Treatment-resistant anxiety disorders: social phobia, generalized anxiety disorder and panic disorder

Resistência ao tratamento nos transtornos de ansiedade: fobia social, transtorno de ansiedade generalizada e transtorno do pânico

Gabriela Bezerra de Menezes,[1] Leonardo F Fontenelle,[1] Sara Mululo,[1] Márcio Versiani[1]

Abstract

Objectives: *Anxiety disorders are common psychiatric conditions that cause significant disability, poor quality of life and enormous social cost. Although treatments with demonstrable efficacy are available a great number of patients fail to respond or remains with clinically significant residual symptoms after treatment. The objective of this study is to review aspects related to treatment resistance and pharmacological strategies to deal with anxiety disorders resistant to treatment.* ***Method:*** *Narrative review.* ***Results:*** *We discuss conceptual aspects related to treatment resistance or refractoriness, predictors of poor treatment outcome, and finally, some strategies to deal with anxiety disorders (including social anxiety disorder, generalized anxiety disorder and panic disorder) that do not respond to standard therapeutic interventions.* ***Conclusion:*** *Treatment resistance in anxiety disorders remains a challenge to clinical practice going from non standardized concepts of response and resistance to a paucity of controlled studies concerning therapeutic strategies.*

Descriptors: *Social phobia; Psychopharmacology; Panic disorder; Generalized anxiety disorder; Drug resistance*

Resumo

Objetivos: *Os transtornos de ansiedade são condições psiquiátricas prevalentes que determinam importante prejuízo funcional, piora na qualidade de vida do indivíduo e um enorme custo social. Embora diversas medicações eficazes para os transtornos de ansiedade encontrem-se disponíveis, um número significativo de pacientes não responde adequadamente ao tratamento e muitos permanecem com sintomas residuais clinicamente significativos. O objetivo deste estudo é rever aspectos relacionados à resistência ao tratamento e estratégias farmacológicas no manejo dos transtornos de ansiedade resistentes ao tratamento.* ***Método:*** *Revisão narrativa.* ***Resultados:*** *São discutidos os diversos aspectos conceituais relacionados à resistência ao tratamento, os possíveis preditores de resistência e, finalmente, algumas estratégias a serem utilizadas no manejo dos transtornos de ansiedade (incluindo transtorno de ansiedade social, transtorno de ansiedade generalizada e transtorno do pânico) que não respondem às abordagens terapêuticas convencionais.* ***Conclusão:*** *A resistência ao tratamento ainda é um desafio para a prática clínica que começa em conceitos não operacionalizados de resposta e resistência e termina na escassez de estudos controlados sobre estratégias de tratamento nesse último cenário clínico.*

Descritores: *Fobia social; Psicofarmacologia; Transtorno do pânico; Transtorno de ansiedade generalizada; Resistência a drogas*

[1] Anxiety and Depression Program, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (IPUB/UFRJ), Rio de Janeiro (RJ), Brazil

Correspondence
Gabriela Bezerra de Menezes
Rua Projetada 32-1 - São Francisco
24360-490 Niterói, RJ, Brazil
E-mail: menezesg@globo.com

Financing: None
Conflict of interest: None

Introduction

Different types of anxiety disorders are characterized by the presence of chronic anxiety symptoms that are clinically significant[1] and are part of the most prevalent group of psychiatric disorders.[2] In the beginning of the 90s, the National Comorbidity Survey[3] demonstrated a 24.9% prevalence rate of anxiety disorders throughout life, and the social anxiety disorder (SAD) was the most frequent one, with a 13.3% prevalence rate. In the same study, generalized anxiety disorder (GAD) and panic disorder (PD) presented prevalence rates of 5.1 and 3.5%, respectively, throughout life.[3]

Anxiety disorders are responsible for a significant social cost due to individual suffering, as well as indirect social costs.[4] There is a huge impact on the health system not only because of the expenses with the treatment, but also because of the more frequent search for medical care caused by the physical symptoms resulting from anxiety.[5]

Patients with anxiety disorders exhibit a significant reduction in their quality of life, less productivity, higher morbidity and mortality, and higher rates of comorbidity.[6] Part of these huge direct and indirect social costs can become even more significant due to the fact that it is a group of disorders typically underdiagnosed, underevaluated, and, often, inadequately treated.[4] Although there are several therapeutic strategies available for the treatment of anxiety disorders, the management of patients who do not respond adequately to the treatment remains a challenge in the clinical practice. Some authors compare the decrease in productivity and quality of life of patients with severe or resistant anxiety disorders to those of patients with schizophrenia.[5] Structured studies regarding resistance in the anxiety disorders, however, are still rare and non-conclusive.

