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Raising Questions about Antidepressants

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Abstract
Antidepressant medication has apparently become the most popular treatment for depression in the USA. Several beliefs about the efficacy of antidepressant medications prevail among mental health professionals and the public. This paper explores relevant research data and raises questions about these beliefs. Many of the common beliefs about these medications are not adequately supported by scientific data. The following issues are raised: (1) industry-funded research studies which result in negative findings sometimes do not get published; (2) placebo washout procedures may bias results in some studies; (3) there are serious questions about the integrity of the double-blind procedure; (4) the 'true' antidepressant drug effect in adults appears to be relatively small; (5) there is minimal evidence of antidepressant efficacy in children; (6) side effects are fairly common even with the newer antidepressants; (7) combining medications raises the risk for more serious complications; (8) all antidepressants can cause withdrawal symptoms; (9) genetic influences on unipolar depression appear to be weaker than environmental influences; (10) biochemical theories of depression are as yet unproven; (11) biological markers specific for depression have been elusive; (12) dosage and plasma levels of antidepressants have been minimally related to treatment outcome; (13) preliminary evidence suggests that patients who improve with cognitive-behavioral psychotherapy show similar biological changes as those who respond to medication, and (14) the evidence suggests that psychological interventions are at least as effective as pharmacotherapy in treating depression, even if severe, especially when patient-rated measures are used and long-term follow-up is considered.

The prevalence of unipolar depression is estimated to be between 3 and 13%, with 20–50% of the adult population having a prior history and as much as 20% experiencing at least some depressive symptoms at any given time [1–3]. Women are consistently found to have rates of depression twice as high as men. Depression is conventionally viewed as a 'medical illness' and drugs appear to be the most commonly delivered treatment for depression in the USA [4]. Antidepressant prescriptions have risen steadily since 1980 and are now prescribed in over 30% of all visits to psychiatrists [5]. By examining the empirical literature, this paper raises questions about the medical model and many of the claims [6] associated with the use

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of antidepressants for nonbipolar, nonpsychotic depression. It is our position that many of the prevailing beliefs about antidepressants are not adequately supported by the available scientific data.

Belief No. 1: Antidepressants Are Conclusively More Effective than Placebo

Reviews and meta-analyses of randomized, double-blind, placebo-controlled, antidepressant studies [7–11] have provided evidence that antidepressants are more effective than placebo. One of the original comprehensive literature reviews by Morris and Beck [9] found that tricyclic antidepressants were superior to a placebo in 63 out of 91 (69%) controlled studies published between 1958 and 1972. Though this review, and the others that followed, generally supported the efficacy of antidepressants, some problems with the publication process and the research paradigm may diminish the strength of this support.

Since drug studies with negative results are likely to be delayed [12] or go completely unpublished [13], a box score summary of published findings about the efficacy of antidepressants may tend to overestimate the strength of the evidence [14]. The extreme view of this publication bias or 'file drawer problem' is that journals are filled with the 5% of the studies that show type I errors (i.e. falsely rejecting the null hypothesis), while the file drawers are filled with the 95% that show nonsignificant results [15]. Though this extreme state of affairs is unlikely, there is evidence of drug companies, which often have veto power in studies they fund, terminating studies before they are completed when results do not favor the study drug [16]. As many as 10–20% of fluoxetine trials go unpublished, a general problem in studies of all antidepressant clinical trials [17]. There is evidence that participation in industry-funded research may create a conflict of interest [18] that is associated with the increased likelihood of results favoring study drugs [19, 20] and with significant delays in publication, i.e. 28% of the time in an attempt to withhold undesirable results [21].

Placebo Washout or Run-In

Most antidepressant drug research includes a single-blind placebo 'washout' or 'run-in' phase that lasts 1 or 2 weeks before the study begins during which all prospective subjects are placed on placebo and taken off any antidepressant drugs [14]. Those prospective subjects who show improvement during the washout phase are eliminated from the pool of subjects prior to random assignment in accordance with standard practice for contemporary FDA clinical trials. The washout is designed to eliminate other antidepressant drugs from the body and to reduce the number of placebo responders. This is purportedly done to get a more accurate estimate of the 'true' drug response. Conservative estimates are that about 5% of patients diagnosed as having unipolar depression show a positive placebo response after 1 week of placebo washout [22]. The actual rate of washout participants who are excluded due to improvement appears to be as high as 20% [23].

The routine placebo washout procedure may selectively eliminate those individuals who tend to have a positive response to placebos. Any patient whose condition was worsened by a prewashout antidepressant would also be eliminated if improvement occurred during the washout. Thus, both drug nonresponders and placebo responders may be eliminated before the study begins. Even before the washout procedure, patients with a history of nonresponse to the study drug are routinely excluded. Therefore, the actual placebo response rate may be underestimated and the actual drug response rate may be overestimated in many antidepressant drug studies.

