TREATMENT AND PREVENTION
OF DEPRESSION

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Summary—Depression is one of the most common and debilitating psychiatric disorders and is a leading cause of suicide. Most people who become depressed will have multiple episodes, and some depressions are chronic. Persons with bipolar disorder will also have manic or hypomanic episodes. Given the recurrent nature of the disorder, it is important not just to treat the acute episode, but also to protect against its return and the onset of subsequent episodes.

Several types of interventions have been shown to be efficacious in treating depression. The antidepressant medications are relatively safe and work for many patients, but there is no evidence that they reduce risk of recurrence once their use is terminated. The different medication classes are roughly comparable in efficacy, although some are easier to tolerate than are others. About half of all patients will respond to a given medication, and many of those who do not will respond to some other agent or to a combination of medications. Electroconvulsive therapy is particularly effective for the most severe and resistant depressions, but raises concerns about possible deleterious effects on memory and cognition. It is rarely used until a number of different medications have been tried.

Although it is still unclear whether traditional psychodynamic approaches are effective in treating depression, interpersonal psychotherapy (IPT) has fared well in controlled comparisons with medications and other types of psychotherapies. It also appears to have a delayed effect that improves the quality of social relationships and interpersonal skills. It has been shown to reduce acute distress and to prevent relapse and recurrence so long as it is continued or maintained. Treatment combining IPT with medication retains the quick results of pharmacotherapy and the greater interpersonal breadth of IPT, as well as boosting response in patients who are otherwise more difficult to treat. The main problem is that IPT has only recently entered clinical practice and is not widely available to those in need.

Cognitive behavior therapy (CBT) also appears to be efficacious in treating depression, and recent studies suggest that it can work for even severe depressions in the hands of experienced therapists. Not only can CBT relieve acute distress, but it also appears to reduce risk for the return of symptoms as long as it is continued or maintained. Moreover, it appears to have an enduring effect that reduces risk for relapse or recurrence long after treatment is over. Combined treatment with medication and CBT appears to be as efficacious as treatment with medication alone and to retain the enduring effects of CBT. There also are indications that the same strategies used to reduce risk in psychiatric patients following successful treatment can be used to prevent the initial onset of depression in persons at risk. More purely behavioral interventions have been studied less than the cognitive therapies, but have performed well in recent trials and exhibit many of the benefits of cognitive therapy.

Mood stabilizers like lithium or the anticonvulsants form the core treatment for bipolar disorder, but there is a growing recognition that the outcomes produced by modern pharmacology are not sufficient. Both IPT and CBT show promise as adjuncts to medication with such patients. The same is true for family-focused therapy, which is designed to reduce interpersonal conflict in the family. Clearly, more needs to be done with respect to treatment of the bipolar disorders.

Good medical management of depression can be hard to find, and the empirically supported psychotherapies are still not widely practiced. As a consequence, many patients do not have access to adequate treatment. Moreover, not everyone responds to the existing interventions, and not enough is known about what to do for people who are not helped by treatment. Although great strides have been made over the past few decades, much remains to be done with respect to the treatment of depression and the bipolar disorders.

Mood disorders are among the most common and debilitating psychiatric disorders. The most common mood disorder is depression, which is the number-one cause of disability worldwide (Murray & Lopez, 1997). However, the term depression encompasses a variety of conditions that differ in both severity and time course. Depressions can range in severity from mild disruptions of normal mood to disorders of psychotic intensity. And although depressions often are episodic and resolve on their own, the majority of afflicted individuals will experience multiple episodes or residual distress, and some depressions last for years. Conventional wisdom once held that mild depressions were chronic and more severe depressions episodic, but the rela-

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tionship between severity and time course is more complex. For example, recent studies indicate that persons with chronic mild depression (dysthymia) have increased risk for experiencing episodes of severe depression (D.N. Klein, Schwartz, Rose, & Leader, 2000).

The majority of mood disorders fall into two categories. Unipolar disorders involve depression only, whereas bipolar disorders involve episodes of elevated mood of varying severity (mania or hypomania), typically in addition to episodes of depression. Unipolar disorders are common, occurring in about 20% of women and about 10% of men, whereas bipolar disorders occur in only 1 to 2% of the population and affect the genders equally (American Psychiatric Association, 1994). Both unipolar and bipolar disorders recur at high rates, and most patients experience multiple episodes. These disorders are often chronic, and even minimal symptoms are associated with increased risk for subsequent episodes and considerable functional impairment (Judd et al., 1998). Suicide is a major concern: About 15% of individuals with mood disorders will commit suicide (depression accounts for about 50% of all suicides). Moreover, other psychiatric or medical conditions often complicate the picture (Kessler et al., 1994).

Several types of treatments have demonstrated efficacy for mood disorders. These include antidepressant medications, electroconvulsive therapy (ECT), interpersonal psychotherapy (IPT), and the cognitive behavior therapies (CBT; American Psychiatric Association, 2000). More traditional psychodynamic and experiential psychotherapies are widely practiced but have not been adequately evaluated. Antidepressant medications are the most widely used treatment; more good studies attest to their efficacy than to the efficacy of any other intervention, but they do not work for everyone and can have problematic side effects. The psychotherapies have been less extensively tested, but some new approaches targeted at depression have fared well in comparisons with medications and can have special benefits not conferred by medications (Hollon et al., in press). These psychotherapies may provide a reasonable alternative to medications for many patients with unipolar depression. No one advocates the use of psychotherapy alone for bipolar patients; rather, work in recent years has focused on whether psychotherapy is a useful adjunct to medication in treating bipolar disorder (Craighead & Miklowitz, 2000).

Despite the availability of efficacious interventions, surveys consistently document that more than 75% of depressed individuals receive no specific treatment or inappropriate care (A.S. Young, Klap, Sherbourne, & Wells, 2001). Even specifically for the bipolar disorders, which tend to be more severe and likely to come to medical attention than unipolar depression, nearly half of all afflicted individuals do not receive appropriate care (Regier et al., 1993). The number of people receiving treatment for these disorders has increased over the past decade, particularly with respect to the use of psychoactive medications, but undertreatment remains a serious problem (Olfson et al., 2002). Undertreatment of mood disorders can be a consequence of societal stigma, lack of recognition by health care providers, or a failure to appreciate the potential benefits of treatment (Hirschfeld et al., 1997).

Left untreated, mood disorders have profound consequences. Their impact on quality of life and economic productivity matches that of heart disease and surpasses the burdens associated with peptic ulcer, arthritis, hypertension, or diabetes (Wells et al., 1989). Suicide remains a leading cause of death across all age groups among people with mood disorders. Effective treatment of mood disorders decreases the utilization of health care resources and increases economic productivity (Sclar et al., 1994). In fact, the direct cost of treating mood disorders pales in comparison with the costs associated with decreased productivity, sick leaves, and premature death (P.E. Greenberg, Stiglin, Finkelstein, & Berndt, 1993).

In this report, we briefly describe the types of mood disorders and the time course of their development and treatment, before reviewing the advantages and limitations of each of the major types of interventions for depression. We focus on the treatment of depression in the context of the unipolar disorders (i.e., depressive disorders), but also address its treatment in the bipolar disorders (along with mania). Medications are widely used in the treatment of both kinds of disorders, whereas the various psychosocial interventions, though long used for unipolar depression, have only recently been systematically applied to the treatment of bipolar disorder.

The monograph's three main sections discuss treatments with considerable empirical support: medication treatment and the somatic interventions, IPT and the dynamic interventions (the latter little studied), and the cognitive and behavioral interventions. There is also a brief section on marital and family therapies, which are only now starting to receive empirical scrutiny. Each of these sections describes the nature of the intervention and its application to the different treatment phases while reviewing the quality of the intervention's empirical support and describing the extent to which it can be applied to special populations. The bulk of the evidence concerns the treatment of adult outpatients with depressive disorders, but there is a growing literature on treatment of bipolar disorder, as well as special populations like children, adolescents, and the elderly.

Clinical practice is too often colored by professional bias; physicians sometimes overvalue the effectiveness of medications, and psychotherapists sometimes demonize their use. Psychotherapists tend to practice what they were trained to do regardless of whether it has empirical support. Interventions that have garnered empirical support (evidence-based interventions) often take too long to make their way into widespread use, whereas approaches based on little more than anecdote or wishful thinking too often sweep through practice at a rapid rate. This disregard of the empirical literature is less likely to be a problem with medication than with other treatments, because the major pharmaceutical companies spend millions of dollars to market novel agents and few physicians identify with a particular medication. Nonetheless, the pharmaceutical industry is hardly an unbi-

ased source of information, and practitioners from all professions need to keep abreast of the latest empirical developments.

TYPES OF MOOD DISORDERS

As a syndrome, depression typically involves negative affect, like sadness, and a pervasive loss of interest in things that were previously enjoyed. It is often accompanied by a profound sense of pessimism (including thoughts of suicide) and negative beliefs about the self. The individual is often less energetic than usual, engages in fewer activities, withdraws socially, and is less productive. There also are often vegetative symptoms, such as difficulty sleeping, loss of appetite, and loss of interest in sex. Conversely, the syndrome of mania typically involves opposite changes in the same signs and symptoms. Mood is typically elevated and often euphoric, interests proliferate, and self-esteem can be inflated to the point of grandiosity. The individual takes on new ventures with reckless abandon and has little need for sleep. Appetites increase and buying sprees and sexual indiscretions are common.

Depression and mania each tend to occur episodically, and episodes are often self-limiting, meaning that they tend to resolve on their own even in the absence of treatment. However, depression especially can be chronic. As shown in Table 1, the current diagnostic nomenclature recognizes two main types of mood disorders (depressive, or unipolar, disorders and bipolar disorders) and several subtypes within each (American Psychiatric Association, 1994). Depressive disorders involve depression only and include Major Depressive Disorder (either a single episode or recurrent episodes), Dysthymic Disorder (a less severe but more chronic version of Major Depressive Disorder), and Depressive Disorder NOS (not otherwise specified). Bipolar disorders are distinguished by the occurrence of one or more maniclike episodes. Two sub-

types are Bipolar I Disorder, in which the person has had one or more fully manic episodes, and Bipolar II Disorder, in which the person has had only a less severe form of mania known as hypomania. Both subtypes are further specified with respect to whether the most recent episode was manic or hypomanic, depressed, or mixed. The bipolar disorders also include Cyclothymic Disorder, a still less severe version of bipolar disorder marked by mood swings in either direction, and Bipolar Disorder NOS.

Both Major Depressive Disorder and Bipolar I Disorder are described with respect to severity (mild, moderate, and severe, with or without psychotic features) and whether they are in partial or full remission. Depressive episodes within either disorder are further characterized with respect to a number of different features. An episode of major depression is said to be chronic when it has lasted for at least 2 years (Dysthymic Disorder by definition requires at least 2 years of mild depression). Individuals who experience an episode of major depression superimposed on a history of chronic dysthymia are said to have "double depression," although this term is not part of the formal nomenclature. Melancholic depressions involve such classic symptoms as a pervasive loss of interest, early-morning awakening, and loss of appetite and interest in sex. Conversely, atypical depressions manifest a different pattern that includes moods that can rise temporarily in response to positive events (mood reactivity), sensitivity to rejection, and reverse vegetative symptoms like oversleeping (hypersomnia) or weight gain and increased appetite. Atypical depression tends to be more common in women of childbearing potential, whereas melancholic depression is more common among men and postmenopausal women. Either depression or mania can occur following childbirth, and the nomenclature specifies disorders with postpartum onset so that they can be explored as possible subtypes.

Table 1. *Types of mood disorders*

- Depressive Disorders (involve depression only; also known as unipolar depression)
  - *Major Depressive Disorder* (more severe disorder that can often be recurrent or chronic)
  - *Dysthymic Disorder* (less severe disorder that lasts at least 2 years)
  - *Depressive Disorder NOS* (not otherwise specified)
- Bipolar Disorders (one or more maniclike episodes)
  - *Bipolar I Disorder* (more severe disorder that involves one or more fully manic episodes; specific episodes can be manic or hypomanic, depressed, or mixed)
  - *Bipolar II Disorder* (less severe disorder that involves one or more hypomanic but no manic episodes; specific episodes can be hypomanic or depressed)
  - *Cyclothymic Disorder* (less severe disorder with mood deflections in both directions)
  - *Bipolar Disorder NOS* (not otherwise specified)
- Mood Disorder Due to General Medical Condition and Substance-Induced Mood Disorder
- Additional features and subtype specifications
  - *Chronic*: episode lasts at least 2 years
  - *Melancholic*: symptoms of pervasive loss of interest and classic vegetative signs (early-morning awakening, loss of appetite, and loss of interest in sex)
  - *Atypical*: symptoms of negative mood that responds to external events (reactivity), rejection sensitivity, "leaden" paralysis (sense of being unable to initiate action), and reverse vegetative signs (sleeping too much and increased appetite or weight gain)
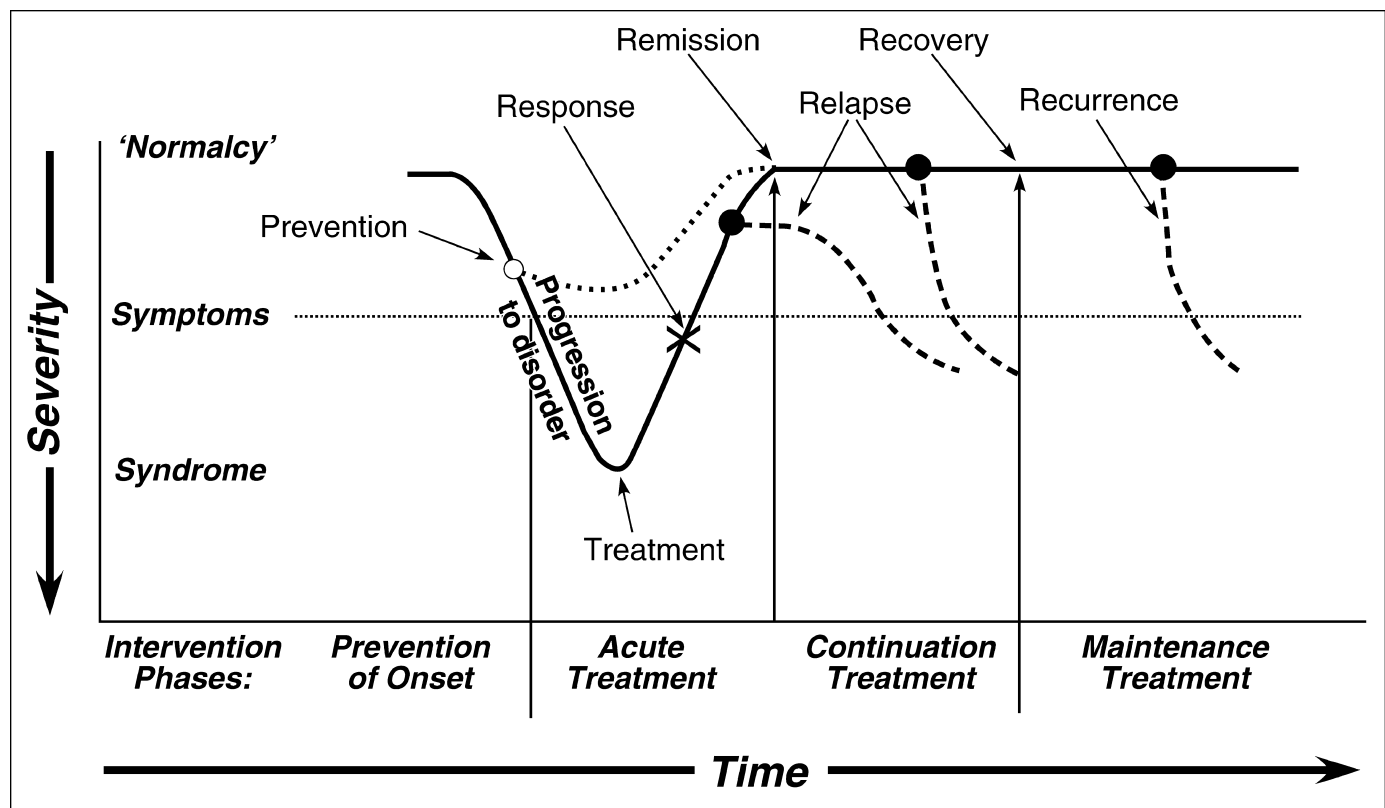
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Finally, separate designations are made for mood disorders that are due to general medical conditions or are substance induced, with the latter coded with respect to the nature of the substance. Depression increases risk for a number of medical conditions, such as heart disease and diabetes; conversely, health problems can lead to depression and even mania in individuals who are so predisposed. For example, strokes that affect the brain's left cortical hemisphere are likely to produce depression, whereas those that affect the right hemisphere can lead to mania or anxiety (Davidson, Pizzagalli, Nitschke, & Putnam, 2002). Similarly, mood disorders can increase the risk for substance abuse, and substance abuse itself can lead to the development of mood disorders. Co-occurrence of mood disorders with other psychiatric disorders (especially the anxiety and the personality disorders) is common.

COURSE OF THE DISORDER AND PHASES OF TREATMENT

Figure 1 depicts the prototypic course of an episode of mood disorder and the associated phases of treatment (Kupfer, 1991). These phases are most applicable to medication treatment, but treatment with psychotherapy is increasingly being described in the same terms. The *acute phase of treatment* covers the period from the start of treatment until the point when the reduction of symptoms is considered acceptable. The initial goal of this treatment phase is to reduce existing symptoms of depression or mania. *Response* is defined as a significant reduction in symptom severity (typically 50%), such that the patient no longer meets criteria for the disorder (Frank, Prien, et al., 1991). *Remission* is a more complete response, defined as a reduction of symptom intensity to a level within the range of a never-ill population. Remission is preferred to response because the former is associated with a lower risk of relapse (Paykel et al., 1995) and a more complete restoration of function (Miller et al., 1998).

Relapse refers to the return of symptoms associated with the treated episode (Frank, Prien, et al., 1991). Treatment may suppress symptoms early on, but these symptoms are likely to reemerge if treatment is discontinued before the underlying episode has been resolved. Ending treatment too early is analogous to discontinuing an antibiotic as soon as a fever breaks but before the underlying infection has run its course; the symptoms of the underlying infection are likely to reemerge. Extending treatment past the point of remission for the purpose of preventing relapse

Fig. 1. Phases of treatment and the five "Rs" of depression: response, remission, relapse, recovery, and recurrence. The solid line represents the course of a prototypical episode of depression, the dotted line represents normalization that occurs if the oncoming episode is prevented, and the dashed lines represent the return of symptoms associated with relapse and recurrence. Adapted from "Long-Term Treatment of Depression," by D.J. Kupfer, 1991, *Journal of Clinical Psychiatry, 52*(Suppl. 5), p. 28. Copyright 1991 by the Physicians Postgraduate Press. Reprinted with permission.

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is called *continuation treatment*, and there is considerable evidence that it does reduce risk (Prien & Kupfer, 1986). It is not clear how long it takes for the underlying episode to completely resolve, but the current convention is to continue treatment on a routine basis for at least 6 months following initial remission. The available evidence suggests that risk for symptom return is highest during the first few months following initial remission and decreases over time in a manner that tracks the length of time it would have taken the episode to remit spontaneously in the absence of treatment (Reimherr et al., 1998).