In the present study, we intend to review 1) several conceptual aspects related to treatment resistance; 2) possible resistance predictors; and 3) pharmacological strategies in the management of treatment-resistant SAD, GAD and PD.

Treatment resistance

Several randomized, double-blind, placebo-controlled clinical trials[7] and meta-analysis studies have demonstrated the efficacy of the antidepressants for SAD,[8] PD[9] and GAD.[10] The serotonin selective reuptake inhibitors (SSRI) are considered the first-choice treatment for these three disorders in clinical algorithms and guidelines. Serotonin and noradrenaline reuptake inhibitors, high-potency benzodiazepines and some anticonvulsant agents also have demonstrated to be efficient.[7] In clinical trials, response rates of 40 to 70% and remission rates of 20 to 47% are described.[11] Resistance to the pharmacological treatment (i.e., no response or insufficient response) affects about one out of three patients with anxiety disorders.

Although the treatment-resistant anxiety disorders are the focus of an increasing number of studies, many questions have not been answered yet, the first of them being the concept of therapeutic resistance itself. If in the depressive disorders there are debates regarding the ideal definitions for response, remission, and resistance to treatment[12] (refer to the study by Vieira-Machado and Soares in the issue), with regard to the anxiety disorders this is even a more complex problem. The reason for such a complexity is that a decrease or absence of anxiety does not necessarily mean response or symptom remission, as it can be seen in patients who effectively avoid the phobic stimuli. The presence of anxiety is not a synonym of resistance or refractoriness either, since it can express inadequate treatment or normal response to an environmental stress factor.[5]

In several studies, the criteria that characterize the treatment resistance of the subject with SAD, PD or GAD are not mentioned[13] or are not very accurate, including absence of response to an "adequate" trial,[14] to "more than one trial"[13] to "several trials",[15] to "first line agents",[16] or to "defined anxiolytic agents".[17] Similarly, the concept of adequate or non-adequate trial is not described[2] or is very heterogeneous, including the administration of a first-choice drug during four,[18] six,[19] eight[13,16,17] or even 12 weeks.[14] The variety and the absence of operationalization of the resistance criteria are only other limiting factors for the understanding of the scarce findings on the treatment of resistant anxiety disorders.

In clinical practice the assessment of the response and remission should be multidimensional, including anxiety symptoms, functional parameters and comorbidities.[5,11,20] Pollack et al. suggested that the concept of response to treatment in the anxiety disorders must include remission or important improvement of the central anxiety symptoms, functional impairment and comorbid depressive symptoms.[11] This would imply a decrease in different magnitudes of the specific scales assessing this parameters, such as the Hamilton Rating Scale for Anxiety, for anxiety symptoms; the Panic Disorder Severity Scale, for PD symptoms; The Liebowitz Social Anxiety Scale, for SAD symptoms; the Sheehan Disability Scale, for functional assessment; and the Hamilton Rating Scale for Depression, for associated depressive symptoms.[11] See Table 1.

Predictors of treatment-resistance

In studies that analyze the predictors of treatment resistance, some clinical variables have been systematically identified, such as higher disease severity, presence of axis I comorbidities and personality disorders, and factors like incorrect diagnosis, inadequate use of antidepressants and absence of cognitive behavioral therapies.[21-23]

In recent reviews, Bystritsky and Pollack listed some of these factors and divided them into aspects related to the disease, the patient and the treatment, or to factors not related to these three items.[5,11] Several variables listed by Bystritsky and Pollack present certain conceptual overlapping, and others are, to date, only clinical impressions that need to be confirmed in future studies.[5,11]