Nevertheless, two meta-analyses comparing studies that reported using a drug washout with studies that did not failed to reveal any evidence that a placebo washout lowered the placebo response rate, increased the drug-placebo difference or affected the drug response rate for outpatients or inpatients or for any antidepressant drug group [24, 25]. However, the definitive study addressing this issue is yet to be done. These meta-analyses relied exclusively on clinician measures and did not include the washout responders in the intent-to-treat outcome analysis. We are unaware of any studies that actually follow the course of the washout responders and count them in the intent-to-treat analysis. It would be illuminating to randomly assign washout responders to treatment conditions with all other subjects and subsequently analyze the data with and without washout responders to understand how such a procedure actually impacts a given study. In the meantime, we think that the practice of excluding patients during the washout procedure should be suspended due to the potential for distorting results in some studies. Knowing the 'true' rate of placebo responders may actually help provide a more accurate calculation of the 'true' drug effect.

Whether or not the placebo washout is disadvantageous to the placebo condition, the placebo response rate in over 30 years of double-blind placebo-controlled antidepressant efficacy studies has consistently been from 30 to 40%, and up to 50% in more recent studies, leading one

psychiatrist to suggest that placebo actually be used as the initial treatment for selected depressed patients [26].

The Integrity of the Double-Blind Procedure

The integrity of the double-blind procedure is open to question. Most controlled drug studies utilize inert placebos which can 'unblind' studies because clinician or patient raters may be able to tell who is receiving the active medication by detecting side effects [14, 27–29]. Guessing the correct condition may result in disparate expectations for positive results, thereby affecting outcome ratings or even outcome itself. Inadequate blinding procedures have been associated with bias and exaggerated effect estimates in other areas [30]. For example, in an outcome study of cocaine dependence, clinical evaluators' subjective ratings of treatment outcome were significantly different depending on whether the clinical evaluator had correctly guessed the patients' condition [31]. Using the same study pool reviewed by Morris and Beck [9], Thomson [32] reviewed 75 placebo-controlled double-blind studies of tricyclic antidepressants published between 1958 and 1972, only 7 of which used an active placebo (i.e. medications not considered antidepressants which produce side effects). Only one of the studies using an active placebo showed the antidepressant to have a superior outcome to the placebo. A more recent meta-analysis of similar literature found that 2 of 9 antidepressant studies using an active placebo (atropine) favored the active drug [33].

The potential for unblinding by side effects is a serious concern since most antidepressant drug studies rely primarily on clinician measures such as the Hamilton Rating Scale for Depression [34] and the Global Assessment Scale [35] rather than patient-rated measures like the Beck Depression Inventory [36]. It has been shown in an extensive meta-analysis [37] that, though they are highly correlated, patient ratings have a significantly smaller effect size than clinician ratings, i.e. patient raters tend to see less improvement than clinician raters. Murray [38] has concluded that patient-rated measures of depression are more objective and have better psychometric properties than clinician-rated measures.

Another meta-analysis [39] reviewed 22 controlled studies (n = 2,230) which compared a placebo (usually inert) with an older tricyclic antidepressant (i.e. imipramine or amitriptyline) and a newer nontricyclic antidepressant (i.e. amoxapine, maprotiline or trazodone). Even if the clinician rater were unblinded by side effects, he or she would presumably have greater difficulty distinguishing between the medication conditions or focusing bias, in effect making these studies somewhat 'blinder'. Overall, the older antidepressants and the newer antidepressants showed a small (average effect size of 0.25 and 0.31, respectively) advantage over placebo on clinician-rated measures. Interestingly, when using patient-rated outcome measures, the old antidepressants were not significantly more effective than placebo. The newer antidepressants did not fare much better. The effect sizes found in this meta-analysis of 'blinder' studies are far smaller than the effect sizes that had emerged from earlier meta-analyses of tricyclic antidepressants. These data suggest that relying on clinician ratings alone could lead to significant biases whenever the blind is penetrated and that patients may not experience improved outcome compared with placebo in blinder studies.

Despite the excitement about the selective serotonin reuptake inhibitors (SSRIs), recent meta-analyses show them to be no more effective than tricyclic antidepressants [11, 27, 40, 41]. In one meta-analysis [40], both clinician and patient outcome ratings correlated significantly with the percentage of patients experiencing side effects, suggesting that side effects may unblind these studies and bias outcome measures. This is likely to be a more serious problem for clinician ratings if the same clinicians evaluate both the drug and placebo groups. Also, the informed consent process is likely to sensitize both patients and clinicians about exactly what side effects to expect [42]. However, just because side effects are correlated with outcome, it does not necessarily follow that the study has been unblinded. It could be that side effects are correlated with a third variable, like blood levels of the drug, that causes good outcome. Additional studies may help shed light on this issue.

Blindness checks are reported in less than 5% of the psychotropic drug literature [43]. Fisher and Greenberg [44] conducted a worldwide literature search for psychotropic drug studies that evaluated whether or not the double-blind design had been penetrated. Of the 26 reports they were able to locate, 23 (88%) indicated that both patients and physicians were able to differentiate who was receiving the drug or placebo at rates significantly better than chance. An assessment of how blind raters remain and how unblinding affects outcome ratings is essential in order to evaluate the validity of the randomized controlled outcome study [33, 45]. We think that such an evaluation should become the standard for any study claiming double-blind methodology.