Recovery refers to the resolution of the underlying episode, either because it has run its course or as a consequence of treatment. By convention, the return of symptoms following recovery is called a *recurrence* and is considered to represent the onset of a wholly new episode (Frank, Prien, et al., 1991). Recurrence typically involves all the same signs and symptoms as relapse and is distinguished more by how much time has passed since remission than by its clinical manifestations. Patients are about 3 times more likely to experience a return of symptoms during the first few months following remission (relapse) than they are to experience the onset of a new episode following complete recovery (recurrence). Extending treatment beyond the point of recovery for the purpose of preventing recurrence is called *maintenance treatment*, and there is considerable evidence that it too can reduce risk (Frank & Thase, 1999). Although not all patients require maintenance treatment, many remain at elevated risk for recurrence even after full recovery, and it is likely that some should remain in maintenance treatment indefinitely (Hirschfeld, 2001). This is particularly likely to be the case for patients with a history of chronic depression or multiple recurrences and for patients with bipolar disorder.

MEDICATION TREATMENT AND THE SOMATIC INTERVENTIONS

Major Depressive Disorder

The antidepressant medications are used for depressive disorders at all levels of severity, whereas ECT is usually reserved for relatively severe disorders and treatment-resistant patients (American Psychiatric Association, 2000). Table 2 lists the commonly used antidepressants, with their dosage ranges and side effects. Some medications, such as the tricyclic antidepressants (TCAs), are named by their chemical structure. Other medications, such as the monoamine oxidase inhibitors (MAOIs) and the selective serotonin reuptake inhibitors (SSRIs), are classified by their neurochemical effects.

The mode of action of the antidepressants is complex and only partly understood. To explicate what is currently understood, it is necessary to consider how the central nervous system functions. Information moves throughout the central nervous system through a series of electrical and biochemical events. When an electrical impulse moves down a neuron, it triggers the release of substances called neurotransmitters into the synaptic space that sep-

arates that neuron from other neurons. Neurotransmitters released by the presynaptic neuron cross the synaptic space, and some lodge by chance in receptors on the postsynaptic neuron; these same neurotransmitters can also be taken back up into the presynaptic neuron or metabolized by enzymes in the synaptic space. If enough of the neurotransmitters are taken up by receptors on the postsynaptic neuron, they cause that neuron to fire, continuing transmission of the information throughout the brain.

Norepinephrine, serotonin, and dopamine are all neurotransmitters that appear to be involved in the regulation of mood and the other vegetative processes involved in depression. It was once thought that the antidepressant medications worked primarily by blocking the reuptake of these neurotransmitters into the presynaptic neuron (thus increasing the amount of neurotransmitter available to trigger firing in the postsynaptic neuron), but it is virtually certain that this mode of action cannot fully explain antidepressants' effects. Manifold effects on presynaptic receptors and the subsequent cascade of biochemical events that go on within the postsynaptic neuron and beyond must also be considered (Duman, Heninger, & Nestler, 1997). These events include gene transcription processes that turn genes on and off and the effects those gene products have on subsequent neurophysiological response systems that control hormonal regulation and the branching and pruning of connections within different neural structures.

It has been widely believed that all available antidepressants have comparable efficacy on average and similar onsets of action (American Psychiatric Association, 2000). Figure 2 shows the results of a meta-analysis that pooled the results from studies comparing response rates for MAOIs, TCAs, SSRIs, and other miscellaneous agents with response rates for a pill placebo. It is clear from the figure that all four categories of medication had higher response rates than placebo, and their advantages over placebo were of a similar magnitude. The figure also shows how each class of medication compared with other medications (typically the other classes); no medication class was clearly superior to the others (Depression Guideline Panel, 1993). Within the context of this presumed parity, selection of an antidepressant for a particular patient is based on personal and familial treatment history, the likelihood of particular side effects, safety in overdose, and expense (American Psychiatric Association, 2000). Moreover, some medications are indicated more than others for certain subtypes of depression.

Antidepressant medications

MAOIs. The MAOIs were the first antidepressants to be identified. As their name suggests, they work by inhibiting the action of monoamine oxidase (an enzyme that breaks down the neurotransmitters in the presynaptic neuron), thus leaving more neurotransmitters available to transmit impulses across the synapse. These agents are particularly efficacious in treating depressions characterized by atypical or reversed vegetative symptoms (Thase, Trivedi, & Rush, 1995). Although they are rarely used any more as first-line treatments of depression, they remain important al-

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Table 2. *Commonly used antidepressants*

Class	Brand name	Usual dose (mg/day)	Prominent side effects[a]
MAOIs			Dry mouth, constipation, nausea, nervousness, difficulty sleeping or daytime drowsiness, tremor (shakiness), blurred vision, increased sweating, fatigue, and muscle jerks (neurologic myoclonus); less commonly headaches, urinary retention, appetite change with weight gain or loss, memory problems, and sexual side effects; especially problematic are orthostatic hypotension (sudden drop in blood pressure upon standing that causes a person to feel dizzy or faint) and hypertensive crisis (potentially life-threatening increase in blood pressure following ingestion of certain foods or medications)
Irreversible			
Isocarboxazid	Marplan	15–30	
Phenelzine	Nardil	45–90	
Tranylcypromine	Parnate	30–60	
Reversible			
Moclobemide	Not yet approved for use in the United States	300–600	
TCAs			Anticholinergic side effects (dry mouth, constipation, difficulty urinating, blurred vision, memory impairment, and confusion); less commonly difficulty sleeping, headaches, tremor (shakiness), appetite change with weight gain, and sexual side effects; especially problematic are orthostatic hypotension (see MAOIs) and cardiac arrhythmias for people with heart problems (can be lethal in overdose for anyone)
Tertiary amines[b]			
Amitriptyline	Elavil	100–300	
Clomipramine	Anafranil	100–250	
Doxepin	Sinequan	100–300	
Imipramine	Tofranil	100–300	
Trimipramine	Surmontil	100–300	
Secondary amines[b]			
Desipramine	Norpramin	100–300	
Nortriptyline	Aventyl	50–200	
Protriptyline	Vivactil	15–60	
Tetracyclics[b]			
Amoxapine	Ascendin	100–400	
Maprotiline	Ludiomil	100–225	
SSRIs			Nausea, diarrhea, insomnia, nervousness, muscle jerks, and especially sexual side effects; less commonly headaches, tremor (shakiness), motor restlessness (akathisia), daytime drowsiness, and vomiting
Citalopram	Celexa	20–60	
S-citalopram	Lexipro	10–20	
Fluoxetine	Prozac	20–60	
Fluvoxamine	Luvox	50–300	
Paroxetine	Paxil	20–50	
Sertraline	Zoloft	50–200	
Others			
NE reuptake inhibitor			
Reboxetine	Not yet approved for use in the United States	8–10	Anticholinergic-like side effects (see TCAs) and insomnia
Mixed reuptake inhibitors			
Bupropion (DA, NE)	Wellbutrin	300–400	Nausea, vomiting, insomnia, headaches, and seizures
Venlafaxine (5-HT, NE)	Effexor	75–225	Nausea, diarrhea, nervousness, increased sweating, dry mouth, muscle jerks, and sexual side effects; less commonly vomiting, insomnia or daytime drowsiness, headaches, tremor (shakiness), and increased blood pressure
Duloxetine	Not yet approved for use in the United States	60–80	Similar to venlafaxine (although risk of increased blood pressure appears to be lower)
5-HT modulators			
Nefazodone	Serzone	150–300	Orthostatic hypotension (see MAOIs), headaches, daytime drowsiness, visual disturbances, and liver damage (in rare instances)
Trazodone	Desyrel	75–300	Orthostatic hypotension (see MAOIs), sedation, and priapism
NE and 5-HT modulator			
Mirtazapine	Remeron	15–45	Weight gain and daytime drowsiness

Note. MAOIs = monoamine oxidase inhibitors; TCAs = tricyclic antidepressants; SSRIs = selective serotonin reuptake inhibitors; NE = norepinephrine; 5-HT = serotonin; DA = dopamine.
[a]For MAOIs, TCAs, and SSRIs, side effects for the entire class are shown; for the other antidepressants, side effects for each agent are shown separately.
[b]Tertiary amines, secondary amines, and tetracyclics are structurally related compounds, which collectively can be grouped together as tricyclics.

ternatives for patients who do not respond to more conventional medications.

Although clearly effective, the MAOIs have not been prescribed widely since the 1960s because they can produce life-threatening interactions with common foods like aged cheese. This so-called cheese effect is the result of inhibition of enzymatic metabolism of tyramine, which can cause a massive release of norepinephrine and a potentially lethal heart attack or

stroke (Thase et al., 1995). The dietary restrictions necessary to prevent this reaction result from the fact that the older MAOIs have an irreversible effect on both of the two forms of monoamine oxidase. There has been continued interest in development of a safer and reversible MAOI that has only a selective effect on one particular subform of monoamine oxidase. One such reversible MAOI, moclobemide, is available in many other countries, but questions about its efficacy persist (Lotufo-Neto, Trivedi, & Thase, 1999). In the midst of the influx of newer antidepressants, the reversible MAOIs appear to have become "orphan" drugs that no pharmaceutical company wants to invest the time and money in to bring to market. Nonetheless, the nonreversible MAOIs continue to be used as second- or third-line agents after others have failed, before taking patients on to ECT.

TCAs. The TCAs were the first-line class of antidepressants for much of the 1960s and 1970s. TCAs either predominantly inhibit norepinephrine reuptake (nortriptyline, protriptyline, and desipramine) or inhibit both norepinephrine and serotonin reuptake (clomipramine, imipramine, and amitriptyline). These latter medications were once thought to affect only serotonin, but it is now known that they each have metabolites that also affect norepinephrine, making them dual reuptake agents that have effects on both neurotransmitter systems (Thase & Kupfer, 1996). Actually, only clomipramine has strong effects on serotonin at moderate therapeutic doses (Bolden-Watson & Richelson, 1993),

which may explain its efficacy in treating obsessive-compulsive disorder (Griest, Jefferson, Kobak, Katzelnick, & Serlin, 1995).

Side effects and potential lethality in overdose are the major drawbacks of the TCAs. On average, up to 30% of patients in controlled trials stop taking TCAs because of side effects (Depression Guideline Panel, 1993). Many of these side effects are caused by blockade of receptors in the brain that have little to do with therapeutic benefit (Preskorn & Burke, 1992). For example, blockade of α_1 norepinephrine receptors may cause fainting due to sudden drop in blood pressure upon standing (orthostatic hypotension), a particular problem for the elderly (Roose, 1992). The TCAs also exert an effect on the heart that may contraindicate use for patients with irregular heartbeats. An overdose of as little as a week's supply of a TCA can result in fatal cardiac arrhythmias, and most outpatients need at least a week's supply of medication to tide them over from session to session (Kapur, Mieczkowski, & Mann, 1992).

TCA treatment is typically initiated at low dosages and then increased as needed, so long as side effects are tolerable, until a clinical response is obtained. Dosage is related to response either linearly (i.e., efficacy increases as doses increase) or curvilinearly (i.e., efficacy increases up to some point as doses increase but then declines as doses increase further; Perry, Zeilmann, & Arndt, 1994). It is easy to test a patient's plasma levels of amitriptyline, desipramine, nortriptyline, or imipramine (i.e., the amount of medication in the fluid part of the blood), and this information
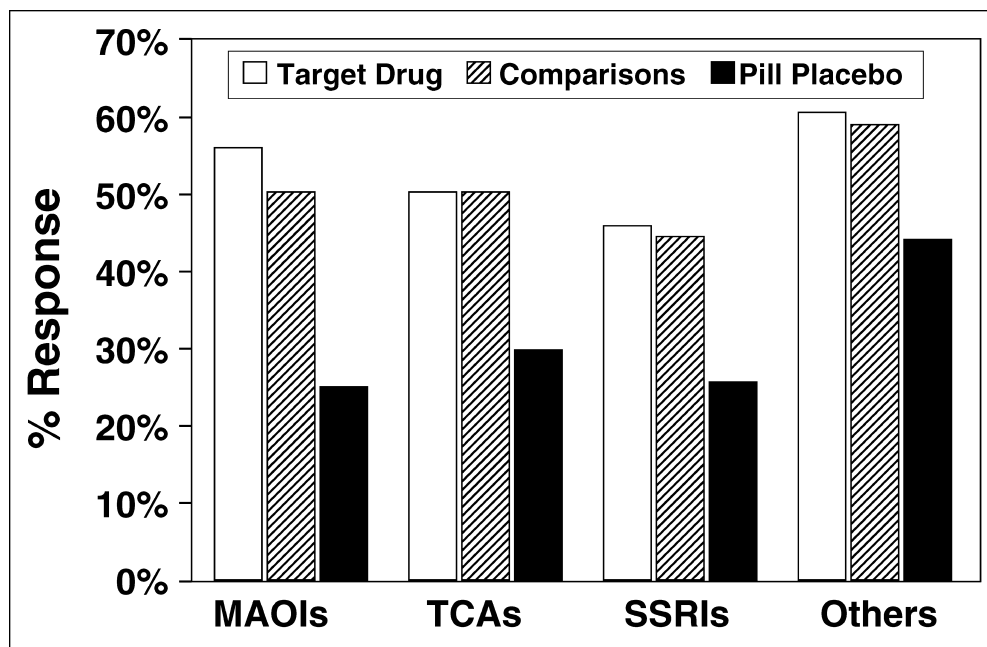
Fig. 2. Percentage of patients responding to treatment as a function of medication class: Each target drug is compared with a number of different alternative medications ("Comparisons") and pill placebo. The figure is based on a meta-analysis conducted for the Agency for Health Care and Policy Research (Depression Guideline Panel, 1993). MAOIs = monoamine oxidase inhibitors; TCAs = tricyclic antidepressants; SSRIs = selective serotonin reuptake inhibitors; Others = other miscellaneous and typically newer medications (listed as "heterocyclics" in the original report).

can be helpful in monitoring cases of exquisite sensitivity to side effects, investigating nonresponse to apparently adequate dosages, or ensuring safety following overdose (Preskorn & Fast, 1991).

The strongest rationale for continued first-line use of the TCAs is their relative cost when prescribed generically (Song, Freemantle, & Sheldon, 1993). Although simple comparisons of purchase costs clearly favor the generic TCAs over other medications that are still under patent, the actual savings are reduced when the costs of necessary blood tests, electrocardiograms, frequent pharmacy visits, and ancillary medications (e.g., stool softeners), as well as noncompliance, are tallied (Henry, 1993). Once the costs of completed suicide, accidental poisonings, and intensive-care days following overdose are taken into account, the TCAs' apparent cost savings virtually disappear. Nonetheless, millions of people who started taking medications in earlier decades when the TCAs were the treatment of choice continue to take these medications for the prevention of recurrent depressive episodes.

SSRIs. The vast majority of American physicians (including psychiatrists) currently favor the SSRIs as first-line medications (Olfson et al., 2002). The SSRIs have replaced the TCAs because of their ease of use, lower level of "nuisance" side effects, and safety in overdose (Thase & Kupfer, 1996). One major drawback of the SSRIs has been their expense, although fluoxetine is now available as a less expensive generic.

The Food and Drug Administration (FDA) has approved four SSRIs for the treatment of depression: fluoxetine, sertraline, paroxetine, and citalopram. A fifth, called fluvoxamine, is approved for treatment of obsessive-compulsive disorder and is used in other countries to treat depression as well. As their name suggests, the principal mechanism of action for the SSRIs is blockade of the reuptake of serotonin back into presynaptic neurons. There are few compelling reasons to pick one SSRI over another for treatment of uncomplicated major depression; the SSRIs are more similar than different (Thase & Kupfer, 1996). However, there are several distinguishing features. These include how long the drug stays in the system after the patient stops taking it, propensity for interactions with other medications, and the antidepressant activity of one or more drug metabolites (Edwards & Anderson, 1999).

SSRI therapy is associated with a number of different side effects, including nausea, diarrhea, headache, tremor, daytime sleepiness, sexual side effects like diminished libido or difficulty having an orgasm, nervousness, and insomnia. The latter two side effects, particularly when coupled with motor restlessness, can be intensely uncomfortable and may help to explain early reports linking SSRI treatment with an increase in thinking about suicide (Teicher, Glod, & Cole, 1990). Despite sensational opinion to the contrary, however, suicidal thinking is no more likely to emerge when taking SSRIs than when taking any other antidepressant, and in those infrequent instances when it does emerge there is little reason to think that it is a consequence of taking medications (Beasley et al., 1991). In fact, there are even indications that the greater reliance on SSRIs over the past decade has been associated with an

overall decrease in the number of deaths from suicide in recent years (Isacsson, 2000). During the acute phase of treatment with SSRIs, typically 10% to 20% of patients stop taking their medication because of side effects; this rate is higher than found with placebo but lower than with the TCAs (Preskorn & Burke, 1992).

The relationship between plasma levels of SSRIs and clinical response is not well defined, so monitoring plasma levels has little value (Preskorn & Burke, 1992). Patients started on low therapeutic dosages tend to have about the same probability of responding as those started on higher dosages (Thase & Kupfer, 1996). Therefore, it is generally cost-effective to begin with a low dose and wait at least 4 weeks to see whether the patient responds. Fluoxetine takes longer than the other SSRIs to reach maximum levels in the bloodstream and requires more time between dose escalations; hence, it may take slightly more time to achieve maximal response with fluoxetine (Edwards & Anderson, 1999).

There are indications that the SSRIs may be less effective than the TCAs for treatment of relatively severe depressions with melancholic features (Nelson, 1994). Although results are inconsistent across individual studies, a meta-analysis of 25 separate randomized controlled trials found a modest advantage for some of the TCAs (e.g., clomipramine and amitriptyline) in studies of hospitalized patients (Anderson, 2000). It is possible that TCAs have an inherent advantage over SSRIs that was obscured in earlier outpatient studies but has emerged in recent trials involving more severe depressions because side effects and dosing are better managed within a hospital milieu than on an outpatient basis. Given their relative safety and ease of management, SSRIs will likely continue to be widely prescribed, particularly in primary-care settings. Nonetheless, there are growing concerns about their efficacy with severely depressed populations.

New antidepressants. Several new antidepressants have potential advantages over the older agents. Bupropion was the first non-SSRI antidepressant to be introduced in the United States following the approval of fluoxetine. Bupropion has a substantially lower incidence of sexual side effects than the SSRIs, and patients who experience side effects during SSRI therapy usually can take bupropion without difficulty (Croft et al., 1999). Bupropion also may be particularly useful for treatment of depressions characterized by weight gain, loss of energy, and oversleeping. Its mechanism of action is not well understood but appears to involve the modulation of transmission involving both norepinephrine and dopamine (Ascher et al., 1995). Its initial formulation required that it be taken more than once a day (divided daily dosing) and was associated with an increased risk of seizures at doses above 450 mg/day. These disadvantages, combined with the clinical perception that bupropion was less effective than other antidepressants for treatment of anxious depressions, limited the use of this otherwise effective medication (Thase & Kupfer, 1996). A sustained-release formulation is now available, and its therapeutic efficacy at doses of 300 to 400 mg/day has been established; it also has been approved as an aid for smoking cessation under the brand name Zyban®.

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Several new antidepressants have multiple direct effects on neuronal systems that may give them an advantage over conventional SSRIs. Venlafaxine, one of these new medications, not only potently inhibits reuptake of serotonin, but also inhibits reuptake of norepinephrine at higher doses, and of dopamine at even higher doses still (Harvey, Rudolph, & Preskorn, 2000). It also is less likely to block the superfluous receptors affected by the dual reuptake TCAs and thus produces fewer noxious side effects than do those agents. It also appears to be less toxic in overdose (Thase, Friedman, & Howland, 2000). At the same time, it appears to share with these agents a relative advantage over the SSRIs in the treatment of relatively severe depression. A pooled analysis of original data from more than 2,000 moderately to severely depressed patients across eight different placebo-controlled trials showed an advantage for venlafaxine relative to a number of different SSRIs (Thase, Entsuah, & Rudolph, 2001). Venlafaxine produces side effects like tremor, headache, sexual dysfunction, and insomnia at rates comparable to those for the SSRIs. Nausea is typically greater with venlafaxine than the SSRIs, but this difference tends to dissipate over time.

