CHAPTER

1

Medication Versus CBT

How Did That Happen?

Mary is a 40-year-old woman who has been in therapy for six months for a severe depression, which developed after her husband of 15 years left her for another woman. Unfortunately, her depressive symptoms include fairly routine and significant insomnia—she wakes up at four A.M. nearly every night. The sleep disturbance has been not responsive to her therapist's suggestions to make her bedtime and waking time the same each day and to employ other sleep hygiene measures. Mary is a pharmacist in a busy chain-operated drugstore. She is in danger of being fired because her work performance has been altered by fatigue and poor concentration. Her therapist is reluctant to refer her for a medication evaluation because she believes Mary's depression has such a clear-cut psychological precipitant.

John is a 60-year-old man who was recently diagnosed with lung cancer. He has developed fairly significant anxiety about an impending surgical procedure to remove the lobe of his lung that contains the primary lesion. He has suffered multiple panic episodes, and in the past month he has started to avoid going out to the mall or to football games. His primary care physician prescribes Clonazepam 0.5 mg twice a day and tells John that it "makes sense" that he would be anxious given his circumstances. He does not refer John for therapy.

Mary and John are both in treatment with practitioners who have beliefs about the origins of their patients' illness that influence the treatment they provide. The decisions we make as clinicians are informed by our understanding of the nature and best available treatment of particular psychological problems. Most of us have a view of combined treatment with medications and CBT that is influenced by how research studies of combined treatment were

conducted in their earliest iterations. It helps to retrace some of this history to assess the quality of the data we use to make clinical decisions.

STUDIES OF COMBINED TREATMENT

Studies conducted about treatment combining medications and CBT evolved with the aim of establishing comparative efficacy. A tremendous increase in effective novel medications for depression and anxiety occurred in the 1960s and 1970s. Although it is an imperfect system, the development of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) meant that researchers were able to make clearer distinctions between groups of patients and actually determine what treatments worked in particular disorders. Structured interviews became available that increased the consistency of diagnoses in patients—so that more homogeneous and accurately diagnosed groups of patients could be studied in either medication or psychotherapy treatment trials. This was a major advance in the field and increased the ability to develop and test new treatments. Once an accurate diagnosis was made, clinicians could treat patients with greater effectiveness.

The previously mentioned explosion in biological treatments was paralleled by substantial new knowledge about manual-based psychotherapeutic treatments—such as CBT and interpersonal therapy (IPT)—that could rapidly and effectively work to treat major depression, panic disorders, and phobias. Medications were considered the "gold standard" as a treatment approach; psychotherapy was evaluated for comparative efficacy. Most research trials were conducted to determine whether individual treatments worked. Unfortunately, investigators who considered the question of whether these treatments were effective were generally quite invested in the approaches they evaluated. Thus, they often framed questions that were inadvertently biased to favor the form of treatment that they espoused. For example, many of the studies that evaluated the efficacy of medication treatment for panic disorder versus the efficacy of CBT were done with patients who did not display agoraphobic avoidance. This would naturally dilute the efficacy of exposure-based procedures in the CBT provided. Certainly the outcome measures chosen to evaluate what constituted response in any study of combined treatment would influence what view we had about the utility of either approach and for which groups of patients. Research about the positive and negative effects of combined treatment was rarely performed in these early comparative studies. Process research that

could inform us about any differential effects of medication or therapy or their combination in particular types of patients is still largely uncharted territory. Pooled data that are evaluated at the end of treatment do not allow us to determine individual differences in response to combined treatment over time. Such studies would be expensive and complicated. Early studies considered outcomes at the end of therapy without any effort to look at process issues, interactions between treatments, or specific patient variables that would make patients more suitable for one particular approach or the combination.

As treatments became more effective, it became more difficult to determine if the combination of two treatments would be even more powerful than either treatment alone. Highly effective treatments require very large studies to determine whether any benefit is derived from their combination. The expense and complexity of such studies limit the frequency with which they occur. Because medication and therapy independently have a substantial impact relative to placebo in depression and anxiety, there is less incentive to conduct complex and costly evaluations of the beneficial or deleterious effects of the combination. Early studies of combined treatment for depression were small, but had some nonsignificant trends toward an increased response rate for those patients who received combined treatment. At least one large-scale clinical trial (Keller et al., 2000) indicates a fairly substantial benefit from combining a form of CBT with medication versus either treatment alone in a group of chronically depressed patients who had a limited response to prior treatment.

Ideally, a heterogeneous group of investigators should develop and execute combined treatment research and pool expertise so that process variables could be measured in the widest possible manner. Gorman and his colleagues (Gorman, Barlow, Ray, Shear, & Woods, 2001) detail the complexity of such a collaboration in an article describing the work they did in evaluating the differential efficacy of CBT, imipramine, and CBT combined with imipramine for panic disorder. Several recent studies, for example, the Treatment for Adolescents with Depression (TADS) study (March et al., 2009), were similarly well designed. They were developed by a multidisciplinary team of investigators and will likely increase our knowledge about variables that influence positive patient outcome.

