosity			$\chi^2=9.35$; d.f.=1; $p=0.002$
Yes	16 (48.5%)	41 (80.4%)	
No	17 (51.5%)	10 (19.6%)	
Occupation			LR=3.65; d.f.=2; $p=0.04$
Unemployed or on medical leave	4 (11.1%)	14 (27.5%)	
Employed, retired or student	32 (88.9%)	35 (68.6%)	
Homemaker	0 (0.0%)	2 (3.9%)	
Social class			LR=5.33; d.f.=2; $p=0.03$
Upper class	20 (54.1%)	18 (35.3%)	
Middle class	16 (43.2%)	26 (51.0%)	
Lower class	1 (2.7%)	7 (13.7%)	
Education			LR=1.31; d.f.=2; $p=0.52$
Basic	4 (10.8%)	7 (13.7%)	
Intermediary	16 (43.2%)	16 (31.4%)	
High	17 (45.9%)	28 (54.9%)	
Course characteristics			
Age at onset	11.6 (5.1)	15.5 (7.0)	$t=-2.80$; d.f.=80; $p=0.006$
Duration of illness	32.1 (14.7)	25.6 (15.1)	$t=1.94$; d.f.=80; $p=0.05$
Insight features			
BABS I	9.1 (4.7)	2.7 (2.3)	$t=7.51$; d.f.=85; $p<0.001$
BABS II	9.1 (4.7)	9.5 (5.9)	$t=-2.80$; d.f.=86; $p=0.78$
Poor insight based on BABS I	10 (27.0%)	0 (0.0%)	Fisher's test $p<0.001$
Poor insight based on BABS II	11 (29.7%)	18 (35.3%)	$\chi^2=0.30$; d.f.=1; $p=0.58$
Severity of symptoms			
BDI	13.1 (9.8)	15.4 (11.1)	$t=-1.00$; d.f.=86; $p=0.31$
SDS	11.4 (8.9)	9.9 (7.8)	$t=0.70$; d.f.=59; $p=0.49$
Work/school work	4.4 (3.3)	2.8 (3.2)	$t=1.85$; d.f.=60; $p=0.07$
Social life/leisure activities	4.5 (3.7)	4.4 (3.7)	$t=1.11$; d.f.=86; $p=0.91$
Family life/home responsibilities	2.9 (3.0)	4.7 (3.7)	$t=-2.44$; d.f.=83.3; $p=0.02$
Days lost	1.0 (2.1)	1.0 (2.4)	$Z=-1.12$; $p=0.26$
Days unproductive	1.6 (2.3)	0.8 (2.0)	$Z=-2.0$; $p=0.05$
Psychiatric comorbidity			
Major depressive episode (lifetime)	18 (50%)	20 (39.2%)	$\chi^2=1.00$; d.f.=1; $p=0.31$
Dysthymia (current)	8 (22.2%)	6 (11.8%)	$\chi^2=1.70$; d.f.=1; $p=0.19$
Bipolar disorder (lifetime)	0 (0.0%)	1 (2.0%)	Fisher's test $p=1.00$
Bipolar II disorder (lifetime)	0 (0.0%)	5 (9.8%)	Fisher's test $p=0.07$
Alcohol dependence (last year)	6 (16.7%)	0 (0.0%)	Fisher's test $p=0.004$
Non-alcohol substance dependence (last year)	3 (8.3%)	0 (0.0%)	Fisher's test $p=0.06$
Panic disorder (lifetime)	2 (5.6%)	10 (19.6%)	Fisher's test $p=0.11$
Generalized anxiety disorder (current)	7 (19.4%)	14 (27.5%)	$\chi^2=0.73$; d.f.=1; $p=0.39$

SAD: Social Anxiety Disorder; OCD: Obsessive–Compulsive Disorder; BABS: Brown Assessment of Beliefs Scale; BDI: Beck Depression Inventory; SDS: Sheehan Disability Scale.

Table 2
Comparison of some treatment adherence features between patients with social anxiety disorder and patients with Obsessive–Compulsive Disorder.

	Patients with SAD	Patients with OCD	Statistics
Has a doctor or other professional ever recommended that you receive CBT for SAD/OCD?	30 (81.1%)	40 (78.4%)	Fisher's test $p=0.79$
Have you ever received CBT for SAD/OCD?	17 (45.9%)	25 (49%)	Fisher's test $p=0.83$
Did you stop attending CBT before completing therapy?	10 (47.6%)	15 (62.5%)	Fisher's test $p=0.37$
Have you ever decided not to participate in CBT despite its being recommended to you by your doctor or another professional?	13 (39.4%)	17 (47.2%)	Fisher's test $p=0.62$
Has a doctor or other professional recommended that you take medication for SAD/OCD?	32 (86.5%)	50 (98%)	Fisher's test $p=0.07$
Have you ever taken any medication for SAD/OCD?	33 (8.3%)	49 (96.1%)	Fisher's test $p=0.64$
Did you ever take the medication less frequently or at a smaller dose than was prescribed, or stopped the medication on your own?	23 (43.2%)	31 (63.3%)	Fisher's test $p=1.00$
Have you ever not taken medication for SAD/OCD, even though it was recommended to you?	16 (43.2%)	26 (52%)	Fisher's test $p=0.51$

This table describes most, but not all items listed on treatment adherence survey-patient version. To avoid multiple comparisons, we have excluded, a priori, comparisons of (i) the number of cognitive behavioral therapy that sessions received, (ii) the total length of time medications were taken, (iii) the reasons why patients did not participate in or stopped attending cognitive-behavioral therapy and (iv) reasons why patients did not receive medication or have taken them less frequently or at a lesser dose than prescribed.

Table 3
Comparison of sociodemographic and clinical features presented by patients with poor- vs. good-insight social anxiety disorder.

	Patients with poor insight SAD	Patients with good insight SAD	Statistics
Socio-demographic features			
Age (in years)	49.4 (12.1)	41.7 (13.6)	$Z=-1.64$; $p=0.10$
Sex			Fisher's test $p=0.44$
Male	8 (80.0%)	17 (63.0%)	
Female	2 (20.0%)	10 (37.0%)	
Marital status			Fisher's test $p=0.02$
Married	7 (70.0%)	7 (25.9%)	
Never married	3 (30.0%)	20 (74.1%)	
Religiosity			Fisher's test $p=0.08$
Yes	1 (14.3%)	15 (57.7%)	
No	6 (85.7%)	11 (42.3%)	
Occupation			Fisher's test $p=1.00$
Unemployed	1 (10.0%)	3 (11.5%)	
Employed	9 (90.0%)	23 (88.5%)	
Social class			LR=0.81;d.f.=2;$p=0.66$
Upper class	5 (50.0%)	15 (55.6%)	
Middle class	5 (50.0%)	11 (40.7%)	
Lower class	0 (0.0%)	1 (3.7%)	
Education			**LR=1.59;d.f.=2;$p=0.45$**
Basic	2 (20.0%)	2 (7.4%)	
Intermediary	3 (30.0%)	13 (48.1%)	
High	5 (50.0%)	12 (44.4%)	
Course characteristics			
Age at onset	13.7 (6.8)	10.8 (4.3)	$Z=-0.94$; $p=0,34$
Duration of illness	35.7 (12.9)	30.8 (15.3)	$Z=-1.07$; $p=0.28$
Severity of symptoms			
SPIN	27.5 (16.7)	43.2 (46.2)	$Z=-1.22$; $p=0.22$
Fear	9.1 (5.4)	12.2 (6.9)	$Z=-1.34$; $p=0.18$
Avoidance	12.7 (7.6)	15.8 (8.2)	$Z=-1.22$; $p=0.22$
Physiological discomfort	5.6 (4.9)	8.4 (6.5)	$Z=-1.14$; $p=0.25$
BDI	8.3 (8.3)	14.9 (9.8)	$Z=-1.92$; $p=0.05$
SDS	10.2 (8.8)	11.8 (9.1)	$Z=-0.08$; $p=0.94$
Work/school work	3.7 (3.1)	4.6 (3.4)	$Z=-0.61$; $p=0.54$
Social life/leisure activities	4.6 (3.8)	4.5 (3.7)	$Z=-0.16$; $p=0.87$
Family life/home responsibilities	2.6 (3.9)	2.9 (2.7)	$Z=-0.84$; $p=0.39$
Days lost	0.3 (1.0)	1.3 (2.4)	$Z=-1.25$; $p=0.21$
Days unproductive	1.7 (2.4)	1.6 (2.3)	$Z=-0.08$; $p=0.93$
Psychiatric comorbidity			
Major depressive episode (lifetime)	4 (40.0%)	14 (53.8%)	Fisher's test $p=0.71$
Dysthymia (current)	2 (20.0%)	6 (23.1%)	Fisher's test $p=1.00$
Bipolar disorder (lifetime)	0 (0.0%)	0 (0.0%)	
Bipolar II disorder (lifetime)	0 (0.0%)	0 (0.0%)	
Alcohol dependence (last year)	3 (30.0%)	3 (11.5%)	Fisher's test $p=0.31$
Non-alcohol substance dependence (last year)	1 (10.0%)	2 (7.7%)	Fisher's test $p=1.00$
Panic disorder (lifetime)	2 (20%)	0 (0.0%)	Fisher's test $p=0.07$
Generalized anxiety disorder (current)	0 (0.0%)	7 (26.9%)	Fisher's test $p=0.15$

SAD: Social Anxiety Disorder; OCD: Obsessive–Compulsive Disorder; BABS: Brown Assessment of Beliefs Scale; BDI: Beck Depression Inventory; SDS: Sheehan Disability Scale.

classical non-psychotic condition that has been more consistently linked with reduced insight (Fontenelle et al., 2010). In fact, the prevalence of poor insight was considerably high in our sample, occurring in approximately 30% of cases. This finding is in sharp contrast to the 1% estimate provided in a previous study that assessed patients' insight into their primary fears as an "all or nothing" phenomenon (Zimmerman et al., 2010). That is, our results suggest that an inability to appraise critically one's own beliefs is in fact a common feature among SAD patients. This observation is therefore consistent with the DSM-5 conceptualization of SAD, which no longer requires patients to recognize their symptoms as irrational.