Several factors initially led to relatively low utilization of venlafaxine. Nausea and the risk of elevated blood pressure were both problematic side effects, and the need for divided daily dosing and a rather broad range of effective doses reinforced the perception that venlafaxine was mostly suited for treatment of severely ill or complicated patients. However, interest in this compound has been renewed by the introduction of an extended-release formulation (Thase, 1997). It has been further spurred by the publication of a number of studies suggesting venlafaxine has greater efficacy than the SSRIs (Mehtonen, Sogaard, Roponen, & Behnke, 2000; Poirier & Boyer, 1999; Rudolph & Feiger, 1999). These findings challenge the conventional wisdom that all antidepressants are equally effective. They also suggest that problems with tolerability may have masked an advantage for the older dual reuptake TCAs over the SSRIs. Replication of these results and studies comparing venlafaxine with a broader range of SSRIs, including sertraline and citalopram, are needed.

Nefazodone is unique in both its chemical structure and its neurochemical effects (Taylor et al., 1995). Nefazodone has only a weak effect in terms of blocking the reuptake of serotonin (and possibly norepinephrine) into the presynaptic neuron, but has a potent blocking effect on postsynaptic 5-HT$_2$ serotonin receptors (Taylor et al., 1995). In contrast to the SSRIs, nefazodone improves sleep (Rush et al., 1998) and has a low risk of sexual side effects (Ferguson et al., 2001). Nefazodone requires divided daily dosing, and its most common side effects include sedation, headaches, and visual disturbances (Preskorn, 1995). In rare cases, it can cause liver damage, leading the FDA to mandate that packaging carry a warning.

Mirtazapine blocks postsynaptic serotonin receptors; it also blocks selected norepinephrine and other receptors. Mirtazapine is also a potent antihistamine and tends to be more sedating initially than most other new antidepressants. Comparative studies have shown that it relieves symptoms sooner than the SSRIs (Quitkin, Taylor, & Kremer, 2001). A modest advantage attributable to sleep improvements was also observed in a recent inpatient study comparing mirtazapine with venlafaxine (Guelfi, Ansseau, Timmerman, & Korsgaard, 2001). Weight gain tends to be the most troublesome long-term side effect, especially for young women (Thase, Howland, & Friedman, 2001). For these and other reasons, mirtazapine is likely to be a "niche drug" for geriatric depression or used in combination with other medications; neither it nor nefazodone is likely to challenge the SSRIs for market share.

ECT

ECT is the best-studied and most effective treatment for patients who have psychotic depressions or do not respond to medications (Sackeim et al., 2001). Nonetheless, ECT is still controversial and remains one of the most stigmatized of psychiatric treatments. In point of fact, when ECT is administered properly, its medical risks are no greater than those associated with other "minor" surgical procedures that require general anesthesia (e.g., tonsillectomy). ECT is a carefully regulated procedure and requires either explicit written informed consent or, much more rarely, the approval of a court-appointed guardian. The current practice of ECT is quite unlike its sensational presentation in the cinema.

ECT typically begins during an inpatient stay and involves a course of 6 to 12 electrically induced grand mal seizures spaced several days apart. Longer courses are sometimes necessary, although patients often are able to continue treatments as outpatients. ECT treatments are most commonly administered on alternating days, and are given under general anesthesia; muscle relaxants and proper respiratory support are used to lessen the musculoskeletal effects of the convulsion. The electrical current is applied either across the nondominant hemisphere of the brain (unilaterally) or bilaterally. Effective therapy may require a dose of current that is at least one and a half times the minimum seizure threshold. It is thought that ECT works by eliciting or provoking compensatory central nervous system mechanisms that regulate the same neurotransmitter systems just described for the antidepressant medications.

The most common immediate side effect is confusion; transient amnesia of varying degrees may be observed for several months. Not uncommonly, there will be some loss of memory of the details of hospitalization or adjacent weeks. Although there is no good evidence of permanent memory loss caused by ECT, some people report this experience, and it remains a legitimate topic for careful longitudinal study. Severe mood disorders can have pronounced effects on cognitive abilities, and it is sometimes difficult to untangle the effects of the illness from those of the treatment. Perhaps it is the experience of having had an acute ECT-induced memory disturbance, coupled with persistent amnesia about details of the weeks surrounding the treatment, that maintains the subjective sense of having persistent memory dysfunction.

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The cost of the treatment and its side effects warrant judicious use for only the most severe and disabling mood disorders. Under these circumstances, the costs are partly offset by a greater probability of improvement, a shorter time to remission, and a significant reduction in post-hospitalization rates of illness and death relative to patients not given ECT. Only 50 to 60% of antidepressant-resistant depressions respond to ECT (Prudic et al., 1996). Relapse is also a problem after successful ECT, particularly among patients who have not responded to antidepressants (Sackeim et al., 1990). Strategies for post-ECT treatment include medication therapy that combines antidepressants and mood stabilizers (especially lithium; Sackeim et al., 2001). Patients who relapse despite medication may benefit from maintenance ECT using a less frequent schedule of treatments (T.B. Clarke, Coffey, Hoffman, & Weiner, 1989; Thienhaus, Margletta, & Bennett, 1990).

Phases of medication and somatic treatment

Acute phase. As Figure 2 shows, about 50% of depressed patients who begin pharmacotherapy in outpatient clinical trials respond to any given antidepressant medication (Depression Guideline Panel, 1993; Mulrow et al., 1999). Approximately 30% of such patients can be expected to respond to a placebo pill alone. This figure includes the effects of spontaneous remission due to factors unrelated to treatment and of nonspecific psychological factors related to the treatment process, such as contact with a helping professional and the expectation for change. Thus, the relative magnitude of an antidepressant's pharmacological effect can be estimated by subtracting the response rate for placebo (which includes the effects of spontaneous remission) from that of active medication; this difference is sometimes referred to as the "true" drug effect. Overall, the average drug-placebo difference in published reports of randomized controlled trials of major depression is about 20% (50% − 30%). Thus, only about 40% of the patients who respond when given antidepressants appear to actually be responding to the specific biological effects of the medication (20%/50%; Depression Guideline Panel, 1993).

Drug-placebo differences are smaller for patients with mild depressive states because they respond to placebo at higher rates than other patients. Patients with severe depressions are less likely to respond to active medications than patients with mild depressions, but they are even less likely to respond to a pill placebo, so that drug-placebo differences remain relatively large for this group (Thase, 1999). Given the high rates of placebo response among patients with mild depression, it is common practice in pharmacological trials to focus on patients who are moderately to severely depressed. This typically means that anywhere from a third to a half of patients who meet criteria for major depression might be excluded from such trials for lack of severity. Chronicity also appears to lower response to both drug and placebo, and factors related to subtype of depression and accompanying illnesses can influence response to different medications. About one third of all published randomized controlled trials fail to show drug-placebo differences (Thase, 1999). This failure is due in part to methodological weaknesses and inadequate sample size, but also to heterogeneity in the populations studied.

Most studies in this literature rely on clinical ratings of depressive symptoms or clinical judgments of global improvement as their major index of change. The Hamilton Rating Scale for Depression (HRSD) is the most widely used clinical rating instrument in the United States (Hamilton, 1960). The number and composition of items varies somewhat from one version of the HRSD to another, although higher scores invariably mean more depression. When its original and most common 17-item version is used, outpatient samples typically have mean ratings in the low- to mid-20s prior to treatment, and ratings drop 8 to 10 points over the next several weeks of treatment. Mean differences after treatment with drug versus placebo typically range between 2 and 4 points, with standard deviations of 6 to 8, yielding average effect sizes that range from .33 to .50. (Effect sizes are calculated by dividing differences between the groups by the standard deviation and represent a common metric for comparing treatment effects across different measures.) An effect of this size is not considered to be particularly impressive, especially when outcome is assessed on a continuous measure like the HRSD (Kirsch, Moore, Scoboria, & Nicholls, 2002).

Response typically is defined as a 50% reduction in HRSD score or a rating of 1 (*fully improved*) or 2 (*much improved*) on clinical ratings of global improvement. Many of the same studies that have produced unimpressive average effect sizes of .50 or less have also produced drug-placebo differences in response rates on the order of 20% or more, which seem considerably more impressive. This apparent discrepancy is partly psychological; people are prone to underestimate the impact of causal processes when they are expressed in terms of the proportion of the variance accounted for, and even small effects can have a major impact (Rosenthal, 1990). However, this discrepancy between average effect size and response rates also reflects the biological diversity of the disorder. Average effects will be reduced by the inclusion of patients who are not pharmacologically responsive to a given agent (Hollon, DeRubeis, Shelton, & Weiss, 2002). If no one got more than the "average" benefit, then the effects of medications would not be very impressive, but for those patients who do respond pharmacologically to a specific agent, the benefits can be profound. When such heterogeneity exists, indices that reflect proportion of patients who respond give a better indication of the value of an intervention than estimates based on the average response across the whole sample.

These estimated effect sizes are based on randomized controlled trials of typically 6 to 8 weeks' duration. Given that the average depressive episode lasts 6 to 9 months, estimates from these trials can be expected to underestimate the amount of spontaneous remission that would occur if the episodes were

allowed to run their course. However, even in these relatively brief trials, spontaneous remission and expectancy factors can account for a considerable portion of the overall response (Kirsch & Sapirstein, 1998). Moreover, these estimates may be inflated by "publication bias." For example, Khan, Warner, and Brown (2000) included unpublished studies in a reanalysis of studies submitted to secure approval from the FDA and found that the average response to medications dropped from 50% down to only 40%, relative to 30% for placebo. Thus, the estimated true drug effect was only 10%, which accounted for only 25% of the total effect of treatment (10%/40%).

Some researchers have gone so far as to question whether the antidepressant medications have any true pharmacological effect at all (Fisher & Greenberg, 1993). They argue that the apparent superiority of antidepressants over placebo is an artifact caused by a problem with the double-blind method; the side effects that patients experience provide clues to which patients are receiving medication and which are receiving placebo. These researchers have further suggested that studies that use active placebos that mimic side effects typically find smaller drug-placebo differences than studies that do not use active placebos (R.P. Greenberg, Bornstein, Greenberg, & Fisher, 1992). They also have suggested that effect size for a given medication typically is smaller when it is used as a comparison agent than when it is itself the focus of attention. However, "breaks in the blind" are often driven as much by perceived response as by side effects, and the studies cited to support the argument just described often fail to hold up under scrutiny (Quitkin, Rabkin, Gerald, Davis, & Klein, 2000). Moreover, there is evidence that placebo response occurs sooner than response to active medication, but is less stable over time (Stewart et al., 1998). Although issues of bias and methodological flaws need to be taken seriously, it seems unlikely that drug-placebo differences are wholly artifactual.

Although most treatment is conducted on outpatients, hospitalization is necessary in about 5 to 10% of cases of acute treatment of depression. The principal reasons for hospitalization are that the severity of the depression is overwhelming, the patient is unable to function in everyday life, or the patient displays suicidal or other life-threatening behavior. The typical length of hospitalization averages just under a week. Such abbreviated stays have reduced costs but necessitate greater transitional or aftercare services. Few severely depressed patients achieve remission after only 1 or 2 weeks of treatment.

One of the major problems compromising the potential effectiveness of acute-phase pharmacotherapy is that patients stop taking their medication too soon, before it is possible to tell if the treatment will be effective. This is particularly problematic in outpatient settings. Attrition rates from clinical trials often are as high as 30 to 40%, and sometimes even higher (Depression Guideline Panel, 1993). Although medication side effects are a principal reason for attrition, other factors are inadequate education of patients (resulting in their having unrealistic expectations about treatment), patients' ambivalence about seeing a

psychiatrist or taking a psychiatric medication, and practical roadblocks (e.g., the cost or accessibility of services).

Another problem is failure of the prescribing physician to monitor how symptoms respond and to change treatments in a timely manner. Antidepressant medications should be changed if there is no clear effect within 4 to 6 weeks at the maximally tolerated dose (Depression Guideline Panel, 1993; Nierenberg et al., 1995; Quitkin et al., 1996). Regardless of the initial medication chosen, about 30 to 50% of patients will not respond, and those patients will often fare better if their medication is changed.

About 50% of patients who do not respond to one medication will respond to a second one (Thase & Rush, 1997). This is clearly the case for changes across medication classes, and there are good theoretical reasons for switching to an agent that mobilizes different underlying mechanisms (see Thase et al., 2002). At the same time, a number of studies without comparison conditions (open trials) suggest that switching to a "classmate" can also be efficacious (e.g., Posternak & Zimmerman, 2001; Thase, Blomgren, Birkett, Apter, & Tepner, 1997; Thase, Feighner, & Lydiard, 2001). Most clinicians prefer to start treatment with a medication that is easy to manage and relatively free of complications, like an SSRI. Until data from more methodologically rigorous trials are available to challenge these open trials, the practice of prescribing at least a second SSRI before switching to an alternate type of medication appears justified.

Switching to a novel compound often requires that the patient first be taken off the ineffective medication or that doses be reduced at the same time that the novel compound is introduced in order to minimize the risk of negative interactions (Thase & Rush, 1997). Patients sometimes feel worse during this process. For most medications, this transitional process takes about a week, although 2 weeks are required when switching from most SSRIs to an MAOI, and 6 weeks when switching from fluoxetine to an MAOI (Beasley, Masica, Heiligenstein, Wheadon, & Zerbe, 1993). Such delays are avoided by augmentation strategies, in which the patient continues to take the original ineffective or only partially effective agent while also taking a new, second medication that can safely be combined with the first. The best-studied strategies of this type are lithium augmentation, thyroid augmentation, and TCA-SSRI combinations, all frequently used with unipolar patients (Nelson, Mazure, Bowers, & Jatlow, 1991; Nierenberg & White, 1990; Thase & Rush, 1997).

Studies have shown that about 30 to 60% of patients who do not respond to a TCA will improve within 4 weeks of beginning lithium augmentation (Thase & Rush, 1995). Lithium augmentation has not been as well studied with the SSRIs and is not as commonly used with them. Lithium is primarily thought of as a mood stabilizer, but it has modest antidepressant properties of its own and appears to enhance serotonin transmission (Price, Charney, Delgado, & Heninger, 1989). Side effects, potential lethality in overdose, and the need to monitor blood levels all limit its use. Thyroid augmentation is generally easier to implement than lithium augmentation but has more equivocal

efficacy. Nonetheless, in the only randomized controlled trial directly comparing thyroid and lithium augmentation, the two strategies were comparable to each other and more efficacious than placebo (Joffe, Singer, Levitt, & MacDonald, 1993).

Increasingly, clinicians are adding medications that also affect norepinephrine, such as desipramine or bupropion, to an ineffective SSRI. Such polypharmacy was anathema in the 1980s, but the relative safety of the newer compounds has permitted a culture shift, reflected in the new term *rational cotherapy*. Nonetheless, the data concerning such combinations are still inconclusive (Thase & Rush, 1997). Moreover, caution is needed when using multiple antidepressants, because doses that are tolerable when each is taken individually can sum to toxic levels in the blood (Nelson et al., 1991).

Continuation phase. Successful acute-phase antidepressant pharmacotherapy should almost always be followed by at least 6 months of continuation treatment for the purpose of preventing relapse (American Psychiatric Association, 2000). During this phase, most patients are seen every other week for the first month or two and then monthly thereafter. Continuation pharmacotherapy reduces the risk of relapse from about 50% to about 20% (Prien & Kupfer, 1986). This reduction is larger in magnitude than the drug-placebo difference during acute-phase treatment and contributes to the notion that the antidepressants have a true pharmacological effect. Moreover, the different medication classes all seem to have an effect of about this size (Hirschfeld, 2001). Relapse during continuation treatment often suggests either that the patient is not taking the medication as prescribed (Myers & Branthwaithe, 1992) or that the initial response was a placebo effect that has disappeared (Quitkin et al., 1993).

A second goal of continuation pharmacotherapy, in addition to preventing relapse, is consolidation of remission into a full recovery, that is, to allow patients to get over the episode. Keeping patients on medications for a number of months following initial remission not only affords protection from relapse, but also allows recovery from the treated episode with its consequent reduction of risk. Exactly how long patients need to keep taking continuation medications remains unclear. However, a recent study that varied the duration of continuation treatment found that keeping patients on medication for 3 months cut relapse risk in half, whereas there was no significant difference between continuing and withdrawing medication after 6 months of continuation treatment (Reimherr et al., 1998). Therefore, the current practice is to provide continuation treatment for virtually all patients who respond to medications, and a significant minority can be withdrawn from antidepressants after 6 to 9 months without provoking a relapse (Frank & Thase, 1999).

Maintenance phase. Maintenance pharmacotherapy is intended to prevent recurrent affective episodes (Himmelhoch, Thase, Mallinger, & Houck, 1991; Kupfer, 1991). In contradistinction to relapse, which represents reactivation of the original epi-

sode, a recurrence is viewed conceptually as the onset of a new episode of illness (Frank, Prien, et al., 1991). Maintenance pharmacotherapy is typically recommended for individuals with a history of three or more depressive episodes or chronic depression, because the risk of recurrence in such patients is high (Kupfer, 1991). Maintenance treatment typically is conducted via monthly or quarterly visits and can extend for years, if not indefinitely (Frank & Thase, 1999). Evidence suggests that maintenance therapy should use the same doses prescribed during acute and continuation treatment (Franchini, Zanardi, Gasperini, & Smeraldi, 1999; Frank et al., 1993).

The magnitude of the drug-placebo difference for prevention of recurrent depressive episodes depends on the inherent risk in the population (i.e., chronicity, age, and number of prior episodes), the length of the treatment, the patient's adherence to the treatment regimen, and the dose of the active agent used. Early studies, which often lowered maintenance dosages following acute-phase treatment, generally documented a twofold advantage for maintenance treatment relative to medication withdrawal, but that advantage more than doubles when doses are kept at the same levels used during the acute phase (Franchini et al., 1999; Frank et al., 1993). Studies of long-term pharmacotherapy with new antidepressants continue to accumulate, and evidence supports their efficacy in preventing recurrence (e.g., Hochstrasser et al., 2001; Thase, Nierenberg, Keller, & Panagides, 2001). No antidepressant with established acute-phase efficacy has been found to lack a preventive effect, and only a handful of negative trials have failed to find this effect. Significant benefits also have been observed in studies of chronic (Keller et al., 1998), atypical (Stewart, Tricamo, McGrath, & Quitkin, 1997), and late-life (Reynolds, Perel, et al., 1999) depression. However, it must be emphasized that this preventive effect exists only so long as the patient continues to take the medication. There is no evidence that medication reduces future risk once its use is terminated.

Fava (1994) has suggested that maintenance antidepressant therapy may suppress risk of recurrence at the expense of inhibiting the natural process of recovery in the central nervous system. Some evidence supports this view. Rates of symptom return following medication withdrawal are similar and often high regardless of how long patients have taken medications (Thase, 2000). The risk of recurrence during the first 6 months after antidepressant withdrawal is 3 to 6 times higher than the rate observed in naturalistic studies in which patients may have been off medications for longer periods (Keller & Boland, 1998). Slow tapering of medication may afford some protection against recurrence, although tapering may need to be extended for a month or more (Baldessarini, Viguera, & Tondo, 1999).

Special populations and problems

Medication treatment in the elderly. By and large, the various antidepressant medications are about as efficacious in the elderly as they are in adults generally (Depression Guideline Panel, 1993). The primary differences in treating this population are the

greater sensitivity to side effects (particularly with the older antidepressants) and problematic interactions with other medications. Depressions often go undetected in the elderly and are sometimes confounded with nonpsychiatric medical and neurological disorders. Most existing studies have been conducted with otherwise medically healthy patients, so the extent to which the results generalize to patients with medical complications remains unclear.