Some predictors of treatment resistance can only be corrected with more wide initiatives at a long-term, such as training of professionals about the diagnosis and the treatment of anxiety disorders, reduction in external stress factors, and maintenance of a functional health system that can provide the patients with regular medical and psychological care. With regard to the psychiatrist, the performance of more accurate diagnosis, either related to anxiety disorders or possible comorbid disorders, so that the treatment can be conducted in a correct

Table 1 – Criteria suggested for remission of anxiety disorders

Assessment Scales	Cutoff points
Hamilton Rating Scale for Anxiety	≤ 7
Sheehan Disability Scales	≤ 1
Hamilton Rating Scale for Depression	≤ 7
Panic Disorder Severity Scale*	< 7
Liebowitz Social Anxiety Scale**	≤ 30

** for assessment of panic disorder*
*** for assessment of social anxiety disorder*

and efficient manner, is crucial for the achivement of better response rates. Efforts to assess the treatment and to optimize the patient's adherence to the treatment must be made before considering the patient as refractory. In addition, confrontation and exposure strategies must be stimulated and psychotherapeutic support must be provided, mainly when prominent stress factors are identified,[11] with the purpose of reducing the risk of resistance.

Management of resistant anxiety disorders

An important clinical issue is related to the best pharmacological intervention when there is resistance to the treatment of anxiety disorders, since there is a small number of controlled studies regarding this issue.[4] Currently, no drug has been approved by the Food and Drugs Administration for the treatment of resistant anxiety, and most pharmacological strategies are based on a limited number of trials, often small and open trials.[11]

Although some reviews suggest that dose increase is an efficient strategy in the management of resistance,[5] there are no controlled studies that support this procedure in treatment-resistant GAD, PD and SAD. As opposed to that, controlled studies that assessed different regular doses of medication, which have been proven to be efficient, did not find a relation between the dose and the response to the treatment in these three disorders.

Regarding GAD, for instance, some studies involving escitalopram[24] and venlafaxine[25] defined that higher doses of these drugs, i.e., higher than 10 mg and 75 mg, respectively, did not show a better response to treatment. With regard to SAD, studies that compared regular doses of venlafaxine[26] and paroxetine[27] also were not able to establish a significant relation between the dose and the response. In the studies involving PD, the scenario is not different. Studies that assess the efficacy of different doses of sertraline concluded that doses higher than 50 mg/day do not mean an increase in the efficacy.[28,29]

There are several options available for the management of resistant anxiety disorder, although not all of them have been adequately tested. These approaches depend on the specific clinical scenario, for example, if there is absence or only insufficiency of response to the treatment. The augmentation, that is, adding up a second drug with a different mechanism of ation would be recommended for patients with partial response to the SSRI and NSRI.[7] In patients with absence of response to the SSRI and NSRI, the most appropriate strategy would be to switch the drugs being used with a drug presenting another mechanism of action.

Augmentation: The augmentation strategy is widely supported in the literature that suggests the involvement of multiple systems of neurotransmission in anxiety disorders,[7] including dopamine, noradrenaline and GABA.[30,31] The association of SSRI and atypical antipsychotics such as risperidone,[18] aripiprazole[32] and olanzapine[19] in the treatment of resistant anxiety disorders has received attention lately[33,34] and has been proven effective in controlled studies.[18,35] Although the use of benzodiazepines, such as clonazepam,[36] is controversial and not supported by controlled clinical trials in all the anxiety disorders reviewed in this study, it has been recommended as a possible approach for resistant patients after considering the possible risks and adverse effects such as sedation and possibility of developing addiction.[5]

Drug switching: The efficacy of different SSRI (e.g.: citalopram and escitalopram) in patients who do not respond to the drugs of the same class was demonstrated in some open studies.[37,38] The monotherapy with atypical antipsychotics (e.g.: olanzapine) or GABAergic agents (such as tiagabine and pregabalin), for instance, was successfully used in some case reports.[39,40] With greater safety regarding the risk of causing addiction and with a less significant anxyolitic action, these substances need to be tested in further studies so that their use can be assessed in a broader manner.[5] The monoamine oxidase enzyme inhibitors (MOAIs), which had their efficacy demonstrated in several anxiety disorders, often are described in text books and literature reviews as an efficient alternative when there is absence of response to the first line drugs. Case reports in which phenelzine is used in treatment-resistant patients with PD[41] and SAD[42] showed the efficacy of these substances in a preliminary manner. However, there are no controlled studies assessing the efficacy of the MOAIs in the resistant anxiety disorders, therefore, new clinical trials are needed so that these drugs can be described as an alternative to the absence of response.

