REVIEW

Treating comorbid anxiety and depression: Psychosocial and pharmacological approaches

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Abstract

Comorbid anxiety with depression predicts poor outcomes with a higher percentage of treatment resistance than either disorder occurring alone. Overlap of anxiety and depression complicates diagnosis and renders treatment challenging. A vital step in treatment of such comorbidity is careful and comprehensive diagnostic assessment. We attempt to explain various psychosocial and pharmacological approaches for treatment of comorbid anxiety and depression. For the psychosocial component, we focus only on generalized anxiety disorder based on the following theoretical models: (1) "the avoidance model"; (2) "the intolerance of uncertainty model"; (3) "the meta-cognitive model"; (4) "the emotion dysregulation model"; and (5) "the acceptance based model". For depression, the following theoretical models are explicated: (1) "the cognitive model"; (2) "the behavioral activation model"; and (3) "the interpersonal model". Integration of these approaches is suggested. The treatment of comorbid anxiety and depression necessitates specific psychopharmacological adjustments as compared to treating either condition alone. Serotonin reuptake inhibitors are considered first-line treatment in uncomplicated depression comorbid with a spectrum of anxiety disorders. Short-acting benzodiazepines (BZDs) are an important "bridging strategy" to address an acute anxiety component. In patients with comorbid substance abuse, avoidance of BZDs is recommended and we advise using an atypical antipsychotic in lieu of BZDs. For mixed anxiety and depression comorbid with bipolar disorder, we recommend augmentation of an antidepressant with either lamotrigine or an atypical agent. Combination and augmentation therapies in the treatment of comorbid conditions vis-à-vis monotherapy may be necessary for positive outcomes. Combination

therapy with tricyclic antidepressants, gabapentin and selective serotonin/norepinephrine reuptake inhibitors (*e.g.*, duloxetine) are specifically useful for comorbid chronic pain syndromes. Aripiprazole, quetiapine, risperidone and other novel atypical agents may be effective as augmentations. For treatment-resistant patients, we recommend a "stacking approach" not dissimilar from treatment of hypertension In conclusion, we delineate a comprehensive approach comprising integration of various psychosocial approaches and incremental pharmacological interventions entailing bridging strategies, augmentation therapies and ultimately stacking approaches towards effectively treating comorbid anxiety and depression.

Key words: Generalized anxiety disorder; Cognitive behavioral therapy; Treatment-resistant mood disorders; Bipolar disorder comorbid with anxiety; Augmentation strategies; Major depressive disorder

Core tip: A comprehensive diagnostic assessment is a critical first step in treating patients with mixed anxiety and depression. Practitioners should be alert to the possibility that this may be a concealed bipolar disorder since misdiagnoses rates can be 70%. Treatment in the patient with uncomplicated non-substance-abusing unipolar disorder may be quite straight forward. However patients are in all likelihood treatment-resistant with probable bipolarity and substance abuse. In the latter instance, more complex regimen of medications with combinations of pharmacotherapy are required. Finally, a "stacking" approach, to cover the full spectrum of available receptors targeted by current pharmacotherapy regimens is recommended.

INTRODUCTION

The article reviews the comorbidity of anxiety and mood disorders, with a primary focus on treatment. For the psychosocial component, we will only focus on the comorbidity of generalized anxiety disorder and major depressive disorder, as a focus on each anxiety disorder would exceed the scope of the current article. However, for the psychopharmacological component, we focus on mood disorders comorbid with the gamut of anxiety disorders. It should be noted that for psychosocial treatments, many of the principles are common to treatment of a spectrum of disorders whereas in psychopharmacology a precise choice of medications may be required for specific presentations.

PSYCHOSOCIAL APPROACHES TO COMORBIDITY OF GENERALIZED ANXIETY DISORDER AND MAJOR DEPRESSIVE DISORDER

Generalized anxiety disorder (GAD) is the most common anxiety disorder in primary care[1] and has a lifetime prevalence of 5.1% or possibly higher[2]. Major depressive disorder (MDD) has, by certain estimates, a lifetime prevalence of 16.2%[3]. The prevalence of the comorbidity of GAD and MDD is as follows; 62% of individuals with GAD also had an MDD episode in their lifetime[4], while 59% had the episode of MDD in the past year[5] and comorbidity of GAD and MDD predicts a poor outcome[6].

THEORETICAL MODELS

In the current article, we describe a range of alternative yet complementary theoretical models of the comorbidity of GAD and MDD. The theoretical models of GAD include: (1) the Avoidance Model of GAD first advanced by Borkovec *et al*[7]; (2) the intolerance of uncertainty (IU) model[8]; (3) the metacognitive therapy model (MCT)[9]; (4) the emotion dysregulation model[10]; and (5) the acceptance-based model[11]. The theoretical models of MDD include: (1) the cognitive model[12]; (2) the behavioral activation model[13]; and (3) the interpersonal model[14].

