

Depression Research Advances, Treatment Lags

Both drugs and psychotherapy have been shown to be effective treatments for depression, but studies show 80% of sufferers never receive treatment

DEPRESSION is the most extensively researched and best understood of the major mental illnesses. This decade in particular has seen significant advances in the epidemiology and treatment of the disorder.

Yet, ironically, the vast majority of cases go untreated. According to a 1983 study by the National Institute of Mental Health (NIMH), about 6% of the population can expect to experience clinical depression within a given 6-month period. Although the suicide rate is 15% for affective (mood) disorders, 80% of the sufferers never see treatment.

The rate of diagnosed depression in this country has increased greatly among people born since World War II, particularly women. The average age of onset has declined, from around 40 years old to the mid-20's, according to NIMH. The likelihood of a major depression is now one in four in the lifetime of a woman, one in ten for a man. Researchers are becoming increasingly aware of the recurrent nature of the illness, which with hospitalized cases has a relapse rate of about 85%. "Depression has a far more pernicious course than is commonly believed," according to a 1984 consensus conference at the National Institutes of Health.

A measure of public ignorance was supplied last year by columnist Ann Landers who received 250,000 requests for an informational pamphlet in response to a column on depression. This gap is largely owing to the stigma attached to all mental disorders and the fact that depression is often not recognized or acknowledged by victims. It is in many ways a hidden scourge, often manifested (and exacerbated) through alcohol and drug abuse.

But public awareness may be changing. Recognition of depression as a health problem has probably received its keenest prod from publicity about the alarming rate of suicide among teenagers. Recently, the NIMH launched a campaign called DART (Depression Awareness, Recognition, and Treatment) to improve public and professional understanding of the illness.

Given the current attention to depression, the preliminary findings of an NIMH treatment study, which suggests that psychotherapy and drugs can be equally effective in treating depression, have attracted a good deal of attention. The study's rigorous methodology, which represents a major step toward quantifying the results of psychotherapy, may be as significant as its findings.

The \$3.4-million Treatment of Depression Collaborative Research Program, launched in 1981, is the largest study of its kind and the most assiduously planned. Two types of therapy were used: cognitive-behavioral therapy, developed at the University of Pennsylvania, which attempts to correct a person's distorted assumptions about self



Gerald Kierman: "The concept of endogeneity is not substantiated by family or follow-up studies."

and the world; and interpersonal therapy, developed by the New Haven-Boston Collaborative Depression Project, which operates on the premise that some depression is caused by role conflicts, grief, and deficient interpersonal relationships. Patients were randomly assigned to one of four groups: a cognitive-behavioral group, an interpersonal group, a group treated with imipramine, a tricyclic antidepressant, and a group on a placebo. The latter two groups also received minimal supportive therapy.

Most studies of psychotherapy for depression have been evaluated by the same people who developed the therapies. The attendant danger of bias was eliminated in this study by administering the same treatments at

three locations—George Washington University in Washington, D.C., the University of Pittsburgh, and the University of Oklahoma (*Science*, 24 April 1981, p. 432).

Participating therapists received extensive training based on treatment manuals for the two psychotherapies, which were developed specifically for the treatment of depression. The therapists were videotaped and monitored to be sure they were following the designated procedures. The drug treatment was also standardized.

The 239 subjects, outpatients with unipolar depression (depression with no mania), had all suffered from "major depressive disorder" for at least 2 weeks and had been depressed, on average, for a year. Seventy percent were female; the average age was 35.

After an average of 16 weeks, between 51 and 57% of the patients in the three treatment groups, as opposed to 29% of the placebo group, had returned to normal according to various depression scales. The fastest results occurred among the patients given imipramine, but by the end of the trial there was no significant difference among the three therapies. Interpersonal therapy, however, seemed to work better than cognitive therapy with the most severely depressed patients. According to NIMH study director Irene Elkin, variation in treatment response according to the site of treatment was greater with regard to the psychotherapy than with the drugs.

Much analysis of the findings remains to be done. One of the big questions is whether those who learned social coping skills and less distorted thinking patterns in the therapy groups will show sustained gains in these areas at the time of the 18-month follow-up next December.

Other areas of investigation will include the responses of those who also had psychiatrically defined "personality disorders." Such disorders, in which depression is aggravated by profound distortions in individuals' attitudes and beliefs, are notoriously difficult to treat and are expected to show less positive outcomes.

