

ANXIETY DISORDERS AND MAJOR DEPRESSION, TOGETHER OR APART

Joseph Levine, M.D.,* Daniel P. Cole, M.D., K. N. Roy Chengappa, M.D., and Samuel Gershon, M.D.

This paper will discuss the relationship between anxiety and depression. We will begin with a brief historical perspective. We will then move into the twentieth century, with a focus on the 1950s, at which time the introduction of pharmacological treatment options revolutionized the field of psychiatry. The use of psychiatric medications and the observation of treatment response provided an additional means of understanding the relationship between anxiety and depression. From the late 1970s to the 1990s, it became apparent that various medications possessed wider therapeutic profiles than were previously recognized. For example, many medications were found to be efficacious in both anxiety and depressive disorders. These expanded therapeutic profiles provided additional clues to fuel our thinking about the relationship between anxiety and depression. The two major objectives of this paper are, first, to describe and formalize a process of pharmacological dissection and, second, to consider how this process might contribute to our search for a better understanding of the relationship between anxiety and depression. Depression and Anxiety 14:94–104, 2001. © 2001 Wiley-Liss, Inc.

Key words: major depression; anxiety disorders; antidepressive agents; antianxiety agents; pharmacological dissection; comorbidity

HISTORICAL PERSPECTIVE

Throughout the Greco-Roman period up to the Renaissance period, and through much of the 18th, 19th, and the beginning of the 20th century, the entity of melancholia was understood to encompass symptoms of both depression and anxiety [Glass, 1994].

Kraepelin [1927] believed that the mental disorders were brain disorders and aimed to define discrete and mutually exclusive psychiatric diseases. Kraepelin differentiated two types of depression. One type was *Angst* (anxiety) that appeared with melancholia in contrast to another type that was *Angestlichkeit*, characterized by helplessness in the face of danger. While Kraepelin made significant contributions to the epistemology of psychiatric diseases, he made no clear distinction between anxiety and depression.

Freud [Fenichel, 1945] was the first to address anxiety as a separate entity. Initially, he proposed that the accumulation of tension due to frustrated sexual discharge was the cause of anxiety. Later in 1926, he drew a distinction between realistic anxiety (in the face of actual danger) and neurotic anxiety (in the face of subjective perception of danger). Freud spoke separately on the issue of melancholia in 1917. According to Freud, melancholia may encompass symptoms of both depression and anxiety. On the whole, though, Freud was more interested in formulating the patient's psychodynamic forces than in formulating a compre-

hensive phenomenological description of signs and symptoms. Thus, his description of neurosis was rather general, including symptoms of both anxiety and depression.

Aubrey Lewis [1970-1] in agreement with Mapother [1926] proposed a new conceptual viewpoint in 1934, suggesting a continuum between anxiety and depression. He regarded anxiety as an integral part of depression. In fact, Lewis [1966, 1970-71] described a variant of manic-depressive illness in which the major form was agitated depression and the minor form was anxiety neurosis. Lewis too failed to draw a distinction between anxiety and depression.

Adolf Meyer [Slater and Roth, 1969] played an important role in the development of DSM I and II [American Psychiatric Association, 1952, 1968]. Meyer suggested that psychiatric disorders were the conse-

Stanley Center for the Innovative Treatment of Bipolar Disorder, Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania

*Correspondence to: Dr. Joseph Levine, Beersheva Mental Health Center, P.O. Box 4600, Beersheva, Israel.
E-mail: levinejmd@hotmail.com

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quence of an individual's reaction to internal and external stressors. In both DSM I and II, differentiation between disorders was based more on precipitants and severity of illness than on the quality of symptoms. Thus, less severe clinical states were diagnosed as "neuroses," while more severe clinical states with no clear precipitants were diagnosed as "psychoses." So, in this schema, the less severe depressive disorder was referred to as depressive neurosis (a neurosis) and the more severe form of depression was referred to as a psychotic depressive reaction (a psychosis). Both states consisted of a similar symptom profile that consisted of depressed mood, psychomotor retardation, apprehension, anxiety, and perplexity. Anxiety neurosis, on the other hand, was said to present with anxiety but was also known to present with symptoms of depression. In the end, neither DSM I nor DSM II drew a clear line to distinguish between anxiety and depression.

Perhaps, the best summary of the relationship between anxiety and depression up to the 1970s was presented by Roth [1972] who stated: "Most of the workers in the field, whether Kraepelinian, psychoanalytic, Meyerian, or Genetical-interactional in their approach towards classification of affective disorder, have conceived of anxiety and depression as closely related and interlocked forms of emotional response in respect to both normal and pathological reaction."