THE AVOIDANCE MODEL OF GAD

In the Avoidance Model of GAD, worry is considered a language- and thought-based activity, which activates somatic and emotional sensations at the same time inhibiting mental images. According to this model, when somatic and emotional experiences are inhibited, emotional processing of fear and avoidance is poorly achieved; which is important for habituation and extinction. This model proposes that worry is "a poor attempt to solve problems and deal with a perceived threat while avoiding the aversive somatic and emotional experiences that occur when confronting the feared stimulus"[15]. On the contrary, "worry becomes negatively reinforced as less distressing thoughts replace catastrophic mental images reducing somatic and emotional experiences"[15]. Here, "worry is maintained by positive beliefs about worrying"[15].

Treatment models that were developed based on the Avoidance Model focus on "self-monitoring of situations, thoughts, feelings, physiological reactions and behaviors"[15]. In addition, the other components include "progressive muscle relaxation exercises and breathing retraining; self-control desensitization such as imaginal practice to develop different, more effective ways of

coping; specific "worry time" which leads to gradual stimulus control; monitoring of worries including what situations are feared, what outcome is feared and what outcome actually occurs; present moment focus and expectancy-free living (realistic expectations)"[15].

The integrative therapy component[16] is associated with the interpersonal problems that are frequently involved in the content of worry which were not included in previous cognitive behavioral therapy (CBT) protocols. This added component to the therapy specifically focuses on interpersonal problems and avoidance of emotions. The results of a comparative study show an effect size of 2.80 for the avoidance CBT model alone and 3.15 for CBT + I/EP (Interpersonal and emotional processing therapy). The response percentage after treating with CBT + SL (supportive listening) was 67% whereas it was 83% with CBT + I/EP.

IU model

The IU model is based on the hypothesis that in individuals with GAD, "uncertain or ambiguous situations are very stressful or uncomfortable and can lead to chronic worry"[15]. According to this model, beliefs about worry include "the idea that worry will prevent some dreaded outcome or prepare the individual in some way for the dreaded outcome"[15]. This model also suggests that individuals have a "negative problem orientation" and engage in "cognitive avoidance" both of which maintain the worry. In negative problem orientation, individuals have "lack of confidence in the ability to solve problems"[15] and, moreover, "problems were perceived as threats and individuals have low frustration tolerance when dealing with problems and become pessimistic about the outcome"[15]. Cognitive avoidance is associated with thought replacement, thought distraction and thought suppression.

The treatment methods that were developed based on the IU model include components like self-monitoring; psycho-education about problem orientation; evaluating worry beliefs; cognitions about core fears that underlie worries; restructuring and exposure and improving problem orientation by cognitive restructuring (CR). The results of IU studies showed that 77% of individuals did not meet criteria for GAD at 6 and 12 mo post-treatment[17].

Dupuy *et al*[18] examined whether comorbid GAD/MDD individuals experienced significantly more IU compared to GAD only individuals. In this sample, the comorbid group differed in severity of GAD symptoms; in addition, they demonstrated greater IU, poorer problem orientation, and higher levels of cognitive avoidance. There was no difference in the level of beliefs about worry (both had similar positive beliefs about worry). This study demonstrates that the comorbid condition adds to the severity of symptoms compared to the GAD only condition.

MCT

The MCT makes distinction between two types of worries known as type 1 and type 2. Type 1 worry is related to "positive beliefs about worry, which helps to cope with, prevent or prepare for dreaded events"[15]. Type 2 worry is related to beliefs about worry that are negative where there is "worry about worry" and here, worry is uncontrollable, and/or considered dangerous. The "ineffective strategies associated with type 2 worry are checking behaviors, thought suppression, distraction, avoidance and reassurance seeking"[15]. These strategies interfere with questioning the validity of beliefs which will increase symptoms of anxiety thus maintaining the worry. The treatment methods that were developed based on the MCT involve exploring worry triggers, and reactions as well as efforts to control/suppress worry; socialization involving psycho-education which focuses on altering beliefs about worry instead of lessening worry directly and thought correction of beliefs about worry, both negative and positive.

The results of an open trial utilizing MCT show that at post-treatment 87% recovered and 75% of individuals maintained symptom recovery after 12 mo of treatment[19]. In a randomized trial, Wells *et al*[20] treated GAD patients with either MCT or applied relaxation (AR) with similar results: 80% recovered at post-treatment compared to 10% in AR; 70% maintained MCT response after 6 mo compared to 10% in the AR condition.

The emotion dysregulation model

The emotion dysregulation model is based on the premise that "individuals with GAD experience their emotions more intensely and/or more easily and quickly and have poor understanding of their emotions, negative attitudes about emotions and maladaptive emotional regulation and management strategies"[15]. The treatment methods that were developed based on the emotion dysregulation model seeks to improve emotional regulation as a means to improve GAD symptoms. The components include: relaxation exercises; reframing of beliefs; education about emotions; emotion skills training and experiential exposure exercises. An open label study results have demonstrated 66.7% of participants (*n* = 21) achieved high end state functioning while 81%-95% experienced significant reduction in mood, worry and other GAD symptoms[21].

The acceptance based model

The Acceptance based model is based on Hayes' model of experiential avoidance[22] and Borkovec's avoidance model[7], both of which deal with a problematic relationship with internal experiences and experiential avoidance and behavioral restriction. In this model, worry is defined as behavioral and cognitive avoidance of internal experiences. Whereas avoidance reduces short-term distress, it reinforces long-term behavioral restriction. The treatment methods that were developed based on the acceptance model comprises psycho-education about worry, avoidance, the reduction in valued

action, how emotions function and how to promote valued actions; mindfulness and acceptance exercises along with present moment awareness with the ultimate goal of behavioral change and valued actions. The results of a study demonstrate that 75% show response to treatment, whereas 62.5% of individuals meet "end-state high functioning" post-treatment[23].

