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Difficulties in the Diagnosis and Treatment of Major Depressive Disorder with Comorbid Anxiety Symptoms

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SUMMARY

Major depressive disorder (MDD) is a common and costly disorder. MDD often occurs with comorbid symptoms of anxiety. While symptoms of anxiety are not part of the diagnosis criteria of MDD, it has been recognized for many years that anxiety may play a critical role in depressive illness. The presence of anxiety has been associated with greater severity of depression and functional impairment, as well as increased suicide risk. Moreover, anxiety symptoms have been associated with reduced antidepressant response, in addition to greater risk of relapse and chronicity. Recently, emphasis has been placed on remission as the goal in the treatment of MDD. Patients who achieve remission have more favorable long-term outcomes than those who have appreciable improvement, but still have residual symptoms. Given the burden of illness caused by MDD, and given that anxiety is a common component of MDD and that full symptom resolution should be the goal of antidepressant therapy, efficacy in treating the symptoms of anxiety associated with depression may be an important component of the overall treatment of depression. Treatment of anxious depression presents unique challenges, optimally involving pharmacological agents that are effective for both depression and anxiety. The likely role of abnormal serotonergic neurotransmission in anxiety is widely supported, while the role of norepinephrine is less clear. A large body of evidence supports the hypothesis that a perturbation in norepinephrine neurotransmission contributes to the symptoms of anxiety. It has been suggested that agents with dual reuptake inhibition of 5-HT and norepinephrine may be particularly effective in treating anxiety.

Key Words: Major depressive disorder, antidepressant, anxiety

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INTRODUCTION

Major Depressive Disorder (MDD), which has lifelong prevalence of 17%-19% and a yearly prevalence of 1%-9% (Angst, 1992), is a common and destructive disorder with long-lasting episodes, a high risk of chronicity, relapse, and recurrence, and causes severe physical and psychological disability. The functional disability caused by depression may be seen in both social and professional life, and may negatively affect the patient's family and economic life. In addition to the patient, depression negatively affects the patient's environment and those who take care of him (Davis and Glassman, 1989). With a death rate of 15% following suicide attempts, MDD is responsible for approximately 50% of all suicidal deaths and is therefore, an exceedingly costly disorder (Angst, 1992).

Studies have shown that anxiety is the most common symptom of depression (Stein et al., 1995). Approximately 50%-60% of adults with a lifelong history of depression also have a history of 1 or more comorbid episodes of anxiety disorder (Kessler et al., 1996). More than 70% of MDD patients who visit primary care clinics also have comorbid anxiety disorder (Olfson et al., 1997). Any anxiety symptom that does not meet the criteria for an anxiety disorder is considered a component of depressive disorder. Of those who have MDD, at least 65% have moderate symptoms and 20%-25% have severe anxiety symptoms (Zimmerman et al., 2000). A study of 200 patients with the diagnosis of MDD revealed that 72% had moderate anxiety, 62% psychic anxiety, 42% so-

matic anxiety, and that 29% had a history of panic attacks (Fawcett and Kravitz, 1983).

The presence of anxiety in MDD causes rapid and sudden changes in mood, increased suicide, relapse risk, and both poor treatment results and course of the disorder (Keller et al., 1983; Fawcett et al., 1990; Joffe et al., 1993; Roy-Byrne, 1996). In addition, the possibility of alcohol and drug abuse increases (Roy-Byrne et al., 2000), resulting which case, use of mental health services increases by 30%-60% (Judd, 1994).