THE 1970S AND EARLY 1980S: ANXIETY AND DEPRESSION APART

In 1972, Roth and colleagues published epidemiological studies on the classification of affective disorders [Roth et al., 1972; Gurney et al., 1972]. In particular, they examined the relationship between anxiety and depression, differentiating the two on the basis of symptom clusters, using "discriminant function analysis." These authors found a bimodality of symptom scores, suggesting that anxiety states and depressive illness characterize two different groups of patients. These findings were incorporated into the definitions of psychiatric illnesses in DSM III.

DSM III [1980] was designed to be an atheoretical, symptom-oriented classification. It introduced explicit inclusion and exclusion criteria, including such data as number and type of symptoms, age of onset, and type and extent of disability. It, thus, established thresholds for various disorders. It allowed for multiple diagnoses on Axis II (personality disorders) and on Axis III (physical disorders). It did not, however, allow for comorbid diagnosis of an anxiety disorder along with major depression in Axis I. Moreover, it gave major depression precedence over anxiety disorders. Simply put, there was no diagnostic mechanism for acknowledging the presence of an anxiety disorder in the context of major depression.

Together, the epidemiologic study of Roth and the diagnostic guidelines of DSM III supported the idea that anxiety and depression were two distinct entities. Of this conclusion, Maser et al. [1995] stated that, "it

brought a (premature) closure to the question of shared vulnerability (matrix) ... for anxiety and depression."

THE LATE 1980S AND 1990S: ANXIETY AND DEPRESSION TOGETHER AGAIN

Various authors challenged the validity of the hierarchical and exclusionary relationship between anxiety and depression, as was put forth in DSM III. So strongly were these ideas challenged that in DSM III-R and DSM-IV the restriction on Axis I was lifted, opening the door for the diagnosis of both anxiety and depressive disorders on Axis I. Soon, it became clear from epidemiological studies that the comorbidity of anxiety and depression was quite frequent.

Table 1 summarizes some of this epidemiologic data in terms of lifetime comorbidity of several anxiety disorders with major depressive disorder. In Table 1, data are reported as rough estimates, since the literature reports a wide range of values for percent of life-time comorbidity. On the whole, Reiger [1988] estimated that the comorbidity between anxiety disorders and either major depressive disorder or dysthymia was 25–40%. This is a much higher percentage of comorbidity than would be expected if the disorders were completely independent (i.e., if comorbidity was solely a function of chance).

So, after less than two decades (the late 1970s and the 1980s), the concept of anxiety and depression being separable entities have again begun to be viewed as less distinct and more overlapping entities.

EXPLORING THE RELATIONSHIP BETWEEN DEPRESSION AND ANXIETY

Table 2 summarizes the possible relationship between anxiety and depression. Several lines of investigation can be used to explore this relationship. A partial list of these investigations include epidemiology (including population genetics), neuropsychological, and CNS pathophysiological studies. Additional approaches involve the comparative analysis of phenomenological clusters and the treatment response to various medications, i.e., pharmacological dissection.

TABLE 1. Estimates of life-time comorbidity depression and anxiety*

Specific anxiety disorder	Anxiety disorders with comorbid major depressive disorder	Major depression with comorbid anxiety disorders
GAD	~60%	~20%
Panic	~40–50%	~30%
OCD	~30%	—
Phobia-soc	~35%	~30%
PTSD	~30–40%	—
Anxiety symptoms	—	~60%
Anxiety disorder	~40%	~60%

*See Gorman, 1997; Kessler, 1994; Ries Merikangas, 1995; Dubson & Chung, 1990; Lydiard, 1996; Weissman, 1994; Gorman, 1996; Pasnau, 1994; Solomon & Bleich, 1998.