CONSIDERATION OF PSYCHOLOGICAL CONSTRUCTS

Regarding psychological constructs of comorbid GAD and MDD, Fresco et al[24] have compared the scores of Penn State Worry Questionnaire (PSWQ), Response Style Questionnaire and Mood and Anxiety Symptom Questionnaire in college students and developed a four-factor solution comprised of two worry factors and two rumination factors which have a significant positive correlation to anxiety and depression. According to that study, excessive and/or pathological worry is not exclusive to anxiety disorders. The GAD group experienced higher levels of worry, including co-morbid GAD/MDD, than MDD alone group. However, the MDD group alone had higher PSWQ scores than a group comprised of non-GAD anxiety disorders[25]. In contrast, rumination is a cognitive, verbal activity associated with MDD[26]. Thus, both worry and rumination factors are separate and distinct cognitive processes but both have significant relationships to depression and anxiety[24].

Clark et al[27] propose their own model which is a modified cognitive neurophysiological model of anxiety and depression in which maladaptive schemas of the self, the surrounding environment and the future are activated through life experiences that lead to biases in information processing and negative, pessimistic or threat-related thoughts, images or interpretations.

MDD MODELS

The cognitive model
The cognitive model of MDD pioneered by Beck[12] is based on the "cognitive triad of defective, inadequate, diseased or deprived (worthless)"[15] thoughts; the "tendency to interpret experiences in a negative way and the pessimistic future with hopelessness"[15]. The treatment methods that were developed based on the cognitive model focus on the use of rating scales: to monitor mood as well as to record thoughts; and the use of techniques such as CR of dysfunctional thoughts, progressive muscle relaxation exercise, role playing and assertiveness training. The treatment was designed to be short-term, from 12 to 16 wk, beginning with an explanation of the rationale (cognitive triad), awareness of the connection between thoughts, feelings and actions, active engagement in correcting cognitive distortions and encouraging the reinstatement of previously avoided activities.

A meta-analysis of randomized controlled studies of

CBT for depression has demonstrated an effect size of 0.90 when compared to a wait-list group, 0.40 when compared to treatment as usual or attention placebo[28]. When compared to medication, CBT was just as effective[29].

The behavioral activation model
The behavioral activation (BA) model of MDD is based on the early work by Lewinsohn et al[30], which demonstrates that depressed individuals have decreased access to pleasant events. The avoidance of positive activity leads to further low mood. The treatment method includes mood and event monitoring (daily pleasant/unpleasant), scheduling of activities, with an emphasis on development of social and time management skills. Patients are encouraged to pursue pleasant activities and to tell themselves that if they do the activity they will feel better, bringing the reward more proximal. They also tell themselves how much worse they will feel if they do not engage in the activity. There is also discussion of problem behaviors with an emphasis on problem solving.

The BA model was tested for efficacy compared to cognitive therapy (CT) and paroxetine and pill placebo in a 16-wk trial. The BA group did just as well as the paroxetine group, but better than the CT group in severely depressed participants[31]. A meta-analysis of activity scheduling[32], a major component of BA, found an effect size of 0.87 compared to a control condition after treatment for depression, but in the same analysis found no significant difference when compared to CT.

The interpersonal psychotherapy model
The interpersonal psychotherapy (IPT) model of MDD is based on Sullivan's interpersonal theory[33] in which "interpersonal relationships play an important role in onset and maintenance of MDD"[15]. This model focuses on interpersonal functioning, which includes unresolved grief, interpersonal disputes, role transitions and social isolation or withdrawal.

IPT, initially a time-limited, weekly outpatient treatment for depressed patients, focuses on the connection between onset of symptoms and current interpersonal problems in the treatment. The first of the three phases of IPT treatment, usually during sessions 1-3, includes diagnostic evaluation and psychiatric history and sets the framework for the treatment. In the middle phase, strategies specific to the interpersonal problem area are pursued. During the final phase, usually the last few sessions, the patient is encouraged to recognize and consolidate therapeutic gains and to develop ways of identifying and countering depressive symptoms should they arise in the future.

The NIMH Treatment of Depression Collaboration Research Program (TDCRP) compared the effectiveness of CBT, IPT and imipramine[34]. Amongst those who completed treatment, 65% responded to CBT, 70% responded to IPT, 69% responded to imipramine while