Our study represents the first attempt to dimensionally assess insight levels in SAD, although some authors have already suggested that patients with primary SAD might occasionally report "psychotic-like" experiences (Armando et al., 2013; Veras et al., 2011). It is surprising that only a few such cases have been described so far. As previously theorized, it must be a very short step, one might suppose, from appraising self-referential thoughts critically to believing "delusionally" that one has been observed (Lewis, 1936). In relation to this, it would be interesting to investigate if insight levels in SAD patients fluctuate over time as has been demonstrated in OCD. Long-term follow-up studies of insight levels in SAD patients will be important in clarifying this relevant clinical issue.

We also investigated whether poor-insight SAD was associated with differential features as reported in many OC-related disorders. However, while in OCD, BDD, and eating disorders poor insight has been associated with greater severity of symptoms (including depression), we found the opposite phenomenon in poor-insight SAD patients, who displayed less severe depression, thus suggesting that different mechanisms may mediate the relationship between insight and depression in SAD. It could be argued, for instance, that patients with poor insight SAD apparently suffer from a purer, but not necessarily milder, form of SAD, as they were less depressed than good insight SAD patients.

One possibility is that by not questioning their SAD beliefs, poor insight SAD patients might adjust to their symptoms and perceive them as less distressful, thus experiencing less

Table 4
Comparison of some treatment adherence features between patients with poor- and good-insight social anxiety disorder.

	Patients with poor insight SAD	Patients with good insight SAD	Statistics
Has a doctor or other professional ever recommended that you receive CBT for SAD/OCD?			Fisher's test $p=1.00$
No	2 (18.2%)	5 (19.2%)	
Yes	9 (81.8%)	21 (80.8%)	
Have you ever received CBT for SAD/OCD?			Fisher's test $p=1.00$
No	6 (54.5%)	14 (53.8%)	
Yes	5 (45.5%)	12 (46.2%)	
Did you stop attending CBT before completing therapy?			Fisher's test $p=0.06$
No	1 (16.7%)	10 (66.7%)	
Yes	5 (83.3%)	5 (33.3%)	
Have you ever decided not to participate in CBT despite its being recommended to you by your doctor or another professional?			Fisher's test $p=1.00$
No	5 (55.6%)	15 (62.5%)	
Yes	4 (44.4%)	9 (37.5)%	
Has a doctor or other professional recommended that you take medication for SAD/OCD?			Fisher's test $p=1.00$
No	1 (9.1%)	4 (15.4%)	
Yes	10 (90.9%)	23 (84.6%)	
Have you ever taken any medication for SAD/OCD?			Fisher's test $p=1.00$
No	1 (10.0%)	2 (7.7%)	
Yes	9 (90.0%)	24 (92.3%)	
Did you ever take the medication less frequently or at a smaller dose than was prescribed, or stopped the medication on your own?			Fisher's test $p=1.00$
No	4 (36.4%)	10 (38.5%)	
Yes	7 (63.6%)	16 (61.5%)	
Have you ever not taken medication for SAD/OCD, even though it was recommended to you?			Fisher's test $p=1.00$
No	6 (54.5%)	15 (57.7%)	
Yes	5 (45.5%)	11 (42.3%)	

This table describes most, but not all items listed on treatment adherence survey-patient version. To avoid multiple comparisons, we have excluded, a priori, comparisons of (i) the number of cognitive behavioral therapy that sessions received, (ii) the total length of time medications were taken, (iii) the reasons why patients did not participate in or stopped attending cognitive-behavioral therapy and (iv) reasons why patients did not receive medication or have taken them less frequently or at a lesser dose than prescribed.

depression. Alternatively, depression may be an understandable outcome of greater awareness into illness and/or lead to an increase in self-criticism, thus resulting in greater insight into SAD beliefs and symptoms. In support of the latter interpretation, some have argued that poor insight symptoms (e.g. persecutory delusions) may be a defense against negative affective processes (Bentall et al., 2001). Finally, being in a stable relationship might also provide a "safer" environment for patients with poor-insight SAD, a situation in which they feel protected and less likely to expose themselves to external evaluators.

No other clinical or demographic feature, including sex, age, employment, age at onset, duration of illness, associated psychiatric disorders, SPIN, and SDS scores, were related to insight levels in SAD. Thus, it appears that poor insight SAD and good-insight SAD might in fact represent the same condition, with poor-insight being an occasional phenomenon reported in SAD, although this possibility can only be considered speculative at this point. Cautionary notes aside, we found that assessing insight in SAD patients might have some important clinical implications, as poor-insight patients might discontinue CBT treatment early. This finding suggests that care should be exercised in applying CBT as a first-line treatment in poor insight SAD cases or conversely that serotonin reuptake inhibitors may be first considered.

It is difficult to compare our findings to those of other studies, as none have employed a methodology similar to ours. For instance, Armando et al. found that SAD patients with psychotic-like experience (PLE) showed higher level of anxiety, depression, and intolerance of uncertainty compared with the SAD without these features (Armando et al., 2013). However, it is not clear how this group compares to poor insight patients in our study. In fact, the instrument employed in their study [Community Assessment of Psychic Experiences (CAPE)] includes symptoms that are qualitatively different from the ones reported in by our patients (e.g. first-rank symptoms).

Our findings have some implications for the differential diagnoses of SAD. For instance, if SAD can be associated with poor insight, then how it could be differentiated from conditions characterized by self-referential delusions or delusion-like ideas? Although this might pose a diagnostic challenge in cases lacking, for instance, gross first-rank symptoms, there are some potential clues that can be relied upon. While high levels of shame and behavioral inhibition are key features of poor insight SAD patients, who also display a more submissive attitude toward their interlocutors (a construct closer to the so-called "bad me" delusions (Trower and Chadwick, 1995)), indignation and disinhibition characterize most paranoid conditions, which also feature a more distrustful and sometimes hostile attitude toward other people ("poor me" delusions (Trower and Chadwick, 1995)).

Our study has some limitations. Firstly, since there were significant differences between SAD and OCD in sociodemographic and clinical terms, it could be argued that the groups could not be compared reliably. However, the extent to which the reported differences between the groups had the potential to affect "delusionality" is debatable. For instance, the SAD group displayed similar or lower insight than the OCD group despite having lower rates of comorbid depression (which is known to decrease insight in most conditions). Secondly, our SAD and OCD samples were relatively small, thus resulting in a reduced proportion of patients with SAD with poor-insight. Conceivably, the latter group might be considered insufficient

large to detect to additional differences in relation to good insight SAD. Finally, future studies should incorporate a greater number of variables, including more clinician-rated scales, as poor insight can theoretically interfere with the ability to report other non-SAD symptoms reliably.

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Considerações finais

Este estudo aponta para a existência de uma parcela significativa de pacientes com *insight* pobre no TAS fundamentado em amostra clínica de pacientes sujeitos a tratamento em ambulatório especializado. De fato, a prevalência de *insight* pobre na nossa amostra foi consideravelmente maior, abrangendo quase 30 % dos indivíduos, comparada ao estudo anterior realizado por Zimmerman e colaboradores (Zimmerman *et al.*, 2010) em que o *insight* foi avaliado de forma categorial e apenas 1% de pacientes não apresentava *insight* no TAS. O resultado sugere que o não reconhecimento do medo ou ansiedade do paciente com TAS como irracional é uma característica comum entre os portadores de TAS, e tal aspecto é condizente com os novos critérios diagnósticos do TAS no DSM – 5.

Talvez mais surpreendente do que a confirmação da existência de um *insight* pobre no TAS tenha sido a correlação positiva encontrada entre *insight* pobre no TAS e maiores sintomas depressivos, um achado completamente discordante do que foi encontrado anteriormente no TOC (Fontenelle *et al.*, 2013), por exemplo. Algumas explicações poderiam auxiliar no entendimento desse achado. Pode-se imaginar que um paciente fóbico social sem *insight* sofra de uma forma mais pura de fobia social mas não necessariamente menos grave, já que esse tipo de indivíduo deprime menos que o fóbico com *insight* melhor. Ou ainda, sem questionar suas crenças, que o fóbico social com *insight* ruim se acomoda aos seus sintomas e assim não experimenta situações estressantes características do fóbico social, deprimindo menos. E uma terceira explicação possível seria que a depressão seria uma consequência compreensível de um maior entendimento sobre sua doença, o que exarcebaria a autocrítica e de que resultaria maior *insight* sobre as

próprias crenças e sintomas característicos da fobia. Além das suposições explicitadas anteriormente para tal achado, convém lembrar que o *insight* se expressa de diferentes formas nas diversas patologias, não somente devido às manifestações clínicas de cada doença, mas também às características individuais de cada sujeito (Marková e Berrios, 1995a e 1995b). Estudos futuros que possam avaliar os pacientes de forma prospectiva e longitudinal possivelmente elucidarão este achado.

Talvez a maior limitação do estudo em questão seja a não identificação de transtornos de personalidade comórbidos ao TAS. Transtornos de personalidade comórbidos no TOC, por exemplo, estão correlacionados com pior *insight* do transtorno primário (Turksoy *et al*., 2002; Alonso *et al*., 2008; Catapano *et al*., 2010). A não investigação desse aspecto nesta pesquisa abre uma janela a novos estudos, como avaliar até quanto a presença de transtorno de personalidade esquivo afetaria, de modo significativo, o *insight* no paciente com TAS.

Novos estudos investigando o impacto das comorbidades e do tratamento no *insight* do TAS são necessários para o maior esclarecimento deste cenário. Além disso, estudos que visem avaliar o *insight* em amostras não clínicas, por exemplo, serão fundamentais para o melhor entendimento do impacto do *insight* na busca pelo tratamento. Mesmo que, intuitivamente, possa-se pensar que um paciente fóbico social em tratamento tenha um *insight* melhor que aquele que nunca foi diagnosticado e/ou tratado, um indivíduo fóbico social pode ir à procura de tratamento por outras comorbidades, sem *insight* sobre o seu diagnóstico primário, enquanto outros pacientes, ainda que percebam suas limitações,

simplesmente não chegam ao tratamento em função de comportamento evitativo ou acomodação familiar.

O presente estudo foi pioneiro em avaliar o *insight* no TAS de forma dimensional e demonstrou a existência de um *insight* pobre no TAS, o que propicia novos questionamentos e necessidade de estudos adicionais para elucidações futuras.