TABLE 2. Possible relationship between depression and anxiety

Both anxiety and depression are reflections of the same phenomenon

1. Both are reflections of the same phenomenon (different parts of the same elephant)
2. One of the two is but a mere reflection of the other
3. One of the two induces changes that lead to the other

There is a common factor for both anxiety and depression

1. There is common factor to both anxiety and depression (e.g., stress, negative affectivity, or vulnerability). Such vulnerability may interact with other parameters leading to anxiety, depression, or mixed anxiety-depression (common factor point of view)

Anxiety and depression are two separate entities

1. These are two separate entities. Mainly they can be either depression or anxiety (sometimes referred to as the traditional point of view)
2. These are two separate entities. However they may frequently appear together (comorbid point of view)
3. These are two separate entities; each can appear at threshold or sub-threshold level. Any combination is possible (mixture subsyndromal point of view)
4. Comorbidity is a common final pathway of two distinct conditions

The method to be used in the remainder of this paper is evaluation of clinical response to psychotropic medications in the context of anxiety and depressive illnesses. First, we will consider a focused review of current data related to the therapeutic profiles of available medications which are currently used in the treatment of anxiety and depressive disorders. The particular disorders that will be considered in this analysis are major depressive disorder and the anxiety disorders including panic disorder, social phobia, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and generalized anxiety disorder (GAD). We will then propose some of the guiding principles that are used in our approach to pharmacological dissection. Finally, we will demonstrate the process by way of a few examples.

MEDICATION TRIALS OF ANXIETY AND DEPRESSION

The process of pharmacological dissection is based upon knowledge of the therapeutic profiles of a variety of medications or treatments. Since such knowledge is fundamental to the process of pharmacological dissection, we will provide some relevant data enabling such dissection. In general, it appears that most medications which are principally used as antidepressants (e.g., TCAs, MAOIs, and SSRIs) are, also, efficacious as anxiolytics (see Table 3). On the other hand, this same reciprocity of therapeutic profiles is not always evident in medications which are principally used as anxiolytics (e.g., various benzodiazepines). When discussing relevant data, (published clinical trials -

predominantly double-blind studies), findings will be grouped by disorder, first focusing on the role of antidepressants in anxiety disorders and then focusing on the role of anxiolytics in major depression. This will provide us with data necessary for a pharmacological dissection between the entities of the anxiety disorders and major depressive disorder. Thereafter, we will discuss the need for higher doses of certain psychotropics in panic disorder and OCD. Although these data are more relevant for a pharmacological dissection within the sphere of anxiety disorders, it will enable us to further demonstrate the usefulness of pharmacological dissection to differentiate disorders.

ANTIDEPRESSANT USE IN ANXIETY DISORDERS

Panic disorder. Klein and Fink [1962] examined behavioral response to imipramine in an open study of 215 inpatients with anxiety disorders. This was the first study to demonstrate the beneficial effect of imipramine in a subgroup of 14 patients who were suffering from panic attacks. At discharge, 79% (11 of 14) were improved and 21% (3 of 14) were much improved. The efficacy of imipramine in treatment of panic attacks was later confirmed by Klein et al. [1964] in a small double-blind study. Thirteen additional double-blind studies have confirmed the efficacy of imipramine in the treatment of panic disorder, phobia plus panic attacks, agoraphobia plus panic attacks, and phobic anxiety [Jefferson, 1997]. Also, Jefferson [1997] summarized the data supporting the efficacy of MAOIs in the treatment of panic disorder, suggesting that the most definitive evidence was provided by Sheehan et al. [1980]. In this study 57 patients with "endogenous anxiety" were treated for 12 weeks with either phenelzine, imipramine, or placebo. At week 6, both drugs were better than placebo. By the end of the study, phenelzine was shown to be more efficacious than imipramine in most of the outcome measures. The SSRIs have also been shown to be effective in panic disorder. Black et al. [1993] compared fluvoxamine with placebo in an 8-week trial. At the end of the study, 81% of patients treated with fluvoxamine were free of symptoms, while only 29% of the placebo group responded. Efficacy of sertraline in panic disorder was demonstrated in a large placebo controlled study of 320 patients [Gorman et al., 1994; Rapoport et al., 1998]. Efficacy of paroxetine in panic disorder was demonstrated in at least two double-blind controlled studies [Jefferson, 1997; Oehrberg et al., 1995]. Efficacy data for fluoxetine is supported by a small double-blind study [Bystritsky et al., 1994]. Efficacy of citalopram was demonstrated in a large double-blind, placebo and clomipramine controlled trial of 475 patients [Wade et al., 1997]. Alprazolam has been shown to be as effective as imipramine and to be more effective than placebo [Ballenger et al., 1988]. Inositol, a simple sugar with antidepressant efficacy [Levine, et al., 1995], has been reported to have efficacy in panic disorder, based

TABLE 3. Efficacy of pharmacological treatments for anxiety disorders and major depression