In clinical trials involving the antidepressants etaperidone and clomipramine, as many as 75% of patients were able to guess correctly whether they had been placed on

antidepressants or placebo and, of those experiencing side effects, as many as 100% were able to guess correctly [46]. Even an independent evaluator, blind to the therapeutic effects of the antidepressant etaperidone, was able to retrospectively distinguish which patients were taking the active drug and which were taking placebo on the basis of reported side effects alone [47]. The fact that the drug condition was unmasked without information about clinical response suggested that side effects are responsible and runs counter to the hypothesis that therapeutic drug effects cause the unblinding. Side effects have been implicated in other studies as a possible factor in the unmasking [27, 48].

A recent meta-analysis attempted to estimate the true antidepressant drug effect by calculating standardized mean response rates for 2,318 depressed patients who had been randomly assigned to either antidepressant medication or placebo in 19 double-blind clinical trials [49]. Using pretreatment assessments (on both clinician and patient ratings) as the comparison, mean effect sizes were 1.55 for the medication response and 1.16 for the placebo response. Across all types of medications, including comparison medications thought to be ineffective for depression, the inactive placebo response was about 75% of the active drug response. From these data it was concluded that only 25% of the drug response was associated with active drug administration, the rest being due to placebo response or nonspecific factors. Because drugs thought to be ineffective for depression showed similar effect sizes, the effect of the active drug may have been due to unblinding from side effects rather than any specific antidepressant effect. Also, the correlation between placebo effect and drug effect was 0.90, indicating that across studies virtually all of the variation in drug effect size was due to the placebo characteristics of the studies. A separate analysis of 19 psychotherapy studies involving 767 patients resulted in mean effect sizes of 1.60 for psychotherapy conditions and 0.37 for no-treatment controls.

Whether the drug response is a true pharmacological effect or an 'enhanced placebo' effect cannot yet be determined because of the relatively small number of studies in which an antidepressant has been compared to both an active and inactive placebo [49]. In order to establish the true drug and placebo responses, it may be necessary to implement four-cell studies using active placebo, inactive placebo, active medication and waiting list control [49]. Atropine, which produces anticholinergic side effects, has been used as an active placebo. A caffeine pill or an antihistamine like diphenhydramine, which mimic some antidepressant side effects, might also be good candidates for this purpose. Even small 'ineffective' antidepressant doses, large enough to cause side effects, have been suggested as a possible control [50].

Blinding is an issue in psychotherapy studies as well [31]. However, studies that claim to be double blind and are not (i.e. most drug studies using an inert placebo) may be more misleading than studies that do not make that claim (i.e. most psychotherapy outcome studies using a waiting list control). In order to get beyond arguments about which literature has better designed studies, randomized controlled studies that compare drugs and psychotherapy can shed light on the relative efficacy of these treatments. In some ways psychotherapy alone, a credible treatment without medical side effects, would seem to be a better comparison intervention for drug treatments than inert placebo. As it turns out, psychotherapy alone may be an even more potent treatment than psychotherapy plus placebo [51], perhaps because patients taking a pill may invest less in the psychological intervention [27] or they may attribute gain to an external agent rather than their own skills.

Antidepressants in Children

Finally, while the foregoing provides some evidence of antidepressant efficacy in adults, the efficacy of antidepressants in children has yet to be adequately demonstrated. Several recent literature reviews uniformly conclude that the preponderance of the evidence shows that tricyclic antidepressants are not more effective than placebo for depressed children or adolescents [23, 52–56]. These data are of particular concern given the estimated 6 million antidepressant prescriptions that are written for children each year [57]. Also of concern is anecdotal evidence of unexpected sudden death in several children on therapeutic doses of tricyclic antidepressants [58].

Regarding SSRIs in children, one controlled study found no advantage of fluoxetine over placebo in adolescent depression [59], while another controlled study found fluoxetine superior to placebo [60] on some clinician-rated measures but not on any patient-rated measures. This latter study spanned 8 weeks and randomly assigned 96 children (ages 7–17 years) with major depression to either fluoxetine or placebo. Any patients who had a history of an adequate trial of fluoxetine were excluded as were 29 patients who improved during the 3-week evaluation period, which included a 1-week single-blind placebo run-in. Despite these apparent relative advantages for the drug condition, complete symptom remission occurred in only 31% of fluoxetine patients and 23% of placebo-treated subjects, a nonsignificant difference.

In summary, industry-funded research studies which result in negative findings sometimes do not get published, placebo washout procedures may bias results in some studies, there are serious questions about the integrity of the double-blind procedure, the 'true' antidepressant drug effect in adults appears to be relatively small and there is minimal evidence of antidepressant efficacy in children.

Belief No. 2: Antidepressants Are Safe and Have Minimal Side Effects

Despite these questions about the efficacy of antidepressants, some patients prefer medications to other treatments and strongly believe in their effectiveness. By prescribing medication, a clinician may take advantage of any associated nonspecific and placebo effects. Also, antidepressants can be prescribed with certain side effects as a desired outcome. In other words, one person's side effect (e.g. sedation, weight gain or loss, ejaculation difficulties) is another person's positive treatment outcome (e.g. longer sleep, improved appetite or weight control, prolonged sexual pleasure). While most clinicians do understand the risk of side effects, they may not appreciate how annoying and distressing, perhaps even depressing, some of the 'minor' side effects can be.