According to the present diagnostic classification systems, depression and anxiety disorders are considered 2 different diagnoses and there is no need for the presence of anxiety symptoms for diagnosing depression. On the other hand, it has been long known that anxiety accompanies depression, and in recent years the relationship between depression and anxiety has been intensely researched (Zung et al., 1990). A series of disorders have been identified in which depression and anxiety symptoms coexist on the level of syndromes and symptoms (Stahl, 1993):

Anxiety disorder with comorbid depressive symptoms (Ad)

Depression with comorbid anxiety symptoms (Da)

Anxiety disorder with comorbid depression (DA)

Depression symptoms with comorbid anxiety symptoms (da)

In this paper, depression at the syndrome level and comorbid anxiety symptoms (Da) will examined. Herein, the effects of anxiety symptoms associated with MDD on the course and treatment of depression, the difficulties involved in the diagnosis and treatment of Da, and the role of dual-effect antidepressants in the treatment of Da, based on the roles of serotonin and noradrenaline systems on the pathophysiology of anxiety, were examined. Moreover, we have compiled all antidepressant studies in the literature with concern to Da treatment. For this purpose, in PubMed and in Türk Medline, the key words, Major Depressive Disorder, Antidepressant, and Anxiety were entered. All domestic and foreign literature between 1968 and 2005 was searched and all full-texts required for the study were obtained.

Defining the Efficacy of Antidepressant Treatment in MDD

Following are the main goals in the treatment of depression, which both threatens public health and is a major public health problem due to the difficulties in its diagnosis and treatment:

1. Reduction of and resolution of all the symptoms of depressive disorder (remission);

2. To return occupational and social functions to the premorbid state;

3. Lowering the rates of relapse and recurrence.

The positive atmosphere at the time of the discovery of antidepressants has turned, in time, into concern for the fact that a certain subgroup does not benefit from the treatment. The two important concepts for the definition of benefits from antidepressants are response and remission. Response to treatment in depression is reported to be 70%-80%, whereas the remission rate is 40%-50% (Nemeroff, 2000). Recently, it has been emphasized that response is not an adequate term for clinical uses and that those who respond to treatment might have residual symptoms (Ferrier, 2001; Bakish, 2001). It is claimed that partial improvement in cases where residual symptoms are observed might be related to the high relapse rate, serious functional impairment, and suicide risk. The concept of remission might be a more appropriate indicator for clinical use because it emphasizes that the person with MDD is well and has no residual symptoms. As a result, in recent studies in which the effectiveness was compared, “remission” has come forward (Ferrier, 2001; Bakish, 2001). Further analysis indicates that only 20%-25% of patients with depressive disorder achieve remission with the first antidepressant they take, irrespective of the drug chosen. This situation is compelling researchers to develop new antidepressants in order to obtain better remission and lower relapse rates (Nemeroff, 2000). However, the cause of the high rate of remission and limitations related to antidepressant therapy has yet to be fully elucidated.

A score of 7 on the Hamilton Depression Rating Scale (HDRS), which is widely used to measure the severity of MDD, is accepted as remission. HDRS includes several items for determining anxiety symptoms. The analysis of the symptoms indicative of the severity of MDD brings forth the importance of anxiety symptoms. A study that analyzes

the HDRS items (Bech et al., 1981) has revealed that the severity of depression is best measured with 5 items. One of these items is "psychic anxiety." The item analysis of HDRS measurements in dual-scope treatment studies has revealed that 6 HDRS items are related to the severity of depression (Gibbons et al., 1993). "Depressive mood", being one of these 6 items, is significantly related to diagnosis, whereas anxiety items (psychic anxiety, somatic anxiety, and agitation) are related to depression severity, which is measured with total HDRS scores. In other words, the symptoms of anxiety that are not required for diagnosis play an important role in determining MDD severity. When we consider that HDRS scores (which measure MDD severity) below a certain level are indicative of remission and that anxiety symptoms play an important role in determining HDRS scores, the low rate of remission achieved with antidepressants brings to mind the question of whether the cause for this is the neglect of anxiety symptoms. Without anxiety symptom resolution, remission of MDD is difficult.