Medication treatment of children and adolescents. Although the older antidepressants are widely used to treat children and adolescents, there is little evidence that they are specifically efficacious for these age groups. A meta-analysis of the dozen available placebo-controlled trials found little differential benefit for the TCAs (Hazell, O'Connell, Heathcote, Robertson, & Henry, 1995), perhaps because of limitations in research design or because children and adolescents have higher rates of spontaneous remission and placebo response than adults. However, the negative results likely also reflect developmental differences linked to age, because the TCAs often target norepinephrine and this neurotransmitter system does not develop fully until early adulthood (Ryan, 1990).

Recent trials suggest greater therapeutic benefit with SSRIs. Emslie et al. (1997) found that children and adolescents between the ages of 7 and 17 were significantly more likely to respond to fluoxetine than to a pill-placebo control, and that there were no differences in response between children and adolescents. Similarly, Keller et al. (2001) found paroxetine (but not imipramine) superior to a placebo pill in an 8-week trial with adolescents. Although it would be premature to claim that the efficacy of SSRIs has been established for these age groups, subsequent studies (some still in progress) support these findings. Yet even if these medications are efficacious, it remains to be seen whether they can (or should) be used for long-term continuation or maintenance treatment in these younger populations.

Chronic depressive states. Chronic depressions are not particularly responsive to placebo (Kocsis et al., 1988) and also have a low rate of spontaneous remission (Keller et al., 1992). The past few years have witnessed a dramatic increase in research on pharmacotherapy of dysthymic disorder and other chronic depressive states (Thase, 1998). It is now fairly well established that many patients with chronic depressive syndromes respond to the various antidepressant medications (e.g., Ravindran, Guelfi, Lane, & Cassano, 2000), as do patients with dysthymic disorder (Thase et al., 1996). In a randomized controlled trial comparing imipramine and sertraline, the two drugs had comparable outcomes for double and chronic major depression, although the SSRI was tolerated better (Keller et al., 1998). Similarly, maintenance treatment appears to provide ongoing relief (Kocsis et al., 1996).

The utility of antidepressants for chronic depression is noteworthy because there previously was a tendency to view these disorders as neurotic or characterologic conditions with largely psychological causes (Akiskal, 1994). Nevertheless, most chronically depressed people have had multiple primary-care contacts without ever having received an adequate course of medication (Wells, Katon, Rogers, & Camp, 1994). In some cases, people with protracted histories of depression report feeling dramatically changed, even transfigured, following only 4 to 6 weeks of pharmacotherapy (Kramer, 1993). Patients with chronic depressions often have interpersonal and vocational difficulties that persist despite adequate pharmacotherapy (e.g., Miller et al., 1998). Combining psychotherapy with pharmacotherapy is therefore particularly beneficial in treating chronic depression, as illustrated by the findings of Keller and his colleagues (2000), something we discuss in a subsequent section.

Bipolar Disorder

Bipolar depression

Recommended pharmacotherapy of bipolar depression typically begins with lithium, divalproex, or an alternate mood stabilizer (American Psychiatric Association, 2002). Mood stabilizers reduce the risk of cycling rapidly between episodes of mania and depressions and have modest antidepressant effects (Sachs & Thase, 2000). For bipolar depressions that do not respond to therapy with a mood stabilizer, or that return after a period of successful treatment, an antidepressant typically is added. Increasingly, that is likely to be one of the newer nonsedating antidepressants like the SSRIs, venlafaxine, or bupropion (Amsterdam, 1998; Nemeroff et al., 2001; Thase & Sachs, 2000; L.T. Young et al., 2000). The MAOIs continue to offer an important alternative treatment for patients who do not respond to standard antidepressants (Himmelhoch et al., 1991; Sachs, Koslow, & Ghaemi, 2000).

The optimal length of continuation-phase pharmacotherapy has not been established empirically for bipolar depression (American Psychiatric Association, 2002). During the continuation phase, the risk of depressive relapse must be balanced against concerns about inducing mania or rapid cycling (Solomon, Keitner, Miller, Shea, & Keller, 1995). Antidepressants may increase mood cycling in vulnerable subgroups, such as women with Bipolar II Disorder (Altshuler et al., 1995).

No recent randomized controlled trials of bipolar disorder have examined the role of antidepressants in preventing recurrent depression. In one well-controlled older study, recurrence rates of more than 60% were observed despite maintenance treatment with lithium, either alone or in combination with imipramine (D.R. Shapiro, Quitkin, & Fleiss, 1989). However, imipramine is a poor antidepressant for bipolar depression, and it is quite possible that newer antidepressants, combined with mood stabilizers, would be more effective.

Mania

Studies over the past two decades have confirmed the limitations of lithium for acute-phase treatment of mania; whereas success rates of 80 to 90% were once the norm, response rates

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of only 40 to 50% are now commonplace (American Psychiatric Association, 2002). This apparent decline in lithium responsiveness may be partly due to sampling bias or factors such as younger age of onset, increased frequency of drug abuse, or shorter treatment periods necessitated by briefer hospital stays (Solomon et al., 1995). About half of all manic episodes still require hospitalization, but the typical stay is now down to less than 2 weeks.

Several medications originally developed for other conditions increasingly are used for patients with bipolar disorder who cannot tolerate or do not respond to lithium. The efficacy of the anticonvulsants carbamazepine and divalproex sodium has been documented in randomized controlled trials (see, e.g., Bowden et al., 2000). These medications are believed to work by stabilizing neuronal membrane systems (Manji & Lenox, 1999). Both can be toxic and require regular monitoring of plasma levels (Tohen, Castillo, Baldessarini, Zarate, & Kando, 1995). Of several other anticonvulsants under study for their antimanic effects, lamotrigine also shows particular promise for the treatment of bipolar depression (Calabrese et al., 1999). Calcium channel blockers may also have antimanic effects, but these initial indications have not yet been tested in large, well-controlled clinical trials (see Janicak, Newman, & Davis, 1992).

Although effective for acute treatment of mania, the conventional antipsychotic medications were relegated to adjunctive use by the very real risk of tardive dyskinesia, an irreversible neurological disorder caused by exposure to these medications. The atypical antipsychotic clozapine, which works through different biological mechanisms and is associated with virtually no risk of tardive dyskinesia, is useful in otherwise refractory manic states (Suppes et al., 2001). However, clozapine therapy necessitates regular blood monitoring to help protect against a potentially lethal disorder of the bone marrow called agranulocytosis. Newer atypical antipsychotic medications, such as olanzapine and risperidone, offer greater safety than clozapine with respect to agranulocytosis, although it is still not clear that they do not cause tardive dyskinesia, which can take up to a decade to emerge. Olanzapine is the most extensively studied and has received FDA approval for treatment of mania (Tohen et al., 1995, 2000). For manic patients who do not respond to pharmacotherapy, ECT remains a viable alternative (Mukherjee, Sackeim, & Schnur, 1994).

The efficacy of lithium for preventing onset of mania also appears to be significantly lower now than in previous decades: Recurrence rates of 40 to 60% are now typical of ongoing lithium therapy (Bowden et al., 2000). Noncompliance with the medication regimen almost certainly plays a role, and there is concern that medication "holidays" may cause patients to lose their responsiveness to lithium (Post, Leverich, Altshuler, & Mikalauskas, 1992). With the growing recognition of the limitations of lithium, anticonvulsants and the atypical antipsychotics are being used increasingly for maintenance therapy of bipolar disorder (American Psychiatric Association, 2002). Concerns about weight gain, hair loss, and, more recently, development of polycystic ovary syndrome may complicate long-term treatment with dival-

proex. Significant weight gain also is associated with long-term therapy with the best-studied atypical antipsychotics, olanzapine and risperidone. It also is possible that these medications will turn out to be associated with some risk of tardive dyskinesia after years of therapy.

Summary

Various antidepressant medications are clearly effective in the treatment of depression and provide protection against relapse and recurrence so long as patients continue to take them. However, not everyone responds to any given medication, and there is no indication that medications reduce risk once discontinued. The different classes of medications appear roughly comparable in efficacy, although they differ in ease of management and the extent to which they produce problematic side effects. The SSRIs are the least problematic and most widely prescribed, but may be less effective than the older, dual reuptake TCAs for more severe patients. Newer agents that affect two or more neurotransmitters may have the efficacy of the older TCAs without some of the most problematic side effects. The MAOIs are rarely used as first-line agents, but remain important in the treatment of atypical depression and depressions that are refractory to other agents. Patients who do not respond to a given medication can be switched to another or treated with a combination of agents, and most patients will respond to one or more of the different medications. ECT remains a valuable treatment for severe or psychotic depressions but is still stigmatized and is associated with at least temporary cognitive impairments.

Treatment of bipolar disorder is less than wholly satisfactory. Although lithium and the anticonvulsant agents are the most effective long-term treatments available, response rates are less impressive than in the past, and for many patients treatment is only partially adequate. Increasing use is being made of the atypical antipsychotics for hard-to-treat bipolar patients, and there is a growing recognition that additional novel strategies are needed to treat this disorder. In summary, although medications and somatic therapies are the best-studied interventions for treatment of mood disorders, they are not as effective as might be desired, and their potential utility is further limited by patients' nonadherence to treatment regimens and by side effects.

INTERPERSONAL AND PSYCHODYNAMIC PSYCHOTHERAPIES

In this section, we discuss two important psychotherapies, IPT and psychodynamic therapy. IPT is relatively new, well researched, and designed to target depression; until recently, it has had little clinical dissemination. Psychodynamic psychotherapy is at the other pole: widely used for many years, relatively nonspecific in its diagnostic indications, and the subject of little outcome research in the treatment of depression. As shown in Figure 3, IPT has fared well in comparisons with medication
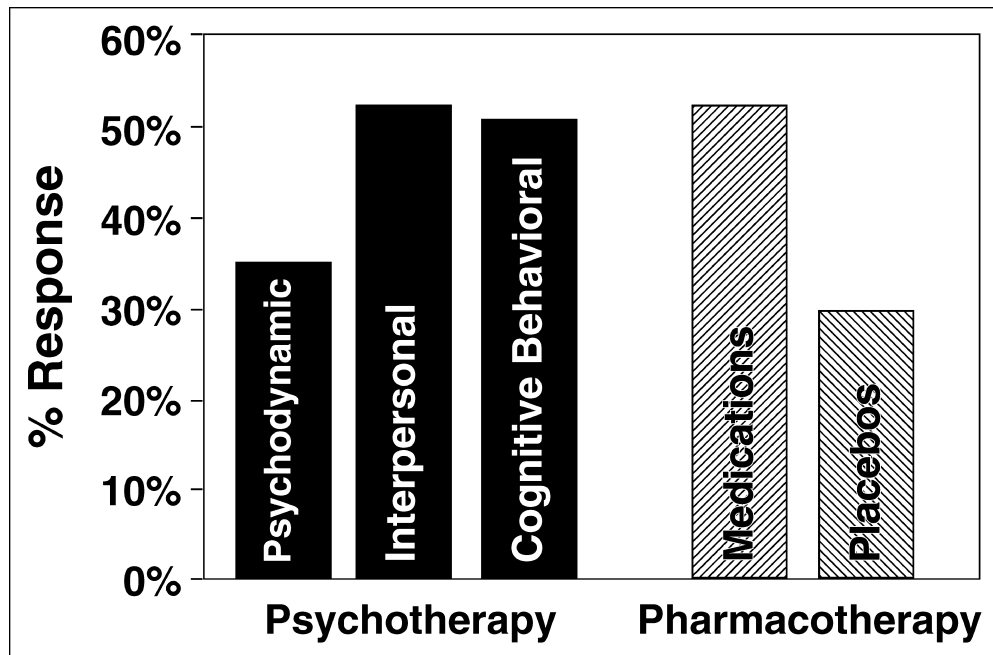
Fig. 3. Percentage of patients responding to psychotherapy versus medications and pill placebo. The estimates for the three kinds of psychotherapies are based on a meta-analysis conducted for the Agency for Health Care and Policy Research (Depression Guideline Panel, 1993); the estimates for medications and placebos are drawn from a subsequent update of that review (Mulrow et al., 1999). Adapted from Hollon (2002).

and other psychosocial interventions, whereas dynamic psychotherapy has been little more effective than placebo pills.

Interpersonal Psychotherapy

IPT is a pragmatic, strategically coherent, time-limited treatment devised by the late Gerald L. Klerman and Myrna M. Weissman in the 1970s for research on adult outpatients with unipolar Major Depressive Disorder. Like most time-limited research interventions, IPT is defined in a treatment manual (Klerman, Weissman, Rounsaville, & Chevron, 1984; updated by Weissman, Markowitz, & Klerman, 2000). IPT has been tested in numerous randomized controlled clinical trials over the past 30 years, but has only recently begun to enter clinical practice (Weissman & Markowitz, 1994).

IPT is based on concepts developed by interpersonal theorists such as Adolph Meyer, Harry Stack Sullivan, and John Bowlby, among others. The key principle derived from these theorists is that life events occurring after the early childhood years influence subsequent psychopathology. This principle contrasts with earlier psychodynamic theory, which emphasized the primacy of early childhood events to the essential exclusion of later life history. IPT therapists presume that the etiology of depressive illness is complex, but use the connection between current life events and the onset of depressive symptoms as an organizing framework to help the patient understand and combat his or her episode of illness. Upsetting life events can precipitate ill-

ness in vulnerable individuals; conversely, depressed mood leads to social withdrawal, fatigue, poor concentration, and consequent further negative life events. IPT helps patients to reverse this negative cycle by engineering positive life events.

IPT therapists define depression as a medical illness, a treatable condition that is not the patient's fault. This framework displaces guilt from the self-blaming patient to the illness, making symptoms seem like something unpleasant that is happening to him or her and not a necessary outgrowth of his or her own personality or limitations. The therapist uses diagnostic categories and clinical rating scales to help the patient understand that he or she is dealing with a common mood disorder having a predictable set of discrete symptoms, rather than with what the patient frequently perceives as a personal failure, weakness, or character flaw. IPT therapists formally give depressed patients the "sick role" (Parsons, 1951), excusing them from self-blame when their illness prevents them from functioning, but also obliging them to work in the patient role in order to ultimately recover the healthy role they have lost.

IPT unfolds in three successive stages. During the first several sessions, the therapist takes a careful history that links the patient's depressive symptoms to his or her interpersonal situation in a formulation that centers on one of four interpersonal problem areas, all of which are connected to life events and social roles (Markowitz & Swartz, 1997). *Complicated bereavement* (grief) results from the loss or death of a significant other. *Role disputes* are struggles based on nonreciprocal expectations

with significant others, such as the struggles involved in a bad marriage. *Role transitions* include any change in life status that alters one's perspective on one's life trajectory. The fourth area, *interpersonal deficits*, covers problems that are not included in the first three categories and that involve the lack of social skills; problems in this area include difficulty in initiating or sustaining relationships, leading to social isolation. Although some patients have multiple interpersonal problems, the goal of the initial stage of IPT is to isolate one or at most two salient problems to serve as a focus of treatment (Markowitz et al., 2000).

During the extended middle stage of IPT, the therapist pursues strategies specific to the identified interpersonal problem area. For complicated bereavement, the therapist facilitates the catharsis of mourning and helps the patient find new activities and relationships to compensate for the loss. For a role dispute, the therapist helps the patient explore the nature of the relationship and the relevant dispute, whether it has reached an impasse, and what options are available for resolving it. For a role transition, the therapist helps the patient learn to manage the change by mourning the loss of the old role, recognizing positive and negative aspects of the uncomfortable new role he or she is assuming, and gaining mastery over the new role. For interpersonal deficits, the therapist helps the patient to develop new relationships and interpersonal skills. Some patients with problems in this category may in fact have dysthymic disorder, for which separate strategies have been developed (Markowitz, 1998).

The final stage of IPT, comprising the last few sessions of acute treatment (or the last few months of maintenance treatment), builds the patient's newly regained sense of independence and competence by recognizing and consolidating therapeutic gains. The goal is to prepare the patient to function without the treatment. Compared with psychodynamic psychotherapy, IPT deemphasizes the end of therapy, which is viewed as a graduation from successful treatment, a type of role transition. The therapist stabilizes the patient's self-esteem by underscoring that the patient's depressive episode has improved because of his or her own actions in changing a life situation. Because depression can recur, the therapist also helps the patient to anticipate interpersonal triggers for and responses to depressive symptoms that might arise in the future.

IPT is an eclectic therapy, using techniques seen in other treatments. Its definition of depression as a medical illness parallels the approach of pharmacotherapy (and makes IPT highly compatible with medication treatment). IPT addresses interpersonal issues in a manner familiar to marital therapists and has been adapted for conjoint sessions for couples with distressed marriages (Klerman & Weissman, 1993). IPT overlaps with psychodynamic psychotherapies, and many of its early research therapists came from psychodynamic backgrounds, yet IPT also meaningfully differs from a psychodynamic approach. It focuses on the present, not the past, and aims to bring about real life change rather than simply self-understanding. It uses a medical model, which psychodynamic psychotherapy does not, and avoids interpreting dreams and the transference relationship be-

tween patient and therapist (Markowitz, Svartberg, & Swartz, 1998). IPT shares with CBT a time-limited format, the targeting of a psychiatric syndrome (major depression), a "here and now" focus, and techniques such as role playing. However, it is considerably less structured, assigns no explicit homework, and focuses on affective responses to interpersonal problems rather than thoughts or behaviors. It is its overall strategies that make IPT unique, not its specific techniques.

Efficacy during different treatment phases

Acute phase. As shown in Figure 3, IPT has fared well in comparison with other types of treatments and control conditions. This conclusion is based on a pair of randomized controlled trials. In the first, 16 weeks of IPT was found to be as efficacious as amitriptyline and superior to a "nonscheduled" control condition in which treatment was available on demand in a sample of 81 outpatients with major depression. Combining medication and IPT showed a nonsignificant advantage over either treatment by itself (Weissman et al., 1979). Patients with endogenous (melancholic) depression did better if they received combined treatment than if they received IPT alone, whereas patients with situational depressions (i.e., depressions with clear external precipitants) did as well with either therapy alone as they did in combined treatment (Prusoff, Weissman, Klerman, & Rounsaville, 1980). Medication produced more rapid symptom relief (especially relief of vegetative symptoms like sleep disturbance and appetitive problems), whereas IPT had somewhat more delayed advantages in improving mood, reducing suicidal thoughts, ameliorating problems at work, and restoring interest (DiMascio et al., 1979). Moreover, patients who were treated with IPT (either alone or in combination with medication) showed greater improvement in social functioning at a 1-year naturalistic follow-up in which treatment was not controlled than did patients treated with medication alone (Weissman, Klerman, Prusoff, Sholomskas, & Padian, 1981).

The second study was part of the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program (TDCRP; Elkin et al., 1989). In that multisite study, 250 outpatients with major depression were randomly assigned to 16 weeks of IPT, CBT, or either medication treatment (with imipramine) or placebo plus clinical management. Clinical management included meeting with a psychiatrist who provided support and encouragement in addition to prescribing medication (or placebo). Patients with pretreatment ratings below 20 on the 17-item HRSD improved equally across the various treatments. Among more severely depressed patients (i.e., HRSD $\geq$ 20), imipramine worked fastest and most consistently outperformed placebo. IPT was comparable to imipramine on most outcome measures (including the HRSD) and superior to placebo for more severely depressed patients. Subsequent reanalyses using more powerful statistical methods suggested that IPT might be more effective than CBT among more severely depressed patients (D.F. Klein & Ross, 1993), although they also sug-

gested that imipramine might be more effective than IPT among patients with the most functional impairment (Elkin et al., 1995).