Even at therapeutic levels there are many observed side effects of tricyclic antidepressants [61]. The anticholinergic side effects include dry mouth, blurred vision, urinary retention, constipation and delirium [62]. There may also be sedative effects, cognitive deficits, speech blockage, excessive perspiration, weight gain and dental caries (related to dry mouth). There is some evidence of risk for extrapyramidal symptoms, seizures, sleep disruption and mania, depending on the dose and type of antidepressant. The cardiovascular risks [63] include heart failure (especially with bundle branch block), hypertension, hypotension, arrhythmias and, rarely, sudden death [64]. Sexual side effects have commonly included decreased libido, erectile dysfunction and orgasm or ejaculatory impairment [65].

Use of antidepressants (primarily tricyclics) in medically ill inpatients has resulted in a 60% unfavorable response rate, with 32% of the patients discontinuing treatment due to significant side effects, the most common of which was delirium [66]. There is even suggestive evidence implicating the long-term use of psychotropic medication, including antidepressants, as a risk factor in the development of breast cancer [67].

Side effects and lack of efficacy cause substantial numbers of patients to drop out of treatment (30 to 60%), no matter which type of antidepressant is used [11, 27, 41, 68–70]. Though the SSRIs may be slightly more tolerable than the old tricyclic antidepressants, there is no evidence of better tolerability of the SSRIs compared with the newer tricyclic or heterocyclic drugs [71]. Dosing and the type of patient population being treated may have as much to do with tolerability as the type of antidepressant [17].

The side effects of most medications, including antidepressants, are severer in the elderly population. A panel of geriatric experts concluded that amitriptyline should be entirely avoided in patients over 65 years because of the serious risk for anticholinergic effects and orthostatic hypotension [72]. In the best designed available studies comparing SSRIs to other antidepressants in the elderly [70], about 76% of the SSRI patients experienced at least some side effects, 25% dropped out due to side effects and about 41% dropped out overall. These results occurred even though most of these studies used only relatively healthy subjects.

Safety

Research suggests that antidepressants are the most common agents used in suicide by poisoning [73] and have been involved in as many as half of serious adult overdoses [74]. However, suicide is a relatively rare event and there is no evidence that antidepressant drugs raise or lower the risk of suicide compared to psychotherapy or placebo treatment [27]. Although SSRIs have about the same risk of overdose as tricyclic antidepressants, death is a less likely outcome with the SSRIs [73].

While the SSRIs are safer than tricyclic antidepressants when used alone, combined with other medications they may be potentially more dangerous due to their pharmacodynamic and pharmacokinetic properties [17, 62, 75]. For example, they can be lethal at therapeutic doses when combined with MAO inhibitors. Fluoxetine has been shown to raise the plasma levels of clomipramine, desipramine, doxepin, nortriptyline, trazodone, amitriptyline and imipramine [76]. The scientific evidence supporting the efficacy of such drug combinations is scant and the practice may be ill advised [76]. Given that antidepressants are prescribed in combination with other psychotropic medications over half the time [5], it is not clear that the newer antidepressants will actually result in safer outcomes. Among drug-related deaths reported by medical examiners in the 1994 Drug Abuse Warning Network, fluoxetine was present and listed as a cause or contributory cause of death in 77 drug-related US suicides, a number

larger than that for doxepin or imipramine [77]. This same data source has been used to highlight the lethality of tricyclic antidepressants [73]. Other evidence [78] has suggested that use of SSRIs may lead to an increase in the concomitant prescribing of anxiolytics, a disturbing possibility given the finding that regular use of minor tranquilizers alone has resulted in worse outcomes than no depression treatment at all [79].

Serotonin syndrome, a potentially lethal neuromuscular activation, is another possible negative consequence of SSRIs, especially when they are combined with other serotonin-enhancing drugs [17, 80]. Serotonin syndrome, which has even been seen in pediatric patients, often results in an admission to an intensive-care unit and the need for artificial ventilation. At least 11 deaths have been attributed to serotonin syndrome [80].

SSRI Side Effects

Even when used alone at therapeutic levels, fairly common side effects (i.e. those experienced by between 5 and 30% of patients) of the SSRIs include nervousness, tremor, anxiety, sleep disruption, nausea, diarrhea, anorexia, loss of weight and sexual problems [17, 62]. In fact, more than half of the patients taking paroxetine or fluoxetine [81] experience at least some adverse gastrointestinal symptoms (nausea, diarrhea or appetite loss). The prerelease studies on SSRIs appear to have grossly underestimated the sexual side effects [82] which can include decreased libido, reduced arousal and diminished intensity or duration of orgasm. Such sexual side effects may affect as many as 73% of all patients who take them [83]. Sexual dysfunction can be a major source of unhappiness for those who experience it.

Though needing replication, the SSRIs have been found to increase the risk of miscarriage [84] and neonatal complications [85], a significant concern given that 67% of antidepressants are prescribed for women [5], many of child-bearing age. For a small minority of patients these new medications may carry a significant risk for mania, akathisia, extrapyramidal effects and even suicide induction [86–88], though the risk of fluoxetine-induced suicide and violence has not been supported by meta-analyses conducted by Eli Lilly and Company [89–91]. However, it can take a very long time for some serious but subtle side effects to be noticed. As an example, fenfluramine, a serotonin-enhancing drug which was popular for weight control, was used in Europe for more than 20 years before any drug-induced heart problems were recognized [92].