Due to the strategies reviewed here and the high occurrence of comorbidity, the use of polypharmacy is a frequent and inevitable reality, in spite of the risks of increasing the adverse effects.[7] Although there is no scientific evidence to validate polypharmacy, several authors defend the idea that this practice is an effective solution for a complex clinical problem.[5]

1. Social anxiety disorder

Randomized, double-blind, placebo-controlled clinical trials have clearly demonstrated the efficacy of several classes of drugs in the treatment of SAD patients who were not under any other drug.[43,44] However, information based on controlled studies remain necessary in order to define the best approach for patients who do not respond to the first line therapies.[23]

The augmentation with atypical antipsychotics was investigated in two open studies, the first one retrospectively assessed the association of aripiprazol with SSRI for 12 weeks,[32] and the second study associated risperidone with SSRI or benzodiazepines for eight weeks.[17] In both cases, the augmentation strategies have been proven efficient, suggesting the necessity of controlled studies that confirm these observations. In an open study conducted by Van Ameringen et al.,[45] the augmentation of SSRI with buspirone in social phobic patients with inadequate response to the treatment also was efficient to improve the symptoms.

Open studies and case reports involving monotherapy have also demonstrated preliminary efficacy in the treatment-resistant SAD. Positive results have been observed whith the use of escitalopram[7] and citalopran[46] in open trials assessing the efficacy in patients who do not respond to other SSRIs. In open studies that described the use of antidepressants agents different from the SSRIs in treatment-resistant social phobic patients (such as phenelzine[42] and venlafaxine[47]), favorable therapeutic response has also been observed. Initial positive studies with atypical antipsychotics (e.g.: olanzapine[48]) and anticonvulsants (e.g.: topiramate[49] and valproic acid[50]) as a monotherapy in non-resistant SAD suggest new perspectives for the therapy provided to treatment-resistant patients.

Augmentation strategies have been preliminarily suggested.[17,45] In the only randomized, placebo-controlled clinical trial involving treatment-resistant SAD, Stein et al. assessed the association of pindolol with paroxetine in 14 social phobic patients resistant to paroxetine administered

for 12 weeks. This association did not show efficacy higher than placebo.[51]

2. Generalized anxiety disorder

More than half of the patients with GAD presents with chronic and persistent symptomatology. However, the optimal management of treatment-resistant GAD has not been well-established yet and there are few studies that assessed possible strategies to deal with the resistance to the GAD treatment.

There is one open study suggesting the efficacy of ziprasidone used as monotherapy (mean dose of 40 mg/day) for seven weeks in resistant patients.[37] Aripiprazol[32,52] and risperidone[17] in association with other treatments were preliminarily assessed in open studies, and were proven to be efficient for resistant GAD. Case reports preliminarily suggest the efficacy of GABAergic agents, including gapapentine[15] and tiagabine.[40]

The efficacy of augmentation strategies with atypical antipsychotics has also been confirmed in two randomized, double-bind, placebo-controlled clinical trials in patients with treatment-resistant GAD.[7] In the first study, patients that remained symptomatic after the use of fluoxetine were randomized so that this treatment could be associated with olanzapine (mean dose of 8.7 mg) or placebo. The augmentation with olanzapine resulted in significantly less severe generalized anxiety symptoms.[53] This finding was replicated by Brawman-Mintzer et al. in a five-week study with risperidone. In this clinical trial, the patients who had not responded to the conventional treatment for GAD and had risperidone (dose between 0.5 and 1.5 mg) associated with their initial treatment presented significant improvement of the symptoms.[54]

3. Panic disorder

Even though several medications have shown positive results in the treatment of PD in controlled clinical trials, a significant percentage of patients remain symptomatic after an adequate period of treatment.

Similarly to SAD and GAD, the management of resistant PD has not been deeply studied and there is no consensus regarding what to do when there is no response.