Eighteen months after the termination of treatment, the TDCRP found a modest advantage for prior IPT or CBT relative to prior medication, but differences were not significant (Shea et al., 1992). Of the patients who showed full remission by the end of acute-phase treatment, relapse rates were 33% for IPT and 36% for CBT versus 50% for imipramine (an unsurprising result, given that medication had been stopped after 16 weeks) and 33% for placebo. Only a minority of the patients remained in remission across the full follow-up (26% of IPT, 30% of CBT, 19% of imipramine, and 20% of placebo subjects). The remaining patients met criteria for neither sustained full remission nor full clinical relapse. The authors concluded that for many patients, 16 weeks of treatment was not sufficient to achieve full and lasting remission leading to recovery.

Continuation phase. IPT also appears to prevent relapse following successful treatment if provided during the continuation phase, although this conclusion is based on a single early study that is open to multiple interpretations. In that trial, 150 depressed women who responded to 4 to 6 weeks of amitriptyline were randomly assigned to continuation medication, withdrawn onto a pill placebo, or withdrawn to no pill at all. Within each of these conditions, some women received an early forerunner of IPT and some did not (Klerman, DiMascio, Weissman, Prusoff, & Paykel, 1974). Patients who continued on medication (either alone or in combination with IPT) had fewer relapses over the next 8 months (around 12%) than patients who received placebo (28–30%, depending on whether they also received continuation IPT) and patients withdrawn from all treatment (36%). Curiously, patients who received IPT alone in the no-pill condition had a relapse rate of 16.7%—almost as good as the rate of patients who continued medication. These results suggested a possible negative interaction between psychotherapy and pill placebos, perhaps due to patients' erroneous belief that they were taking an active medication, and led to the inclusion of comparable conditions in several subsequent studies (Hollon & DeRubeis, 1981).

More interesting still were indications that patients given continuation IPT showed improved social functioning over time, although this effect did not emerge until after 8 to 10 months of continuation treatment (Weissman, Klerman, Paykel, Prusoff, & Hanson, 1974). This result is reminiscent of the delayed effect that IPT had on the quality of interpersonal life following acute-phase treatment in the study by Weissman et al. (1981). Patients who received combined treatment received the benefits of both modalities; they were no more likely to relapse than patients treated with continuation medication alone and showed the same improvement over time in social functioning as patients treated with IPT alone. This is a theme to which we return in later sections: Combined treatment typically retains the specific advantages associated with each therapy by itself, although on any single outcome it does not enhance the effects of the more effective intervention (Hollon & Shelton, 2001).

Maintenance phase. IPT also appears to prevent recurrence following recovery when extended into the maintenance phase. This conclusion is based on a pair of studies conducted at the University of Pittsburgh. One was a study of geriatric patients and is discussed later in this section, where we focus on special populations. The other was a study of 128 adult outpatients with a history of two or more prior depressive episodes (at least one within the last 2.5 years). During the acute phase of treatment, they received a combination of high-dose imipramine ($\geq$200 mg/day) and weekly IPT. Those who responded to treatment then remained on high-dosage medication while IPT was tapered to monthly sessions during a 4-month continuation phase (Frank et al., 1990; Frank, Kupfer, Wagner, McEachran, & Cornes, 1991). Patients who remained in remission and could therefore be considered recovered were then randomly assigned to 3 years of (a) ongoing high-dose medication plus clinical management, (b) high-dose medication plus monthly IPT, (c) monthly IPT alone, (d) monthly IPT plus placebo, or (e) placebo plus clinical management. IPT alone was included in order to check for any possible negative psychotherapy-placebo interaction.

As shown in Figure 4, medication treatment with imipramine was particularly efficacious, protecting about 80% of patients over the ensuing 3 years. In contrast, most patients withdrawn onto placebo alone became depressed again within the first few months; fewer than 20% survived the full 3 years without recurrence. Monthly IPT was less efficacious than medication and did little to enhance the effects of medication when combined with it. However, it was superior to the placebo condition, and there was no indication of any negative psychotherapy-placebo interaction. It is possible that IPT would have done better still had it been maintained at a "higher dose" than monthly sessions; in effect, the study compared low-dose IPT with high-dose imipramine.

The modal depressed patient is a woman of childbearing age, and there may be risks to her unborn child if she becomes pregnant while on medication. Although IPT was not as effective as medication in preventing recurrence, the median survival time of 82 weeks without recurrence for IPT alone would protect many women with recurrent depression long enough to complete pregnancy and nursing without medication. Thus, these findings suggest that maintenance IPT may be a viable alternative to medications for women who are at high risk for recurrence but want to come off medications to have a child. Further study is required to determine the efficacy of IPT relative to the SSRIs and newer medications and the efficacy of maintenance IPT at more than monthly "doses."

Subsequent analyses revealed that the results for certain groups were noticeably different from these overall results. For example, maintenance IPT was less effective for patients characterized by reduced slow-wave (delta) sleep, suggesting that patients with an underlying biological abnormality may do less well in psychotherapy than on medications (Kupfer, Frank, McEachran, & Grochocinski, 1990). At the same time, it was substantially more effective for patients who participated in patient-therapist dyads that were rated as above average on a measure of adherence to
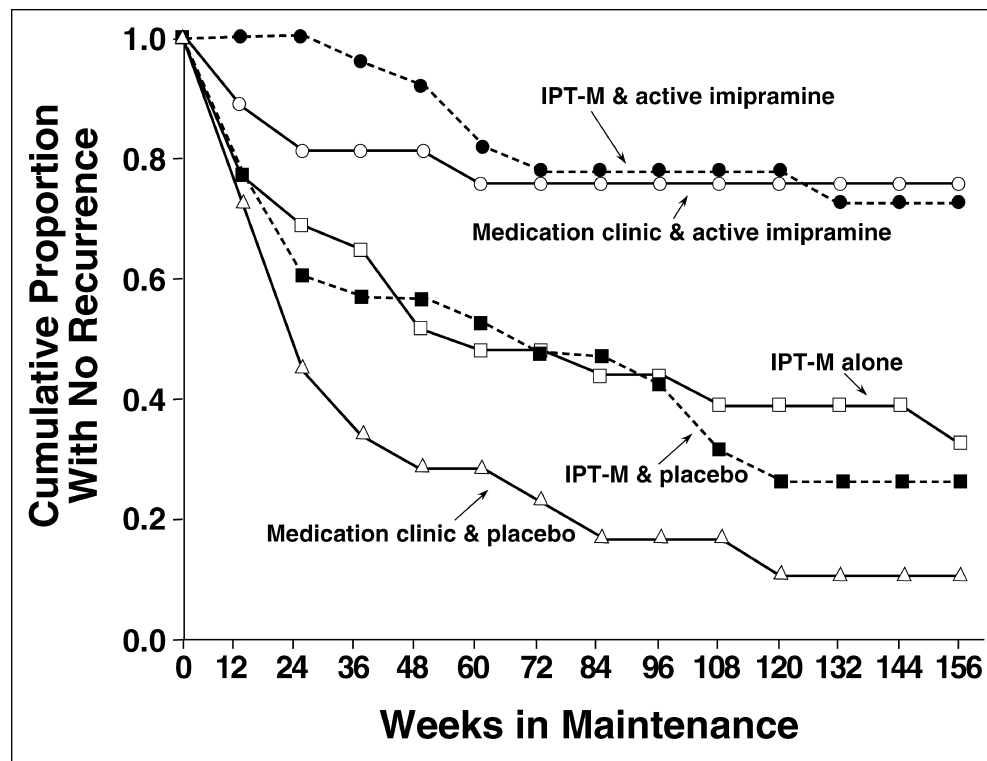
Fig. 4. Results of maintenance treatment with interpersonal psychotherapy and imipramine. The graph shows the proportion of patients who did not experience a recurrence of depression, separately for five treatment groups: medication alone, maintenance interpersonal psychotherapy (IPT-M) alone, medication and IPT-M combined, IPT-M and placebo combined, and placebo. From "Three-Year Outcomes for Maintenance Therapies in Recurrent Depression," by E. Frank et al., 1990, *Archives of General Psychiatry, 47*, p. 1097. Copyright 1990 by the American Medical Association. Reprinted with permission.

the specified IPT regimen (Spanier, Frank, McEachran, Grochocinski, & Kupfer, 1996). Patients in these dyads who had normal delta sleep had a 73% 3-year survival rate with maintenance IPT alone, a rate comparable to that observed for pharmacotherapy. By contrast, within 12 months of withdrawal from imipramine, depression recurred in 100% of the patients in the below-average dyads who also had reduced delta sleep (Spanier et al., 1996). Thus, the potency of IPT as a preventive strategy appeared to depend on both the biological characteristics of the patient and the quality of the treatment process.

Special populations and problems

IPT in geriatric depression. Geriatric patients often have trouble with medication side effects. IPT was originally adapted for the elderly in an attempt to see if it could be helpful in increasing their adherence to prescribed medication treatments, although in recent years it has since been used as a stand-alone treatment (Sholomskas, Chevron, Prusoff, & Berry, 1983). As might be expected, grief and role transitions are common foci of treatment in these patients. Specific modifications for the elderly include increased flexibility in the length of sessions, greater use of practical advice and support, and recognizing that major role changes may

be impractical or detrimental. A 6-week trial found IPT superior to nortriptyline in 30 geriatric depressed patients, largely because of higher attrition in the medication group due to side effects (Sloane, Stapes, & Schneider, 1985).

Reynolds, Frank, et al. (1999) used this modified version of IPT in the second of the long-term IPT maintenance trials at the University of Pittsburgh. In that study, 187 geriatric patients with recurrent major depression were first treated with the combination of IPT and nortriptyline; when they reached recovery, they were randomly assigned to one of four maintenance conditions: medication alone, IPT plus pill placebo, medication plus IPT, and pill placebo alone. Over the next 3 years, patients assigned to medication alone or IPT plus placebo were less likely to experience a recurrence than patients withdrawn onto placebo (43% and 64% vs. 90%). Patients maintained on combination treatment did best of all (20% recurrence). Patients over the age of 70 were more likely, and more quick, to have a recurrence than were younger geriatric patients, whereas patients whose sleep quality normalized during the continuation phase were likely to remain well during maintenance regardless of treatment. These results suggest that biological characteristics can be used to predict whether treatment will be successful, and in this sense are reminiscent of the results observed with respect to sleep

dysfunction (Kupfer et al., 1990) in the larger study by Frank and her colleagues (1990; Frank, Kupfer, et al., 1991). However, an important difference is that combined treatment had a greater advantage in this geriatric sample than in the younger population of that earlier study.

As in the first IPT maintenance study (Frank et al., 1990; Frank, Kupfer, et al., 1991), IPT might have been more effective had sessions been conducted more frequently: Session frequency was cut back from acute-phase levels, whereas medication doses were maintained at full strength. A study of the effects of varying session frequency of maintenance IPT for depressed patients is under way in Pittsburgh. Similarly, given the earlier indication that adding an inert placebo might reduce the efficacy of IPT (Klerman et al., 1974), it was unfortunate that Reynolds and his colleagues (Reynolds, Frank, et al., 1999; Reynolds, Perel, et al., 1999) did not include a condition in which patients received IPT alone. Of course, such a condition was included in the earlier IPT maintenance trial (Frank et al., 1990; Frank, Kupfer, et al., 1991), and no evidence of a negative psychotherapy-placebo interaction was found.

IPT for depressed adolescents. Mufson, Moreau, and Weissman (1993) modified IPT to incorporate developmental issues in adolescents (IPT-A), adding in particular a fifth problem area addressing life in a single-parent family. Following a promising feasibility study, Mufson, Weissman, Moreau, and Garfinkel (1999) proceeded to a 12-week controlled clinical trial comparing IPT-A with clinical monitoring alone in 48 clinic-referred 12- to 18-year-olds with major depression. Patients receiving IPT-A reported significantly greater improvement of depressive symptoms and overall social functioning (including functioning with friends and problem-solving skills); 75% of the patients in IPT-A met criteria for full remission, compared with 46% of control patients. The results suggest that IPT-A may be effective in treating depressed adolescents. Mufson and her colleagues are currently testing IPT-A in a large-scale effectiveness study in school-based clinics and are also pilot-testing a group format for depressed adolescents.

Rossello and Bernal (1999) also tested the efficacy of IPT in treating depressed adolescents, although they did not use the modifications developed by Mufson and her colleagues. Their study compared outcomes for 71 Puerto Rican adolescents (ages 13 to 18) who met the criteria for major depression or dysthymia. Patients were randomly assigned to receive 12 weeks of IPT or CBT, or to be placed on a waiting list for treatment (control condition). Both IPT and to a lesser extent CBT were more efficacious than the control condition in reducing adolescents' self-rated depressive symptoms. IPT was more effective than CBT in increasing self-esteem and social adaptation.

Together, these two studies suggest that IPT is effective in the treatment of depressed adolescents. The fact that the two studies were conducted by different research groups using different versions of the same approach speaks to the robustness of the effect.

IPT for dysthymic disorder. Medication benefits roughly half of dysthymic patients, but nonresponders may need psychotherapy, and even patients who respond to medication may benefit from combined treatment (Markowitz, 1994). IPT is designed as a response to recent life events, yet some illnesses are chronic, requiring a shift in the model. A modification of IPT for dysthymic disorder encourages patients to reconceptualize what they have considered lifelong character flaws as chronic but treatable "states" rather than immutable "traits" (Markowitz, 1998). Therapy itself is defined as a "role transition" from believing oneself flawed in personality to recognizing and treating the mood disorder. In a pilot study (an open trial with no control group) that used this approach, none of the 17 subjects worsened, and 11 went into remission (Markowitz, 1994). Similarly, combining IPT with moclobemide produced a nonsignificant advantage relative to moclobemide alone in a small sample of dysthymic patients (Feijò de Mello, Myczowisk, & Menezes, 2001). On the basis of these findings, in a study under way at Cornell University, Markowitz and his colleagues are investigating the efficacy of IPT in treating dysthymic disorder; specifically, in the 16-week trial, the experimental groups are receiving IPT alone, sertraline pharmacotherapy alone, or a combination of the two, and the control group is receiving a supportive psychotherapy.

IPT for bipolar disorder. Frank and her colleagues have modified IPT to make it suitable for use as an adjunct to maintenance medication in the treatment of bipolar disorder. This adaptation is based on a theory that suggests that social *Zeitgebers* (interactions and expectations) serve to provide order and regularity in life that help maintain affective balance (Ehlers, Frank, & Kupfer, 1988). Specific elements added to conventional IPT in this adaptation include scheduling activities and regularizing sleep schedules (Malkoff-Schwartz et al., 2000). The resulting approach, called interpersonal social rhythms therapy (IPSRT), was found to reduce the frequency of depressive symptoms, but not manic episodes, when used in combination with medications (Frank et al., 1999). Subsequent analyses indicated that switching patients from IPSRT to medication alone increased the risk for recurrence of depression (Frank, Swartz, & Kupfer, 2000). Although still preliminary, these findings suggest that IPSRT may have a role to play in the treatment of bipolar disorder, particularly bipolar depression.

IPT for depressions associated with medical conditions. Markowitz and his colleagues modified IPT for depressed HIV patients, emphasizing shared issues of illness and death, grief, and role transitions (Markowitz, Klerman, Perry, Clougherty, & Mayers, 1992). They tested the approach in a randomized controlled trial in which 101 depressed HIV-positive patients were randomly assigned to 16 weeks of this adapted version of IPT, CBT, imipramine plus supportive psychotherapy, or supportive psychotherapy alone (Markowitz, Kocsis, et al., 1998). IPT and medication each produced significantly greater symptomatic and functional improvement than either CBT or supportive psycho-

therapy alone, a pattern reminiscent of the findings for more severely depressed patients in the NIMH TDCRP. Interestingly, many patients reported improvement in physical symptoms that had been attributed to HIV infection.

Pregnancy and the postpartum period are times of depressive risk when it may be advisable for women to avoid medication. Spinelli (1997) has adapted IPT to address concerns about pregnancy, parenting, and altered relationships, also adding *complicated pregnancy* as a fifth interpersonal problem area; a controlled trial comparing this version of IPT with parent education in a sample of depressed pregnant women is under way. O'Hara, Stuart, Gorman, and Wenzel (2000) found IPT reduced depressive symptoms and improved social function relative to a waiting-list control condition in a sample of 120 women with postpartum depression. Similarly, Klier, Muzik, Rosenblum, and Lenz (2001) found significant reductions in distress among 17 women with postpartum depression in an open trial with no control group that used 9 weekly group sessions and a 10th individual termination session. In a particularly interesting study, Zlotnick, Johnson, Miller, Pearlstein, and Howard (2001) found that high-risk pregnant women provided with four sessions of group IPT were less likely to subsequently develop postpartum depression than women provided only with treatment as usual. Although clearly in need of replication, this is the first study to suggest that IPT might have an enduring effect in reducing risk following termination of treatment.

Schulberg and his colleagues adapted IPT for use with depressed ambulatory medical patients, largely by integrating it into the routine of a primary-care setting (Schulberg, Scott, Madonia, & Imber, 1993). In a randomized controlled trial, they found that primary-care patients treated with 4 months each of acute- and continuation-phase IPT did as well as patients treated with nortriptyline for a comparable duration; both IPT and nortriptyline were superior to usual care provided by a primary-care physician (Schulberg et al., 1996). Approximately 70% of the patients who completed each of these treatments met criteria for recovery after 8 months, compared with only 20% of the patients receiving usual care, which could include medication or referral to a mental health specialist within the primary-care clinic. This result suggests that specialty care with IPT or medication may be superior to usual care in primary-care clinics. Patients with a history of panic disorder were less responsive to either treatment than were patients without such a history (Brown, Schulberg, Madonia, Shear, & Houck, 1996), a finding replicated elsewhere (Frank, Shear, et al., 2000).

IPT has been adapted for use in a brief format, called interpersonal counseling, that is suitable for use by nurse practitioners and other personnel not trained in formal psychotherapy (Klerman et al., 1987). A recent trial conducted with elderly hospitalized medical patients with minor depressive symptoms showed that 10 sessions of interpersonal counseling administered by nonpsychiatric nurses produced greater improvement in depressive symptoms and self-rated health and lower rates of subsequent rehospitalization than usual care (Mossey, Knott, Higgins, & Talerico, 1996). These findings suggest that brief in-terpersonal counseling may have a role to play in the treatment of minor depression in general medical settings. Work also is under way testing the applicability of conventional IPT for depressed patients who are recovering from heart attacks (Stuart & Cole, 1996) or have cancer or other disorders (Weissman et al., 2000). The IPT focus on life events makes it applicable to patients with medical illness.

Summary

IPT has demonstrated efficacy as an acute and maintenance therapy for Major Depressive Disorder, both by itself and as a component of combined treatment. Because therapy with either IPT or medication alone is likely to suffice for most depressed patients, combined treatment is probably best reserved for severely or chronically ill patients (Rush & Thase, 1999). How best to combine IPT with pharmacotherapy, for which patients and in what sequence, is an important area for future research. The success of IPT in treating depression has led to its expansion to non-mood disorders. IPT has also been tested for couples and group therapy, as a telephone intervention, and in a patient self-help guide. Its success in empirical studies has led to its endorsement in practice guidelines (American Psychiatric Association, 2000; Depression Guideline Panel, 1993) and a growing demand for IPT training in psychiatric residencies, graduate psychology programs, and continuing-education courses for medical personnel (Markowitz, 1995). Because of this success, IPT has spread from the United States to other parts of the globe, and an International Society for Interpersonal Psychotherapy was formed in May of 2000.