Another substudy will compare outcomes between patients with "endogenous" depressions not apparently triggered by any life event with a group suffering "situational" and nonendogenous depressions. This one should add fodder to the perennial debate within psychiatry over the definition and significance of "endogenous" depression. Endogeneity has been defined in many ways, according to psychiatrist Robert Hirschfeld of NIMH. It has been used to denote extreme severity of symptoms, depression that falls like a bolt from the blue (nonsituational), depression unresponsive to environmental stimuli, or depression in a

person with an otherwise normal and non-depressive personality. The common thread of all these definitions is the attempt to designate a biological basis to the illness. Nowadays, the definition of endogenous is more directly biological: it refers to depression with strong "vegetative" features—that is, insomnia, loss of interest in food and sex, energy loss, and psychomotor retardation, as well as extremely depressed mood.

This type of depression has been commonly thought to be predominantly nonsituational and to occur most frequently in those with a family history of depression. It is also thought to respond better to drugs. But recent research, particularly from another NIMH collaborative study, on the psychobiology of depression, is casting these assumptions into question. Says investigator Gerald Klerman of the Cornell-New York University Medical Center: "One of the most surprising findings is that the concept of endogeneity is not substantiated by family or follow-up studies."

In one study, endogeneity could not be predicted from dividing depressives into situational versus nonsituational. In another, according to Martin Keller of Massachusetts General Hospital, the same people can show endogenous depression in one episode, and nonendogenous in another. "The hope was that endogeneity would lead to an understanding of etiology," says Keller, but it seems that the severity of symptoms is not related to family prevalence.

Psychologist Myrna Weissman of Yale University has found that, although the families of depressives suffer from about three times as much depression as the general population, this could not be predicted on the basis of a depressed individual's history or symptomatology. The only predictors for increased family prevalence, she says, were early age of onset, alcoholism, or anxiety disorder in the depressed patient.

The situation is much clearer when it comes to separating out manic depression, or bipolar disorder, from unipolar depression. Bipolar illness is strongly influenced by genes, as shown by studies that reveal up to 80% concordance between identical twins, and by adoption studies showing that rates of the illness in adoptees correlate with their biological parents and not with their adopted parents.

The relationship of unipolar to bipolar illness carries strong implications for the biological status of unipolar depression. Frederick Goodwin, director of intramural research at NIMH, believes a case can be made for categorizing unipolar illness according to its recurrence patterns rather than symptomatology. "My own strong feeling," he says, "is that recurrent unipolar

and manic depression are closely related. The issue of recurrence and cyclicity may be more meaningful and unifying than the concept of polarity." He says evidence for a relation between the two is that, among unipolars who seem to have regular cycles, lithium is as successful as it is with bipolars in preventing recurrences. This, however, is controversial.

One thing everyone agrees on is that the incidence of bipolar illness is probably higher than the conventionally used figure of 1%. This appears to be partly because, until the past decade, cases of mania were often incorrectly diagnosed because many of the symptoms resemble those of schizophrenia. The other reason is that antidepressants can trigger manic episodes in many people who would otherwise be diagnosed as having unipolar depression. Goodwin says that probably one-third of cases of severe depression are bipolar illness. The true incidence could be higher—Janice Egeland of the University of Miami School of Medicine, in her study of the Amish, found the ratio to be 50–50 (*Science*, 2 May 1986, p. 575).

NIMH psychiatrist Elliot Gershon, who heads intramural research on the genetics of mental illness, believes that unipolar illness may progress along two spectrums. Family

posite symptoms (sleeping and eating too much, and different diurnal fluctuations) from endogenous depression. It would also include dysthymia, meaning chronic depression without acute fluctuations.

Currently, quite a bit of work is going on in an effort to differentiate unipolar from bipolar depression through biochemistry. But so far the answers are tentative. At present the only way to chemically distinguish a bipolar from a unipolar is to administer antidepressants and see if "switching" to mania occurs.

A number of possible markers for bipolar illness have been proposed. Joseph Schildkraut of Harvard University, the author in 1965 of the catecholamine hypothesis of affective disorders, has found that people with full-fledged cases of manic depression have low levels of urinary MHPG (3-methoxy-4-hydroxyphenylglycol), a metabolite of norepinephrine, when they are in the depressed phase (and high levels in mania). Unipolar depressives, however, cluster in three groups, with low, high, and intermediate levels. Schildkraut has further found that, by using a statistical method called multivariate discriminate function equation, he can discriminate who among the "lows" are also susceptible to mania.