The combination of drugs has been described in anecdotal studies. The association of imipramine and moclobemide,[55] tricyclics and fluoxetine,[56] benzodiazepines and sodium valproate[57] or d-fenfluramine,[58] and lithium carbonate and clomipramine[59] were described in case reports with preliminary positive results. Cases of positive response due to the augmentation with phenelzine, tiagabine and gabapentine were also reported by Buch, Schwartz and Pollack, respectively.[15,40,42]

Some substances were described as efficient when used as monotherapy to treat resistant PD. Case reports suggested the efficacy of trimipramine,[60], tiagabine[61] and clonazepan.[36] In an open study with reboxetine (8 mg/day) for six weeks, there was a significant improvement of the symptoms in patients who had presented treatment resistance previously.[62] In a study conducted by Baets et al. involving patients with PD and mood instability, divalproate has proven to be efficient in the treatment of PD symptoms.[63]

Similarly to the other resistant anxiety disorders, the use of atypical antipsychotics has been receiving attention, with open studies demonstrating the efficacy of aripiprazol[32] and risperidone[17] associated with SSRI or benzodiazepines, and case reports in which the association of olanzapine with paroxetine[37,64] or the previously used treatment[65] has shown to be efficient. In an open study, Sepede et al. found favorable results after treating, with 5 mg of olanzapine for 12 weeks, 31 patients who had not responded to the previous treatment with SSRI.[19] Olanzapine has also shown to be efficient as monotherapy in an open study conducted by Hollifield[39] with 10 patients who received a mean dose of 12.3 mg for eight weeks.

The only randomized, double-blind, placebo controlled clinical trial involving augmentation strategies in treatment-resistant PD assessed the association of beta-blocker pindolol with SSRI. Pindolol (7.5 mg per day) associated with fluoxetine (20 mg per day) for a period of four weeks was effective in the decrease in the severity of PD symptoms compared to placebo.[13]

Conclusion

Anxiety disorders, in addition to being prevalent, are associated with important functional impairments. Even though there have been recent advances in the management and understanding of these disorders, the treatment of anxiety remains a challenge for the clinical practice. Several interventions have proven to be efficient to reduce anxiety symptoms; however, many patients remain symptomatic and disabled.

Treatment resistance is especially relevant for anxiety disorders. The reason why it is so important is that the clinical conditions are associated with higher mortality and morbidity rates, worse quality of life and high social cost in a large group of individuals. There are several factors involved in the absence of treatment response and the adequate understanding of this phenomenon is crucial to help the patients. Although the relevance of the topic is undeniable, there are few studies systematically investigating the inadequate response to the treatment in anxiety disorders. The development of new and

Table 2 – Factors associated with lack of response to the treatment of anxiety disorders

Factors associated with lack of response according to Bystritsky	Factors associated with lack of response according to Pollack
Related to the pathology Lack of knowledge on the pathophysiology; participation of multiple neurotransmitters; inaccurate diagnostic system; limitation of the biological treatments	**Related to the patient** Comorbidity; lack of adherence to the treatment
Related to the patient Severity; clinical and psychiatric comorbidities; non-adherence to the treatment; cultural factors	**Related to the treatment** Incomplete diagnosis; inadequate intervention; insufficient dose and duration of drug use
Related to the professional Lack of knowledge on primary health care; lack of training in cognitive behavioral therapy; limitation of the relationship between doctor and patients due to the cost of the treatment	**Related to the logistics** Lack of training; inadequate health system
Related to the environment Severe or persistent stress factors; childhood stress factors; life cycles	

effective strategies to deal with this problem is very important. New therapeutic approaches and clear evidence-based strategies can mean higher response rates and less impairment associated with these disorders.