Withdrawal Symptoms

There is a well-documented withdrawal phenomenon associated with tricyclic medication, even when doses are gradually tapered [93]. The most common withdrawal symptoms, which may last up to 2 weeks following drug discontinuation, include general somatic or gastrointestinal distress (in as many as 21–55% of patients following withdrawal) with or without anxiety and agitation, sleep disturbance characterized by excessive and vivid dreaming and initial and middle insomnia, movement disorder, and psychic and behavioral activation extending on a continuum to mania. Children may be even more sensitive to tricyclic antidepressant withdrawal than adults [93].

A recent study found that 12% of patients discontinuing SSRIs reported adverse effects including dizziness, paresthesia, lethargy, nausea, vivid dreams, irritability and lowered mood [94]. In severe cases, dizziness was exacerbated by slight head or eye movements and associated with jerking or blurring vision. The majority of cases occurred despite slowly tapered withdrawal and the symptoms persisted for up to 21 days after onset. No withdrawal symptoms were recorded in patients who had been on the SSRI for less than 7 weeks.

In summary, side effects are fairly common even with the newer antidepressants, combining medication raises the risk for more serious complications and all antidepressants can cause withdrawal symptoms.

Belief No. 3: Antidepressants Are Necessary to Redress a Chemical Imbalance Caused by a Genetic Predisposition

It is estimated that somewhere between 9 and 18% of depressions are the result of an underlying medical condition [95, 96], suggesting that physical examination is important in the comprehensive treatment of depression. However, the vast majority of depressions are not attributable to identifiable medical causes. Other data suggest that genetic influences account for 16% of the variance in total depression scores [97], and that life experiences are the statistically most important influence on self-reported depressive symptoms [97] or clinician-assessed depressive disorder [98, 99]. Genetic influences on major depression, dysthymia and depressive adjustment disorder appear to be weak and cannot account for the increases in depression for age cohorts born after World War II [100].

Nevertheless, many promotional materials for antidepressants posit the existence of a genetically transmitted 'chemical imbalance' with the clear implication that

chemicals are required to correct this imbalance. Current biochemical theories propose that depression is caused by a deficiency of available serotonin or a disruption in the sensitivity of key serotonin receptors [101]. However, environmental influences have been at least as powerful as genetic influences on serotonin levels in primate studies [102], and other studies have not shown serotonergic activity to be lowered in depressive states [103].

The SSRIs were developed to correct the hypothesized deficiency by interfering with serotonin reuptake. However, the brain quickly (as soon as 2 days in animal studies) compensates for this increase in serotonin through the process of downregulation or reduction in the number of serotonin receptors [101, 104]. Though speculative, current theories suggest that antidepressant treatment returns the receptors to their normal sensitivity through this downregulation [105]. The permanence of these changes and the potential long-term consequences are not clear. Fava [106, 107] and Baldessarini [108] have speculated that the receptor changes, similar to those found in tardive dyskinesia, may in some cases be irreversible, and may increase the biological vulnerability to depression in some patients following drug withdrawal, especially after long-term use. Baldessarini [108] has suggested that since some studies show a shorter time to relapse after drug discontinuation than would be expected from pretreatment history and the rate of drug removal predicts the time to the first recurrent episode, the combination of long-term drug treatment followed by withdrawal may be a causal factor in depression recurrence. He goes on to raise the possibility that it may take months to reestablish a predrug level of neurophysiological and neuropsychological homeostasis. Further research is needed to evaluate this possible risk.

Closely related to the chemical imbalance hypothesis is the postulated need for adequate doses to achieve a therapeutic response [109]. However, the tricyclic antidepressant dose has not been related to outcome in a naturalistic study [110] and only weak relationships have emerged between plasma levels and clinical response to imipramine or amitriptyline [10, 111, 112]. Regarding the SSRIs, no relationship has been demonstrated between therapeutic response and dosage or plasma concentrations of the drugs [17, 27, 113]. The efficacy of antidepressants does not appear to be related to selectivity or potency for either norepinephrine or serotonin uptake blockade [101]. Despite years of experimentation, there is yet no convincing consistent evidence for disrupted receptor sensitivity in depressed patients (without a history of antidepressant treatment) or the biochemical theory of causation [27, 101] and the mechanism of action for antidepressants in treating depression has not been firmly established [101].

Biological markers for depression continue to be elusive. Some potential markers include abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis as measured by nonsuppression in the dexamethasone suppression test (DST), impaired lymphocyte glucocorticoid sensitivity and abnormal sleep EEG patterns [114]. While the baseline DST does not predict antidepressant treatment response or outcome after hospital discharge, research has suggested that the DST tends to return to normal as a result of antidepressant treatment [114, 115] or cognitive behavior therapy [116]. Abnormal DST results that persist after treatment and EEG sleep abnormalities have been associated with poor prognosis and higher relapse rates [114, 117].