William Potter, an NIMH psychopharmacologist, has also identified a subset of unipolar depressives whose chemistry differentiates them from bipolars and from other unipolars. If you look at "melancholics," another term for those with severe endogenous symptoms, he says, you find the level of plasma norepinephrine is two or three times as high as it is in bipolars. This suggests to him they are secreting too much, but are making inefficient use of it—"the brain's not getting it." The same holds true with serum cortisol. These "hypersecreters"—equivalent to Schildkraut's high MHPG group—are regarded by Potter as the most likely candidates for drug treatment. He also says he "will bet money" that they will also show higher familial prevalence of affective disorder than other unipolar depressives.

The dexamethasone suppression test is an older assay that some have hoped would serve as a measure of severity, and perhaps of an inherited vulnerability to unipolar depression, by pointing up patients whose cortisol levels are not suppressed by the test. George Winokur of the University of Washington at St. Louis has found that patients whose family members show a high prevalence of depression (he calls this "familial pure" depression) show more nonsuppression than do patients whose family members manifest a high rate of alcoholism and personality disorders ("depression spectrum



Myrna Weissman: *Codeveloper, with Klerman, of interpersonal therapy.*

prevalence data suggest to him that there is one genetic spectrum starting with unipolar depression, shading into bipolar depression, and ending with schizoaffective disorder, a combination of affective and thought-disordered symptoms. This reading is suggested by the fact that 30% of the first-degree relatives of schizoaffectives have mood disorders, the most common being manic depression. Gershon believes other types of depression may occupy a strictly unipolar spectrum. This would include "atypical" depression, so named because it manifests op-

disorder"). But other researchers say these findings have not been replicated. The dexamethasone test has been found to signal that a depressed patient is not fully recovered, but it fails to identify many severe cases and is not specific for depression, says Potter.

Unipolar depression is really a "heterogeneous wastebasket," as Goodwin puts it, a product of myriad causes including physical and other mental illnesses, biochemical imbalances, character disorders, addictions, stress, and grief. Any depression that is severe enough will manifest itself in biological changes, not all of which are treatable by antidepressant medications.

So, new avenues continue to be explored. For example, some investigators find that certain depressions can be temporarily alleviated by interfering with biorhythms—sleep deprivation, for instance, has a magical temporary effect for some people, suggesting the involvement of melatonin, secreted by the light-sensitive pineal gland. Larger cycles are implicated in the newly identified "seasonal affective disorder," which afflicts some people in the winter and which NIMH researchers have found to be responsive to several hours a day of exposure to strong light.

Schildkraut believes the understanding of depression is at best rudimentary: "Our most complex thoughts about this disorder, I think, are orders of magnitude oversimplified." But if research has more questions than answers, it still has a lot more answers than are actually reaching depressed patients. Some observers have likened the treatment situation to the status of hypertension 15 years ago, which went largely untreated until the National Heart Institute staged a prolonged campaign on education and treatment.

Several recent studies, in addition to the 1983 NIMH catchment area project, indicate that depression is being undertreated or inappropriately treated. One was published in 1982 as part of the NIMH collaborative psychobiology study. This study looked at 217 patients admitted to five university centers after being treated for depression by doctors or therapists "in the community." The study found, for example, that tranquilizers, which are generally contraindicated for depression, were prescribed more often than antidepressants. Of the 34% who received antidepressants, "high proportions did not receive somatotherapy long enough or at a high enough dose."

A follow-on to this study, published this year,* comes up with even more surprising information: widespread undertreatment of

Manic Depression and Creativity

The apparent link between genius and insanity has long been noted and much debated, particularly in the Romantic era. Modern science has taken next to no interest in exploring the connection. But there are a few studies that indicate that bipolar or manic depressive illness may be the mental disorder which (next to alcoholism) is most often found among creative artists.

The first study using modern diagnostic criteria was conducted in 1973 by psychiatrist Nancy Andreasen of the University of Iowa. Andreasen interviewed 15 writers at Iowa's prestigious Writers Workshop and compared them with 15 controls matched for age, education, and sex. Ten (67%) of the writers had been treated for affective disorder as opposed to 13% of the controls. Two of the ten were diagnosed as manic depressive, and almost all reported mood swings including manic or hypomanic (mildly manic) states. Six (40%) of the group were also alcoholic, compared with two of the controls.