Psychodynamic Psychotherapy

In contrast to IPT, psychodynamic psychotherapy has a long history but limited empirical support. It was the first real psychotherapy, deriving from Freud's psychoanalysis and based on his use of free association and dream analysis to explore unconscious conflicts arising from childhood relationships and the way these conflicts are transferred onto the relationship with the therapist. Psychodynamic psychotherapy differs from psychoanalysis largely in intensity and setting; it usually consists of one to three sessions weekly rather than the four or five typical of psychoanalysis, and the patient sits and faces the therapist rather than lying on a couch. Because of the focus on free association and the transference phenomenon, psychodynamic sessions tend to be relatively unstructured, and the therapist is more silent than in IPT or CBT.

Paucity of empirical tests

For many years, and particularly following the Second World War, psychodynamic psychotherapy was the predominant psychosocial intervention in the United States and much of Europe. Yet despite its widespread clinical use, it lacks a research tradition (DeRubeis & Crits-Christoph, 1998). Reasons for this are

several: Each case was seen as being unique, such that treatment could not be standardized; duration tended to be open-ended; and an emphasis was put on intrapsychic conflicts rather than standardized diagnoses defined by observable symptoms that could be reliably measured. On the infrequent occasions when its effects were studied, psychodynamic psychotherapy was often used as a control condition by researchers who lacked allegiance to it or expertise in its use (Luborsky et al., 1999). When psychodynamically oriented researchers have led studies, they typically have not focused on a particular diagnosis; few of the manuals written in recent decades have addressed patients with major depression or other mood disorders (see, e.g., Strupp & Binder, 1984). Although manuals on psychodynamic therapy do exist, they vary considerably in their emphases, and many of even the treatments defined in manuals have not been tested. As a result of this paucity of research, psychodynamic psychotherapy has been in the odd position of being widely used but little studied, a large edifice supported by a slender evidential stalk (Barber, 1994).

The lack of research does not mean that there has been no interest in depression on the part of psychodynamic theorists. Indeed, by focusing on empirical bases, this monograph must give psychodynamically oriented psychotherapy short shrift. Early writings describing psychoanalytic understanding of depression date from nearly a century ago; Abraham (1948) viewed depression as aggression turned inward, and Freud (1917/1975) elaborated this model. Other important modifications to theory have followed (see Karasu, 1990, for a review). They provide rich clinical descriptions and interesting hypotheses about depression, but no clinical testing.

Efficacy

Only a handful of comparative studies have examined psychodynamic psychotherapy. In the earliest such trial, Daneman (1961) found that adding imipramine greatly improved the outcomes produced by dynamically oriented individual psychotherapy. Covi, Lipman, Derogatis, Smith, and Pattison (1974) found that dynamically oriented psychotherapy provided in a group format was less effective than medication alone (and no more effective than pill placebo) and did nothing to enhance the effects of medications when added in combination. These early studies contributed to the perception that psychotherapy is less effective than medications in the treatment of depression, although it was not clear that psychodynamic psychotherapy was adequately implemented in the latter trial, particularly given that it was provided in a group format. This same research group conducted a later study that again relied on a questionable implementation of psychodynamic psychotherapy in a brief group format. In that study, brief dynamic group psychotherapy was less effective than either group cognitive therapy alone or a combination of group cognitive therapy with medications (Covi & Lipman, 1987).

McLean and Hakstian (1979) compared behavior therapy, amitriptyline, and a relaxation control with a psychodynamic psy-chotherapy in a 10-week trial for 178 depressed patients. They found an initial advantage (lower attrition and greater improvement in levels of depression) for behavior therapy over psychodynamic therapy, although there was little evidence of any continued advantage at a subsequent follow-up. Hersen, Bellack, Himmelhoch, and Thase (1984) found no differences between a psychodynamic psychotherapy and social skills training or amitriptyline in the acute-phase treatment of 120 women with major depression. In a study of geriatric patients with major depression, Gallagher and Thompson (1982) found no differences at the end of treatment among patients treated with brief psychodynamic therapy, cognitive therapy, or behavior therapy, although patients treated with dynamic therapy were more depressed than the other groups at a subsequent follow-up. In a subsequent study, this same research team found no differences between brief dynamic psychotherapy and either cognitive or behavior therapy (with each superior to a waiting-list control condition) at the end of treatment (Thompson, Gallagher, & Breckenridge, 1987) or at a 2-year follow-up (Gallagher-Thompson, Hanley-Peterson, & Thompson, 1990).

Psychodynamic-interpersonal psychotherapy is an amalgam of elements from psychodynamic therapy and IPT that, despite its title, many theorists would consider representative of neither form of therapy. D.A. Shapiro et al. (1994) compared the results of psychodynamic-interpersonal psychotherapy and a somewhat idiosyncratic version of CBT among 117 patients with major depression. They were categorized into three different levels of depression and randomly assigned to receive one of the treatments for either 8 or 16 weeks. There were no overall differences between treatments. Patients with the most severe depressions had better outcomes if they received 16 weeks of treatment rather than only 8. At a 1-year follow-up, patients treated with eight sessions of psychodynamic-interpersonal therapy had a poorer outcome than did patients in the three other treatment conditions. A smaller replication again showed advantages for 16 over 8 weeks of treatment (Barkham et al., 1996).

Supportive-expressive psychotherapy, an important and relatively well researched form of psychodynamic psychotherapy for which a manual is available, has shown promise in the treatment of other types of psychiatric patients (Luborsky, 1984). Supportive-expressive psychotherapy lies at the more interpersonal end of the psychodynamic spectrum and thus bears some resemblance to IPT. Diguer, Barber, and Luborsky (1993) found that brief supportive-expressive psychotherapy was effective in reducing levels of depression in patients with uncomplicated depressions, but did less well with patients who had underlying personality disorders. Barber and his colleagues currently are conducting a placebo-controlled study comparing the effectiveness of supportive-expressive psychodynamic psychotherapy and an SSRI in treating major depression (J. Barber, personal communication, October 10, 2001).

Some meta-analyses have included IPT as a type of psychodynamic psychotherapy, although one of us has argued against this elsewhere (Markowitz, Svartberg, & Swartz, 1998). Psycho-

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dynamic psychotherapy has looked more impressive in those meta-analyses that have included IPT (e.g., Crits-Christoph, 1992) than in those that have not (Svartberg & Stiles, 1991). Although few of the available comparative studies show a great disadvantage for psychodynamic psychotherapy, none shows any real advantage. The dearth of studies and their methodological limitations make conclusions about the efficacy of psychodynamic psychotherapy tentative at best. Moreover, results obtained from the time-limited psychodynamic psychotherapy examined in such studies may not generalize to psychodynamic psychotherapy as it is typically practiced in the community, because of differences in implementation. In the community, psychodynamic psychotherapy is often longer term and more open-ended. For example, a recent survey conducted at a prestigious center for psychoanalytic training found that medication was prescribed to nearly a third of the patients, usually for the purpose of treating depression (Roose & Stern, 1995). In that study, depressed patients who did not receive medication typically did not improve or dropped out of psychoanalysis. This suggests that open-ended, long-term psychodynamic psychotherapy as typically practiced in the treatment community may be particularly poorly suited to the treatment of depression when not combined with medications.

Summary

Psychodynamic psychotherapy today is a discipline threatened by its own lack of research. This is unfortunate. The fact that it has not been adequately tested does not necessarily mean that it is ineffective, any more than the fact that it is widely practiced guarantees that it has an effect. It remains unknown whether it is truly lacking in efficacy or just not adequately tested. Given the richness of the approach and the numbers of patients who receive this kind of treatment, careful empirical testing is long overdue to either validate or disqualify its use in the treatment of psychiatric disorders, including major depression.

COGNITIVE AND BEHAVIOR THERAPIES

The cognitive and behavior therapies represent a diverse array of interventions based on the premises that mood disorders are either caused or exacerbated by learned beliefs and behaviors and that interventions based on learning principles can prevent or treat those disorders. The more cognitively based interventions emphasize the role of aberrant beliefs and maladaptive information processing strategies, whereas the more behaviorally oriented approaches focus on external contingencies and their role in shaping specific behaviors. Because most extant interventions blend cognitive and behavioral strategies, many reviews simply refer to CBT, as if the approaches the label encompasses represent a single entity (American Psychiatric Association, 2000). Nonetheless, there are differences in history and emphasis among the several types of CBT that may prove important, and although none are purely cognitive in their emphasis, some are purely behavioral.

In general, the cognitive and behavioral interventions have fared well in controlled trials, although many of these trials have been conducted in samples that do not meet criteria for major depression, if it was even assessed. Moreover, most of these studies have relied on self-report instruments like the Beck Depression Inventory (BDI; A.T. Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). These interventions typically have outperformed minimal-treatment controls like waiting-list or assessment-only conditions. In these studies, effect sizes have been large (.85 and above), and treatment typically has reduced scores on the BDI for the average participant from about 2.5 standard deviations above the mean for the general population to within 1 standard deviation above the mean (Robinson, Berman, & Neimeyer, 1990). That corresponds to a drop of about 10 points from a mean of 21.8; untreated control subjects typically drop less than 3 points. (Scores on the BDI can be divided into 10-point ranges, with scores below 10 indicating no depression, scores from 10 to 19 indicating mild depression, scores from 20 to 29 indicating moderate depression, and scores of 30 and above indicating severe depression; Kendall, Hollon, Beck, Hammen, & Ingram, 1987).

However, few of the studies involving minimal-treatment controls were conducted with actual clinical samples seeking treatment; most used recruited volunteers or college student samples. Most of the studies of actual patients have compared presumably active treatments without including a minimal-treatment control condition, in part because investigators have been reluctant to withhold treatment from actual patients. Such clinical samples typically have been more severely depressed than the samples recruited for the studies that have included minimal-treatment controls (mean BDI scores in the high 20s or low 30s for the clinical samples vs. in the low 20s for the recruited samples). Moreover, outcomes in such studies, at least those from the early years, may be suspect because many were conducted by research groups with a vested interest in a particular treatment (Gaffan, Tsaousis, & Kemp-Wheeler, 1995). In this section, we emphasize work done in fully clinical populations.

Cognitive Therapy and Related Cognitive Behavioral Interventions

Cognitive therapy was one of the earliest of the cognitive behavioral interventions and is perhaps the best established empirically. Developed by A.T. Beck in the early 1960s, it is based on the notion that how an individual interprets life events plays a role in determining how he or she responds to those events (A.T. Beck, 1991). Depressed patients are seen as being unduly negative in their beliefs and suffering from the use of maladaptive information processing strategies. Cognitive therapy seeks to teach patients to identify their aberrant beliefs and processing proclivities and to systematically test the accuracy of those beliefs and proclivities. Although largely emphasizing cognitive mechanisms in its theory of disorder, cognitive therapy makes frequent use of behavioral strategies, to structure patients' lives and particularly to test their beliefs. In fact, the use of behavioral

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strategies is so fully integrated into the approach that it is sometimes referred to as CBT, despite the fact that there are other approaches, differing in some respects, to which this label would apply just as well. In essence, patients in cognitive therapy are encouraged not just to examine the accuracy of their beliefs, but to engage in a series of "experiments" in which they systematically vary their behaviors in order to test the accuracy of those beliefs.

Cognitive therapy consists of a number of strategies designed to help patients identify and correct their inaccurate beliefs and distorted information processing (A.T. Beck, Rush, Shaw, & Emery, 1979). These strategies often incorporate behavioral elements, such as scheduling activities to increase pleasure or to provide a sense of mastery, but always in the service of testing underlying beliefs. Patients are encouraged to predict what they think will happen and then to collect data or run experiments that explicitly test those predictions. More often than not, depressed patients find that they are unduly pessimistic in their estimation of the likelihood of success and unnecessarily negative in their estimation of their own abilities. Particular attention is paid to helping patients learn to recognize and question their own beliefs by entertaining alternative explanations and implications and reviewing the evidence for each. Throughout, an emphasis is placed on realism over optimism; the goal is not to think "happy thoughts," but rather to become more accurate in one's self-assessments and perceptions of the world and the future. Similarly, much time is spent teaching patients how to evaluate the accuracy of their own beliefs, rather than just doing it for them; the goal is to teach patients how to use these tools themselves, so that they can use these skills long after therapy is over.

Acute-phase treatment

Cognitive therapy has performed well in a number of controlled trials in fully clinical populations (Hollon & Shelton, 2001). It was the first psychosocial intervention to hold its own with medications in the treatment of clinical depression, and early trials suggested that it might even be superior to the antidepressants in some populations (Blackburn, Bishop, Glen, Whalley, & Christie, 1981; Rush, Beck, Kovacs, & Hollon, 1977). In fact, early meta-analyses sometimes suggested that cognitive therapy was superior to medications in the reduction of acute distress (Dobson, 1989; Robinson et al., 1990).

However, medication treatment often was less than adequately implemented in those early trials (Meterissian & Bradwejn, 1989). For example, Rush et al. (1977) started medication withdrawal 2 weeks before the end of treatment; the subsequent increase in depression levels among patients in that condition contributed to the apparent superiority of cognitive therapy. Similarly, in the study by Blackburn et al. (1981), the response to medication was so low among patients in a general medical-practice sample as to raise questions about whether this treatment was implemented correctly in that setting. Subsequent stud-

ies that have implemented pharmacotherapy in a more adequate fashion typically have suggested that medication and cognitive therapy have comparable efficacy in outpatient samples (Hollon et al., 1992; Murphy, Simons, Wetzel, & Lustman, 1984).

The one study to suggest that cognitive therapy was less efficacious than medication was the NIMH TDCRP (Elkin et al., 1989). As shown in Figure 5, cognitive therapy was less effective than medications and not significantly more effective than pill placebo plus clinical management among patients with HRSD scores of 20 or higher (Elkin et al., 1995). Because this study was large and the first major comparison to include a pill-placebo control, the TDCRP dampened enthusiasm for cognitive therapy considerably. Even though this negative finding was limited to a single study, the notion that cognitive therapy is less effective than medications in treating severely depressed patients became the central premise of a generation of treatment guidelines (American Psychiatric Association, 2000; Depression Guideline Panel, 1993).

However, findings varied across sites within the TDCRP. Among severely depressed patients, cognitive therapy did as well as medication treatment at one of the three sites and considerably less well than medications at the other two sites (Jacobson & Hollon, 1996). Although the TDCRP did not identify which results came from which sites, it is clear from examining the sample sizes and other methodological information that the site with the most experienced cognitive therapists was the site that obtained the best response with respect to cognitive therapy. Moreover, other studies typically have found cognitive therapy to be as effective as medications. This was shown by a recent study that reanalyzed data from a number of independent trials, comparing the outcomes for individual patients who met criteria for severe depression and were treated with either cognitive therapy or medications (DeRubeis, Gelfand, Tang, & Simons, 1999). As shown in Figure 6, the TDCRP was the only relevant study to show an advantage for medication among the severely depressed patients; in the other three relevant studies, patients treated with a cognitive therapy (labeled "cognitive behavior therapy" by the authors) did at least as well as patients on medication.

However, none of those other studies included a placebo control. In the absence of such controls, it is not always possible to tell whether medication treatment was adequately implemented or whether any portion of the sample showed a true drug effect (D.F. Klein, 1996). Two recent studies speak to both issues. In the first, Jarrett et al. (1999) found cognitive therapy as effective as an MAOI, and each superior to a pill-placebo control, in the treatment of atypical depression. Although not all the patients in this study were severely depressed, many were, and all met the criteria for major depression. Thus, in contrast to the TDCRP, this study showed cognitive therapy to be comparable to medications in a placebo-controlled trial that demonstrated a true drug effect in a pharmacologically responsive sample.

The second study is an as yet unpublished multisite trial testing whether medications are superior to cognitive therapy in treating severe depression, as the TDCRP results suggested.
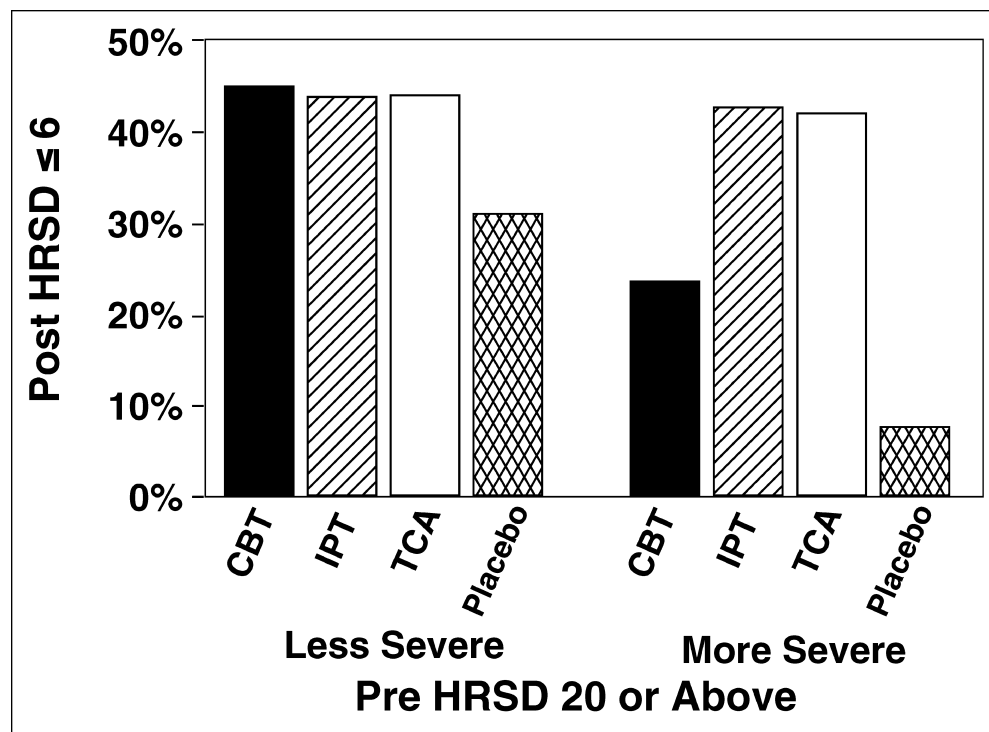
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In this second study, conducted at Vanderbilt University and the University of Pennsylvania, cognitive therapy and treatment with an SSRI (plus augmentation) were both found to be superior to a pill placebo and did not differ from one another in their effectiveness (DeRubeis, Hollon, Amsterdam, & Shelton, 2001). The cognitive therapists at Vanderbilt were less experienced than those at the University of Pennsylvania and did less well than them early in the study, but caught up as they gained additional training and experience. Quality of implementation can be as much a problem with psychotherapy as with pharmacotherapy. Given the differences across sites in the TDCRP and the absence of any advantage for medications in subsequent studies, the TDCRP may have underestimated the relative efficacy of cognitive therapy, much as earlier studies underestimated the relative efficacy of medication treatment (Hollon & Shelton, 2001).

Nonetheless, important questions remain. Cognitive therapy depends on the quality of its implementation, and not all therapists appear to be able to implement it adequately, at least for patients with relatively severe depressions or otherwise complicated conditions. Differences in results across sites (or studies) typically have been found only with such patients (DeRubeis et al., 2001; Elkin et al., 1989). We suspect that the explanation is not that cognitive therapy cannot be effective with such patients, but that the therapist's expertise makes a greater difference the more difficult the depression is to treat.