However, HPA abnormalities have a relatively low prevalence limiting the practical utility of the DST [117]. EEG profiles may offer a somewhat more promising marker because sleep abnormalities are more common. EEG abnormalities were predictive of outcome in depressed patients treated with interpersonal therapy [117] but not in depressed patients treated with cognitive-behavioral therapy [118]. To date we are unaware of any randomized controlled trials comparing somatic and psychotherapeutic interventions with patients who have such sleep abnormalities.

Even if biochemical change is the goal, drug treatment may not be the only way to accomplish it. There is PET imaging evidence that improvement in cognitive therapy (in patients with obsessive-compulsive disorder) is associated with therapeutic alterations in brain chemistry similar to those found with medications [119]. Biondi [120] has suggested that it may be possible to conceptualize the positive effects of psychological treatments as acting at a biochemical level as is done with drug treatments. To support this idea, he cites consistent evidence that most of the classical neurotransmitters and neuropeptides are highly sensitive to emotional stressors. He also cites evidence of the therapeutic neuroendocrine impact of relaxation and social support.

In summary, genetic influences on unipolar depression appear to be weaker than environmental influences, biochemical theories of depression are as yet unproven, biological markers specific for depression have been elusive, dosage and plasma levels of antidepressants have been minimally related to treatment outcome, and there is preliminary evidence that patients who improve with cognitive-behavioral psychotherapy show similar biological changes as those who improve with drug treatments.

Belief No. 4: Antidepressants Are More Effective than Psychotherapy, Especially for Severe or Recurrent Depression

Several meta-analyses have evaluated controlled studies comparing antidepressants with psychotherapy or combined treatment. Bearing in mind the limitations of meta-analyses [121–123], these studies, involving thousands of depressed patients, have found that (1) psychotherapy has an outcome that is comparable [124, 125] or better [126, 127] than that of pharmacotherapy alone, (2) combined psychotherapy and drug treatment do not appear to be clearly superior to either therapy alone [124, 125, 128], (3) when the dropout rate is considered, pharmacotherapy alone has a substantially worse outcome than psychotherapy alone or combined treatment [129] and (4) treatment with cognitive therapy (with or without drugs) during the acute episode appears to reduce the risk of subsequent relapse following termination [124]. Several reviews have concluded that the preponderance of the evidence does not support the differential effectiveness of psychotherapy and antidepressants in more severely depressed nonpsychotic outpatients [27, 130–132]. Actually most drug studies exclude some of the most severely depressed (e.g. acutely suicidal) patients due to the risk of overdose.

In clinical practice, many patients are kept on antidepressants, usually prescribed by general practitioners, virtually indefinitely and at very high cost. One Nevada HMO found that patients on SSRIs, 80% of whom had never seen a psychiatrist, had been taking the antidepressants for an average of 3 years (over half for more than 9 months) without being withdrawn [133]. In studies advocating long-term maintenance on antidepressants for relapsers [134–139], recovery from depression has typically been defined in terms of symptomatic remission for a specified period of time [140]. For a patient to be considered recovered in these studies, there is no requirement that treatment be discontinued, even though the concept of recovery implies the possibility that treatment can be discontinued [114]. In this sense, patients who are both symptom free and drug free are equated with patients who are symptom free but receiving medication. From our perspective, it makes more sense to consider the latter group of patients to be in remission but not fully recovered until treatment is no longer necessary.

Even with full-dose maintenance drug treatment, as many as 40% of patients drop out or relapse [106]. The maintenance phase of treatment is conducted only with the responders. Since psychotherapy alone is not offered to patients initially in most of these studies, the maintenance phase of treatment is essentially restricted to drug responders and those patients who can tolerate the side effects. Baldessarini [108] suggests that the interpretation of findings in maintenance studies may be confounded by comparing patients with a pharmacologically induced placebo-associated risk with low-risk patients on continued treatment. Therefore, the patient samples in most drug maintenance studies should not be considered representative of the general population of depressed patients who have not first been medicated. Further, patients with drug refractory depression ought not to be considered treatment refractory if systematic psychosocial interventions have not been provided, especially given evidence that many of these patients may respond and maintain a good follow-up with cognitive-behavioral psychotherapy [141–143].

It has been shown that the therapeutic alliance is strongly and positively related to outcome in drug treatment, just as it is in psychotherapy [144]. One reason may be that the drug condition usually involves weekly contact combined with supportive psychotherapy [145], a higher level of drug treatment than is usually delivered in the typical outpatient setting. Further, more effective therapists are more psychologically minded, eschew biological interventions in their ordinary clinical practice and expect outpatient treatment of depression to take longer than do moderately and less effective therapists [146].

The comparative outcome literature almost exclusively involves tricyclic antidepressants. Currently under way are several NIMH-funded randomized clinical trials comparing cognitive-behavioral therapy and SSRIs. No current data suggest that the outcome will be any different from that of tricyclic drugs [27]. In one recent study comparing the efficacy of fluoxetine and cognitive therapy [147], after 16 weeks of treatment there were no statistically significant group differences in treatment response, though there was a trend for more patients assigned to fluoxetine to drop out than those assigned to cognitive therapy (33 vs. 9%).