In the context of the early "horse race" model designed to evaluate the differential efficacy of medications, therapy, or both, many of the completed and published studies evaluate combined treatment with medications that are currently not in common use. A majority of the studies in depression and

anxiety investigate the efficacy of tricyclic antidepressants alone, compared to, and in combination with CBT, for example. Unfortunately, the data we have from these studies has limited applicability to current practice. The vast majority of patients do not take these medications for depression or anxiety because of the debilitating side effects and risk of suicide inherent in their use. There is less incentive to pursue combined treatment research with newer medications, because CBT has been established as an effective treatment for depression and anxiety and newer antidepressants have not been found to be more effective than tricyclic antidepressants, so that testing them head-to-head with CBT and evaluating the combination has less value to researchers.

Another limitation to generalizing the research data available about combined treatment to clinical practice is that research studies do not employ optimal or acceptable standards of care. Separate clinicians deliver each treatment in research studies with minimal, if any, communication with one another. Medications in most clinical trials are prescribed with limited dosage adjustments, if at all. If there is no response, research protocols prohibit switching or augmenting medications. Patients generally continue on the same medication for the full duration of the study, regardless of their response, when in clinical practice another method of treatment would be added if medication was ineffective. Pharmacotherapy protocols in research studies generally do not allow for any addition of pharmacological treatments for debilitating and common symptoms when they are incompletely treated by the prescribed medication. Insomnia or severe anxiety would typically be managed by additional medications in the acute treatment of a severely ill patient. Providers who prescribe in research trials are often instructed to limit the interpersonal interactions they have with patients to reduce any study error caused by variation in therapy time. Murphy and colleagues (Murphy, Carney, Knesevich, Wetzel, & Whitworth, 1995) have shown that antidepressant medication is far less effective when providers are instructed to not interact with patients in a positive and engaged way—largely because of adherence issues. In a meta-analysis, Pampallona and colleagues (Pampallona, Bollini, Tibaldi, Kupelnick, & Munizza, 2004) determined that 33% of patients in treatment with antidepressants who are not provided therapy drop out of treatment and do not take medication. Gorman and colleagues (2001) describe a situation in the combined treatment study of CBT and imipramine in panic disorder in which one practitioner had an unusually low response rate to the medication provided. Upon review, this practitioner was interacting minimally with patients because of his concern

that he could confound the study results by providing additional therapy. Therefore, medication treatment provided with minimal interaction with care providers may not accurately reproduce clinical outcomes with optimal care. Therapists with a positive attitude toward medication can enhance the placebo response to medication (Barrett & Wright, 1984). This potentiating effect is absent in blinded combined treatment trials.

In the psychotherapy arm of research projects, therapy is often unlike clinical practice. It is generally manual-based with less emphasis on individual patient conceptualization. Patients are assessed with multiple measures throughout treatment—which could alter patient expectations and motivation in a positive or negative way. If patients have co-morbid Axis II psychopathology, there is rarely the flexibility to slow the therapeutic process to allow for the type of alliance-building that is necessary to employ CBT effectively.

Another difficulty we face in determining the best evidence-based option to recommend to a patient is that patients who are eligible to participate in clinical trials represent a very narrow spectrum of the individuals afflicted by a particular diagnosis. An estimated 80% of applicants to antidepressant trial research are excluded (Posternak, Zimmerman, Keitner, & Miller, 2002). Zimmerman and his colleagues (Zimmerman, Mattia, & Posternak, 2002) looked at the medical records of patients seen in a large general psychiatry clinic to see how many of them would be eligible for a clinical trial of antidepressant medications. Of 803 patients, 346 had major depression. Of these patients, 86%—all but 41—would be excluded from a typical efficacy trial due to co-morbidity, chronic illness, severity, or suicidal ideation. Patients seen by therapists and prescribers in routine clinical practice are often far more complicated and have more chronic conditions than those who participate in clinical trials. Bockting and colleagues (2008) determined that patients with greater numbers of episodes of illness derive the most benefit from combined treatment—again, these patients were often excluded from early efficacy trials. The complexity of the typical patient who seeks mental health care makes it more difficult to determine what treatment makes sense; studies of patients with co-occurring disorders are even scarcer. Patients who respond to treatment in typical efficacy trials may be very different from the typical patient who seeks treatment, accepts and adheres to treatment, and recovers and stays well.

In summary, the research evidence that we have available to us about when combined treatment might be helpful has limits to its clinical applicability and may not reflect the potential benefits or detractions of combined treatment in

a particular patient. What may help us best is to consider the combination of genetic/biological, interpersonal/developmental, and temperamental risk factors that any patient has in order to determine who might benefit from combined or sequenced treatment until we have better data to help us to make determinations about what would constitute optimal care. Newer practical clinical trials will hopefully help us to determine the best interventions to help a patient obtain and sustain a full recovery.