Medication class	Spectrum of Efficacy					
	MDD	Panic	Social phobia	OCD	PTSD	GAD
Traditional antidepressants						
SSRIs (including clomipramine)	x	x	x	x	x	x
TCA's (excluding clomipramine)	x	x			x	x
MAOIs (including RIMAs)	x	x	x	x	x	
Traditional anxiolytics						
Benzodiazepines (diazepam, clonazepam)		x	x			x
Triazolobenzodiazepines (alprazolam)	x	x	x			x
Buspirone	x			x		x

upon a 4-week double-blind cross-over study [Benjamin et al., 1996]. While the literature addressing efficacy of the newer antidepressants in panic disorder is inadequate in terms of placebo controlled studies, data from one site (n=25) of an 8-week multi-site double blind study of venlafaxine for treatment of panic disorder has demonstrated a trend toward efficacy of venlafaxine as compared to placebo [Pollack et al., 1996].

Charney et al. [1986] found trazodone to be less effective than imipramine or alprazolam in treating panic disorders, and bupropion does not appear to be effective [den Boer and Westenberg, 1988]. Interestingly, bupropion does not seem to be effective in panic disorder [Sheehan, 1983].

Social phobia. Keck and McElroy [1997] surveyed the literature on social phobia, finding seven double-blind studies of antidepressants being used in the treatment of social phobia. Five of these studies assessed the efficacy of MAOIs and/or RIMAs (reversible inhibitors of monoamine oxidase) in social phobia. Liebowitz et al. [1992] conducted an 8-week study comparing parallel groups of phenelzine vs. atenolol vs. placebo. Response rates were 64% for phenelzine, 30% for atenolol, and 23% for placebo. Gelernter et al. [1991] conducted a 12-week study that compared parallel groups of phenelzine vs. alprazolam versus placebo. Response rates were 69% for phenelzine, 38% for alprazolam, and 20% for placebo. Versiani et al. [1992] also conducted a parallel group study for 16 weeks that compared phenelzine vs. moclobemide vs. placebo. Response rates were 91% for phenelzine, 82% for moclobemide, and 43% for placebo. Another parallel group study was performed by van Vliet et al. [1992]. This 8-week study compared brofaromine with placebo and response rates were 79% for brofaromine (belonging to the RIMA class) and only 14% for placebo. The final study on MAOIs/RIMAs in social phobia was again a parallel design, this time for 12 weeks, which compared brofaromine with placebo. Response rates were 79% for brofaromine and 26% for placebo [Fahlen et al., 1995]. The remaining two double-blind studies assessed the efficacy of SSRIs in social phobia. Van Vliet et al. [1994] studied parallel groups of fluvoxamine versus placebo. Response rates were 47% for fluvoxamine and 8% for placebo. Katzelnick et al.

[1995] performed a cross-over study of sertraline vs. placebo, which demonstrated response rates of 50% for sertraline and 9% for placebo.

Obsessive-compulsive disorder. The treatment of OCD with clomipramine has been demonstrated in a large multicenter study (n=520) [Anonymous, Clomipramine Collaborative Study Group, 1991]. An average reduction in OCD symptoms of 40% was reported in the clomipramine group, while only a 4% reduction of symptoms was seen in the placebo group. Several of the newer SSRIs have also demonstrated efficacy in OCD [Chouinard, 1992; Griest et al., 1995a,b]. In a multi-center meta-analysis, Griest et al. [1995a] found that placebo controlled trials have demonstrated that clomipramine, fluoxetine, and sertraline are superior to placebo. Clomipramine, however, did have a larger effect size as compared to the other SSRIs. Trazodone was found not to be an effective anti-obsessional agent in OCD in one double-blind controlled study [Pigott et al., 1992].

Posttraumatic stress disorder. Three studies have evaluated TCAs in the treatment of PTSD. Frank et al. [1988] compared imipramine, phenelzine, and placebo. Both imipramine and phenelzine were found to be superior to placebo. Davidson et al. [1990] showed in an 8-week trial that amitriptyline up to 300 mg/day may improve some PTSD symptoms as compared with placebo. Reist et al. [1989] evaluated the efficacy of desipramine vs. placebo and found the desipramine group had improvement of depressive symptoms but no significant improvement of the core PTSD symptoms. A double-blind placebo controlled study by van der Kolk et al. [1994] demonstrated superiority of fluoxetine over placebo.