References

1. Ballenger JC. Anxiety and depression: optimizing treatments. *Prim Care Companion J Clin Psychiatry*. 2000;2(3):71-9.
2. Kessler RC, Demler O, Frank RG, Olfson M, Pincus HA, Walters EE, Wang P, Wells KB, Zaslavsky AM. Prevalence and treatment of mental disorders, 1990 to 2003. *N Engl J Med*. 2005;352(24):2515-23.
3. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51(1):8-19.
4. Stein DJ, Seedat S. Unresolved questions about treatment-resistant anxiety disorders. *CNS Spectr*. 2004;9(10):715.
5. Bystrisky A. Treatment-resistant anxiety disorders. *Mol Psychiatry*. 2006;11(9):805-14.
6. Wittchen HU, Fehm L. Epidemiology, patterns of comorbidity, and associated disabilities of social phobia. *Psychiatr Clin N Am*. 2001;24(4):617-41.
7. Ipser JC, Carey P, Dhansay Y, Fakier N, Seedat S, Stein DJ. Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. *Cochrane Database Syst Rev.* 2006;(4):CD005473.
8. Mitte K, Noack P, Steil R, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. *J Clin Psychopharmacol*. 2005;25(2):141-50.
9. Mitte K. A meta-analysis of the efficacy of psycho- and pharmacotherapy in panic disorder with and without agoraphobia. *J Affect Disord*. 2005;88(1):27-45.
10. Blanco C, Schneier FR, Schmidt A, Blanco-Jerez C, Marshal RD, Sanchez-Lacay A, Liebowitz MR. Pharmacological treatment of social anxiety disorder: a meta-analysis. *Depress Anxiety*. 2003;18(1):29-40.
11. Pollack MH, Otto MW, Roy-Byrne PP, Coplan JD, Rothbaum BO, Simon MN, Gorman JM. Novel treatment approaches for refractory anxiety disorders. *Depress Anxiety*. 2007; [Epub ahead of print].
12. Keller MB. Issues in treatment-resistant depression. *J Clin Psichiatry*. 2005;66(Suppl 8):5-12.
13. Hirschmann S, Dannon PN, Iancu I, Dolberg OT, Zohar J, Grunhaus L. Pindolol augmentation in patients with treatment-resistant panic disorder: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol.* 2000;20(5):556-9.
14. Pallanti S, Quercioli L. Resistant social anxiety disorder response to Escitalopram. *Clin Pract Epidemiol Ment Health.* 2006;2:35.
15. Pollack MH, Matthews J, Scott EL. Gabapentin as a potential treatment for anxiety disorders. *Am J Psychiatry*. 1998;155(7):992-3.
16. Snyderman SH, Rynn MA, Rickels K. Open-label pilot study of ziprasidone for refractory generalized anxiety disorder. *J Clin Psychopharmacol.* 2005;25(5):497-9.
17. Simon NM, Hoge EA, Fischmann D, Worthington JJ, Christian KM, Kinrys G, Pollack MH. An open-label trial of risperidone augmentation for refractory anxiety disorders. *J Clin Psychiatry*. 2006;67(3):381-5.
18. Brawman-Mintzer O, Knapp R, Nietert P. Adjunctive risperidone in generalized anxiety disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2005;66(10):1321-5.
19. Sepede G, De Berardis D, Gambi F, Campanella D, La Rovere R, D'Amico M, Cicconetti A, Penna L, Peca S, Carano A, Mancini E, Salerno RM, Ferro FM. Olanzapine augmentation in treatment-resistant panic disorder: a 12-week, fixed-dose, open-label trial. *J Clin Psychopharmacol*. 2006;26(1):45-9.
20. Bandelow B, Baldwin D, Dolberg O, Andersen HF, Stein DJ. What is the threshold for symptomatic response and remission for major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder? *J Clin Psychiatry*. 2006;67(9):1428-34.
21. Pollack MH, Meoni P, Otto MW, Simon N, Hackett D. Predictors of outcome following venlafaxine extended-release treatment of DSM-IV generalized anxiety disorder: a pooled analysis of short- and long term studies. *J Clin Psychopharmacol.* 2003;23(3):250-9.
22. Katerndahl DA. Predictors and outcomes in people told that they have panic attacks. *Depress Anxiety.* 2003;17(2):98-100.