WHAT MECHANISMS COULD INFLUENCE COMBINED TREATMENT EFFECTS?

We can generate hypotheses about the possible effects of combined treatment by considering the mechanisms of action of the individual effects of medications and psychotherapy. To benefit from psychotherapy, patients must be able to learn. Wright (2003) details the ways that medication or psychiatric illness could each alter attention, memory, and the ability to integrate new information. We know that a substantial number of psychiatric disorders interfere with the acquisition and retention of information. Severe anxiety, depression, mania, and psychosis, for example, can hamper normal learning. Sleep problems are common in major psychiatric disorders, and insomnia can decrease the capacity to learn and remember. Distractibility is common to many Axis I disorders—rumination, hallucinations, flight of ideas, and attention to threat can interfere with patient attentiveness. The speed of thought can be accelerated or decreased by mood disorders, hindering attention and recall. Therapy can proceed more effectively if these impediments to learning are addressed by pharmacotherapy. CBT, in particular, is primarily a treatment that relies on the patient's ability to learn new skills, so a fundamental requirement is that patients must have the ability to learn and to remember.

The downside can also be true—combined treatment has the potential to impede learning and memory. Prescribers must be aware of medications that can sedate patients and interfere with learning. Anticholinergic side effects were once a predominant feature of medications used for depression and psychosis. This particular side effect could interfere with new learning and memory functions in all patients. Specific side-effect profiles of many tricyclic antidepressants listed possible alterations in memory, including problems with word-finding. This type of alteration in memory could slow therapeutic progress. Benzodiazepines can also impair learning and recall, so when they are used for

anxiety, they could interfere with exposure treatment by preventing new learning as well as habituation.

So a practitioner may ask "Why is this important? If medication and therapy are each so effective, what difference does it make?" And the answer—obvious to anyone in clinical practice for very long—is that our treatments, although better than ever, are still not that good. In the best hands, response to a single-modality treatment for depression in the limited, uncomplicated population studied in most clinical trials is a bit better than 50%. Our treatments are better than placebo, but many patients do not respond. Mental illness is dangerous, painful, and debilitating. We need to consider the costs of treatment and deliver it as efficiently as possible in real-world settings.

In standard clinical practice, a good clinician faced with an unresponsive patient would try to obtain better results by changing medications or therapy type or by combining treatments. Results from the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) pharmacotherapy are concerning regarding initial treatment response. STAR*D trial (Gaynes et al., 2009) was a large practical clinical trial where entry criteria were broadly defined and inclusive and patients were enrolled from psychiatric and primary care clinics. The results of this trial emphasize that antidepressant treatment is unlikely to be effective if a patient does not respond to the initial medication prescribed. In the "real world," patients with no response after two vigorous medication trials have a very low probability of recovery from depression. Patients who do not attain a remission of depression with typical medications would likely require more complicated medication regimens with complicated side effects. These more complicated treatments have less certain success. If one could improve the likelihood of an initial response to medication by adding CBT to medication it could have a substantial impact on the course of the illness. In addition, the STAR*D trial showed that 67% of those patients who responded to medication also had residual symptoms of depression (Trivedi et al., 2006)—these continual symptoms could represent a significant burden for a patient, a risk factor for relapse, and be an additional indication for and benefit from combined treatment.

Another reason to consider combined treatment is that existing pharmacological treatments for depression and anxiety do not produce a durable recovery over time, both when taking medication and once medication is withdrawn. Relapse in psychiatric illness is more the rule than the exception. Initial hypotheses offered to account for frequent relapse often included nonadherence

to medication treatment, particularly in those patients who were treated with earlier medications that had undesirable side effects. Paykel (2007) did a prospective study of patients who were hospitalized for depression and who had recovered. Over a ten-year period two-thirds of patients had a recurrence, half of these within 24 months of recovery. The follow-up data the study obtained included subject interviews, prescription records, and antidepressant blood levels. These indicated that patients in the study had good adherence and still relapsed. Combined treatment may have the potential to increase coping skills in a patient with a significant genetic diathesis for depression so that they are more capable of sustaining a durable recovery.

Clinicians face a number of other challenges in the "real world." We must provide a credible rationale for our recommendation of different treatments to patients. Our interventions must be acceptable and understandable to the patient to ensure adherence. The goal of treatment should be a durable recovery (not just improvement) whenever possible. We do not reach this goal at present for too many of our patients. Treatment resistance is common and partial response is more common. Patients with co-morbid disorders and chronic illness are also those who do the least well with a single method of treatment. They are the patients who, intuitively, would be most responsive to combined treatment.