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Anexo 1:

A review on predictors of treatment outcome in Social Anxiety Disorder

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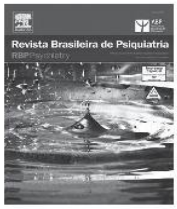

REVIEW ARTICLE

A review on predictors of treatment outcome in social anxiety disorder

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DESCRIPTORS
Phobic Disorders;
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Abstract
Objective: This article aims to review the clinical features and therapeutic characteristics that may predict treatment response in patients with social anxiety disorder (SAD). *Methods*: A systematic review of trials identified through databases of ISI, Medline, PsycInfo, Cochrane, LILACS, Current Controlled Trials, and in references of previously selected articles published in English up to December 2010. In our literature search, we used the words prediction/predictors and social anxiety disorder or social phobia. *Results*: Early onset, greater disease severity, comorbidity with other anxiety disorders (including generalized anxiety disorder and simple phobia), and high expectations about the role of the therapist emerged as potential predictors of less effective treatment in SAD. *Conclusions*: Knowledge of various clinical and treatment features may help professionals to predict possible responses to therapeutic interventions in patients with SAD. However, given the diversity of measures used to assess response, further studies should be performed with standardized methods to investigate the aspects related to treatment resistance in SAD.
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DESCRITORES:
Transtornos fóbicos;
Fatores de predição;
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Ensaios clínicos.

Uma revisão sobre fatores de predição de resposta ao tratamento no transtorno de ansiedade social

Resumo
Objetivo: Este artigo tem por objetivo descrever as principais características clínicas e terapêuticas que possam predizer resposta ao tratamento em pacientes com transtorno de ansiedade social (TAS). *Métodos*: Revisão sistemática de ensaios clínicos identificados através das bases de dados *ISI*, *Medline*, *PsycInfo*, *Cochrane*, *LILACS*, *Current Controlled Trials* e em referências bibliográficas de artigos previamente selecionados publicados em inglês até dezembro de 2010. As seguintes palavras-chave foram utilizadas em nossa busca bibliográfica: *prediction/predictors* e *social anxiety disorder ou social phobia*. *Resultados*: Início precoce, maior gravidade da doença, comorbidade com outros transtornos de ansiedade (incluindo o transtorno de ansiedade generalizada e fobia simples) e alta expectativa sobre o papel do terapeuta emergiram como potenciais fatores de predição menor eficácia do tratamento do TAS. *Conclusões*: O conhecimento de uma variedade de características clínicas e de tratamento pode auxiliar os profissionais a preverem possíveis respostas às intervenções terapêuticas nos pacientes com TAS. No entanto, devido à diversidade de medidas utilizadas para avaliar a resposta, novos estudos com o objetivo de investigar aspectos relacionados à resistência ao tratamento do TAS devem ser realizados com métodos mais padronizados.
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Introduction

Social anxiety disorder (SAD) is characterized by intense and persistent fear of being negatively evaluated by others, which leads to significant avoidance or intense psychological distress in various social situations.[1] SAD has high prevalence rates, early and insidious onset, and a chronic course.[2] It is associated with low levels of quality of life; significant feelings of incapacity; and notorious social, educational, and occupational disability.[3] Despite remaining largely underdiagnosed,[4] recent studies are beginning to unveil SAD neurobiological underpinnings, thus leading to greater knowledge regarding its pathophysiology.[5]

Currently, the most empirically effective treatments of SAD include pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs), and cognitive behavioral therapy (CBT), either together or separately.[6,7,8] Although these strategies lead to a therapeutic response in a large proportion of individuals, a significant number of patients with SAD (up to 50%) does not respond at all or remain significantly symptomatic after being submitted to first-line treatments.[9,10,11]

This article aims to review the clinical and therapeutic characteristics that have been reported to be associated with response to treatment prescribed to patients with SAD. Potentially, the characterization of these features may save patients' time by avoiding ineffective treatments, which may be sometimes associated with severe side effects and/or economic burden. It could also help to identify factors that should be taken into account if one aims at elaborating more specific treatment for SAD individuals who do not respond to conventional strategies.

Methods

A systematic review of clinical trials that describe the profile of patients with SAD who respond to treatment was performed in the following databases: ISI/Web of science, Medline, PsycInfo, Cochrane Library, LILACS, and Current Controlled Trials (articles not published yet). An additional search for articles of interest was performed in the bibliographic list of selected articles. The following keywords were used in the bibliographical search: prediction/predictors and social anxiety disorder or social phobia. Clinical trials originally published in English up to December 2010 were assessed.

Inclusion criteria consisted of studies composed of subjects with a primary diagnosis of SAD according to the DSM-III-R or DSM-IV and describing an assessment of treatment response predictors in this condition. We included papers that addressed the following aspects as potential response predictors: (i) clinical features (age of onset, duration of SAD, severity of symptoms, generalized subtype of SAD, family history of SAD, and psychiatric comorbidity); (ii) sociodemographic characteristics (age, gender, educational level, and marital status); and (iii) treatment features (treatment history, duration of current treatment, expectancy regarding treatment, and group cohesion [in case of group therapy]). For the sake of space, other potential predictors (e.g., personality traits) were not addressed in our review.

Results

Medline search identified 392 articles, of which 10 met the inclusion criteria. In PsycInfo, from the 58 studies identified, 5 were included. The ISI/Web of Science database led to the identification of 679 articles, of which 4 were included. A Cochrane search resulted in 158 studies, of which 11 were selected, including 10 that had already been localized on Medline and Psyinfo, and one that appeared for the first time.

A LILACS search led to only one article, which did not meet the inclusion criteria. Unpublished articles searched on Current Controlled Trials were not found as well. Four additional articles were identified in the reference lists

of previously selected articles. These combined search strategies led to a total of 24 selected articles. Most studies (n = 19) reported independent predictors of response using regression analysis, while the remaining ones[12-16] used univariate analysis.

Clinical characteristics

Studies describing the impact of different clinical characteristics (including age of onset, duration, symptom severity, subtype, and family history) on SAD treatment outcomes are listed in Table 1.

Age of onset

The impact of the age of SAD onset on treatment outcome was investigated in four studies. In one of them, no impact of age of onset on the response of 57 patients treated with group CBT was found.[17] In the second trial with 204 patients treated with sertraline or placebo, patients with late-onset (≥ 19 years) generalized SAD tended to have a better response to treatment with sertraline than those with early-onset generalized SAD.[18] Accordingly, in two additional studies; e.g., one including 102 patients with generalized SAD submitted to individual or group CBT[19] and the other including 80 SAD patients treated with individual and group cognitive or interpersonal therapy,[20] early (childhood) onset emerged as a predictor of poor response to treatment.

Duration of illness

Duration of SAD was not associated with a worse therapeutic outcome in four studies, including trials with moclobemide,[21] brofaromine and fluvoxamine,[22] paroxetine,[23] and group CBT.[17] Only one placebo-controlled trial found baseline duration of generalized SAD to be a significant predictor of poor response to treatment (in this case, sertraline).[24] In this study, none of the independent variables were significant as predictors of response to placebo.

Severity

The impact of SAD severity on treatment outcome was analyzed in three studies.[22,23,25] Increased severity of symptoms predicted worse response in 30 patients treated with brofaromine or fluvoxamine (with higher Symptom Checklist-90 interpersonal sensitivity scores and heart rate predicting 92% of non-responders),[22] and in 76 patients submitted

Table 1 Studies describing the impact of different clinical characteristics on treatment outcomes of social anxiety disorder

Study	Design	Intervention	N	Clinical characteristics	Influence on response
Brown et al.[28]	Controlled clinical trial	CBTG ESTG PHE PLO	NI	Generalized subtype	Negative
Slaap et al.[22]	Controlled clinical trial	BROFARO FLUVO	15 15	Short duration of SAD Greater Severity Generalized subtype Family history	Neutral Negative Neutral Negative
Turner et al.[12]	Controlled clinical trial	Flooding ATE PLO	NI	Generalized subtype	Neutral
Versiani et al.[21]	Naturalistic	MCLO	93	Short duration of SAD Generalized subtype	Neutral Negative
Scholing et al.[25]	Open trial	CBTG and/or individual	73	Greater Severity	Negative
Van Ameringen et al.[24]	Controlled clinical trial	SERT PLO	NI	Short duration of SAD	Positive
Stein et al.[23]	Controlled clinical trial	PARO PLO	491 329	Short duration of SAD Greater Severity	Neutral Neutral
Van Ameringen et al.[18]	Controlled clinical trial	SERT PLO	NI	Early onset of SAD	Negative
Lincoln et al.[26]	Naturalistic	CBTG	287	Generalized subtype	Negative
Chen et al.[17]	Open trial	CBTG	57	Early onset of SAD Short duration of SAD Generalized subtype	Neutral Neutral Neutral
Dalrymple et al.[19]	Open trial	CBTG and/or individual	102	Early onset of SAD	Negative
Marom et al.[27]	Naturalistic trial	CBTG	219	Generalized subtype	Negative
Borge et al.[20]	Controlled clinical trial	COTG and individual IT individual and group	40 40	Early onset of SAD	Negative

ATE: Atenolol; BROFARO: Brofaromine; CBTG: Cognitive Behavior Therapy Group; ESTG: Educational Supportive Therapy group; FLUVO: Fluvoxamine; IT: Interpersonal Therapy; MCLO: Moclobemide; NI: Not Informed; PARO: Paroxetina; PLO: Placebo; SAD: Social Anxiety Disorder; SERT: Sertraline; PHE: Phenelzine; COTG: Cognitive Therapy In Group.

to individual or group CBT[25] (with greater impairment or Global Clinician rating of Social Phobia severity predicting a slight proportion [4-8%] of treatment outcome). In the third study,[23] the severity levels (according to the baseline scores on the Liebowitz Social Anxiety Scale) of 829 SAD patients did not predict differences in outcome after treatment with paroxetine or placebo.

Subtype

No differences in terms of response to treatment was found between generalized and non generalized SAD patients in three clinical trials: one article with brofaromine or fluvoxamine,[22] one involving group CBT,[17] and one comparing atenolol to exposure psychotherapy (EXP) with flooding.[12] However, in other four studies using group CBT,[26,27] moclobemide,[21] or a set of interventions (including group CBT, educational support therapy, phenelzine, and placebo pill),[28] generalized SAD patients exhibited worse response to treatment compared to non-generalized patients in the post-test. In one of these studies, the generalized subtype was characterized by a trend towards worse short-term response in group CBT, although this difference reached statistical significance after one-year of follow up.[26]

Family history

Only one article suggested that the presence of a family history of SAD predicts worse response to treatment with brofaromine or fluvoxamine in SAD patients.[22] Therefore, the relationship between family history and response to treatment should be considered relatively fragile at this moment.