23. Van Ameringen M, Mancini K, Pipe B, Bennet M. Optimizing treatment in social phobia: a review of treatment resistance. *CNS Spectr.* 2004;9(10):753-62.
24. Rickels K, Zaninelli R, McCafferty J, Bellew K, Iyengar M, Sheehan D. Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2003;160(4):749-56.
25. Baldwin DS, Huusom AK, Maehlum E. Escitalopram and paroxetine in the treatment of generalised anxiety disorder: randomised, placebo-controlled, double-blind study. *Br J Psychiatry*. 2006;189:264-72.
26. Stein MB, Pollack MH, Bystritsky A, Kelsey JE, Mangano RM. Efficacy of low and higher dose extended-release venlafaxine in generalized social anxiety disorder: a 6-month randomized controlled trial. *Psychopharmacology* (Berl). 2005;177(3):280-8.
27. Liebowitz MR, Stein MB, Tancer M, Carpenter D, Oakes R, Pitts CD. A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder. *J Clin Psychiatry*. 2002;63(1):66-74.
28. Londborg PD, Wolkow R, Smith WT, DuBoff E, England D, Ferguson J, Rosenthal M, Weise C. Sertraline in the treatment of panic disorder. A multi-site, double-blind, placebo-controlled, fixed-dose investigation. *Br J Psychiatry*. 1998;173:54-60.
29. Sheikh JI, Londborg P, Clary CM, Fayyad R. The efficacy of sertraline in panic disorder: combined results from two fixed-dose studies. *Int Clin Psychopharmacol*. 2000;15(6):335-42.
30. Robinson HM, Hood SD, Bell CJ, Nutt DJ. Dopamine and social anxiety disorder. *Rev Bras Psiquiatr*. 2006;28(4):263-4.
31. Johnson MR, Marazziti D, Brawman-Mintzer O, Emmanuel NP, Ware MR, Morton WA, Rossi A, Cassano GB, Lydiard RB. Abnormal peripheral benzodiazepine receptor density associated with generalized social phobia. *Biol Psychiatry*. 1998;43(4):306-9.
32. Worthington JJ 3rd, Kinrys G, Wygant LE, Pollack MH. Aripiprazole as an augmentor of selective serotonin reuptake inhibitors in depression and anxiety disorder patients. *Int Clin Psychopharmacol.* 2005;20(1):9-11.
33. Blier P, Szabo ST. Potential mechanisms of action of atypical antipsychotic medications in treatment-resistant depression and anxiety. *J Clin Psychiatry*. 2005;66(Suppl 8):30-40.
34. Nemeroff CB. Use of atypical antipsychotic in refractory depression and anxiety. *J Clin Psychiatry*. 2005;66(Suppl 8):13-21.
35. Pollack MH, Simon NM, Zalta AK, Worthington J, Hoge EA, Mick E, Kinrys G, Oppenheimer J. Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: a placebo controlled study. *Biol Psychiatry*. 2006;59(3):211-5.
36. Tesar GE, Rosenbaum JF. Successful use of clonazepam in patients with treatment-resistant panic disorder. *J Nerv Ment Dis.* 1986;174(8):477-82.
37. Khaldi S, Kornreich C, Dan B, Pelc I. Usefulness of olanzapine in refractory panic attacks. *J Clin Psychopharmacol.* 2003;23(1):100-1.
38. Pallanti S, Quercioli L. Resistant social anxiety disorder response to Escitalopram. *Clin Pract Epidemol Ment Health.* 2006;2:35.
39. Hollifield M, Thompson PM, Ruiz JE, Uhlenhuth EH. Potential effectiveness and safety of olanzapine in refractory panic disorder. *Depress Anxiety.* 2005;21(1):33-40
40. Schwartz TL. The use of tiagabine augmentation for treatment-resistant anxiety disorders: a case series. *Psychopharmacol Bull.* 2002;36(2):53-7.
41. Buch S, Wagner M. Successful use of phenelzine in treatment-resistant panic disorder. *J Clin Psychiatry*. 2007;68(2):335-6.
42. Aarre TF. Phenelzine efficacy in refractory social anxiety disorder: a case series. *Nord J Psychiatry.* 2003;57(4):313-5.
43. Stein DJ, Ipser JC, van Balkom AJ. Pharmacotherapy for social anxiety disorder (Review). *The Cochrane Library.* 2005, Issue 3.