Table 1 Descriptions of studies conducted in support of theoretical model

	n	Treatments	Diagnosis	Response rates
Avoidance model				
Integrative therapy	24	CBT + SL *vs* CBT + I/EP	GAD	CBT + SL = 66.7%
Newman *et al*[16]		14 sessions		CBT + I/EP = 83.3%
Intolerance of uncertainty model				
Ladouceur *et al*[81]	26	CBT *vs* wait list	GAD	CBT = 77%
Metacognitive model				
Wells and King[19]	10	MCT	GAD	87.5%
				MCT = 80%
Wells *et al*[20]	20	MCT *vs* AR	GAD	AR = 10%
Acceptance based model				
Roemer *et al*[23]	31	ABBT *vs* wait list	GAD	ABBT = 78%
				Wait list = 17%
TDCRP				
Elkin *et al*[34]	50	CBT		CBT = 40%; 58%
	56	IPT	MDD	IPT = 47%; 60%
	49	IMI-CM		IMI = 49%; 61%
	50	PLA-CM		PLA = 26%; 50%
Cognitive model				
Thoma *et al*[28] (meta-anlaysis)	29	CBT *vs* wait list	MDD/minor depression/dysthymia	ES = 0.90
	18	CBT *vs* TAU		ES = 0.40
	26	CBT *vs* other[1]		ES = 0.05
	23	CBT *vs* medication		ES = 0.10
Behavioral activation				
Dimidjian *et al*[31]	45	CT		High severity
	43	BA	MDD	CT = 56%; 48%
	100	ADM		BA = 60%; 76%
	53	PLA	High and low severity	ADM = 40%, 49%
Interpersonal psychotherapy model				26 wk
Peeters *et al*[37]	63	CT	MDD	CT = 41%; ES = 1.3
	56	IPT	Nonrandomized trial	IPT = 39%; ES = 1.5
	34	CT-PHT		CT-PHT = 35%; ES = 1.0
	21	IPT-PHT		IPT-PHT = 33%; ES = 1.0

First percentage refers to response rates using Hamilton Rating Scale of Depression while second refers response rates using Beck Depression Inventory. [1]Other treatments include psychodynamic, behavior, humanistic and interpersonal psychotherapy. CBT: Cognitive behavior therapy; SL: Supportive listening; I/EP: Interpersonal and emotional processing; MCT: Metacognitive therapy; AR: Applied relaxation; ABBT: Acceptance-based behavior therapy; IPT: Interpersonal therapy; IMI-CM: Imipramine plus clinical management; PLA-CM: Placebo plus clinical management; TAU: Treatment as usual; ADM: Antidepressant medication; PHT: Pharmacotherapy.

51% responded to placebo. Amongst those who were in the "intent to treat" group, 49% responded to CBT, 56% responded to IPT, 53% responded to imipramine while only 40% responded to placebo. Imipramine demonstrated greater efficacy for severe MDD rather than IPT in this sample, whereas in less severe MDD, all the groups were equivalent. When comparing medication discontinuation to both cognitive approaches and BA, both are effective in relapse prevention[35], however, BA was more effective than cognitive therapies in severe MDD[36].

A Dutch study[37] offered MDD patients the choice of treatment: CT or IPT with or without antidepressant medication with the collaboration of their clinician. Treatment duration was up to 26 wk. At 8 wk, only 20% remitted based on Beck Depression Inventory, but by 26 wk 35% remitted. All the treatments were similarly effective, even the combination of antidepressants and therapy with effect sizes ranging from 1.3 to 1.5.

DeRubeis *et al*[29], after concerns about how well the CT was administered in the TDCRP trial, tested the effectiveness of CT and antidepressant medication (paroxetine or desipramine) *vs* placebo for 16 wk in a group of depressed individuals. The results showed that both active treatments were superior to placebo at 8 wk and at 16 wk and were equivalently effective.

A listing of all the research studies conducted on the various theoretical modals can be found in Table 1.

COMPARISON OF PSYCHOSOCIAL MODELS

There are differences and similarities in all the models described above. The most notable differences include: the emotional dysregulation and the acceptance models focuses on emotional experience and exposure respectively, the CBT and the intolerance model focuses on cognitions (worries), the BA model focuses on behavior but not on CR whereas the IPT model focuses on relationships *via* behavior without any emphasis on CR. In contrast, the most notable similarities for all the models described above include the components: psycho-education, homework, CR, progressive muscle relaxation exercises and exposure.

There are many studies comparing the effectiveness

of two different types of psychosocial treatments as well as meta-analyses for response in specific disorders, such as major depression. A full inclusion of all such studies is beyond the scope of this article, but a few salient studies will be covered. Hofmann and Smits[38] conducted a meta-analysis of CBT randomized controlled studies for all adult anxiety disorders which revealed that those who completed any form of CBT were four times more likely to respond than those who were given a placebo treatment (usually a sham treatment). Hunot *et al*[39] conducted a meta-analysis of CBT treatment for GAD and found that in comparison to treatment as usual or waiting list, CBT was more effective; but when CBT was compared to supportive psychotherapy, both were equally as effective suggesting that active treatment is more effective than no treatment but good treatment is generally similarly effective.

Arch *et al*[40] compared CBT *vs* acceptance and commitment therapy (ACT) in a randomized controlled trial of 128 individuals for mixed anxiety and depression demonstrating that both were effective in reducing anxiety and improving mood with similar gains maintained at 12-mo follow-up. Although both were effective, the authors concluded that the treatments targeted different mechanisms; namely that CBT improved quality of life and ACT improved psychological flexibility.