Comorbidities

Studies describing the impact of different psychiatric comorbidities (including personality, anxiety and mood disorders, and substance abuse) on SAD treatment outcomes are depicted in Table 2.

Personality disorders

Eleven trials assessed the influence of avoidant personality disorder (PD) on treatment response of patients with SAD. In five of these studies, patients with SAD and avoidant PD displayed worse outcome after treatment (including moclobemide,[21] atenolol or EXP with flooding,[12] group CBT,[29] EXP,[13] and moclobemide or individual cognitive therapy)[30] compared to patients with SAD without avoidant PD. Nonetheless, in one of these studies,[30] this difference did not remain significant after 15 months of treatment.

In five additional articles, the comorbidity of SAD with avoidant PD did not predict differences in response to interventions with sertraline,[18] EXP,[14] individual or group CBT,[25] individual or group cognitive therapy, individual or group interpersonal therapy[20] and a set of interventions (including group CBT, educational support therapy, phenelzine and placebo pill).[28] Finally, in contrast to the results described above, a study with 295 generalized SAD patients reported that patients with avoidant personality disorder (APD) had exhibited greater changes in SAD early in treatment than those without APD.[15]

Two studies reported that other types of PD (e.g., obsessive-compulsive and dependent) had no influence in response of 84 SAD patients who received either atenolol or EXP with flooding treatment,[12] and 93 SAD patients who were treated with moclobemide.[21] Histrionic PD co-morbidity with SAD, on the other hand, had a negative impact on response to treatment with atenolol or EXP with flooding.[12]

Anxiety disorders

A study with 52 SAD patients treated with group CBT plus video feedback of exposures revealed that co-morbidity with any anxiety disorder was associated with a worse therapeutic outcome.[31] Similarly, the presence of simple phobia had a negative impact on treatment response of 84 patients with SAD treated with atenolol or EXP with flooding.[12] Finally, generalized anxiety disorder (GAD) was associated with worse treatment response of 93 patients with SAD treated with moclobemide,[21] and of 84 patients treated with atenolol or EXP with flooding.[12]

Mood disorders

The influence of comorbid mood disorders on the treatment outcome of patients with SAD was associated with mixed results. For instance, in at least three studies,[25,26,29] the presence of major depression was associated with worse response of SAD patients treated with group and individual CBT[25] or group CBT,[26,29] respectively. Similarly, comorbid dysthymia had a negative impact on response to treatment with atenolol or EXP with flooding[12] and with moclobemide.[21] However, in one of these articles, the negative influence of depression on the therapeutic outcome was not maintained in the 18-month follow up.[25]

In two trials[27,32] no difference was found in the post-test of SAD patients with comorbid depression treated with group CBT. However, in one of these studies,[27] patients with SAD and comorbid depression displayed an increased relapse rate after one year. On the other hand, the presence of previous episode of depression in patients treated with moclobemide did not predict any difference in treatment outcome.[21]

Alcohol abuse

In one of the studies described above,[21] the occurrence of alcohol abuse co-morbidity was by far the strongest predictor of worse therapeutic outcome in 93 SAD patients treated with moclobemide.

Sociodemographic characteristics

Studies describing the impact of different sociodemographic features (including age, gender, educational level, and marital status) on SAD treatment outcomes are listed in Table 3.

Age

According to several aforementioned studies, the patient's age did not predict the therapeutic response of SAD patients to sertraline,[18] moclobemide,[21] paroxetine,[23] brofaromine or fluvoxamine,[22] group CBT,[17,32] and group or individual CBT.[19]

Gender

Similarly, no impact of gender on treatment response of SAD patients was found in most trials reviewed above, including studies that used group CBT,[17] group or individual CBT,[19]

Table 2 Studies describing the impact of different comorbidities on treatment outcomes of social anxiety disorder

Study	Design	Intervention	N	Comorbidities	Influence on response
Brown et al.[28]	Controlled clinical trial	CBTG	NI	Avoidant PD	Neutral
		ESTG			
		PHE			
		PLO			
Turner et al.[12]	Controlled clinical trial	Flooding	NI	Avoidant PD	Negative
		ATE		Obsessive Compulsive PD	Neutral
		PLO		Dependent PD	Neutral
				Histrionic PD	Negative
				GAD	Negative
				Simple Phobia	Negative
				Dysthimia	Negative
Versiani et al.[21]	Naturalistic trial	MCLO	93	Avoidant PD	Negative
				Obsessive Compulsive PD	Neutral
				Dependent PD	Neutral
				GAD	Negative
				Dysthimia	Negative
				Previous Depression	Neutral
				Alcohol Abuse	Negative
Chambless et al.[29]	Open trial	CBTG	62	Avoidant PD	Negative
				Depression	Negative
Feske et al.[13]	Naturalistic trial	EXP	48	Avoidant PD	Negative
Van Velzen et al.[14]	Open trial	EXP	61	Avoidant PD	Neutral
Scholing et al.[25]	Open trial	CBTG and/or individual	73	Avoidant PD	Neutral
				Depression	Negative
Oosterbaan et al.[30]	Controlled clinical trial	COT individual	28	Avoidant PD	Negative
		MCLO	27		
		PLO	27		
Van Ameringen et al.[18]	Controlled clinical trial	SERT	NI	Avoidant PD	Neutral
		PLO			
Lincoln et al.[26]	Naturalistic trial	CBTG	287	Depression	Negative
Huppert et al.[15]	Controlled clinical trial	FLU	NI	Avoidant PD	Positive
		CBTG			
		FLU+CBTG			
		CBTG+PLO			
Marom et al.[27]	Naturalistic trial	CBTG	219	Depression	Neutral
Alfano et al.[32]	Controlled clinical trial	CBTG	NI	Depression	Neutral
		TNE			
Chen et al.[31]	Open trial	CBTG+VF	52	Anxiety Disorders	Negative
Borge et al.[20]	Controlled clinical trial	COTG and individual	40	Avoidant PD	Neutral
		IT individual and group	40		

ATE: Atenolol; CBTG: Cognitive Behavior Therapy Group; EXP: exposure psychotherapy; COT: Cognitive Therapy; COTG: Cognitive Therapy In Group; ESTG: Educational Supportive Therapy Group; FLU: Fluoxetine; GAD: Generalized Anxiety Disorder; IT: Interpersonal Therapy; MCLO: Moclobemida; NI: Not Informed; PD: Personality Disorder; PHE: Phenelzine; PLO: Placebo; SERT: Sertraline; TNE: Treatment not Specific; VF: Video feedback.

paroxetine,[23] moclobemide,[21] brofaromine or fluvoxamine.[22] In one naturalistic study, no difference regarding treatment outcomes was found when CGI scores of both genders were compared at the end-point after treatment with SSRIs and/or benzodiazepines.[16] However, male gender was associated with worse response of SAD patients to sertraline or placebo[18] and to group plus video feedback CBT.[31]

Educational/Marital status

Educational and marital status had no impact on the response of 57 SAD patients in group CBT in one study,[17] and of 102 patients treated with group or individual CBT in another one.[19]

Treatment characteristics

Studies describing the impact of different therapeutic features on the outcome of SAD (including history, duration and expectancy of current treatment, and group cohesion [in case of group therapy]) are listed in Table 4.

Previous treatment

In three aforementioned studies, previous treatment (either pharmacotherapy or psychotherapy) had no impact on the response of SAD patients to moclobemide,[21] brofaromine and fluvoxamine,[22] and in group CBT.[17]

Table 3 Studies describing the impact of different sociodemographic features the treatment outcomes of social anxiety disorder

Study	Design	Intervention	N	Sociodemographic characteristics	Effect on response
Slaap et al.[22]	Controlled clinical Trial	BROFARO FLUVO	15 15	Age Gender	Neutral Neutral
Versiani et al.[21]	Naturalistic trial	MCLO	93	Age Gender	Neutral Neutral
Stein et al.[23]	Controlled clinical Trial	PARO PLO	491 329	Age Gender	Neutral Neutral
Van Ameringen et al.[18]	Controlled clinical Trial	SERT PLO	NI	Age Female Gender	Neutral Positive
Chen et al.[17]	Open trial	CBTG	234	Age Gender Educational Marital status	Neutral Neutral Neutral Neutral
Dalrymple et al.[19]	Open trial	CBTG and/or individual	57	Age Gender Educational Marital status	Neutral Neutral Neutral Neutral
Menezes et al.[39]	Naturalistic trial	SSRI and/or BENZO	34	Gender	Neutral
Alfano et al.[32]	Controlled clinical Trial	CBTG TNS	NI	Age	Neutral
Chen et al.[31]	Open trial	CBTG+VF	80	Male Gender	Negative

BENZO: Benzodiazepine; BROFARO: Brofaromine; CBTG: Cognitive Behavior Therapy Group; FLUVO: Fluvoxamine; MCLO: Moclobemide; NI: Not Informed; PARO: Paroxetine; PLO: Placebo; SERT: Sertraline; SSRI: selective serotonin reuptake inhibitors; TNS: Treatment not Specific; VF: Video feedback.

Table 4 Studies describing the impact of different treatment characteristics on treatment outcomes of social anxiety disorder

Study	Design	Intervention	N	Treatment characteristics	Effect on Response
Slaap et al.[22]	Controlled clinical trial	BROFARO FLUVO	15 15	Previous treatment	Neutral
Versiani et al.[21]	Naturalistic	MCLO	93	Previous treatment	Neutral
Chambless et al.[29]	Open trial	CBTG	62	Low expectancy regarding treatment effectiveness	Negative
Stein et al.[23]	Controlled clinical trial	PARO PLO	491 329	Short duration of treatment	Negative
Erwin et al.[33]	Controlled clinical trial	CBTG	234	Low expectancy regarding treatment effectiveness	Negative
Chen et al.[17]	Open trial	CBTG	57	Previous treatment Short duration of treatment	Neutral Neutral
Taube-Schiff et al.[35]	Open trial	CBTG	34	Group cohesion	Positive
Delsignore et al.[34]	Open trial	CBTG	49	Low expectancy regarding the therapist role	Neutral
Borge et al.[20]	Controlled clinical trial	COTG and individual IT individual and group	40 40	Low expectancy regarding treatment effectiveness	Negative

BROFARO: Brofaromine; CBTG: Cognitive Behavior Therapy Group; COTG: Cognitive Therapy in Group; FLUVO: Fluvoxamine; IT: Interpersonal Therapy; MCLO: Moclobemide; PARO: Paroxetine, PLO: Placebo.