44. Versiani M. A review of 19 double-blind placebo-controlled studies in social anxiety disorder (social phobia). *World J Biol Psychiatry*. 2000;1(1):27-33.
45. Van Ameringen M, Mancini C, Wilson C. Buspirone augmentation of selective serotonin reuptake inhibitors (SSRIs) in social phobia. *J Affect Disord*. 1996;39(2):115-21.
46. Simon NM, Korbly NB, Worthington JJ, Kinrys G, Pollack MH. Citalopram for social anxiety disorder: an open-label pilot study in refractory and nonrefractory patients. *CNS Spectr.* 2002;7(9):655-7.
47. Altamura AC, Pioli R, Vitto M, Mannu P. Venlafaxine in social phobia: a study in selective serotonin reuptake inhibitor non-responders. *Int Clin Psychopharmacol*. 1999;14(4):239-45.
48. Barnett SD, Kramer ML, Casat CD, Connor KM, Davidson JR. Efficacy of olanzapine in social anxiety disorder: a pilot study. *J Psychopharmacol.* 2002;16(4):365-8.
49. Van Ameringen M, Mancini C, Pipe B, Oakman J, Bennett M. An open-label trial of topiramate in the treatment of generalized social phobia. *J Clin Psychiatry*. 2004;65(12):1674-8.
50. Kinrys G, Pollack MH, Simon NM, Worthington JJ, Nardi AE, Versiani M. Valproic acid for the treatment of social anxiety disorder. *Int Clin Psychopharmacol*. 2003;18(3):169-72.
51. Stein MB, Sareen J, Hami S, Chao J. Pindolol potentiation of paroxetine for generalized social phobia: A double-blind, placebo-controlled, crossover study. *Am J Psychiatry.* 2001;158(10):1725-7.
52. Menza MA, Dobkin RD, Marin H. An open-label trial of aripiprazole augmentation for treatment-resistant generalized anxiety disorder. *J Clin Psychopharmacol.* 2007;27(2):207-10.
53. Pollack MH, Simon NM, Zalta AK, Worthington JJ, Hoge EA, Mick E, *Kinrys G, Oppenheimer J*. Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: a placebo controlled study. *Biol Psychiatry.* 2006;59(3):211- 5.
54. Brawman-Mintzer O, Knapp RG, Nieter PJ. Adjunctive risperidone in generalized anxiety disorder: a double-blind, placebo- controlled study. *J Clin Psychiatry*. 2005;66(10):1321-5.
55. Boerner RJ. Treatment refractory panic disorder -success of a combined treatment with imipramine, moclobemide and behavior therapy. *Psychiatr Prax.* 1995;22(1):30-2.
56. Tiffon L, Coplan JD, Papp LA, Gorman JM. Augmentation strategies with tricyclic or fluoxetine treatment in seven partially responsive panic disorder patients. *J Clin Psychiatry*. 1994;55(2):66-9.
57. Ontiveros A, Fontaine R. Sodium valproate and clonazepam for treatment-resistant panic disorder. *J Psychiatry Neurosci.* 1992;17(2):78-80.
58. Hetem LA. Addition of d-fenfluramine to benzodiazepines produces a marked improvement in refractory panic disorder—a case report. *J Clin Psychopharmacol.* 1996;16(1):77-8.
59. Cournoyer J. Rapid response of a disorder to the addition of lithium carbonate: panic resistant to tricyclic antidepressants. *Can J Psychiatry.* 1986;31(4):335-8.
60. Cerra D. Trimipramine for refractory panic attacks. *Am J Psychiatry.* 2006;163(3):548.
61. Zwanzger P, Baghai TC, Schule C, Minov C, Padberg F, Moller HJ, Rupprecht R. Tiagabine improves panic and agoraphobia in panic disorder patients. *J Clin Psychiatry*. 2001;62(8):656-7.
62. Dannon PN, Iancu I, Grunhaus L. The efficacy of reboxetine in the treatment-refractory patients with panic disorder: an open label study. *Hum Psychopharmacol.* 2002;17(7):329-33.
63. Baetz M, Bowen RC. Efficacy of divalproex sodium in patients with panic disorder and mood instability who have not responded to conventional therapy. *Can J Psychiatry.* 1998;43(1):73-7.
64. Chao IL. Olanzapine augmentation in panic disorder: a case report. *Pharmacopsychiatry.* 2004;37(5):239-40.
65. Etxebeste M, Aragues E, Malo P, Pacheco L. Olanzapine and panic attacks. *Am J Psychiatry.* 2000;157(4):659-60.