The effect of Serotonin and Noradrenaline Antidepressants on Anxiety Symptoms and Remission Rate in MDD

The fact that Selective Serotonin Reuptake Inhibitors (SSRI) are not as effective as Tricyclic Antidepressants (TSAs) in the treatment of depression and the knowledge that the effects of TSAs on the noradrenergic system are more dominant have led to the search for different treatments of depression (Schatzberg, 2000).

Yet, in spite of our pre-clinical work and observations, our knowledge about antidepressants and their effect mechanism is limited. The efforts to disclose the unseen section of the iceberg have taken us ahead of the "monoamine hypothesis." TSAs are dominantly effective on the noradrenergic system. However, it is not known whether the superiority of TSAs, which also demonstrate serotonergic characteristics, to varying degrees, compared to SSRIs is related only to their dominant effects on the noradrenergic systems. In some studies, it was shown that drugs that exhibit selective effects through serotonin and noradrenaline exhibit their effects without any interaction between these 2 systems; whereas in other studies, they were effective in the treatment of depression with some unknown level of interaction between these 2 systems (Delgado and Moreno, 2000; Racagni and Brunello, 1999; Frazer, 2000).

The role of noradrenaline on the pathophysiology of anxiety suggests that drugs that have an effect through multiple systems resolve anxiety by influencing the noradrenergic system. At the moment, it is yet unclear as to whether the real reason this group of antidepressant has better remission rates than SSRIs in the treatment of MDD is on account of this efficacy.

Serotonergic and noradrenergic systems and their roles on anxiety pathophysiology

Although the pathogenesis of anxiety has not been fully explained, reports indicate that perturbation in both serotonergic and noradrenergic systems exist in depression and anxiety disorders. While a decrease in serotonergic functions causes depression and anxiety disorders, irregularities in serotonin transport can cause anxiety symptoms (Ressler and Nemeroff, 2000). However, the role of noradrenaline in the pathophysiology of anxiety is more complicated. According to our present knowledge, it is clear that in depression and anxiety disorders there is a perturbation in the noradrenergic system and that this system interacts with several chemical transporter systems that contribute to depression and anxiety symptoms (Leonard, 2000; Sullivan et al., 1999; Ressler and Nemeroff, 2000). Most of the data reveal that in depression and anxiety disorders, there is an increase in noradrenergic function and receptor sensitivity (Ressler and Nemeroff, 2000). An increase in the noradrenaline level causes autonomic and emotional anxiety symptoms, such as a sense of fear, tachycardia, tremors, dryness of the mouth, increased blood pressure, increased peristaltic movements of the gastrointestinal system, sweating, and dilation of the pupils (Ninan, 1999). It is revealed that noradrenaline organizes the functions of the areas of the brain related to anxiety, such as the amygdala (Feldman and Weidenfeld, 1998). It is observed that gamma-amino butyric acid (GABA) receptors also exist in high concentrations in the noradrenergic neuron bodies in the locus ceruleus. Based on this, it is suggested that noradrenergic inhibition through GABA in the locus ceruleus also contributes to the efficacy of benzodiazepines on anxiety (Stahl, 1996).

Clinically, it is observed that anxiety-resolving drugs cause changes in the locus ceruleus and noradrenergic systems, and their dispersion areas (such as, decrease of .2-adrenoreceptor intensity in the locus ceruleus due to chronic use of imipramine). It is revealed that desipramine and mapro-

tiline, which show selective noradrenergic activity, decrease the firing speed in locus ceruleus noradrenergic neurons, and consequently cause stimulation of prefrontal cortex neurons. With respect to all this data, it can be suggested that the noradrenergic system plays an important role in the pathophysiology of anxiety. The positive effects of noradrenergic drugs on anxiety add additional proof of this (Sullivan et al., 1999).

Treatment of MDD with Comorbid Anxiety Symptoms

Patients with anxious depression are not properly diagnosed due to the confusion in psychiatric diagnostic systems, and as a result, they are not offered appropriate treatment (Kamerov, 1988). However, it is widely supported that the presence of anxiety symptoms with varying severity can change the response to treatment (Fawcett and Kravitz, 1983), and that early diagnosis of depression and associated anxiety can positively affect treatment results (Liebowitz, 1993).