Duration of treatment

In a study with 829 SAD patients,[23] treatment with paroxetine for 12 weeks was associated with increased response compared to treatment for only 8 weeks. Conversely, another study that used group CBT with a protocol of 11-20 sessions found that the number of treatment sessions did not predict response of 57 patients with SAD.[17]

Expectancy regarding treatment effectiveness

Low expectancy regarding treatment effectiveness and reduced confidence concerning treatment predicted worse response in studies that comprised 62[29] and 234 patients[33] with SAD assigned to group CBT, and 80 patients with SAD assigned to cognitive therapy or interpersonal therapy.[20]

Expectancy regarding the therapist role

In one study, the expectations of 49 SAD patients about the role of the therapist in their treatment did not have any influence on their response in group CBT in the short-term.[34] However, in the three-month follow up, patients who attributed greater responsibility for change to their therapists had worse therapeutic response.

Group cohesion in group CBT

The perception of group cohesion of individuals attending group CBT and its impact on treatment outcome were studied in 34 patients with SAD.[35] In this study, increases in group cohesion ratings over the course of treatment significantly predicted therapeutic response.

Discussion

The present work aimed at reviewing the overall profile of individuals with SAD who respond and not respond to standard treatment, with the ultimate purpose of contributing to future research on the development of more effective interventions.[36] We found that early onset, increased duration and severity of illness, presence of generalized subtype, positive family history of SAD, and male gender were all predictors of worse response to treatment in at least one study. Among these, early onset and severity of illness were the most replicated findings.

In terms of co-morbidity, major depression, dysthymia, generalized anxiety disorder, simple phobia, avoidant and histrionic PD, and alcohol abuse predicted negative responses to treatment in at least one trial. Among these conditions, anxiety disorders emerged as a predictor of poor therapeutic response in more than one study.

Finally, regarding treatment characteristics, low expectancy regarding treatment efficacy, high expectancy regarding the role of the therapist in treatment, and decreased group cohesion (in case of group cognitive behavioral treatment) were associated with worse therapeutic responses. Among the later, low expectancy regarding treatment efficacy was the most replicated finding.

Importantly, we found a handful of studies suggesting the association between early onset of SAD and poor response to treatment. While this finding provides some support to the view that the early-onset of SAD represents a valid subtype of SAD, with greater psychiatric comorbidity, higher levels of incapacitation, and worse prognosis,[19] there is still controversy on this subtype definition, as different studies used different age criteria for "early" or "late" onset. Previous reviews suggested that the unwelcome influence of both age at onset and severity of symptoms on treatment outcome holds true for other anxiety disorders.[37]

Furthermore, we also found some evidence that greater severity of social anxiety symptoms predicts decreased efficacy in the response of patients with SAD to different types of treatment (both pharmacotherapy and psychotherapy). This finding is particularly relevant when one considers that all studies reporting them focused their analysis on patients who completed treatment (and not on an intention-to-treat sample), thus suggesting that decreased treatment efficacy cannot be ascribed to the tendency that patients with more severe symptoms have to discontinue treatment more frequently.

Data supporting an effect of comorbid psychiatric disorders in SAD treatment response are mixed, particularly for depression. It is difficult to explain these findings because, while major depression and dysthymia could perpetuate and strengthen SAD patients negative beliefs about themselves, some of the SAD treatments (including SSRIs and cognitive re-structuring) may effectively treat some forms of depression, particularly those that are secondary. Accordingly, it is interesting to note that many of the comorbid conditions found to predict worse response of SAD to treatment (e.g., alcohol abuse,[21] specific phobia,[12] histrionic PD[12]) are not clearly responsive to treatment (e.g., antidepressants) themselves. It is worth noting that findings regarding the role of several comorbid conditions were assessed in only one study, which restrains us to consider these results as conclusive.

Finally, we also found that low expectancy regarding treatment effectiveness,[29] which might be related to comorbid depression,[38] was associated with worse response to treatment in different studies. Clearly, patients with SAD might believe that the treatment will not work in their case, that they will not be able to follow the therapeutic steps, or that another person will be totally responsible for his improvement. These cognitive distortions should be identified and managed early in the treatment.

Conversely, lower expectations about the role of the therapist were related to better treatment outcomes, particularly in the follow-up sessions.[34] Likewise, in one study, increased feelings of group cohesion between participants and therapist in group CBT was associated with better outcomes.[35] It would be interesting to test whether add-on strategies (aimed at increasing treatment expectancy, attributing responsibility for change to patients, and stressing the importance of group cohesion in group CBT) increase the effectiveness of treatment provided to patients with SAD.

Indeed, our review has a number of limitations. First, several sociodemographic and clinical variables associated with worse outcomes (e.g., previous treatment, dependent and obsessive compulsive PD comorbidity) had their relationship with outcome assessed by a very small number of studies. Second, as there is no current consensus on what should be the optimal criteria for treatment response in SAD, one should examine our results with caution.[12,25,29] It has been argued that the concept of response and remission in SAD must be multidimensional,[39] embracing the

reappraisal of the diagnosis,[40] social anxiety symptoms, and comorbid conditions.[36] Of note, none of the reviewed studies adopted such criteria. Third, there is a clear methodological heterogeneity among selected studies, including study design,[15,17,23] type of intervention,[21,25-27,29,32] and duration of treatment (varying from five or seven days[26] to two years).[21] Accordingly, one must consider that, regardless of treatment, longer follow-ups are usually associated with substantial reduction in anxiety symptoms, a phenomenon that can be explained by the tendency of SAD individuals to orientate their life choices so that anxiogenic situations become less prominent.[41]

Conclusion

The recent increase in the number of studies in the field of response and resistance in SAD is complicated by the difficulty of replicating and comparing these studies. Even when they are conducted with similar patients, treatment, and methods, a considerable variety of treatment response and resistance definitions is used.[25] As a consequence, the current sociodemographic and clinical profile of SAD patients who respond to treatment remains elusive, as it does not point to a very clear direction.

To date, early onset, severity of illness, comorbid anxiety disorders (particularly generalized anxiety disorder and simple phobia), and low expectancy regarding treatment efficacy emerged as potential correlates and/or predictors of low therapeutic response. Clearly, the field of treatment response needs conceptual and methodological redefinitions if it aims to lead to more solid results. A better knowledge about the profile of the significant proportion of SAD patients who remain resistant to treatment is important for discussing the emergence of novel therapeutic alternatives, both in terms of psychotherapy and pharmacotherapy.

Disclosure

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Anexo 2:

Second-generation antidepressants in Social Anxiety Disorder: meta-analysis of controlled clinical trials.

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REVIEW

Second-generation antidepressants in social anxiety disorder: meta-analysis of controlled clinical trials

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Abstract
Rationale A growing number of controlled clinical trials suggest that different second-generation antidepressants (SGA) may be effective in the treatment of social anxiety disorder (SAD).
Objectives The aim of the present study is to evaluate the effectiveness of SGA in SAD and to investigate possible differences in their efficacy.
Methods We performed a systematic review and meta-analysis of all double-blind, randomized, controlled clinical trials involving second-generation antidepressants in adult patients with SAD published on PubMed/MEDLINE, PsycINFO, and Current Controlled Trials databases until July 2009. Our analyses were based on changes in Liebowitz Social Anxiety Scale (LSAS), Clinical Global Impression (CGI), and standardized mean difference (SMD).
Results Twenty-seven controlled clinical trials, comprising ten different SGA, were selected. When comparing the reduction of LSAS scores, the group receiving active drugs showed a significantly greater reduction compared to those observed in the placebo group [pooled weighted mean −11.9 (IC 95% −14.5 to −9.4)]. The combined relative risk (RR) for the different drugs revealed a 62% increase in treatment response (final CGI ≤2) for those using SGAs, compared to those receiving placebo [RR 1.62 (95% CI 1.44–1.81)]. The combined SMD for the SGAs was −0.43 (IC 95% −0.49 to −0.37).
Conclusion Second-generation antidepressants are efficacious treatment for patients with SAD. However, our results do not suggest differences of efficacy among different drugs.

Keywords Anxiety · Drug · Social anxiety disorder · Social phobia · Pharmacological treatment · Second-generation antidepressants · Meta-analysis

Abbreviations

SGA	Second-generation antidepressants
SAD	Social anxiety disorder
LSAS	Liebowitz Social Anxiety Scale
CGI	Clinical Global Impression
SMD	Standard mean difference

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Introduction

Social anxiety disorder (SAD) is a prevalent, chronic, and disabling disorder (Westenberg 1998). A recent epidemiological study, the *National Comorbidity Survey Replication*, found a lifetime prevalence of SAD of 12.1% and a 12-month prevalence of 4.5% (Kessler et al. 2005), placing it among the most common psychiatric disorders and making it the most prevalent anxiety disorder. Given the early onset of symptoms (typically in adolescence) and the chronic course, SAD is associated with impairment in the development of interpersonal relationships (Ballenger et al. 1998) and significant functional impairment, including occupational, academic, and social dysfunction (Katzelnick and

Greist 2001). The diagnosis of SAD is associated with higher unemployment rates, lower educational levels, and greater frequency of single or divorced individuals (Wittchen et al. 1999).

SAD is highly comorbid with other mental disorders (Lecrubier 1998; Lydiard 2001). Studies estimate that 50% to 80% of patients with SAD have at least one additional psychiatric disorder (Ballenger et al. 1998; Wittchen and Fehm 2001). Indeed, SAD often precedes the onset of comorbid disorders (Kessler et al. 1999) and is believed to be a risk factor for the development of other mental diseases like major depression and substance abuse (Stein and Stein 2008).