Generalized anxiety disorder. GAD, perhaps, has had the least clear results. Hoehn-Saric et al. [1988] studied outpatients with GAD in a double-blind trial comparing alprazolam and imipramine for 6 weeks. Both medications were comparable in terms of reducing anxiety. Imipramine was superior to alprazolam in terms of reducing depressive symptoms, obsessive and somatic symptoms, hyperarousal, and interpersonal sensitivity. Rickels et al. [1993] compared imipramine, trazodone, diazepam, and placebo over an 8-week period in 230 GAD patients. At 3 weeks, all active drugs

were superior to placebo. At week 4 imipramine was superior to trazodone and diazepam. By the end of week 6 only imipramine was superior to placebo. No correlation between baseline depression and the outcome was found. However, in a subgroup meeting also criteria for major depression, imipramine and trazodone were superior to diazepam and placebo. Roca et al. [1997] conducted an 8-week double-blind study of paroxetine, imipramine, and 2-chlorodesmethyldiazepam in 81 outpatients with GAD. All three medications showed significant improvement after 8 weeks. However, conclusions drawn from these results should be taken with caution for the lack of a placebo group. Casacalenda and Boulenger [1998] summarize the results of these antidepressant drug trials in GAD concluding that TCAs and the SSRI paroxetine demonstrate efficacy in GAD compatible to that of the benzodiazepines.

ANXIOLYTIC USE IN MAJOR DEPRESSIVE DISORDER

While many antidepressants are quite effective in the treatment of a variety of anxiety disorders, this same reciprocity does not appear to be the case for the use of anxiolytics in the treatment of depression. Schatzberg and Cole [1978] reviewed 20 double-blind studies and concluded that benzodiazepines are not particularly effective for the treatment of depression. A possible exception is the use of the triazolo-benzodiazepine, alprazolam. Casacalenda and Boulenger [1998] surveyed 21 double-blind controlled studies comparing alprazolam, TCAs, and/or placebo in adult subjects with major depression. These authors conclude that alprazolam in doses up to 4 mg daily appear to have an acute effect comparable to that of several TCAs in outpatients with mild to moderate major depression [Rickels et al., 1985, 1987; Feighner et al., 1983]. However, alprazolam does not seem to be effective in inpatients with severe major depression or significant psychomotor retardation or decreased REM latency [Hubain et al., 1990; Eriksson et al., 1987; Rush et al., 1985].

Some writers have suggested that high doses of benzodiazepines may be effective in the treatment of depression [Tyrer and Tyrer, 1994]. However, Petty et al. [1995] and Lipman et al. [1986] demonstrated in double-blind placebo controlled studies that chlordiazepoxide was not efficacious in the treatment of depression. In a more recent review on this topic, Birkenhager et al. [1995] commented that comparative studies with classical (non-triazolo) benzodiazepines in major depression show that these agents do not alleviate the core symptoms of depression. They do, though, have an effect on sleep and anxiety. Classic benzodiazepines show some efficacy in minor depression, but this conclusion, again, may be related to efficacy in patients suffering from anxiety disorders rather than depression. Triazolo-benzodiazepines, mainly alprazolam (mean doses approximately 2.5 to 4 mg/day), have been

found to be effective in mild to moderate depression, although they have been shown to be inferior to tricyclic antidepressants (TCAs) in patients with endogenous or melancholic depression. Furthermore, it is questionable whether triazolo-benzodiazepines ameliorate the core symptoms of depression [Casacalenda and Boulenger, 1998].

Buspirone, an anxiolytic drug [Rickels et al., 1990; Fulton, 1997], has shown some efficacy in reducing depressive symptoms in patients diagnosed with major depression which was associated with significant anxiety symptoms. Robinson et al. [1990] reported these results in a large (n=382) double-blind placebo controlled study, noting that higher doses (40–90 mg per day) were used and that particular items of improvement on the Hamilton Depression Rating Scale represented some of the core depressive symptoms, such as depressed mood, guilt, work and interest, anergia, and diurnal variation of mood. Fabre et al. [1990] studied 140 outpatients and reported that buspirone (41–54 mg daily) was better than placebo in the treatment of major depression up to 6 weeks (but not in week 8). Buspirone was superior to placebo in a subgroup of patients with severe melancholic depression. However, since the analysis used was intent-to-treat and the drop-out rate was very high, these results should be viewed with caution. Rickels et al. [1997] studied 155 patients suffering from major depression with moderate anxiety. Twenty-nine percent of buspirone and 40% of placebo treated patients discontinued treatment before 8 weeks. Thirty-five percent of subjects taking placebo and 70% of buspirone-treated patients were rated moderately to markedly improved at 8 weeks. Casacalenda and Boulenger [1998], surveying the literature on buspirone in major depression, concluded that buspirone has modest antidepressant efficacy especially in patients exhibiting anxiety symptoms and that one cannot rule out that at least part of the improvement seen was due to an antianxiety effect of buspirone.