In a study of relapse prevention[41], participants who had remitted from at least three previous episodes of MDD, were randomized to mindfulness-based cognitive therapy (MBCT), an active comparison treatment similar to MBCT except without meditation called cognitive psychological education or treatment as usual (continuing on medication and regular clinical visits). The follow-up period was 12-mo with the results that both active treatments were effective in preventing relapse but the MBCT group was most effective for individuals with significant trauma history.

Yovel *et al*[42] compared the core components of CBT and ACT in an attempt to understand how each of the treatments work. CR in CBT and cognitive diffusion (CD) in ACT are the core elements that target rumination and worry in both GAD and MDD. CR works to logically evaluate each thought and change the thought while CD works to accept the thoughts and not change them. In this study of 142 individuals, subjects were asked to identify a distressing thought through the recall of a sad, autobiographical event. After an induction task for rumination regarding the thought, they completed one of four brief interventions using either analogue CR, CD or a control intervention that included either distraction from the distressing thought or an exploration of different aspects of the thought. Results demonstrated improvement in mood about equally in both CR and CD - neither was superior to the other.

Thoma *et al*[28] conducted a meta-analysis comparing CBT to a second treatment, *e.g.*, psychodynamic or medication for major depression and/or dysthymia, with an added focus on quality of research conducted. This meta-analysis employed a rating system to evaluate methodological quality of the trials. The authors were surprised to discover that certain CBT studies, especially early ones, had "poor" quality which clearly detracted from the effect size. From 120 studies, in the regression analysis, there were four groups: CBT *vs* waiting list; CBT *vs* attention control or treatment as usual; CBT *vs* another treatment; CBT *vs* medication. They found that there was no significant difference in outcome between CBT and another treatment (*e.g.*, psychodynamic treatment) with the caveat that many of the studies were of poor quality.

CHOOSING A MODALITY

In general terms, we would advocate BA and medication as the first-line treatment for severe MDD/GAD or other mixed anxiety and mood states. For moderate to mild MDD/GAD there is no evidence supporting an intervention order. Depending on what clients describe as their primary problem (*i.e.*, anxiety or depression), we would advise focusing on interventions targeting that particular aspect of the comorbid condition. Since most of the studies comparing head-to-head modalities for anxiety or depression have demonstrated fairly similar effectiveness, we are not recommending any particular modality. Often the choice is based on what modality the clinician is most proficient or comfortable conducting. What is yet missing from the research literature is which treatment method is most effective for a particular patient. Until that is known, any of the modalities detailed in this article have demonstrated effectiveness when conducted by a knowledgeable clinician. Medication may be combined with psychotherapy and the discussion of those approaches follows.

PHARMACOLOGICAL APPROACHES TO COMORBID MOOD AND ANXIETY DISORDERS

Treating anxiety and depression

Treating anxiety comorbid with mood disorders requires an adjustment of pharmacological approaches when compared to treating only anxiety or only depression. We discuss how anxiety disorders may manifest with variations of depression and how we should adapt pharmacotherapy for a range of situations that may be encountered. Conversely, when patients are being treated for bipolar disorder or major depression, anxiety disorders commonly go unnoticed. For instance, data obtained from the first 500 participants in the systematic treatment enhancement program for bipolar disorder indicated that lifetime comorbid anxiety disorders were extremely common, occurring in over one-half of the sample. Bipolar disorder comorbid with anxiety disorders was associated with younger age at onset, decreased likelihood of recovery, poorer quality of life, less time euthymic, and greater likelihood of suicide attempts[43]. In one study, panic disorder (PD) occurred

at higher rates in patients with bipolar compared to unipolar mood depression[44]. Similarly, in cross-national epidemiological surveys, patients with major were shown to be at increased risk for comorbidity with substance abuse and anxiety disorders at all sites[45].

Diagnostic considerations

First, we need to pay attention to the evidence for major depression comorbid with significant anxiety. Sub-syndromal symptoms of either anxiety or depression should be noted. Not all anxiety falls into diagnostic categories but may be non-specific[46]. Positive family history of anxiety and/or depression will corroborate the diagnosis. Bipolar disorder commonly causes anxiety and depression symptoms. Therefore, a family history of bipolar disorder should raise a red flag for covert bipolarity in the patient. Non-response to previous treatments should also serve as an alert for covert bipolarity. Finally, comorbid substance abuse needs independent treatment but will also direct pharmacotherapy[47].

PHARMACOTHERAPY FOR THE ANXIETY DISORDER COMPONENT

Addressing initial anxiety

For uncomplicated cases, to achieve rapid control of anxiety symptoms in patients without substance abuse, use of a benzodiazepine (BZD) may still constitute the best option. Long half-life BZDs such as clonazepam or alprazolam XR are favored and reduce the likelihood of "mini-withdrawal" symptoms. Careful titration is always necessary, so we recommend starting at a dose of 0.5 -1.0 mg/d (or lower) for each of the aforementioned medications and double following 3 d. Night time dosing is preferred because it minimizes side effects. We advocate use of immediate release BZDs, such as alprazolam, on an as needed basis (PRN), for panic attacks or panic-inducing social situations. BZDs are an important "bridge strategy" since antidepressant onset of action will generally take 3-4 wk; (perhaps the duration of onset may be shorter for vilazodone, although studies are conflicting). The extent of use of PRN dosing serves as an indicator of the extent of increase necessary for the standing BZD dose[48].