Considering the high prevalence rates and the dysfunction associated with SAD, effective treatment of these patients has great public health value (Blanco et al. 2003). Accordingly, the effectiveness of different types of drugs has been studied in SAD. At first, clinical trials pointed out the efficacy of irreversible monoamine oxidase inhibitors (MAOIs; Gelernter et al. 1991; Versiani et al. 1992) and tested the value of beta-blockers (Liebowitz et al. 1992). Later, the usefulness of reversible MAOIs (van Vliet et al. 1992) and high-potency benzodiazepines (Davidson et al. 1993; Versiani et al. 1997) was also demonstrated. More recently, clinical trials have focused on drugs that selectively block serotonin and/or noradrenalin transporters [i.e., second-generation antidepressants (SGAs)], antagonize both serotonin and dopamine receptors [i.e., atypical antipsychotics (Barnett et al. 2002; Vaishnavi et al. 2007)], or act as GABAergic agonists [i.e., anticonvulsivants (Pande et al. 1999)].

The SGAs represent the most studied and prescribed agents for the treatment of SAD. Indeed, although previous clinical trials, systematic reviews, and meta-analytic studies compared the efficacy of different SGAs in patients with SAD, they were unable to point out any comparative superiority of any single drug in the treatment of this condition (Blanco et al. 2003; Gould et al. 1997; Hidalgo et al. 2001; Hedges et al. 2007; Hansen et al. 2008; Ipser et al. 2008; Hedges et al. 2009). Therefore, important questions regarding the pharmacotherapy of SAD remain unanswered, challenging the clinical practice and showing the need of further investigation.

Unfortunately, the heterogeneous design of the clinical trials and the biased selection of studies that employ the same assessment instrument for SAD symptoms, e.g., Liebowitz Social Anxiety Scale (LSAS), determined the exclusion of many potentially relevant controlled clinical trials in previous meta-analyses, a strategy that may have reduced the possibility of finding potential differences between different SGAs or classes of SGAs. The standardized mean difference (SMD) method (Deeks et al. 2001), a statistical approach in which the absolute score values are converted into number of standard deviations, allows the comparison of clinical trials using different rating scales for the assessment of change.

In this meta-analysis, our aim was to estimate the effect size of different SGAs and to compare their efficacy in order to clarify whether any drug or group of drugs was more effective in the treatment of SAD. To do so, we adopted three different approaches, i.e., the measurement of changes in the LSAS, in the Clinical Global Impression (CGI), and to capture a greater number of clinical trials, the SMD.

Methods

We searched relevant studies in PubMed, PsycINFO, and Current Controlled Trials databases combining the terms (social phobia OR social anxiety disorder) AND (clinical trial OR treatment OR placebo), in order to identify double-blind, placebo-controlled randomized drug trials performed in patients with SAD (social phobia). Reference lists of retrieved articles were also explored. Our searches had no language restriction and covered studies published until July 2009.

Controlled clinical trials involving pharmacological treatment in monotherapy compared with placebo and including adult patients (>18 years) diagnosed with SAD according to DSM-III or later editions criteria were selected. Clinical trials comparing more than one drug were included when at least one comparison group received only placebo. The first and second authors (GB and EC) retrieved data from each study. Authors were contacted in order to obtain information missing in the articles.

Statistical analysis

Analyses were stratified according to the type of drug used. Categorical and continuous outcomes were evaluated. Firstly, we estimated the pooled measures using fixed-effects models. In the presence of heterogeneity, we used random effects models.

Continuous data (scores)

We decided to combine the difference of mean score changes (final-baseline) between the placebo and the intervention groups. When the studies used the same scale, we calculated the weighted mean differences (Deeks et al. 2001). When the scales were different, we used the standardized mean differences (Deeks et al. 2001), which transform the absolute values of scores into numbers of standard deviations.

Differences in means were calculated so that values less than zero indicated greater reduction in scores (final-baseline) in the intervention group. In some studies, there was no information about the standard deviation (SD) of the scores changes (baseline-final), but only of the baseline and final scores. In this case, we used the formula presented by Higgins and colleagues (Higgins et al. 2008):

$$SD_{change} = \sqrt{SD^2_{baseline} + SD^2_{final} - (2 \times corr \times SD_{baseline} \times SD_{final})}$$

The correlation value for the above formula (*corr*) was estimated from studies that had standard deviation for both baseline and final scores and for score changes (final-baseline) using the formula:

$$corr = \frac{SD^2_{baseline} + SD^2_{final} - SD^2_{change}}{2 \times SD_{baseline} \times SD_{final}}$$

The impact of these estimates was evaluated through sensitivity analysis, comparing the combined measures with and without the presence of these studies. Two studies reported values of standard deviations whose magnitude was more compatible with those of standard error (Muehlbacher et al. 2005; van Ameringen et al. 2001). The authors were contacted but did not clarify the issue. Simulations were made using these values either as standard deviation or as standard error. Ultimately, data analysis assumed that these were standard errors, since the results were more consistent with those observed in other studies.

Categorical data (responders vs nonresponders)

In this case, estimates of studies' relative risk were combined. This parameter was constructed so that values greater than one indicate a greater proportion of improvement in the intervention group.

Heterogeneity analysis

The heterogeneity evaluation of effects was firstly conducted with the visual inspection of confidence intervals in the "forest plots" and with the I^2 index (Higgins et al. 2003). Values above 30% were considered indicative of heterogeneity between the studies. This assessment was completed with the chi-square heterogeneity test. The sensitivity analysis was also used to assess the impact of discrepant results (outliers) on the combined values.

Indirect comparisons

In order to contrast the efficacy between different drugs, "indirect comparisons" were performed using the methodology proposed by Bucher et al. (1997). This method can be applied when all trials use a common control group (control group as a standardizing factor), and has the advantage of preserving the randomization of the originally assigned patient groups. In our particular review, all studies involved monotherapy compared with placebo.

Results

Twenty-seven double-blind, placebo-controlled, randomized clinical trials, comprising ten different SGAs, were included in the analysis (Fig. 1). Of note, the search performed in the Current Controlled Trials database did not result in the inclusion of any study not found in PubMed or PsycINFO. When two substances were compared with placebo in different arms of the same clinical trial, both of the medications were included in our evaluation. In three studies, where fixed doses of the active drug were compared (Liebowitz et al. 2002; Lader et al. 2004; Stein et al. 2005), each one of the different arms was analyzed separately. The 27 selected studies included 21 comparisons involving selective serotonin reuptake inhibitors and eight comparisons involving other SGA. The characteristics of these studies are depicted in Table 1.

There were three head-to-head trials comparing two active drugs. In the first one (Lader et al. 2004), fixed doses of escitalopram (5, 10, and 20 mg) were compared with paroxetine (20 mg). Statistically significant greater reduction on LSAS score was reported for patients on higher doses (20 mg) of escitalopram compared with paroxetine (20 mg) in the observed cases analysis. However, the

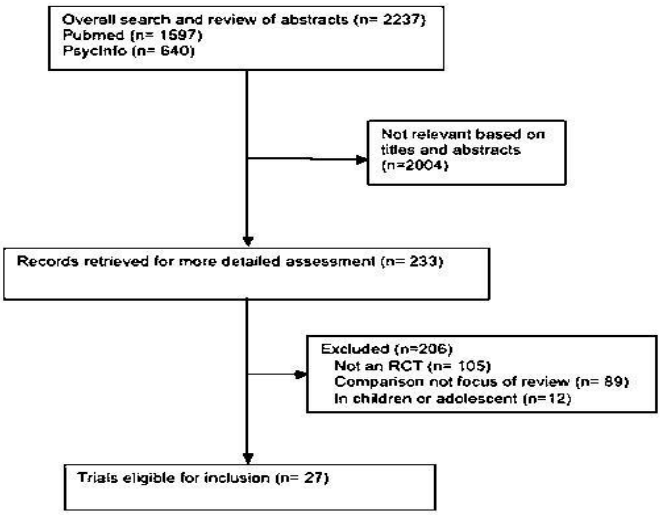

Fig. 1 Flowchart of study selection

Table 1 Clinical trials included in revision

Drug	Clinical trial	Mean dose (mg/day)	Year	Sample size	Duration (weeks)	Percentage of female	Mean baseline LSAS	Scale
Fluvoxamine	van Vliet (van Vliet et al. 1994)	150	1994	30	12	56.7	68.1	LSAS
	Stein (Stein et al. 1999)	202	1998	92	12	35.8	81.0	LSAS
	Asakura (Asakura et al. 2007)	150–300	2007	265	10	32.4	87.9	LSAS
Fluvoxamine CR	Davidson (Davidson et al. 2004a)	174	2004	279	12	35.8	90.1	LSAS
	Westenberg (Westenberg et al. 2004)	209	2004	300	12	52.3	94.8	LSAS
Paroxetine	Stein (Stein et al. 1998)	37	1998	187	12	56.7	78.0	LSAS
	Baldwin (Baldwin et al. 1999)	35	1999	290	12	54.1	87.6	LSAS
	Algullander (Allgulander 1999)	–	1999	92	12	47.8	70.4	LSAS
	Liebowitz[b] (Liebowitz et al. 2002)	20	2002	384	12	41.4	79.8	LSAS
		40					77.5	
		60					76.9	
	Algullander[a] (Allgulander et al. 2004a)	44.2	2004	434	12	52	83.9	LSAS
	Lader[a] (Lader et al. 2004)	20	2004	839	12	53	94.1	LSAS
	Liebowitz[a] (Liebowitz et al. 2005a)	46	2005	440	12	46.4	87.2	LSAS
Paroxetine CR	Lepola (Lepola et al. 2004)	12.5–37.5	2004	370	12	50	94.1	LSAS
Sertraline	Katzelnick (Katzelnick et al. 1995)	133	1995	12	10	33.3	65.5	LSAS
	Blomhoff (Blomhoff et al. 2001)	–	2001	387	24	60.4	–	SPS
	van Ameringen (van Ameringen et al. 2001)	146.5	2001	204	20	44.1	–	MFQ –SP
	Liebowitz (Liebowitz et al. 2003)	158.8	2003	415	12	40.4	91.3	LSAS
Fluoxetine	Kobak (Kobak et al. 2002)	50	2002	60	14	58	81.9	LSAS
	Davidson (Davidson et al. 2004b)	43.6	2004	295	14	46.4	–	BSPS
Escitalopram	Lader[a]; [b] (Lader et al. 2004)	5	2004	839	12	53	94,3	LSAS
		10					92,4	
		20					94	
	Kasper (Kasper et al. 2005)	17.6	2005	358	12	45.5	96.3	LSAS
Citalopram	Furmark (Furmark et al. 2005)	40	2005	36	6	52.8	–	CGI
Venlafaxine	Stein[b] (Stein et al. 2005)	75	2004	386	28	34.3	–	LSAS
		150–225						
	Algullander[a] (Allgulander et al. 2004b)	192.4	2004	434	12	52	83.2	LSAS
	Rickels (Rickels et al. 2004)	152–178	2004	272	12	42.5	87.3	LSAS
	Liebowitz (Liebowitz et al. 2005b)	75–225	2005	271	12	45.3	91	LSAS
	Liebowitz[a] (Liebowitz et al. 2005a)	201.7	2005	440	12	46.4	86.2	LSAS
Mirtazapine	Muehlbacher (Muehlbacher et al. 2005)	30	2005	66	10	100	71.9	LSAS
Nefazodone	van Ameringen (van Ameringen et al. 2007)	494	2007	105	14	52.3	88.6	LSAS
Hypericum	Kobak (Kobak et al. 2005)	1676	2005	40	12	52.5	76.9	LSAS