Recently, with improvements in antidepressants, positive developments have been made in the treatment of depressive disorder. Many studies emphasize the efficacy of antidepressants in the resolution of anxiety in depression (Van Praag, 1998); however, when anxiety is associated with depression, the symptoms of anxiety do not respond favorably to standard treatment. It has been reported that associated anxiety is an important factor and that it can affect the choice of treatment (Lydiard and Brawman-Mintzer, 1998). Therefore, it is critical to measure and resolve resistant anxiety to ensure fast and efficacious treatment of depression (Fawcett, 1997). For that reason, it is important to know if the anxiety-resolving effects of antidepressants with similar effectiveness are at different levels (Triverdi et al., 2001).

The primary goal in the treatment of patients who exhibit depression and anxiety symptoms is the resolution of depression. Therefore, when reviewing alternatives for treatment, drugs with proven efficacy for both depression and anxiety should be preferred. Amelioration of the symptoms of anxiety may provide fast and definite response to MDD treatment. Studies have revealed that with effective treatment of severe anxiety and agitation, the risk of sudden suicide is lowered, despite the continuing symptoms of depression (Fawcett, 1997). Hence, antidepressants that quickly reduce anxiety and agitation are important. Drugs that act upon the serotonergic and/or noradrenergic system, or others that work through multiple transport systems are used for this purpose, including TSAs, SSRIs, and Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) (Bakish, 1999).

Drugs used in the treatment of depression with comorbid anxiety symptoms

Tricyclic antidepressants

TSAs have sedative effects and provide positive improvement in sleep and anxiety symptoms, especially in the first weeks of treatment, due to their efficacy on histaminergic receptors. TSAs' sedative effects, which are perceived as a distinct advantage during the first weeks of treatment, may interfere with social functioning due to psychomotor activity limitations (Boyer and Feighner, 1998). TSAs have also been used for treatment of anxiety disorders; however, they are not preferred as the primary treatment due to their side-effect profiles. When used in high dosages in cases of depression with comorbid anxiety, they are not safe due to a high risk of suicide (Mavissakalian and Perel, 2000).

Coplan et al. (1993), and Joyce and Paykel (1989) have suggested that TSAs are effective with persons who have depression with comorbid anxiety symptoms. Some studies have revealed that TSAs have advantages over benzodiazepines in treating anxiety symptoms in association with depression (Kahn et al., 1986), while other studies have determined their efficacies to be equal (Haskell et al., 1978).

Selective Serotonin Reuptake Inhibitors

SSRIs have fewer side effects than TSAs; therefore, they are safer and cause fewer compliance problems. SSRIs can result in a temporary increase in restlessness, anxiety, and agitation in the first days of treatment, and this may give rise to a sense of increased depression severity. For that reason, in order to reduce the risk of suicide, close observation, attention, information exchange, and review of treatment alternatives, when necessary, are important during SSRI treatment of people with anxious or agitative depression (Rotchild and Locke, 1991; Wirshing et al., 1992).

A series of studies have revealed that SSRIs are effective in the resolution of anxiety symptoms in MDD (Dunbar and Fuell, 1992; Sonawalla et al., 1999; Boerner and Moeller, 1999; Spalletta et al.,

2002). When compared to benzodiazepines (Laws et al., 1990) and TSAs (Montgomery, 1989; Sheehan et al., 1992; Tollefson et al., 1994; Ravindran et al., 1997; Marchesi et al., 1998; Beasley et al., 2000), SSRIs were shown to exhibit equivalent activity. However, there are also some studies that reveal that they are more advantageous than TSAs (Baca et al., 2003; Versiani et al., 1999) or that they act more rapidly than TSAs (Dunbar et al., 1991). SSRIs have demonstrated similar efficacy to TSAs in the resolution of anxiety symptoms in MDD (Aguglia et al., 1993; Fava et al., 2000); however, it was also found that the efficacy of paroxetine, the SSRI with the greatest anxiety resolving activity, starts to act sooner than fluoxetine (De Wilde et al.,1993).