For patients whose course is complicated by substance abuse, instead of using a BZD, we advise using an atypical antipsychotic for comorbid anxiety. Quetiapine is the only atypical antipsychotic, to our knowledge, to be shown effective in GAD as monotherapy at 50 mg QD[31]. Lower doses can be used (start at 25 mg QHS, go to 75 mg QHS over 5 d, or even lower). Doses may have to be raised to 400 or even 600 mg in certain patients. Other atypical agents require further study. Weight "neutral" atypical agents, for example, lurasidone, are in need of further investigation. Quetiapine XR shows, to our knowledge, no advantage over the generic form of quetiapine[49].

Antidepressant strategies

The selective serotonin reuptake inhibitors (SSRIs) are probably the treatment of choice in treating depression and a gamut of comorbid anxiety disorders. The most used SSRI is escitalopram. Long-term problematic side effects include sexual side effects and weight gain. Although sexual side effects were initially viewed as uncommon with SSRI's, certain critical reviews have cited rates of > 80% of subjects experiencing some form of sexual side effect[50]. In another independent study, paroxetine showed the highest incidence rate of overall sexual dysfunction (64.71%) which was followed by fluvoxamine (58.94%)[51]. Although weight gain is frequently observed with prolonged SSRI treatment in clinical practice, a paucity of systematic data gathered over an extended period are available. In over 20000 adult patients who began receiving a medication of interest with available weight data over a 12 mo period, compared with citalopram, when adjusting for sociodemographic and clinical features, significantly decreased rate of weight gain was observed among individuals treated with bupropion, amitriptyline and nortriptyline; the latter two tricyclics have long been associated with weight gain, suggesting SSRI's are associated with greater weight gain than the older tricyclics antidepressants[52]. A meta-analysis of available studies suggested weight gain with paroxetine but not other SSRIs although only short-term data were available on certain SSRIs (*e.g.*, fluoxetine[53]). There is now a restriction by the FDA on citalopram doses above 40 mg per day due to QT interval prolongation although the relevance of this warning to escitalopram is unclear. We recommend starting at 5-10 mg/d and aim for a final dose of 10-30 mg/d with escitalopram. All anxiety disorders, with the exception of specific anxiety disorder, respond to SSRIs and SSRIs have been FDA approved for their treatment[54].

Vilazodone is a novel compound - an SSRI + 5-HT1$_A$ partial agonist. The 5-HT1$_A$ partial agonist binding is reportedly seven times more potent than buspirone[55]. Although the mechanisms are unknown, data to date indicate weight neutrality and much lighter burden for male and female sexual side effects. For this reason, Vilazodone may conceivably displace SSRIs as a first line. The dosing starts at 10 mg/d and is raised to 40 mg/d although lower doses may be effective. Vilazodone is only approved for depression, but in our hands it has worked as an excellent anxiolytic in GAD and PD with comorbid MDD[56].

Serotonin norepinephrine reuptake inhibitors (SNRIs) as a first line choice for comorbid GAD and MDD are a perfectly legitimate choice. We specifically recommend the use of duloxetine for comorbid fibromyalgia, osteoarthritic back pain or, for that matter, any other form of pain. The starting dose is 20-30 mg/d and the prescriber should aim for 60-120 mg. Other SNRIs, such as venlafaxine acts like an SSRI up to a dose of 150 mg/d and only then manifests noradrenergic reuptake properties. Des-venlafaxine may have fewer side

Pharmacotherapy of the bipolar patient with mixed anxiety/depression

Frequently a patient with bipolar disorder presenting with mixed anxiety and depression is on an antidepressant. Bipolar disorder can be comorbid with any of the anxiety disorders and is frequently comorbid with substance abuse (approximately 70%)[58]. Approximately 70% of bipolar disorders are misdiagnosed[59] and if it is not appreciated that a patient has bipolar disorder, the patient will, in all likelihood, remain treatment-resistant. Although controversial, we generally recommend not discontinuing the antidepressant, but rather recommend augmentation of the antidepressant with a medication with mood-stabilizing properties. Bipolar patients are less likely to respond to psychotherapy including CBT, yet psychotherapy is an integral part of stabilization[60].

LAMOTRIGINE

Lamotrigine works especially well for a hypomanic/anxious or depressed presentation although data for this position is scant. Slow dosage increase, a major disadvantage, is recommended to avoid maculopapular rashes and Steven-Johnson syndrome. For example, increasing dose from 25 mg/d up to 200 mg/d at weekly increases of 25 mg is recommended which takes a total of 8 wk. Bridging strategies include using BZDs and use of concomitant atypical antipsychotics is frequently indicated. Lamotrigine does not show any evidence of efficacy for any specific anxiety disorder. A major drawback of lamotrigine is the remote risk of a rash secondary to Steven-Johnson's syndrome but low weight gain or sexual side effects have been documented[61].

Atypical antipsychotics

The risks *vs* benefits of atypical antipsychotics need to be weighed whenever using this class of drug in patients with mood and anxiety disorders. We have reviewed the risk of tardive dyskinesia in a long-term follow-up study of patients treated with atypical antipsychotics for mood and/or anxiety disorders[62]. Although the risk was significant, in most instances it resolved following cessation of the offending agent.