LSAS Liebowitz Social Anxiety Scale; *SPS* Social Phobia Scale; *MFQ-SP* Marks Fear Questionnaire-Social Phobia; *BSPS* Brief Social Phobia Scale; *CGI* Clinical Global Impression

[a] Head-to-head trial

[b] Fixed dose trial

difference was not statistically significant in the intention-to-treat analysis. The other two head-to-head trials compared paroxetine and venlafaxine (Allgulander et al. 2004a; Liebowitz et al. 2005a). Mean doses of the substances were comparable in both trials, and no statistically significant differences in the reduction of LSAS scores were reported between venlafaxine and paroxetine. The numbers of responders [characterized by a rating of 1 ("very much" improved) or 2 ("much" improved) on the CGI-I] did not differ significantly between the groups in any of the trials.

Table 2 Weighted mean differences (WMD), 95% confidence intervals, and weights of the studies, for drug

Drug/trial	WMD	95% confidence interval	% Weight
Paroxetine (I^2=0.00)			
Stein 1998	−16.00	−23.33–8.67	11.63
Baldwin 1999	−13.80	−21.42–6.18	10.75
Liebowitz 2002 20 mg	−19.10	−27.68–10.52	8.50
Liebowitz 2002 40 mg	−9.50	−18.15–0.85	8.35
Liebowitz 2002 60 mg	−10.20	−18.82–1.57	8.40
Algullander 2004	−16.30	−23.03–9.56	13.78
Lepolla 2004	−13.10	−18.02–8.18	25.83
Liebowitz 2005	−17.00	−24.00–10.00	12.75
Venlafaxine (I^2=0.00)			
Stein 2004 75 mg	−14.60	−23.25–5.95	12.08
Stein 2004 150 mg	−14.10	−22.60–5.60	12.52
Algullander 2004	−16.99	−23.57–10.41	20.85
Rickels 2004	−11.71	−18.90–4.524	17.50
Liebowitz 2005 (JCP)	−12.32	−19.21–5.43	19.06
Liebowitz 2005 (AGP)	−12.80	−19.89–5.71	17.99
Fluvoxamine (I^2=0.00)			
Stein 1998	−14.20	−22.81–5.59	16.38
Davidson 2004	−13.80	−19.78–7.82	33.90
Westenberg 2004	−8.80	−15.88–1.72	24.20
Asakura 2006	−8.10	−14.99–1.20	25.52
Nefazodone (I^2=NA)			
van Ameringen 2007	−8.60	−18.89–1.69	100.00
Hypericum (I^2=NA)			
Kobak 2005	1.75	−13.04–16.54	100.00
Mirtazapine (I^2=NA)			
Muehlbacher 2005	−20.20	−44.00–3.60	100.0
Escitalopram (I^2=NA)			
Kasper 2005	−7.50	−13.39–1.61	100.0

LSAS Liebowitz Social Anxiety Scale, I^2 Variation in WMD attributable to heterogeneity, *NA* Not applicable (only one trial)

All scores were obtained by LSAS. Weights were estimated by random effects model

LSAS score changes

The efficacy of different medications was initially assessed considering the LSAS score reduction (comparing the baseline scores with the final scores of the LSAS). In this first meta-analysis, 17 studies, comprising seven different drugs, were included, allowing 22 comparisons with placebo (Table 2 and Fig. 2).

When LSAS scores in the SGAs and placebo groups were compared, the weighted mean reduction from baseline

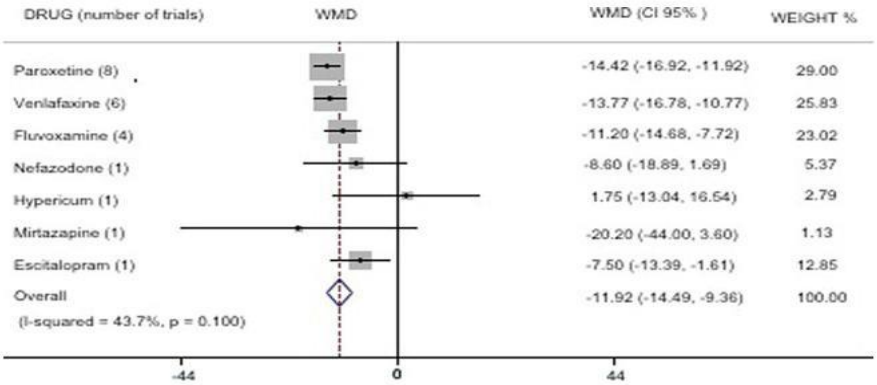

Fig. 2 Forest plot of the WMD for the seven drugs. Weights were estimated by random effects model

scores was 14.4 points larger for paroxetine, 13.8 points for venlafaxine, 11.2 points for fluvoxamine, and 8.6 points for nefazodone. Escitalopram, *Hypericum perforatum*, and mirtazapine were included in the analysis with one study each. The group using citalopram showed a 7.5 points reduction in comparison with the control group. Differences were not statistically significant in the mirtazapine and in the *H. perforatum* groups. The combined weighted mean difference for the seven drugs was −11.9 points (IC 95% –14.5 to −9.4; Fig. 2).

Although the estimates of weighted mean difference for paroxetine, venlafaxine, and fluvoxamine against placebo were different, indirect comparisons were performed to contrast the effects of the main three drugs showed in

Table 3 RR for symptoms improvement, 95% confidence intervals, and weights of the studies, by drug

Drug/trial	RR	95% confidence interval	% Weight
Paroxetine (I^2=55.8%)			
Stein 1998	2.34	1.55–3.52	7.89
Baldwin 1999	2.06	1.59–2.67	12.31
Algullander 1999	8.45	3.24–22.03	2.13
Liebowitz 2002 20 mg	1.60	1.08–2.35	8.40
Liebowitz 2002 40 mg	1.63	1.11–2.40	8.43
Liebowitz 2002 60 mg	1.52	1.03–2.25	8.27
Algullander 2004	1.86	1.44–2.42	12.23
Lader 2004	1.44	1.21–1.73	15.30
Lapolla 2004	1.87	1.46–2.41	12.55
Liebowitz 2005	1.73	1.34–2.23	12.49
Venlafaxine (I^2=0.00)			
Stein 2004 75 mg	1.73	1.30–2.31	16.18
Stein 2004 150 mg	1.74	1.31–2.32	16.28
Algullander 2004	1.94	1.50–2.50	19.97
Rickels 2004	1.48	1.10–1.98	15.17
Liebowitz 2005 (JCP)	1.47	1.07–2.02	12.89
Liebowitz 2005 (AGP)	1.62	1.25–2.11	19.51
Fluvoxamine (I^2=63.4%)			
van Vliet 1994	7.00	0.98–50.16	2.88
Stein 1998	1.92	1.02–3.62	16.58
Davidson 2004	2.06	1.32–3.20	23.10
Westenberg 2004	1.09	0.85–1.40	30.92
Asakura 2006	1.48	1.04–2.11	26.53
Escitalopram (I^2=0.00)			
Lader 2004 5 mg	1.38	1.15–1.65	27.46
Lader 2004 10 mg	1.32	1.09–1.59	26.27
Lader 2004 20 mg	1.42	1.19–1.70	28.53
Kasper 2005	1.39	1.11–1.74	17.73
Sertraline (I^2=0.00)			
Blomhoff 2001	1.69	1.07–2.65	20.30
van Ameringen 2001	1.83	1.22–2.73	25.70
Liebowitz 2003	1.80	1.36–2.37	54.01
Fluoxetine (I^2=0.00)			
Kobak 2002	1.33	0.66–2.69	29.28
Davidson 2004	1.61	1.02–2.52	70.72
Nefaxodone (I^2=NA)			
van Ameringen 2007	1.33	0.70–2.53	100.00
Citalopram (I^2=NA)			
Furmak 2005	6.00	0.84–42.59	100.00

I^2 Variation in RR attributable to difference between trials, *NA* Not applicable (only one trial)

Weights were estimated by random effects model

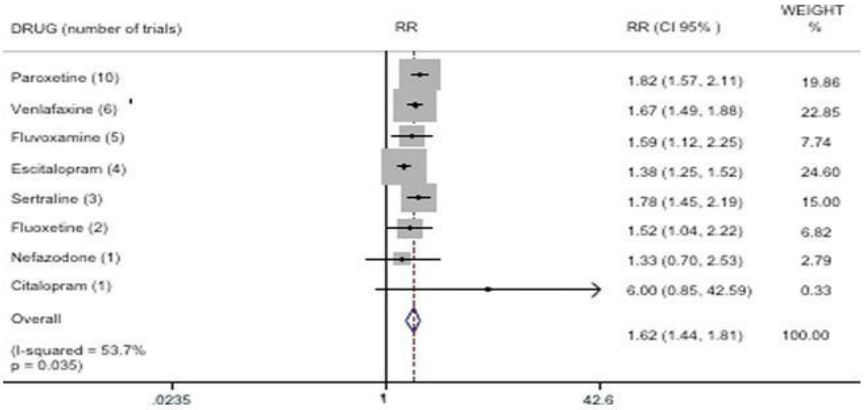

Fig. 3 Forest plot of the RR for the eight drugs. Weights were estimated by random effects model

Fig. 2. The mean difference and respective 95% confidence intervals were:

1. Paroxetine vs venlafaxine: −0.6 (−4.5 to 3.3).
2. Paroxetine vs fluvoxamine: −3.2 (−7.5 to 1.1).
3. Venlafaxine vs fluvoxamine: −2.6 (−7.2 to 2.0).