Continuation and maintenance treatment

Recent work by Jarrett and her colleagues suggests that continuing cognitive therapy past the point of initial remission can reduce risk for subsequent relapse and possibly recurrence. An early sequential nonrandom comparison suggested that patients who continued therapy following remission were less likely to relapse than patients who were simply withdrawn from treatment (Jarrett et al., 1998). In a subsequent randomized trial, patients who continued monthly cognitive therapy sessions were significantly less likely to relapse than patients whose sessions terminated after the end of acute treatment (Jarrett et al., 2001). Moreover, there were indications that continuation therapy may

Fig. 5. Results from the National Institute of Mental Health Treatment of Depression Collaborative Research Project: Response to treatment as a function of the severity of patients' depression prior to treatment. Scores on the Hamilton Rating Scale for Depression (HRSD) were used to categorize patients as having more or less severe depression prior to treatment ("Pre"). The graph shows the percentage of patients whose posttreatment ("Post") HRSD ratings dropped to 6 or below. Results are shown separately for four treatment groups: cognitive behavior therapy (CBT), interpersonal psychotherapy (IPT), tricyclic antidepressants (TCA; imipramine), and placebo. From "National Institute of Mental Health Treatment of Depression Collaborative Research Program: General Effectiveness of Treatments," by I. Elkin et al., 1989, *Archives of General Psychiatry, 46*, p. 976. Copyright 1989 by the American Medical Association. Reprinted with permission.

have reduced risk for symptom return over an extended 36-month follow-up, at least for high-risk patients with an early age of onset or relatively unstable remission. Similarly, Blackburn and Moore (1997) found that maintenance treatment with cognitive therapy was at least as effective as maintenance medications in a sample of patients at risk for recurrent depression. These findings suggest that high-risk patients may benefit from continuation and maintenance cognitive therapy, just as they do from continuation and maintenance medication or IPT.

Does cognitive therapy have an enduring effect?

Cognitive therapy may have an enduring effect that extends beyond the end of treatment. Several studies have shown that patients treated to the point of remission with cognitive therapy are only about half as likely to relapse following the termination of treatment as are patients who enter remission after treatment with medications (Blackburn, Eunson, & Bishop, 1986; Evans et al., 1992; Kovacs, Rush, Beck, & Hollon, 1981; Simons, Murphy, Levine, & Wetzel, 1986). In fact, this enduring effect appears to be at least as great as the effect of keeping patients on continuation medication (Evans et al., 1992). This

finding was recently replicated in the Vanderbilt-Pennsylvania study comparing cognitive therapy and medications in the treatment of severely depressed outpatients (Hollon, DeRubeis, Shelton, & Amsterdam, 2001). In that study, 25% of the patients treated with cognitive therapy relapsed during the year following the termination of treatment, whereas 81% of the patients treated with medication relapsed within a year of when their treatment ended. In fact, the patients who had received cognitive therapy were no more likely to relapse during the year following treatment than were patients continued on medications (40%).

Cognitive therapy appears to have an enduring effect regardless of whether it is provided alone or in combination with medications during acute treatment (Evans et al., 1992), or whether it is added sequentially after medication is used to reduce acute symptoms (Paykel et al., 1999). Few studies have continued medication treatment long enough to get beyond risk for relapse, but a recent trial by Fava, Rafanelli, Grandi, Conti, and Belluardo (1998) suggests that cognitive therapy's enduring effect may extend to the prevention of recurrence. In that study, all patients were treated with medications, first to the point of remission and then to the point of recovery. At the end of the continuation phase, the patients were randomly assigned to receive either 10
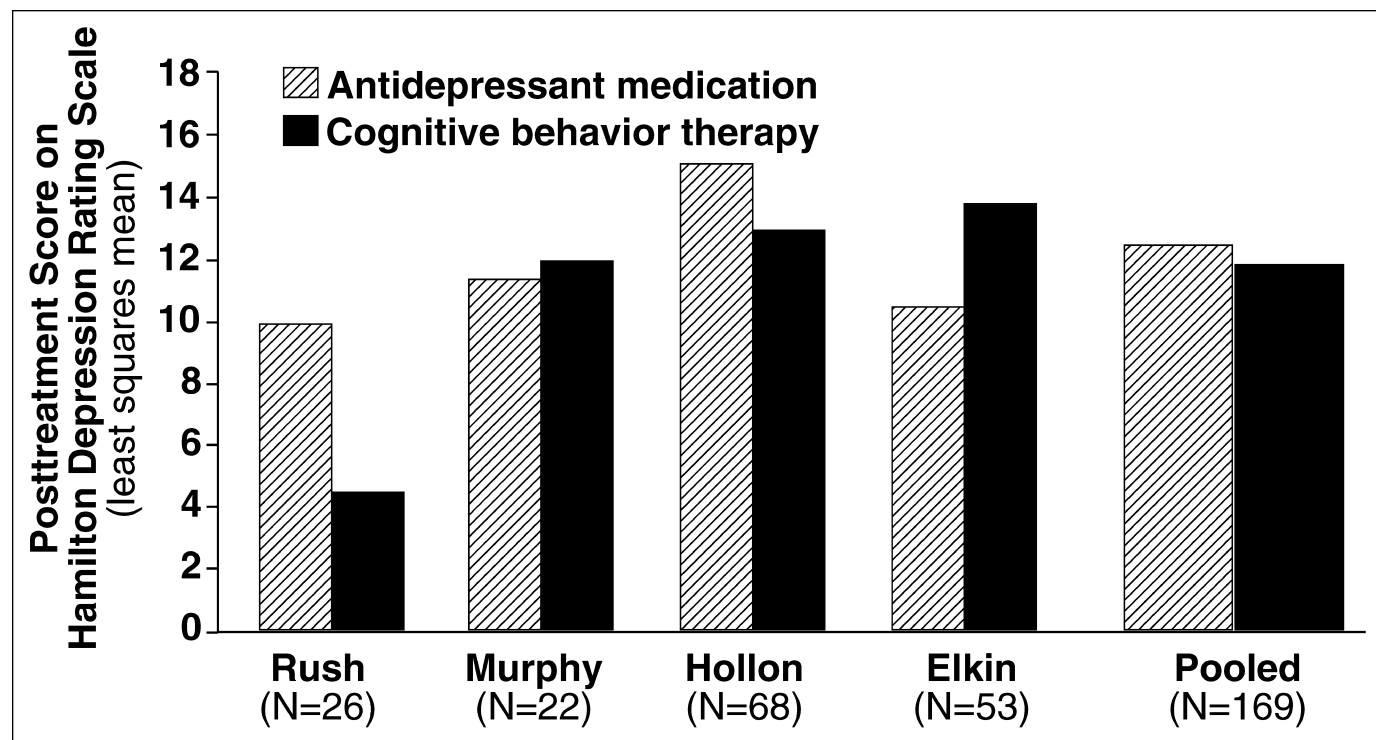
Fig. 6. Average response to cognitive behavior therapy versus antidepressant medications in severe depression. The graph shows the results from four randomized comparisons: Rush, Beck, Kovacs, and Hollon (1977); Murphy, Simons, Wetzel, and Lustman (1984); Hollon et al. (1992); Elkin et al. (1989). In addition, the results from all four studies are pooled. Treatment outcome is measured by posttreatment scores on the Hamilton Rating Scale for Depression (within each study, these scores were adjusted for differences in pretreatment levels across individuals). Higher scores indicate more severe depression. From "Medication Versus Cognitive Behavior Therapy for Severely Depressed Outpatients: Mega-Analysis of Four Randomized Comparisons," by R.J. DeRubeis, L.A. Gelfand, T.Z. Tang, and A.D. Simons, 1999, *American Journal of Psychiatry*, *156*, p. 1010. Copyright 1999 by the American Psychiatric Association; http://ajp.psychiatryonline.org. Reprinted with permission.
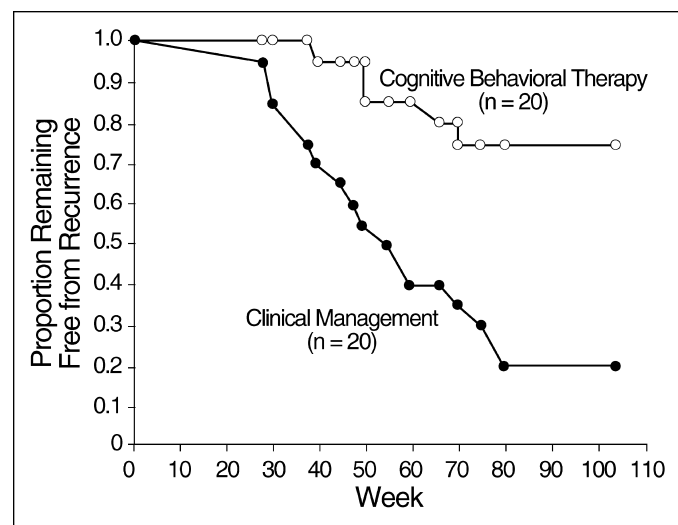
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sessions of a modified version of cognitive therapy or conventional clinical management over the next 20 weeks, during which time they were also tapered off medications. The modifications to cognitive therapy involved attention to beliefs and behaviors designed to increase positive affect and enhance life satisfaction. All patients were then followed across the remainder of a 2-year interval, during most of which (from Week 20 on) they were treatment free and no longer on medications. As shown in Figure 7, the patients who were exposed to cognitive therapy (labeled "cognitive behavioral therapy" by the authors) were considerably less likely to experience a recurrence following treatment termination than were the patients who had received clinical management only.

It remains to be seen whether other studies will replicate this effect (the sample was small and the cognitive behavioral intervention was provided by a single therapist), but if they do, the implications could be important. The standard perception is that pharmacotherapy is more cost-effective than psychotherapy, but that may not be the case over the long run if cognitive therapy and related cognitive behavioral interventions truly have an enduring effect. Although treating a patient to the point of remission typically costs more with CBT than with medica-

tions, the cumulative expense of maintaining patients on medications indefinitely will eventually exceed the cost of providing a time-limited course of CBT. If CBT prevents recurrence, this cost differential could extend over decades.

Other related cognitive behavioral interventions also appear to have enduring effects. Mindfulness-based cognitive therapy draws on strategies from dialectic behavior therapy (acceptance and meditation) to help teach patients to distance themselves affectively from their depressive ruminations (Teasdale, Segal, & Williams, 1995). Unlike conventional cognitive therapy, it focuses more on the process than on the content of thinking. Patients are encouraged not so much to examine the accuracy of their beliefs as to recognize their occurrence without responding to them affectively. In the only trial to date, this form of cognitive therapy had an enduring effect that reduced risk for relapse among patients with major depression who were first treated with medication (Teasdale et al., 2000). Given that the intervention can be provided in an economical group format and that meditation has already gained widespread acceptance, mindfulness-based cognitive therapy is likely to have considerable popular appeal if subsequent efforts at replication confirm its effects. It also will be interesting to see whether its enduring effect extends to the prevention of recurrence and whether it can be used to enhance acute treatment, but the approach has already generated considerable interest in the field.

*Does combined treatment enhance response?*

Combining drugs and cognitive therapy (or related cognitive behavioral interventions) appears to provide only a modest increment in efficacy, at least with respect to acute response, which typically is increased by about 10 to 20% (Conte, Plutchik, Wild, & Karasu, 1986). However, as has been found for IPT, combined treatment does appear to retain the specific advantages of each single modality (i.e., medication is sometimes faster and more dependable, whereas cognitive therapy protects against subsequent return of symptoms; Hollon & Shelton, 2001). Thus, there may be pragmatic reasons for combining medication and cognitive therapy, especially for patients with complex or difficult-to-treat disorders.

Moreover, combining medication with cognitive therapy or related cognitive behavioral interventions may be effective for certain kinds of patients, particularly those with chronic depression. In a recent trial, the combination of medication with a newly developed cognitive behavioral intervention with strong interpersonal overtones proved considerably more effective than either single therapy alone (Keller et al., 2000). Patients selected had all been continuously depressed for at least 2 years (most for considerably longer). Some met criteria for chronic major depression, others for double depression, and still others for recurrent major depression with incomplete remission between episodes. The newly developed intervention, called Cognitive Behavioral Analysis System of Psychotherapy (CBASP), is an innovative blend of cognitive, behavioral, interpersonal, and psychodynamic components. CBASP is predicated on the

Fig. 7. Proportion of patients remaining free from recurrence after receiving cognitive behavior therapy versus clinical management only (continued contacts with their psychiatrist): All patients were first treated to the point of recovery with medications alone and then randomly assigned to receive either cognitive therapy (extended to include attention to well-being) or clinical management only; they were then withdrawn from medication and followed across the rest of a 2-year follow-up. Randomization to the two treatment conditions occurred just prior to Week 0 in the figure, and medication withdrawal was completed and all other treatment stopped by Week 20; from that point forward, all patients received no further treatment. From "Prevention of Recurrent Depression With Cognitive Behavioral Therapy," by G.A. Fava, C. Rafanelli, S. Grandi, S. Conti, and P. Belluardo, 1998, *Archives of General Psychiatry, 55*, p. 819. Copyright 1998 by the American Medical Association. Reprinted with permission.

notion that patients with chronic depression have particular difficulty learning from experience in problematic interpersonal relationships (McCullough, 2000). As shown in Figure 8, patients provided with the combined treatment showed both the early gains over the first 4 weeks associated with medication treatment and the later gains shown by CBASP that allowed it to catch up with medication treatment over the last several weeks. Overall the combination was considerably more effective than either therapy by itself. It remains unclear whether this enhanced effect for combined treatment was unique to the specific modalities utilized or a more general characteristic of treatment with chronic patients. Moreover, CBASP needs to be assessed in a placebo-controlled trial. Nonetheless, this study has generated renewed interest in combined treatment in general and CBASP in particular.

Cognitive therapy and related interventions have been adapted for inpatient populations with generally good results, particularly when combined with medications (Stuart, Wright, Thase, & Beck, 1997). Thase, Bowler, and Harden (1991) found that over 80% of unmedicated inpatients with major depression responded to up to 20 sessions of cognitive therapy over a 4-week period. However, a subsequent study by the same group found a somewhat lower rate of response, particularly among patients with the highest severity scores at the beginning of hospitalization (Si-mons & Thase, 1992). Bowers (1990) found that adding cognitive therapy (or relaxation) to inpatients' medication treatment reduced their depressive symptoms more than medication alone; 80% of the patients who received cognitive therapy were considered fully recovered at discharge, versus 20% of the patients treated with medication alone. Miller, Norman, Keitner, Bishop, and Dow (1989) found that adding either cognitive therapy or social skills training increased rates of response relative to standard hospital care, including medications, although those trends did not reach significance until after further outpatient treatment. Hautzinger, de Jong-Meyer, Treiber, and Rudolf (1996) found cognitive therapy as efficacious as medication and no less effective than combined treatment in a sample of patients who did not meet criteria for endogenous depression, about 40% of whom were inpatients. A companion study found that adding cognitive therapy did little to enhance the effects of medication in a sample of depressed inpatients with endogenous features, although combined therapy was somewhat more effective for outpatients (de Jong-Meyer, Hautzinger, Rudolf, & Strauss, 1996). On the whole, cognitive therapy appears to be a useful adjunct to standard inpatient treatment, including medications; whether it is sufficient in the absence of medications remains an open question.
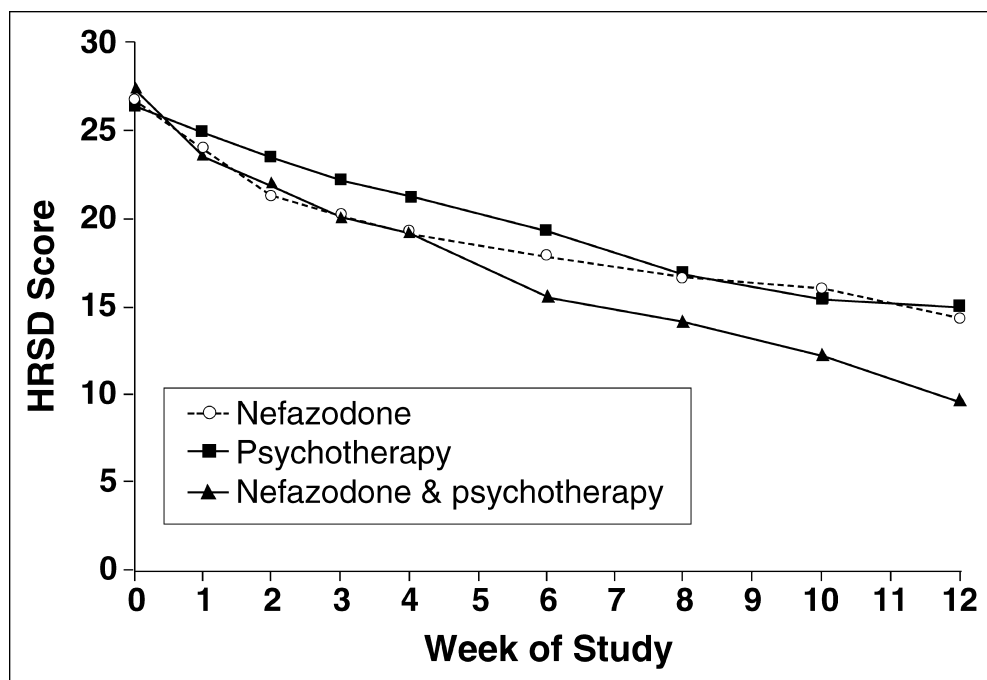
Fig. 8. Average score on the Hamilton Rating Scale for Depression (HRSD) as a function of the number of weeks of treatment for chronically depressed patients who received nefazodone alone, Cognitive Behavioral Analysis System of Psychotherapy (CBASP) alone, or a combination of the two treatments. Higher scores indicate more severe depression. From "A Comparison of Nefazodone, the Cognitive Behavioral-Analysis System of Psychotherapy, and Their Combination for the Treatment of Chronic Depression," by M.B. Keller et al., 2000, *New England Journal of Medicine, 342*, p. 1466. Copyright 2000 by the Massachusetts Medical Society. Reprinted with permission.

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Behavior Therapy

Interest in behavior therapy for depression dates at least to the advent of the cognitive interventions, but the behavioral approaches have never been as popular in clinical practice. A central premise of early behavioral theories was that depression is a consequence of a low rate of positive reinforcement, which might itself be due to problems in the environment or a lack of necessary social skills (Lewinsohn, Biglan, & Zeiss, 1976). Interventions that take a relatively pure behavioral approach include contingency management, social skills training (including assertiveness training), problem-solving therapy, and training in self-control. Although not tested as extensively as the cognitive behavioral interventions, behavior therapy has done well in controlled trials, most in mildly depressed populations (American Psychiatric Association, 2000). Behavior therapy typically has been found to be superior to minimal treatment and about as effective as other interventions (see Jarrett & Rush, 1994, for a review). Nonetheless, comparisons with other approaches in fully clinical populations have been few, and poor implementation of the comparison conditions has clouded interpretation of results in those studies that have found differences in outcomes.

For example, McLean and Hakstian (1979) found that behavior therapy based on contingency management had a modest advantage on some measures relative to either medications alone or brief dynamic psychotherapy. However, the drug doses were low, and the quality of the alternative psychotherapy was questionable. Conversely, Hersen et al. (1984) found no differences between social skills training (combined with either medications or pill placebo) and either amitriptyline alone or brief dynamic psychotherapy in a sample of women with major depression. In that study, drug doses were more adequate, and experts in the respective approaches oversaw the implementation of the comparison treatments.

Lewinsohn and his colleagues have been active in developing interventions based on social learning theory for the treatment of depression. Early work focused on efforts to increase engagement in pleasant activities and was often conducted in a group format (Lewinsohn, Weinstein, & Alper, 1970). Over the years, Lewinsohn and his colleagues evolved a more integrative model that incorporated cognitive, affective, and interpersonal features into their basic behavioral approach. This theoretical expansion led to the development of a multicomponent cognitive behavioral intervention that targeted a number of problem areas, including discomfort in social situations, low rate of engagement in pleasant activities, irrational and negative thoughts, and poor social skills (Lewinsohn, Muñoz, Youngren, & Zeiss, 1986).