Considering that cognitive-behavioral treatments can be successfully delivered in a group format [148–150] or even as bibliotherapy with minimal therapist contact [151–153] and good long-term outcome [154], psychotherapy can be very cost-effective. A recent cost-effectiveness analysis that considered acute outcome, long-term outcome, dropout rates, relapse rates and side effects concluded that individual cognitive-behavioral therapy alone would cost about 33% less than fluoxetine alone and 23% less than combined treatment over a 2-year period of standard treatment [155].

Conclusions

This paper has raised questions about the validity of double-blind placebo-controlled drug studies, the side effects and safety of medication interventions, evidence for biological theories of depression and the relative efficacy of medication treatments and psychotherapy. It is unfortunate that in any debate over the relative merits of psychological and biochemical approaches to depression, claims of disciplinary bias inevitably enter the discussion. This will likely occur despite the fact that the pioneers in the development of psychological interventions have come from both psychology (e.g. David Barlow, Albert Ellis, Myrna Weissman, Peter Lewinsohn, Donald Michenbaum, Lynn Rehm) and medicine (e.g. Aaron Beck, Herbert Benson, David Burns, Edmund Jacobson, Gerald Klerman, Isaac Marks, Joseph Wolpe). Recent depression treatment guidelines [156, 157] do not seem to adequately reflect this tradition or the scientific evidence supporting these interventions. Current practice guidelines are considered by some [27, 130–132] to be inconsistent with the scientific literature in that they overstate the benefits of antidepressant medications and the combined treatment, understate the risks and side effects associated with pharmacotherapy, and understate the efficacy of psychotherapy. For example, the AHCPR summary guidelines [156] recommend two unsuccessful trials of antidepressant medication before even considering referral for psychotherapy. The APA practice guidelines [157] recommend that most patients receive antidepressant medication combined with psychotherapeutic management or psychotherapy. Though the debate continues [158–161], perhaps it is time to carefully reevaluate these practices, which follow directly from the beliefs critiqued in this paper. Since a primary principle of the Hippocratic dictum is 'first, do no harm', an argument can be made that if there are alternative medically benign treatments of equivalent efficacy, they should be tried first. A new model [162] of collaboration between patient and doctor which promotes a healing partnership and enhances the patient's capacity for self-healing through psychotherapy may provide a safe and effective first choice.

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References

1 Amenson CS, Lewinsohn PM: An investigation into the observed sex difference in prevalence of unipolar depression. J Abnorm Psychol 1981;90:1–13.

2 Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen H, Kendler KS: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Arch Gen Psychiatry 1994;51:8–19.

3 Oliver JM, Simmons ME: Affective disorders and depression as measured by the diagnostic interview schedule and the Beck Depression Inventory in an unselected adult population. J Clin Psychol 1985;41:469–477.

4 Narrow WE, Regier DA, Rae DS, Manderscheid RW, Locke BZ: Use of services by persons with mental and addictive disorders: Findings from the National Institute of Mental Health Epidemiological Catchment Area Program. Arch Gen Psychiatry 1993;50:95–107.

5 Olfson MD, Klerman GL: Trends in the prescription of antidepressants by office-based psychiatrists. Arch Gen Psychiatry 1993;150:571–577.

6 Kramer P: Listening to Prozac. New York, Viking, 1993.

7 Davis JM, Wang Z, Janicak PG: A quantitative analysis of clinical drug trials for the treatment of affective disorders. Psychopharmacol Bull 1993;29:175–181.

8 Joffe R, Sokolov S, Streiner D: Antidepressant treatment of depression: A meta-analysis. Can J Psychiatry 1996;41:613–616.

9 Morris JB, Beck AT: The efficacy of antidepressant drugs: A review of research (1958 to 1972). Arch Gen Psychiatry 1974;30:667–674.

10 Quality Assurance Project: A treatment outline for depressive disorders. Aust NZ J Psychiatry 1983;17:129–146.

11 Song F, Freemantle N, Sheldon TA, House A, Watson, Long A, Mason J: Selective serotonin reuptake inhibitors: Meta-analysis of efficacy and acceptability. BMJ 1993;306:683–687.

12 Ioannidis JPA: Effects of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 1998;279:281–286.

13 Jadad AR, Rennie D: A randomized controlled trial gets a middle-aged checkup. JAMA 1998;279:319–320.

14 Greenberg RP, Fisher S: Examining antidepressant effectiveness: Findings, ambiguities, and some vexing puzzles; in Fisher S, Greenberg RP (eds): The Limits of Biological Treatments for Psychological Distress: Comparisons with Psychotherapy and Placebo. Hillsdale, Erlbaum, 1989, pp 1–37.

15 Rosenthal R: The 'file drawer problem' and tolerance for null results. Psychol Bull 1979;86:638–641.

16 Pushing drugs to doctors: Consumer Reports 1992, February, pp 87–94.

17 Gram LF: Fluoxetine. N Engl J Med 1994;331:1354–1361.

18 Campbell EG, Louis KS, Blumenthal D: Looking a gift horse in the mouth: Corporate gifts supporting life sciences research. JAMA 1998;279:995–999.