A more recent study was conducted in 1983 at Oxford University by Kay Jamison, a psychologist at the University of California at Los Angeles. She surveyed 47 top British artists and writers, 87% of whom were male with an average age of 53. Thirty-eight percent had sought treatment for affective illness. Writers experienced the most problems, and of these, poets topped the list—with half of them reporting medical intervention (drugs, hospitalization, or both) for depression. Almost two-thirds of the playwrights, 20% of the biographers, and 13% of the painters had been treated for depression, mainly with psychotherapy.

One-third of the 47 reported suffering from severe mood swings, particularly the poets and novelists. Whereas the biographers—those least likely to be caught by "creative fire," says Jamison—reported no mood swings, 17% of the poets had been treated for mania.

Another psychiatrist interested in the subject is Hagop Akiskal of the University of Tennessee. Akiskal conducted an unpublished study of 750 patients with mood disorders and schizophrenia to see if there were any subtypes manifesting a differential rate of creativity from the rest of the population. He found that the severe cases of bipolar illness (bipolar I) had high levels of antisocial behavior. But among those with moderate cases (bipolar II and cyclothymia), between 9% and 10% qualified as creative artists.

Akiskal did not see any excess creativity among those who suffered only from depression. He and others think that many artists plagued by depression also enjoy hypomanic episodes which are likely to be perceived simply as optimal functioning. Bahman Sholevar, a poet and psychiatrist at Thomas Jefferson Medical College in Philadelphia, says: "most artists I know are at least cyclothymic." Akiskal is currently conducting a study in Paris with Salpêtrière Hospital which involves exhaustive personal interviews with several dozen writers, painters, and musicians.

If artists are more prone to mood disorders, are the emotionally ill more creative? There is only one contemporary study that explores this angle, conducted with Danish subjects by Ruth Richards of Harvard University's McLean Hospital and Inge Lunde of the Kommune Hospitalet in Copenhagen. The subjects were 17 manic depressives, 16 cyclothymes, and 11 normal first-degree relatives of the patients. Creativity (judged by participation in arts and crafts) was found to be significantly higher among the subjects than the controls, with the most creative group being the normal relatives of the manic depressives.

Richards concludes that "creativity may be enhanced, on the average, in subjects showing milder and perhaps 'subclinical' expressions of potential bipolar liability." She also notes similarities in "cognitive style" between the creative and the emotionally disturbed—a "breadth of cognitive capacity" that when carried to an extreme "bears similarity to some primitive and potentially pathological patterns."

No one has offered a hypothesis as to why a tendency to manic depression might enhance creativity, although hypomania is a high-energy state conducive to focused concentration and tremendous productivity. Descriptions of manic states also bear a strong resemblance to descriptions of artistic raptures and some mystical states. But, says Akiskal, "bipolarity may have more to do with achievement than creativity per se" in view of the fact that manic depression is one of the few mental disorders that shows higher prevalence in upper socioeconomic groups. ■ C.H.

*M. B. Keller *et al.*, "Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients," *Arch. Gen. Psychiatry* 43, 458 (1986).

depression even in the five major centers participating in the project. Of 250 hospitalized patients, 31% got no or very low doses of antidepressants, and 19% received less than 30 minutes of psychotherapy per week. Of the 88 outpatients, 54% got no drugs or very low doses, and 52% got less than 30 minutes of therapy a week. The outcomes are not impressive—after 8 weeks, 67% of the patients had not recovered and 38% still had “marked symptoms” of depression.

These findings came as a “surprise,” says Keller, who adds that investigators anticipated that this population—urban and all Caucasian—would be getting high levels of treatment. Interestingly, the authors recount that symptomatology did not predict treatment course in either study. In fact, the only significant predictor was geographical location. In Boston and New York, where psychiatry has a strong psychoanalytic tradition, drugs are less likely to be prescribed than they are in Iowa City and St. Louis.

Another study, at Cornell–New York University Medical Center’s Payne-Whitney Clinic, also reveals a reluctance to use drugs. According to investigator James Kocsis, this study focused on chronic depression or dysthymia. Most of the 38 subjects had been in long-term individual psychotherapy. Only seven were getting antidepressant medication. Upon referral to the clinic, they were put on imipramine. Between 50 and 60% exhibited “dramatic improvement” according to Kocsis. He says most medication studies have been short-term ones on acute depressive episodes, but the Cornell study shows there is a “definite role for antidepressant medication in a substantial percentage of patients with chronic depression.”