VARIABLE DOSAGE REQUIREMENTS

Benzodiazepines in panic disorder versus GAD. Charney and Woods [1989] studied alprazolam and lorazepam in 48 patients with panic attacks with or without agoraphobia. Both benzodiazepines were shown to have similar efficacy in reducing the panic attacks. It is of note, though, that the doses required to achieve such response were double those required for the treatment of generalized anxiety (mean daily dose of alprazolam and lorazepam, administered for panic disorder at week 6 of the study, were 2.7 and 6 mg, respectively). Similar results, that is, that higher doses of benzodiazepines were required in the treatment panic disorder, were reported by Schweizer et al. [1988].

Clomipramine and SSRIs in OCD versus major depression. In the meta-analysis by Greist et al. [1995a], fixed-dose studies revealed that the “best” doses of fluoxetine and sertraline were 60 mg and 200

mg, respectively. The recommended doses of these drugs for major depression are in general about 20 mg of fluoxetine [i.e., Patris et al., 1996]. This data suggests that higher doses of serotonergic antidepressants are necessary for effective treatment of OCD as compared to those in major depression.

SUPERIOR EFFICACY OF VARIOUS TREATMENTS IN PARTICULAR ILLNESSES OR SUBGROUPS OF ILLNESSES

Superior efficacy of serotonergic antidepressants in OCD. Whereas other anxiety disorders respond to a greater variety of antidepressants, OCD appears to respond more selectively to clomipramine and the SSRIs [Lydiard, 1994]. These medications seem to represent one class of antidepressants based on our current understanding of putative mechanisms of action, i.e., serotonergic modulation.

AN APPROACH TO PHARMACOLOGICAL DISSECTION

While the intuitive process of pharmacological dissection is not novel, there is no established method by which this process is carried out. Toward this end, we draw on the rule of logic known as “Ockham’s Razor,” which was proposed by William of Ockham (1285–1349). Essentially, this rule states that, when seeking to explain the nature of something, the simplest explanation is more likely to be true than a more complicated explanation. The elegant simplicity of this principle was a noticeable departure from other philosophical approaches of the time and it has been suggested that Ockham’s Razor paved the way for modern science [Audi, 1995].

Using Ockham’s Razor as a guide, we shall formalize an approach to pharmacological dissection by presenting three basic rules that will be used to compare anxiety and depression. In brief, The Rule of Shared Efficacy describes situations that suggest biological similarity; The Rule of Unshared Efficacy describes situations that suggest biological differences; and The Rule of Limited Efficacy describes situations that suggest both shared and unshared biological attributes.

RULE OF SHARED EFFICACY

If a single medication is efficacious in two disorders, then we will assume that these disorders share a common biological dysfunction. If this shared efficacy exists for more than one class of medication, then the disorders may share more than one biological property.

RULE OF UNSHARED EFFICACY

If a single medication is efficacious in one disorder but not the other then we will assume that these disorders have different biological attributes.

RULE OF LIMITED EFFICACY

If a medication is efficacious in one disorder, but has a lower rate of response or requires significantly higher doses in a second disorder, then we will assume that there is some biological similarity between these disorders. However, this situation of limited efficacy, also, suggests that there is unshared biological attributes.

The intention of our pharmacological dissection is to gain some insight into the shared and unshared biological characteristics of anxiety and depression. It is important to note that, by these rules, we are attributing “biological similarity” based on pharmacological dissection but not other dissecting tools. So, the conclusions that we reach through this analytic process will need to be considered as suggestive only [see also Fyer et al., 1990].

EXAMPLES OF PHARMACOLOGICAL DISSECTION

Three examples will be provided in order to demonstrate the process of pharmacological dissection. The first example will consider the relationship between MDD and panic disorder and the second will consider the relationship between MDD and OCD. A third example will consider the relationship between panic disorder and GAD, particularly to demonstrate the Rule of Limited Efficacy.

MDD AND PANIC DISORDER

By the Rule of Shared Efficacy, we conclude that there is some degree of biological similarity between these two disorders. Medications from each of the three major antidepressant groups (TCAs, SSRIs, and MAOIs) have demonstrated efficacy in both MDD and panic disorder [Gorman, 1994, 1996, 1997]. The two best studied members of the TCA class are imipramine and clomipramine. Studies suggest that these two medications are either equivalent in terms of panic disorder efficacy or that clomipramine may be superior [Boyer, 1995; Modigh et al., 1992]. Good efficacy for both disorders has been demonstrated with the SSRIs as well as MAOIs.