Aripiprazole augmentation

Aripiprazole is FDA approved for augmentation of an antidepressant for partially responsive depression. Aripiprazole can be effectively used in a unipolar mixed anxiety/mood disorder patient who is not doing adequately well and is FDA-approved for the maintenance of bipolar disorder should a bipolar component be suspected. Aripiprazole works well for patients with bipolar mixed anxiety/depression, especially while waiting for lamotrigine to work. The onset of aripiprazole action is rapid (1-2 wk). Starting with low dosages (1-2 mg) is recommended, to avoid intolerable akathisia. The dosage goal is 5-10 mg per day, but is not imperative. The major downfall is weight gain; even at mini-doses (few are spared). Weight gain is associated with metabolic complication such diabetes mellitus. However, aripiprazole is known to cause less weight increase and metabolic burden than other second-generation antipsychotics[63]. The anxiolytic effects of aripiprazole as an augmentation are not, to our knowledge, specific to any anxiety disorders[64].

QUETIAPINE AUGMENTATION

Quetiapine is FDA approved as a monotherapy for bipolar depression and has also been shown to be equivalently effective to duloxetine in unipolar depression[65]. Efficacy for GAD has been demonstrated but was rejected by the FDA for unclear reasons. We previously presented an abstract that quetiapine was effective for PD as an add-on. Sedation, an important side effect due to potent anti-histaminergic (H_1) effects, can be handled by careful titration. The sedating side effect of quetiapine and also olanzapine can be beneficial to patients who suffer from insomnia. Quetiapine also is reported to show less extra pyramidal effect. If one maintains low doses (< 200 mg/d), metabolic consequences and weight gain can be significantly averted in certain patients[66].

OTHER ATYPICALS AGENTS USED FOR BIPOLAR DISORDER, ANXIETY DISORDERS AND MDD

Risperidone, a potent D_2 receptor antagonist, is a treatment option for augmenting SSRIs for obsessive compulsive disorder (OCD) but is an "unforgiving" weight-gainer even at low doses. Ziprasidone is approved for maintenance of bipolar disorder and its utility remains limited. Olanzapine is FDA approved for bipolar depression and is used as an add-on in GAD studies. Olanzapine has amongst the worst metabolic profiles but can be considered if choices are limited. Paliperidone has been better tolerated than risperidone in specific cases and has excellent antimanic properties[67].

Newer atypicals agents

Lurasidone, along with D_2 and $5HT_{2a}$ antagonist properties, is a $5HT_7$ antagonist and has a favorable metabolic profile. Lurasidone does not need to be titrated and is useful if an additional atypical is necessary. It has recently been approved for bipolar depression. Anxiolytic effects of $5HT_7$ antagonists have been documented preclinically and a role for mixed anxiety/depression is envisaged. Asenapine is also a $5\text{-}HT_7$ antagonist and $5\text{-}HT_{1A}$ partial agonist. Asenapine has to be given sublingually BID and is approved for bipolar disorder. Iloperidone is a basic $D_2/5HT_{2a}$ antagonist but also has D_3 antagonist properties. It is only approved for schizophrenia but bears similarity to sulpiride in its

effects[57].

receptor binding profile; the latter has been used for decades for mood disorders[68]. Its future role is unexplored.

Anticonvulsant agents - gabapentin

Gabapentin is useful in patients with anxiety disorders comorbid with substance abuse disorders but does not have antidepressant properties. Gabapentin, effective for GAD and social anxiety disorder (SAD), may have modest mood stabilizing properties, improves sleep quality, and me be very useful for comorbid chronic pain syndromes such as irritable bowel syndrome, fibromyalgia, interstitial cystitis, prostatitis and vuvlvodynia. Gabapentin necessitates combination with a high potency BZD or SSRI for PD or combined with an SSRI for OCD[69].

Buspirone

Buspirone is only effective in GAD. Buspirone does not have antidepressant effects or efficacy for any other anxiety disorders. In fact, buspirone is useful as a "placebo" prescription, with attendant ethical implications, and perhaps has some value as an augmenting agent to an antidepressant. Buspirone, moreover, has minimal side effects and minimal withdrawal[70].

Antidepressants- tricyclic antidepressants

Tricyclic antidepressants (TCAs) cover both depression and certain anxiety disorders including GAD and PD. However, TCAs are ineffective in SAD and post traumatic stress disorder where SSRIs are required. OCD can be treated with clomipramine which is a TCA with selective serotonin and norepinephrine reuptake inhibitor properties.

Side effects of TCAs stem from its anticholinergic and antimuscarinic properties. TCAs are also dangerous in overdose and produce cardiac conduction defects in patients with differing degrees of heart block. However, TCAs are especially useful in patients with functional pain syndromes such as irritable bowel syndrome, fibromylagia and neuropathic pain, probably by virtue of their noradrenergic reuptake blockade effects. In addition, TCAs promote sleep integrity which is key to treating disorders such as fibromyalgia and chronic fatigue syndrome[71]. Functional pain syndromes are especially comorbid with mixed anxiety and depression and can be comorbid with bipolar disorders.