This intervention was further refined for use as a psychoeducational course that could appeal to a broad spectrum of individuals who did not generally meet the criteria for Major Depressive Disorder and might not otherwise make use of formal mental health services. The Coping With Depression (CWD) course consists of 12 weekly sessions, with the first 2 sessions providing a basic social learning perspective on depression and the last 2 sessions integrating the basic skills learned during the course. The intervening 8 sessions teach specific skills, with 2 sessions each devoted to relaxation training, increasing pleasant activities, identifying and challenging negative and irrational thoughts, and social skills training, including training in assertion (Lewinsohn, Hoberman, & Clarke, 1989). The approach has been adapted for use with a wide range of formats and populations.

In general, studies have shown that the CWD course is efficacious. A recent meta-analysis indicates that it has shown an effect size of .65 relative to minimal treatment (Cuijpers, 1998). This corresponds to a drop of more than 12 points on the BDI and an advantage of nearly 7 points over control conditions, benefits comparable to those for other cognitive and behavioral interventions in another prominent meta-analysis (Robinson et al., 1990). The one caveat is that neither meta-analysis included many studies with fully clinical populations. Similarly, CWD has rarely been compared with medications or other types of psychotherapies. Thus, although the CWD course appears to be effective in reducing depressive symptoms in subclinical populations, its value in fully clinical populations remains unknown. Although it might prove to be a useful adjunct therapy, it seems unlikely to suffice for patients with clinical levels of depression.

Two other approaches typically are classified as behavior therapies, although each contains cognitive elements. Self-control therapy involves teaching patients to evaluate their own behaviors more positively by using more reasonable standards, and to reward themselves when they meet those standards (Rehm, 1977). Problem-solving therapy teaches patients to define life problems in a systematic fashion that facilitates generating solutions that can be implemented behaviorally (Nezu, 1986). Both of these therapies have been found to be superior to minimal treatment and comparable to related interventions in numerous studies with recruited samples with mild depressions, but studies in fully clinical populations have been few. Self-control therapy did enhance response relative to "treatment as usual" in a day-treatment setting (Van den Hout, Arntz, & Kunkels, 1995), and problem-solving therapy was comparable to amitriptyline and superior to placebo in the treatment of depression in a sample drawn from general medical practice (Mynors-Wallis, Gath, Lloyd-Thomas, & Tomlinson, 1995). These studies suggest that each of these behavior therapies may be helpful in treating at least some depressions. However, these approaches have had little impact on clinical practice because they have been so rarely studied in psychiatric samples that meet criteria for major depression.

Two studies have examined the efficacy of behavioral marital therapy in the treatment of depression. The first, restricted to couples with marital distress, found behavioral marital therapy as effective as cognitive therapy and superior to a waiting-list control (O'Leary & Beach, 1990). The second found behavior marital therapy as effective as cognitive therapy in reducing depression for patients with marital distress, but less effective than cognitive therapy for patients without marital problems (Jacob-

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son, Dobson, Fruzzetti, Schmaling, & Salusky, 1991). Both studies suggested that behavioral marital therapy was more effective than standard cognitive therapy for depression in reducing marital distress (Baucom, Shoham, Mueser, Daiuto, & Stickle, 1998). Similarly, conjoint IPT in which spouses are included appears to be more effective than individual IPT in reducing marital distress (Foley, Rounsaville, Weissman, Sholomskas, & Chevron, 1989). Given the importance of intimate relationships and the known associations between marital distress and depression, this work seems most promising.

Despite the generally good showing by these various behavioral interventions, interest in behavior therapy stagnated until recently, when an analysis of the different components of cognitive therapy showed that behavioral strategies designed to increase the patient's activity were as efficacious as the full treatment package (Jacobson et al., 1996). Moreover, patients exposed to only the behavioral components were no more likely to relapse following the termination of treatment than patients who were also exposed to cognitive-change techniques (Gortner, Gollan, Dobson, & Jacobson, 1998). These findings were so unexpected that they led Jacobson and his colleagues to develop a more comprehensive version of behavioral activation that emphasized the role of the external environment in determining behavior (Martell, Addis, & Jacobson, 2001). A recent placebo-controlled trial, as yet unpublished, suggests that behavioral activation is as effective as paroxetine in reducing acute distress (see Hollon, 2000, for a description of the preliminary findings). Moreover, this same study suggests that the effects of behavioral activation may be as enduring as those of cognitive therapy. This work should help to revive interest in behavioral interventions.

Special Populations and Problems

CBT for older adults

Several studies have examined the efficacy of CBT for older adults. Steuer et al. (1984) found that a group intervention adapted for geriatric patients from cognitive therapy was superior to psychodynamic group therapy in improving self-reported depression. Gallagher and Thompson (1982) found no differences at the end of treatment between cognitive therapy, behavior therapy, and insight-oriented dynamic psychotherapy in a sample of elderly depressed outpatients, although differences at a 1-year follow-up favored the two cognitive behavioral interventions. In a subsequent study, Thompson et al. (1987) again found no differences among cognitive, behavioral, and dynamic interventions in an elderly population, and all three of these treatments were superior to a waiting-list control. Treatment gains were largely maintained at a 2-year follow-up, with residual symptoms at the end of treatment predicting greater risk for relapse (Gallagher-Thompson et al., 1990). Beutler et al. (1987) found a main effect for group CBT but not alprazolam (an anti-anxiety agent) in a geriatric sample. Curiously, there are no comparisons between CBT and antidepressant medications in this population. Finally,

Scogin and his colleagues have found sustained reductions in levels of distress for older adults with mild depression who read self-help manuals (bibliotherapy) designed to expose people to the principles and techniques of CBT (Scogin, Hamblin, & Beutler, 1987; Scogin, Jamison, & Gochneaur, 1989).

CBT for children and adolescents

Numerous studies have suggested that the various cognitive behavioral interventions are effective in the treatment of children and adolescents (Curry, 2001). These interventions typically emphasize more behavioral strategies with younger children and more cognitive strategies with adolescents. The bulk of studies done with preadolescent children have been conducted in school-based settings with samples selected on the basis of self-reported (but not diagnosed) depression. In most instances, CBT proved superior to a variety of comparison conditions ranging from waiting-list control conditions through standard school counseling (see Curry, 2001, for a review). In a particularly elegant study, Weisz, Thurber, Sweeney, Proffitt, and LeGagnoux (1997) found that the effects of CBT were maintained up to 9 months after treatment.

The bulk of the studies in adolescent populations have been conducted in clinical settings with participants who had diagnosable depressions. In almost all instances, CBT has been found to be superior to minimal treatment (see Curry, 2001). Among the more notable examples are two studies by Lewinsohn and his colleagues, who adapted their CWD course for adolescents and found it superior to a waiting-list control condition in adolescents with diagnosable major depression (G.N. Clarke, Rohde, Lewinsohn, Hops, & Seeley, 1999; Lewinsohn, Clarke, Hops, & Andrews, 1990). In perhaps the most clinically representative study in this literature, Brent et al. (1997) found CBT superior to either systematic behavioral family therapy or nondirective supportive therapy for depressed and suicidal adolescents in an outpatient setting. They adapted CBT to place additional emphasis on the exploration of issues of autonomy and the acquisition of problem-solving and affect-regulation skills (e.g., finding ways to deal with anger beyond lashing out verbally or physically). On the whole, it appears that the cognitive behavioral interventions are effective treatments for depression in children and adolescents.

Finally, there are indications that the same strategies that reduce subsequent risk in adult psychiatric patients can be used to prevent the initial onset of depression in at-risk adolescents with no history of prior episodes (Gillham, Shatte, & Freres, 2000). In a pair of studies, G.N. Clarke and his colleagues found that training in CBT reduced the incidence of depressive episodes in at-risk adolescents selected on the basis of their scores for symptoms of depression (G.N. Clarke et al., 1995, 2001). Similarly, Seligman and his colleagues found that a preventive intervention modeled on cognitive therapy reduced risk for symptom onset in college students selected on the basis of having a problematic information processing style (Seligman, Schulman, DeRubeis, & Hollon, 1999). This same intervention has been adapted for use in school settings with young adolescents ap-

proaching the age of risk (Jaycox, Reivich, Gillham, & Seligman, 1994). These findings, combined with the work with adult psychiatric patients pointing to an enduring effect of CBT, suggest that cognitive behavioral interventions may be more than palliative and can be used to prevent the onset of affective distress.

CBT for dysthymia and the personality disorders

CBT was originally intended to be a brief intervention that focused on current life concerns, but it has become clear in recent years that patients with long-standing problems may require longer courses of treatment. This group includes patients with chronic depressions (including dysthymia), as well as those who have depression superimposed on an underlying personality disorder. Work by McCullough (2000) with CBASP has already been described, but even standard cognitive therapy has been modified in recent years to better deal with such patients' long-standing needs (A.T. Beck, Freeman, & Associates, 1990).

The crux of this modification is an approach called schema-focused cognitive therapy, which is designed to identify and change deep-seated core beliefs regarding the self, the world (usually interpersonal), and the future (J.S. Beck, 1995). In a schema-focused approach, the therapist pays specific attention to the childhood antecedents and the nature and quality of the working alliance between patient and therapist, something Beck calls the "three-legged stool." Conventional cognitive therapy attends to childhood issues only late in the course of treatment (if at all), and the patient-therapist relationship only if problems arise. In schema-focused cognitive therapy, the therapist is encouraged to attend to each "leg of the stool" in every session when working through any given issue. The assumption is that clients with long-standing problems have no way of looking at things other than through the flawed beliefs that gave rise to their problems in the first place. It also is assumed that it will take longer to help such patients develop a new view of themselves and the world than it does to help patients who have discrete episodes and a more balanced perspective between episodes. Schema-focused cognitive therapy resembles more psychodynamic approaches in some respects, although it does not posit the existence of unconscious sexual and aggressive motivations, and it retains the emphasis on running behavioral experiments to test underlying beliefs that is common to all cognitive behavioral interventions.

Schema-focused cognitive therapy remains largely untested, but early indications from ongoing clinical trials are encouraging. Both dysthymic and personality-disordered patients appear to benefit from identifying and testing their core beliefs and engaging in behaviors that differ greatly from their more typical compensatory strategies and safety behaviors. It would be premature to claim that conventional cognitive therapy is uniquely effective with such patients, as was done in one recent treatment guideline (see American Psychiatric Association, 2000). However, this might well prove to be the case for schema-focused cognitive therapy once it is adequately tested (Hollon & Shelton, 2001).

CBT for bipolar patients

As for IPT, there is a growing interest in adapting CBT to the treatment of bipolar disorder. This interest is fueled in part by the recognition that medications alone often are not sufficient to control symptoms or resolve residual social or vocational impairment (see the earlier section on medications). Early studies focused primarily on using CBT to enhance patients' compliance in taking their medication as prescribed (see, e.g., Cochran, 1984). More recent work has focused not just on enhancing compliance, but also on regularizing everyday routines and coping with events, as well as redressing the social and vocational complications of illness (Basco & Rush, 1996). In the only randomized controlled trial published to date, Lam et al. (2000) found that adding CBT to ongoing medication treatment reduced the occurrence of subsequent episodes and improved residual functioning in a small sample of Bipolar I patients who were not currently in distress. It would be premature to claim, on the basis of this single study, that CBT is effective in preventing bipolar episodes, but work is currently under way to see if these findings can be replicated. No one would claim that CBT should be used alone in the treatment of bipolar disorder, but there is reason to think that it might provide a useful adjunct to medication.

Summary

The cognitive behavioral interventions appear effective in reducing acute depression and may have an enduring effect beyond the end of treatment. These interventions compare favorably to medications in all but the most severely depressed patients and do well with those patients in the hands of experienced therapists. Moreover, they are relatively free from complications or side effects. Cognitive therapy has been the most extensively tested of the cognitive behavioral interventions and has generally fared well, but several other newly developed interventions also appear promising. These include CBASP for the treatment of chronic depression and mindfulness-based cognitive therapy for the prevention of relapse and recurrence. At the same time, the more purely behavioral interventions are starting to attract renewed interest, driven largely by the success of a contextual approach to behavior activation.

Indications that CBT might have a preventive effect that reduces future risk are especially exciting. Given that depression is often a chronically recurrent disorder, teaching people to deal with or prevent their own affective distress could be a real boon to public health. Particularly promising are the indications that the same strategies that work to protect psychiatric patients from relapse or recurrence following successful treatment may also reduce risk for initial onset in children and adolescents who have never been depressed. Even the most efficacious treatments rarely have long-lasting benefits; they often control symptoms, but do little to resolve the underlying causes. Although it is premature to claim that CBT provides such resolution, the presence of an enduring effect leaves open that possibility.

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MARITAL AND FAMILY THERAPY

Marital and family problems are common in the course of depression and can trigger episodes and complicate their treatment (American Psychiatric Association, 2000). In addition to the behavioral approaches already described, traditional marital and family approaches and newer psychoeducational interventions have all been used to reduce family conflict and relieve distress.

Traditional Marital and Family Therapies

Traditional marital and family therapies have been often used but little studied in the treatment of depression. Friedman and his colleagues conducted an early trial in a sample of 196 depressed women with marital distress. Some women got antidepressants and others got a placebo, and within each of these groups some women received dynamic marital therapy and others received supportive therapy (Friedman, 1975). Medications were better than marital therapy in reducing acute distress, whereas marital therapy produced greater changes in the quality of the relationships. Although combined treatment did little to improve on either single modality, it retained the benefits of each. This was one of the studies that led to the belief that psychotherapy was less effective than medications in treating depression and did little to enhance their effects.

Psychoeducational Programs for Families

Psychoeducational approaches are designed to provide patients and family members with information about depression and other disorders that they can use to protect themselves from the disorders' effects. Recent work on psychoeducation builds on the notion that depressed people often provoke hostile responses from people around them and that the resultant perceived criticism often aggravates distress (Hooley & Teasdale, 1989). Psychoeducational approaches modeled on work done with families of schizophrenic patients have been designed for depression. Their goal is to relieve the burden on family members that sometimes leads them to criticize and withdraw from the loved one with depression. Although most of the work on psychoeducational approaches to depression has been conducted with bipolar populations, some research on unipolar depression is also being conducted. For example, Clarkin et al. (1990) found that adding psychoeducational family therapy enhanced response to standard inpatient medication treatment among female patients regardless of diagnosis. However, only women with bipolar disorders maintained those gains over the subsequent 18 months; bipolar women also showed gains in social functioning. Male patients, particularly those with unipolar disorders, actually did worse in the combined condition than in standard treatment. Why they did worse is not clear, but a complex interaction between gender and polarity may moderate treatment response. Whether this finding is replicable remains to be seen, but researchers should be alert to the possibility that women respond better than do men to psychoeducational treatment programs.

Family-Focused Therapy (FFT) for Bipolar Patients

FFT is a structured psychosocial treatment for bipolar disorder based on the notion that the family or marital environment moderates the expression of underlying biological vulnerabilities (Miklowitz & Goldstein, 1997). The resultant symptomatic states themselves become a source of stress to which families and spouses often respond with high levels of expressed emotion, which in turn triggers subsequent exacerbation of symptoms or relapse. FFT for bipolar patients is modeled on work in schizophrenia. The patients and their relatives are first provided with information about bipolar disorder and taught to recognize its signs and symptoms and to develop a relapse-prevention plan. A second stage of treatment teaches communication skills with an emphasis on active listening and providing positive feedback. The final stage teaches patients and their relatives to define and solve specific family problems in a manner that enhances a sense of cooperation and reduces emotional conflict. FFT for bipolar patients is intended to be done in conjunction with, and not as a substitute for, medication treatment.

FFT was found to reduce risk for relapse in two successive studies. In the first, FFT led to lower rates of relapse in 101 medicated bipolar patients than did conventional crisis management designed to simply deal with the immediate problem (Miklowitz et al., 2000). Both patients and family members engaged in more positive interactions following FFT, as would be expected if interactional processes played a role in reducing risk for relapse (Simoneau, Miklowitz, Richards, Saleem, & George, 1999). An as yet unpublished companion project indicated a comparable advantage for FFT over individual counseling (see Craighead & Miklowitz, 2000, for a description). These studies suggest that family psychoeducation can efficaciously reduce risk for relapse and buffer the consequent stress of having a family member with bipolar disorder.

Summary

These studies suggest that marital and family therapy may have a role to play in the treatment of depression, although the studies are still too few and the results too disparate to permit firm conclusions. Nonetheless, the results are promising, particularly for the more recently developed FFT, which shares with IPT a focus on relational issues and with CBT an interest in teaching specific skills in a structured fashion. Given the limitations of current approaches to the treatment of bipolar disorder, any innovation in this area is welcome indeed. Further work is clearly warranted in this area.

CONCLUSIONS AND RECOMMENDATIONS

Several types of interventions appear to be effective in the treatment of depression. Each has advantages and disadvantages, and none is universally effective. The antidepressant medications have the most extensive empirical support and generally are efficacious so long as they are continued or maintained, but can

produce troublesome side effects and do little to reduce risk after their use is terminated. ECT remains the single most effective intervention for the most severe depressions, but its use needs to be weighed against concerns regarding possible effects on memory and cognition. IPT has had good results in a number of different populations (including relatively severely depressed outpatients) and may enhance the quality of relationships, but is still not widely available to the general public. CBT appears to be effective for all but the most severe depressions (and maybe those as well); it may have an enduring effect that reduces subsequent risk, but its effectiveness may depend on the competence of the clinician. FFT appears to be a promising adjunct to medications in preventing relapse in bipolar patients, but is yet not widely practiced. Treatment that combines two different modalities (e.g., medication plus FFT) tends to incorporate the advantages of each treatment component and may enhance outcomes for chronically or severely ill patients.

Despite real progress over the past 50 years, many depressed patients still do not respond fully to treatment. Only about half of all patients respond to any given intervention, and only about a third eventually meet the criteria for remission. Clinical experience suggests that many patients who do not respond to one intervention will respond to another or, in the case of the empirically supported psychotherapies, to extended treatment. However, there is little clear empirical guidance for what to do for patients when treatment fails. Moreover, most patients will not stay well once they get better unless they receive ongoing treatment. Although depression is an eminently treatable disorder (compared with other forms of severe psychopathology), it may require nearly continuous treatment in order to ensure that symptoms do not return. In that sense, it may be more like other chronic recurrent disorders, such as hypertension or diabetes, than it is like the infectious diseases that can often be cured with the right antibiotic. That is why indications of an enduring effect for CBT are so exciting. Similarly, indications that IPT (and possibly FFT) may enhance the quality of interpersonal relations also should be explored, because most patients are as concerned with the quality of their interpersonal lives as they are with their specific symptoms.

Finally, too few patients have access to empirically supported treatments. Depression often goes unrecognized, especially in primary-care settings, and access to competent treatment is not always easy to obtain. Surveys of clinical practice suggest that many physicians fail to provide antidepressant medications in adequate doses or prescribe the wrong medications. At the same time, empirically supported interventions like IPT and FFT are still not widely available, and many practitioners still prefer more traditional psychotherapies of unknown efficacy. CBT has become fashionable in practice settings, but many of the therapists who identify with the approach do so only in name.

Although considerable progress has been made, more clearly needs to be done. Existing treatments need to be improved and new approaches developed to deal with patients who currently do not respond. Research is needed to clarify how to combine or sequence existing interventions, and practitioners need better guidelines for selecting the best possible treatment for a given individual. Access to empirically supported interventions must be improved, and researchers and practitioners alike need to do a better job of monitoring the efficacy of treatments over time. Most important of all, the field needs to emphasize efforts at prevention that build on existing indications that people can learn strategies to reduce future risk.

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