By the Rule of Unshared Efficacy, it is important to note that bupropion, while it is effective in the treatment of MDD, does not appear to be efficacious in the treatment of panic disorder [Sheehan, 1983].

In conclusion, this pharmacological dissection suggests that there is a biological similarity between MDD and panic disorder. This is supported by the observation that three classes of antidepressants demonstrate efficacy in both disorders. The fact that bupropion is ineffective in panic disorder suggests there are also unshared biological attributes between these disorders.

Speculating briefly about possible meanings in

terms of shared biological attributes, the most consistent similarity in terms of putative mechanisms of action is the role of 5-HT enhancement. Support for this assertion derives from the idea that the most effective antidepressants in the treatment of panic disorder are the more pro-serotonergic agents, such as clomipramine and the SSRIs [Boyer, 1995; Modigh et al., 1992]. Additionally, the apparent lack of efficacy in panic disorder of bupropion, which lacks significant serotonergic effects, suggests a less significant role for the NE and DA systems in this illness [Ascher et al., 1995].

MDD AND OCD

By the Rule of Shared Efficacy, we can again conclude that there is biological similarity between MDD and OCD. Primarily, the SSRIs and clomipramine have been shown to be efficacious in both MDD and OCD.

By the Rule of Unshared Efficacy, we note that non-serotonergic antidepressants do not display reciprocal efficacy in OCD. While there have been case reports that suggest limited efficacy of several of the MAOIs, and of the more noradrenergic TCAs, there are no controlled studies that support the efficacy of these agents.

Speculating about shared biological attributes, serotonergic mechanisms of action of clomipramine and the SSRIs suggest that a disordered serotonergic system may represent a common biological property between MDD and OCD.

PANIC DISORDER AND GAD

By the Rule of Shared Efficacy, we conclude that there is biological similarity among panic disorder and GAD. Since Klein's demonstration of therapeutic efficacy in the 1960s, imipramine is known to be an effective treatment for panic disorder. More recently, it has been shown that imipramine is also an effective treatment of GAD [Rickels et al., 1993]. Additionally, the SSRI paroxetine is clearly effective in the treatment of panic disorder and has been suggested in one recent study [Rocca et al., 1997] to have efficacy in GAD (this was neither double-blind nor placebo controlled).

By the Rule of Limited Efficacy, we consider the case of the benzodiazepines. While standard doses of benzodiazepines appear to demonstrate efficacy in the treatment of GAD, this is not the case for panic disorder. Panic disorder appears to be more responsive to higher doses of benzodiazepines, such as alprazolam and lorazepam [Charney and Woods, 1989].

In conclusion, this pharmacological dissection supports the existence of both shared and unshared biological properties for these two disorders. Biological commonality is demonstrated by the efficacy of imipramine in both illnesses. Preliminary findings suggest that the SSRIs may also prove to be efficacious in both anxiety disorders. The limited efficacy of the GABA-ergic medications in panic disorder suggests that beside shared biological attributes there may be unshared biological attributes between GAD and panic disorder.

Speculating briefly about the possible meaning of these similarities, the strongest association between GAD and panic disorder is demonstrated by the efficacy of imipramine, thus suggesting a role for the NE system in these illnesses. While not yet definitively demonstrated, there may be efficacy with paroxetine as well. This may eventually lead to recognition that the 5-HT system may be involved in GAD as well. Alternatively, it may reveal that even the relatively small NE effects of paroxetine or some other actions of paroxetine are involved in the pathology of GAD. The gamma aminobutyric acid (GABA) system, the apparent active site of the benzodiazepines, may be involved to a greater degree in GAD and to a lesser extent in panic disorder.

If these rules are applied to MDD and other anxiety disorders, such as GAD, PTSD, and social phobias, it will be noted that MDD has shared biological properties with these disorders as well. However, space constraints and lack of double-blind studies of several classes of antidepressants in these anxiety disorders prevents us from elaborating further. For example, there is lack of good data on TCAs in social phobia and MAOI and SSRI antidepressants in GAD.