Benzodiazepines

Antidepressants and benzodiazepines are often used together in the treatment of anxiety symptoms in depression; it is suggested that this increases patient compliance with treatment (Danacı et al., 2000). However, when used together, the presence of drug interaction, reduced effectiveness of benzodiazepines after prolonged use, withdrawal symptoms, paradoxical agitation related to loss of inhibition, abuse, and dependence problems limits their range of application (Keller and Hanks, 1995). Furthermore, although anxiolytic drugs act fast and positively on sleep and anxiety symptoms, they are not, by themselves, as effective as antidepressants in the treatment of anxiety symptoms in MDD (Feighner, 1999; Rickels et al., 2000). An antidepressant that can resolve depression and anxiety symptoms at the same time will reduce the need for anxiolytic drugs.

Serotonin and Noradrenaline Reuptake Inhibitors

It is reported that SNRIs are effective in the treatment of anxiety symptoms (Rudolph et al., 1998; Feighner et al., 1998; Khan et al., 1998; Dilbaz et al., 1999; Dunner et al., 2003; Akkaya et al., 2004), that their effectiveness is equal to TSAs (Lecrubier et al., 1997), and greater than SSRIs (Silverstone and Ravindran, 1999; Saiz-Ruiz et al., 2002; Davidson et al., 2002; De Nayer et al., 2002). Data shows that in anxiety treatment, drugs that cause changes in noradrenaline transport are at least as effective as those that produce changes in serotonin transport (Silverstone, 2004). Since the roles of serotonin and noradrenaline in the treatment and pathogenesis of anxiety disorders have been identified, it is believed that in anxiety therapy, antidepressants derived from SNRIs, which jointly organize the functions of both chemical transport systems, are more effective than drugs that are selectively effective in only one system (Silverstone, 2004).

CONCLUSION

Recently, in the treatment of MDD, remission has been emphasized more than response; therefore, attention has been drawn to the role of anxiety in this remission. Remission is the main goal in the antidepressant treatment of MDD. HDRS items related to anxiety are effective in the determination of total HDRS points and the severity of depression; hence, effective resolution of anxiety in depression is important for reaching the primary goal of the treatment of depression (Dunner et al., 2003).

Treatment of anxious depression is fraught difficult problems. Are anxiety symptoms a component of MDD, or do they represent a different condition, which requires a different treatment plan? Can the anxiety-resolving effects of antidepressants be independent of the effects of antidepressants? Can the anxiety-resolving effects of the noradrenergic system be considered independently of its direct or indirect relationship with other chemical transport systems? Answers to such questions are important for the development of treatment plans in cases of depression with comorbid anxiety symptoms, in addition to clarifying the etiopathogenesis of depression.

Despite all of these questions, it seems as though drugs with noradrenergic activity have anxiety resolving effects. In that case, fast and powerful resolution of anxiety symptoms in MDD with "dual-effective" drugs and improved treatment results of MDD with these agents compared to SSRIs may be related to the improvement of the functional failures of the noradrenergic system by the action of these agents. However, it is difficult to say if the advantages emanate from antidepressant effectiveness or anxiety resolution effectiveness. The role of the noradrenergic system, by itself, in these results is worth further investigation.

In conclusion, the data currently available suggests that functional impairment of the noradrenaline system can also affect the resolution of anxiety, which is a symptom of major depression.

Therefore, influencing the function of this system with "dual-effective" drugs can reduce the symptoms of anxiety in depression, thus constituting an improved response to treatment. In order to show that such a result is actually related to the improvement of noradrenaline functioning, comprehensive clinical studies of the SNRI, reboxetine, might prove beneficial.

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