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) are now generally outmoded. They have become unpopular because of dietary restrictions and the risk of tyramine-induced hypertensive crisis. They can cause significant weight gain, especially phenelzine. However, prior to SSRIs, MAOIs were uniquely effective for SAD and atypical depression. Newer agents (selegiline patch) do not require diet restriction but are restricted by the low dosage recommendations. A major downfall of the MAOIs is that, because of the risk of serotonin syndrome, patients have to undergo a 2-wk washout (4 wk with fluoxetine) of other antidepressants[72]. Nevertheless, MAOIs may serve as the treatment of choice for treatment-resistant depression in its later stages and might be suitable for certain subtypes of depression such as atypical depression, anergic bipolar depression and anxious/phobic-associated depression[73]. It has been advised that the risk-benefit ratio is optimally managed not by avoiding MAOIs but rather, by assessing and discussing safety measures in a direct and continuous manner. Careful attention to medication storage and administration and securely controlling dosages and quantities of pills is recommended. Certain authors have opined that there may well be a greatly less occurrence of treatment-resistant depression if more practitioners were willing to prescribe optimal therapeutic doses of MAOIs[74].

Buproprion

Buproprion is an effective antidepressant but it does not have specific anti-anxiety effects for PD, OCD or SAD. Buproprion may have a non-specific anxiolytic effect, but it has an excellent side effect profile by not inducing weight gain or sexual side effects. Thus, the weight gain and sexual side effects that are implicit to SSRI treatment, is obviated. Treating depression with buproprion can be performed, but for GAD, PD or SAD, concomitant high-potency long-acting BZDs are necessary[75].

SPECIFIC SCENARIOS

The treatment resistant mixed patient

If patients are resistant to treatment and show mixed anxiety/depression symptoms, patients may well suffer from a bipolar disorder. Then, having patients on a combination of an SSRI, lamotrigine and aripiprazole can be considered. In our experience, many treatment-resistant patients will respond to this combination of therapies. Regarding the use of antidepressants in bipolar disorder has been controversial. The 2002 American Psychiatric Association (APA) guidelines for the treatment of bipolar disorder recommended a more conservative use of antidepressants, including discontinuation because of the risk of mood cycling. The Munich group published a critique of the recommendations of the APA guidelines indicating that anticonvulsants when used as monotherapy in the absence of antidepressants have not been demonstrated to exhibit antidepressant properties[76]. Certain authors, including experts such as Ghaemi *et al*[77], argue that conceptually and empirically, there is a strong rationale for a cautious approach to antidepressant use in bipolar disorder, consistent with the APA guidelines. Certainly, antidepressant treatment of bipolar depression has been associated with manic switch and cycle acceleration. However, it has been argued that

many clinicians continue to employ antidepressants, especially in the management of severe depression that is unresponsive to mood stabilizers alone[78]. Certainly, in our experience, if antidepressants can be avoided, they should not be used. But in the context of more treatment-resistant mood disorders with comorbid anxiety they may well be necessary although a high level of vigilance for mood cycling is warranted. If the patient is still unresponsive, adding quetiapine without subtracting any medications, which is called a "stacking approach", is advised[79]. Many patients will respond but the side effect load may well become higher, especially weight gain. It is recommended to reserve lithium, because of nephrotoxicity risk, for the most treatment-resistant. If the patient is lithium treatment-resistant, a discussion of ECT should be initiated.

Mixed anxiety/depression patient with hypomania from an SSRI

Frequently, patients with OCD, SAD or PD with comorbid depression may have become manic or hypomanic in the past because SSRIs can induce a mania, a bipolar type Ⅲ pattern. If SSRIs can be avoided, using lamotrigine plus gabapentin for GAD or SAD is encouraged. Otherwise, one has to "cover" for the possibility of a manic occurrence and an example is administering lamotrigine 200 mg/d. Many of these patients will require SSRIs for OCD as no alternatives are available. Vigorous treatment with concomitant CBT is required.

The bipolar mixed anxiety/depression patient with ADHD

Many patients with a bipolar or unipolar mixed anxiety/depression have a childhood history of ADHD that has continued into adulthood. Many of the patients with these diagnoses may have undiagnosed ADHD. ADHD also may contribute to anxiety symptoms. Stimulants may serve as augmenters of antidepressants. However, the practitioner should make sure that comorbid bipolarity is stabilized before using stimulants. For substance-abusing patients, using the prodrug lisdexamfetamine, atomoxetine or guanfacine is recommended[80].

CONCLUSION

In summary, a careful and comprehensive diagnostic assessment is a critical first step in treating the patient with mixed anxiety and depression. The practitioner should be alert to the possibility that this may be a concealed bipolar disorder since misdiagnoses rates can be 70%. Treatment in the patient with uncomplicated, non-substance-abusing unipolar disorder may be quite straight forward entailing the use of SSRIs and BZDs. However, the norm is far more complex. Patients are in all likelihood, treatment-resistant with probable bipolarity and substance abuse. In the latter instance a much more complex regimen of medications has to be used with careful attention being played to pros and cons of side effects and other comorbidities. Therefore, not infrequently, combinations of pharmacotherapy are

required. Finally, a "stacking" approach, as is used in hypertension, to cover the full spectrum of available receptors targeted by current pharmacotherapy regimens is recommended.

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