DISCUSSION

Since the earliest conceptualizations of melancholia, this malady was considered to be comprised of both anxiety and depressive symptoms. Modern pharmacological treatment for anxiety and depression began in the 1950s. During the 1960s and early 1970s, the existing knowledge and experience suggested that the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were efficacious for treatment of depression and that benzodiazepines (BNZs) were efficacious for treatment of anxiety, but not vice versa (see Table 4). In contrast to the pharmacological dichotomy between anxiety and depression, diagnostic manuals prior to DSM III [1980] essentially grouped together what appeared to be pharmacologically distinct entities. In DSM III, however, a specific effort was made to distinguish between anxiety and depression. By prohibiting the co-diagnoses of major depressive disorder along with any of the anxiety disorders, it became necessary to separate anxiety and depression, choosing the most accurate of the two diagnoses in cases of ambiguity. However, a growing body of psychiatric knowledge, based upon clinical observation and treatment with available medications (see Table 4) demonstrated that the goal of full separation between anxiety and depression was unattainable. Thus, subsequent diagnostic manuals (DSM III-R and DSM IV) have opted to allow, on Axis I, both diagnoses of major depressive disorder and one or more anxiety disorders. Furthermore, in DSM IV, anxiety disorder NOS is defined as a mixture of anxiety and depressive symptoms. DSM IV also introduces the diagnostic consideration of mixed anxiety-depressive disorder.

TABLE 4. Evolution of the indications for pharmacological treatments for anxiety and depression during the last five decades

	Treatment for major depression	Treatment for anxiety disorders	Phenomenological attitude towards anxiety and depression
Until 1950		Barbiturates	Anxiety and depression together
1950s and 1960s	MAOIs Tricyclics	Benzodiazepines	Anxiety and depression together
1970s and early 1980s		Alprazolam Buspirone	Anxiety and depression apart
Late 1980s and 1990s	SSRIs RIMAs		Anxiety and depression together

Upon reflection, the current conceptualization of the relationship between anxiety and depression is not fundamentally different from the conceptualization of several hundred years ago. Anxiety and depression, both then and now, appear to be closely linked. Perhaps, the greatest difference is that present day views are supported not only by clinical observation but also by biological data. It is important to realize the value of this accumulating data, since it is a means by which we are able to recognize both similarities and differences between the currently defined clinical entities of anxiety and depression. In essence, techniques used to gain biological data serve as dissection tools to better define clinical entities. These dissecting tools include, for example, phenomenological, endocrinologic, neuro-receptor, and genetic investigations.

Another available approach for studying the relationship between anxiety and depression is pharmacological dissection. In the preceding pages, we have offered an approach based upon three basic rules that can be applied in order to perform such a dissection. Along with other biological findings, this pharmacological dissection tool can be used to suggest possible shared and unshared biological matrices for anxiety and depressive disorders. Several biological findings support the similarity between anxiety and depression. A few examples of shared characteristics include 1) blunted growth hormone response to clonidine [Siever et al., 1992; Coplan et al., 1995; Uhde, 1986], 2) dysregulation of the hypothalamic-pituitary-adrenal axis [Butler and Nemeroff, 1990], and 3) dysfunction of brain response to serotonergic challenge [Mann et

al., 1996]. Additionally, genetic studies have suggested similarity in terms of shared genetic risk in both anxiety and depression [Kendler et al., 1987, 1992]. Other findings suggest differences between anxiety and depression. A few examples of unshared characteristics in anxiety and depression include shortened REM latency and increased REM density during the first REM period in depression but not in anxiety disorders [Stein et al., 1994], different patterns in platelet receptor binding [Cameron et al., 1984], and low electrodermal activity in major depression compared with high values in anxiety disorders [Stein et al., 1994].

Thus we argue that the long-standing perception along with the accumulating biological evidence and pharmacological dissection suggests both shared and unshared characteristics for these two clinical disorders.

Such suggestions may effect future research by focusing on shared and unshared biological characteristics instead of concentrating on either entity alone. It may also affect the development of newer drugs for these conditions. For instance, research evaluating drugs for major depression tend to overlook drugs that show efficacy in models for anxiety disorders and vice versa [Robinson and Kurtz, 1990].

In the above dissection, we treated anxiety disorders and major depression without referring to the evolution of these disorders and their different stages. Differences in treatment response to the different classes of medications may vary depending upon the "stage" of the illness. Also, we did not refer to the severity or the heterogeneity of the clinical presentation of these disorders (i.e., major depression with melancholia vs.

major depression without melancholia). Still another important variable is the length of the pharmacological treatment, since there may be a difference between the result of pharmacological dissection done with short-term treatment trials (few weeks) compared with long-term trials (several months to years). Future dissections may need to consider these issues.

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