As all confidence intervals included the null value (zero), we could not conclude on the superiority of one drug over the other based on the weighted mean difference. Furthermore, sertraline could not be included in this analysis since the four studies investigating this drug employed three different scales.

CGI outcome (responders vs non responders)

Table 3 describes relative risks (RR) according to the CGI score in 24 different trials comprising eight drugs that allowed 32 comparisons with placebo. In this analysis, we considered as responders those patients with CGI-I scores ≤2 in the final evaluation. The combined RR for the different drugs (Fig. 3) was 1.62, which represents an increase of 62% in the response rate among the patients receiving SGA, in comparison with those receiving placebo.

In the paroxetine and fluvoxamine groups, we observed inconsistency between the findings of individual studies, with the I^2 statistic indicating moderate heterogeneity (I^2 >50%). In the paroxetine group, this inconsistency was due mainly to the study by Algullander and colleagues (Allgulander 1999), while for the fluvoxamine group, the same resulted from the inclusion of the study by van Vliet et al. (van Vliet et al. 1994). Both studies have wide confidence intervals (low precision) due to the small size of their samples and had little influence on the pooled estimates of efficacy (weight less than 3% in the pooled RR). The only included study evaluating citalopram showed a very high RR, but with very low accuracy because of the small sample size. The withdrawal of the study of citalopram did not alter these results, given the negligible weight of this study in the combined RR.

There was significant symptom improvement in the paroxetine, venlafaxine, fluvoxamine, sertraline, fluoxetine, and escitalopram groups. Compared to placebo, the CGI

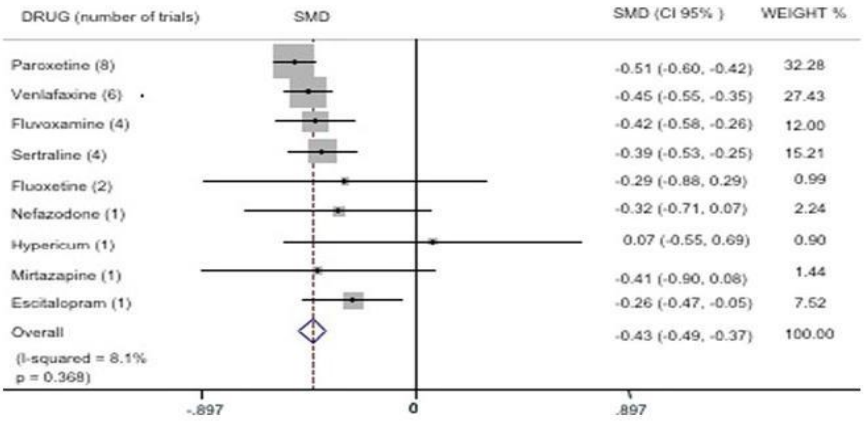

Fig. 4 Forest plot of the SMD for the nine drugs. Weights were estimated by random effects model

response rate was statistically significant for paroxetine (82%), venlafaxine (67%), fluvoxamine (59%), escitalopram (38%), sertraline (78%), and fluoxetine (52%). When we used indirect comparisons for these drug, we found that escitalopran presented less effect compared to paroxetine (RR=1.32; 95% CI 1.10–1.57), venlafaxine (RR=1.21; 95% CI 1.04–1.41), and sertraline (RR=1.29; 95% CI 1.03–1.62). No statistically significant differences were found for the other indirect comparisons. Escitalopram low efficacy accounted for the moderate heterogeneity observed among the different substances (I^2=53.7%). Withdrawing this drug from the analysis made the antidepressants efficacy rise from 62% to 71%, suggesting that escitalopram has the lowest efficacy among the four substances.

Different scales score changes (SMD)

In order to include trials in which different scales were used, the SMD was calculated, converting absolute score values of different rating scales into number of standard

Table 4 SMD, 95% confidence intervals, and weights of the studies, by drug

Drug/trial	SMD	95% confidence interval	% Weight
Paroxetine (I^2=0.00)			
Stein 1998	−0.63	−0.92–0.33	9.40
Baldwin 1999	−0.42	−0.65–0.18	14.94
Liebowitz 2002 20 mg	−0.63	−0.92–0.34	9.64
Liebowitz 2002 40 mg	−0.31	−0.60–0.03	9.90
Liebowitz 2002 60 mg	−0.33	−0.62–0.05	9.98
Algullander 2004	−0.59	−0.84–0.34	13.14
Lepolla 2004	−0.54	−0.75–0.33	18.82
Liebowitz 2005	−0.57	−0.81–0.33	14.18
Venlafaxine (I^2=0.00)			
Stein 2004 75 mg	−0.41	−0.66–0.17	16.31
Stein 2004 150 mg	−0.41	−0.65–0.16	16.32
Algullander 2004	−0.63	−0.87–0.38	16.12
Rickels 2004	−0.40	−0.64–0.15	16.57
Liebowitz 2005 (JCP)	−0.43	−0.67–0.18	17.17
Liebowitz 2005 (AGP)	−0.43	−0.66–0.19	17.52
Fluvoxamine (I^2=30.7%)			
Stein 1998	−0.67	−1.09–0.25	12.55
Davidson 2004	−0.54	−0.78–0.30	29.39
Westenberg 2004	−0.28	−0.51–0.05	31.27
Asakura 2006	−0.32	−0.58–0.06	26.80
Sertraline (I^2=0.00)			
Katzelnick 1995	−0.85	−2.04–0.34	1.84
Blomhoff 2001	−0.29	−0.58–0.00	31.11
van Ameringen 2001	−0.55	−0.85–0.26	23.03
Liebowitz 2003	−0.35	−0.55–0.15	67.06
Fluoxetine (I^2=71.9%)			
Kobak 2002	0.03	−0.47–0.54	45.74
Davidson 2004	−0.57	−0.94–0.20	54.26
Nefazodone (I^2=NA)			
van Ameringen et al. 2007	−0.32	−0.71–0.07	100.00
Hypericum (I^2=NA)			
Kobak et al. 2005	0.07	−0.55–0.69	100.00
Mirtazapine (I^2=NA)			
Muehlbacher 2005	−0.41	−0.90–0.08	100.0
Escitalopram (I^2=NA)			
Kasper et al. 2005	−0.26	−0.47–0.05	100.0

I^2 Variation in SMD attributable to heterogeneity, *NA* Not applicable (only one trial)

SMD was standardized by the respective standard deviations. Weights were estimated by random effects model

deviations. In this analysis, 23 studies were included, comprising nine different drugs allowing 28 comparisons with placebo (Fig. 4 and Table 4).

Comparing baseline scores with final scores in antidepressant and placebo groups, the mean reduction achieved by the group using paroxetine was 0.5 standard deviations greater than the one of the placebo group. The reduction of the groups receiving venlafaxine, fluvoxamine, and sertraline was approximately 0.4 standard deviations. In the citalopram group, this value was around 0.3 standard deviations. Although the paroxetine group showed the greatest reduction in the symptoms score, we could not assert that this latter antidepressant is more effective than the others (p=0.24). Nefazodone, mirtazapine, and *Hypericum* had only one study each, and the differences compared with the placebo group were not statistically significant. The combined standardized mean difference for the seven drugs was −0.43 (IC 95% −0.49 to −0.37; Fig. 4).

In the group of studies with fluoxetine, we observed an inconsistency between the findings of individual studies, with the I^2 statistic indicating an important heterogeneity (I^2=72%). In fact, there were only two clinical trials evaluating this drug, and they presented conflicting results. The data described by Davidson and colleagues (Davidson et al. 2004b) are more consistent with those presented in most studies (Table 4).

Discussion

Our results support the effectiveness of most SGAs in the treatment of SAD, similar to what has been reported in other meta-analyses (Hedges et al. 2007; Hansen et al. 2008). Paroxetine, sertraline, fluvoxamine, escitalopram, and venlafaxine have shown, consistently, to be more effective than placebo. Citalopram, mirtazapine, and nefazodone have been evaluated in only one clinical trial, all with a small number of subjects, which may have contributed to the nondetection of the efficacy of these drugs. *H. perforatum*, also evaluated in a single trial, was not more effective than placebo. No studies with duloxetine and bupropion were identified in our review.

Fluoxetine was evaluated in two clinical trials that showed conflicting results, making difficult to conclusively assess its effectiveness. Accordingly, in a study conducted by Clark et al. (2003), not included in our analysis due to the absence of appropriate placebo control, the authors found that cognitive therapy was better than both self-exposure plus fluoxetine and self- exposure plus placebo, and the two last groups were found to be equally effective. Taken together, these studies suggest that the utility of fluoxetine in the treatment of SAD remains unclear.

Unfortunately, the SMD approach, aimed at included greater number of studies in our analyses and increasing the possibility of identifying differences between SGAs, did not result in any finding clearly divergent from the previous strategies that were solely based on either the LSAS or the CGI. In other words, it was not possible to identify a difference in efficacy among the various drugs when comparing the combined measures of each antidepressant. Although paroxetine showed higher means than the other drugs in the three analyses presented here, the differences were not statistically significant when compared with venlafaxine, fluvoxamine, and sertraline. Only escitalopram showed a somewhat lower performance, even when four studies were included (Fig. 4).

Of note, in only three studies, the effectiveness of different drugs was assessed directly in head-to-head trials. Studies comparing venlafaxine and paroxetine (Allgulander et al. 2004b; Liebowitz et al. 2005a) showed no difference in efficacy between these two substances. In a study by Lader et al. (Lader et al. 2004), comparing paroxetine and escitalopram, the highest dose of escitalopram (20 mg) was more effective than paroxetine (20 mg) in one analysis that took into account the reduction of LSAS. However, in the intention-to-treat analysis, there was no statistically significant difference between the drugs.

Some limitations of this review should be taken into account. There were relatively a few controlled clinical trials in the treatment of SAD, and some antidepressants have been evaluated in only one controlled clinical trial. In addition, the studies were quite heterogeneous, with various doses of active drug being used and variable duration of therapeutic intervention being employed (6 to 28 weeks). There were also a few studies evaluating fixed doses of SGA (Liebowitz et al. 2002; Lader et al. 2004; Stein et al. 2005), which makes it hard to conclusively assess whether higher doses are associated with higher response rates. Indeed, although there are a wide range of clinical trials and reviews showing the effectiveness of the SGA in the treatment of SAD, it is not possible to precisely identify the difference in efficacy among the different substances.

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