More information on chronic depression is expected from an unusually long (176 weeks) treatment study now under way at the Western Psychiatric Institute and Clinic, in Pittsburgh, called “maintenance therapies in recurrent depression.” Investigator David Kupfer says this will supply valuable data on two little-studied questions: the effects of long-term treatment, and adequate levels of treatment for maintenance.

The study involves 230 outpatients with histories of quite severe depression, 90% of whom have been diagnosed “definite or probably” endogenous. They are receiving acute treatment combining drugs and psychotherapy for 6 to 8 months until they can achieve three consecutive weeks free of symptoms. They are then divided into five groups for maintenance treatment: an imipramine group, an interpersonal therapy group, a combination drug and therapy group, a placebo and therapy group, and a placebo group. They are being followed up for 3 years (or until depression recurs). Data

are also being gathered on family prevalence of depression, personality characteristics and psychopathology, and biological measures such as neuroendocrine functions and sleep electroencephalograms.

So far, report Kupfer and Ellen Frank, a 4-month study has shown that “normal” (that is, prompt) responders to the combination of treatments also have more biological abnormalities, namely hyperexcretion of serum cortisol and short REM latency (the onset of rapid eye movement sleep comes earlier than with nondepressed people). Slower responders tend to be more emotionally disturbed and to show higher levels of neuroticism. Frank and Kupfer believe this means that those with the more biologically based depressions are responding primarily to the drugs, while those with more personality problems are responding primarily to the (slower acting) psychotherapy.



Martin Keller: Findings about low levels of treatment came as a surprise.

The heterogeneous nature of depression obviously poses challenges for treatment, but there are many other reasons for the undertreatment of the illness. Some have to do with patient reluctance to admit to emotional problems, or to take medication for them (antidepressants, unlike tranquilizers, have no subjectively obvious psychoactive effect). Most depressed patients who seek help are treated by general practitioners for secondary symptoms, such as anxiety, chronic pain, or insomnia.

Keller, who headed the two NIMH-sponsored studies, suggests a variety of reasons for undertreatment by mental health professionals. One is misdiagnosis: a practitioner oriented to psychotherapy may seek to explore underlying character problems while failing to recognize that the depression has taken on a life of its own. There is also a reluctance to go to tricyclics because of their initial unpleasant side effects, such as dizziness and dry mouth, and the delay in therapeutic action which may take several weeks. (Monoamine oxidase inhibitors, which have

few side effects but involve dietary restrictions, are still little used in this country.) And, there is just plain pharmacological ignorance, which includes prescriptions of inadequate dosages and failure to explore another drug when one doesn’t work.

Psychiatrist Donald Klein of Columbia University adds that many professionals tend to have an “either/or” mentality about drugs and therapy which reflects the orientation in their schooling. Schools for nonmedical therapists such as psychologists and social workers have not responded to changes in drug prescribing, he says, and some medical schools cling to a psychoanalytic orientation that downplays drugs.

Others, such as Morton Reiser of Yale University School of Medicine believe that the problem is a generational one. Many psychiatrists in private practice are very reluctant to prescribe drugs, and, says Reiser, “there is still a lot of empirical seat-of-the-pants pharmacology going on.” But he believes that those who have graduated from medical school within the past decade are more sophisticated about drugs and accustomed to combining pharmacotherapy with psychotherapy.

The 1980’s may well emerge as a major turning point in the treatment of depression. This decade has seen the refinement of diagnostic criteria, widespread adoption of structured interviews, important new epidemiological information, and the development of rigorous studies on psychotherapy compared with drugs. There is growing interest in family prevalence and in the long-term course of the illness. New antidepressant drugs are in the offing. Private funding for research is likely to increase with the formation of new advocacy groups for the mentally ill, the latest of which is the National Alliance for Research on Schizophrenia and Depression, a fund-raising coalition that started operation in July.

The greatest problem with depression today is the fact that, at best, there is a large lag time between onset of the disorder and treatment for it. And it is costly indeed. According to European data, says Goodwin, patients with recurrent depression spend about one-fifth of their adult lives hospitalized, and another 20% are chronically disabled by their symptoms. NIMH likes to boast that the introduction of lithium for manic depression has saved the country \$6.5 billion in medical costs over the past 15 years. Earlier recognition and treatment of depression might produce similarly impressive results. ■ **CONSTANCE HOLDEN**

ADDITIONAL READING

M. B. Keller *et al.*, “Treatment received by depressed patients,” *J. Am. Med. Assoc.* **248**, 1848 (1982).

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