19 Cho MK, Bero LA: The quality of drug studies published in symposium proceedings. Ann Intern Med 1996;124:485–489.

20 Stelfox HT, Chua G, O'Rourke K, Detsky AS: Conflict of interest in the debate over calcium-channel antagonists. N Engl J Med 1998;338:101–106.

21 Blumenthal D, Campbell EG, Anderson MS, Causino N, Louis KS: Withholding research results in academic life science: Evidence from a national survey of faculty. JAMA 1997;277:1224–1228.

22 Loebel AD, Hyde TS, Dunner DL: Early placebo response in anxious and depressed patients. J Clin Psychiatry 1986;47:230–233.

23 Sommers-Flanagan J, Sommers-Flanagan R: Efficacy of antidepressant medication with depressed youth: What psychologists should know. Pro Psychol Res Prac 1996;27:145–153.

24 Greenberg RP, Fisher S, Riter JR: Placebo washout is not a meaningful part of antidepressant drug trials. Percept Mot Skills 1995;81: 688–690.

25 Trivedi MH, Rush J: Does a placebo run-in or a placebo treatment cell affect the efficacy of antidepressant medications? Neuropsychopharmacology 1994;11:33–43.

26 Brown WA: Placebo as a treatment for depression. Neuropsychopharmacology 1984;10: 265–269.

27 Greenberg RP, Fisher S: Mood-mending medicines: Probing drug, psychotherapy, and placebo solutions; in Fisher S, Greenberg RP (eds): From Placebo to Panacea: Putting Psychiatric Drugs to the Test. New York, Wiley & Sons, 1997, pp 115–172.

28 Hughes JR, Krahn D: Blindness and the validity of the double-blind procedure. J Clin Psychopharmacol 1985;5:138–142.

29 Margraf J, Ehlers A, Roth WT, Clark DB, Sheikh J, Agras WS, Taylor CB: How 'blind' are double-blind studies? J Consult Clin Psychol 1991;59:184–187.

30 Schulz KF, Chalmers I, Hayes RJ, Altman DG: Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408–412.

31 Carroll KM, Rounsaville BJ, Nich C: Blind man's bluff: Effectiveness and significance of psychotherapy and pharmacotherapy blinding procedures in a clinical trial. J Consult Clin Psychol 1994;62:276–280.

32 Thomson R. Side effects and placebo amplification. Br J Psychiatry 1982;140:64–68.

33 Moncrieff J, Wessely S, Hardy R: Meta-analysis of trials comparing antidepressants with active placebos. Br J Psychiatry 1998;172:227–231.

34 Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;12:56–62.

35 Endicott J, Spitzer RL, Fleiss JL, Cohen J: The Global Assessment Scale: A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976;33:766–771.

36 Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J: An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571.

37 Lambert MJ, Hatch DR, Kingston MD, Edwards BC: Zung, Beck, and Hamilton rating scales as measures of treatment outcome: A meta-analytic comparison. J Consult Clin Psychol 1986;54:54–59.

38 Murray EJ: Measurement issues in the evaluation of pharmacological therapy; in Fisher S, Greenberg RP (eds): The Limits of Biological Treatments for Psychological Distress: Comparisons with Psychotherapy and Placebo. Hillsdale, Erlbaum, 1989, pp 39–67.

39 Greenberg RP, Bornstein RF, Greenberg MD, Fisher S: A meta-analysis of antidepressant outcome under 'blinder' conditions. J Consult Clin Psychol 1992;60:664–669.

40 Greenberg RP, Bornstein RF, Zborowski MJ, Fisher S, Greenberg MD: A meta-analysis of fluoxetine outcome in the treatment of depression. J Nerv Ment Dis 1994;182:547–551.

41 Anderson IM, Tomenson BM: The efficacy of selective serotonin re-uptake inhibitors in depression: A meta-analysis of studies against tricyclic antidepressants. J Psychopharmacol 1994;8:238–249.

42 Brownell K, Stunkard A: The double-blind in danger: Untoward consequences of informed consent. Am J Psychiatry 1982;139:1487.

43 Ney PG, Collins C, Spensor C: Double blind: Double talk or are there ways to do better research? Med Hypotheses 1986;21:119–126.

44 Fisher S, Greenberg RP: How sound is the double-blind design for evaluating psychotropic drugs? J Nerv Ment Dis 1993;181:345–350.

45 Basoglu M, Marks I, Livanou M, Swinson R: Double blindness procedures, rater blindness, and ratings of outcome: Observations from a controlled trial. Arch Gen Psychiatry 1997;54: 744–748.

46 Bystritsky A, Waikar SV: Inert placebo versus active medication: Patient blindability in clinical pharmacological trials. J Nerv Ment Dis 1994;182:485–487.

47 White K, Kando J, Park T, Waternaux C, Brown WA: Side effects and the 'blindability' of clinical drug trials. Clin Res Reports 1992; 149:1730–1731.

48 Rabkin JG, Markowitz JS, Stewart J, McGrath P, Harrison, Quitkin FM, Klein DF: How blind is blind? Assessment of patient and doctor medication guesses in a placebo-controlled trial of imipramine and phenelzine. Psychiatry Res 1986;19:75–86.

49 Kirsch I, Sapperstein G: Listening to Prozac, but hearing placebo? A meta-analysis of antidepressant medication. Prev Treat;1998;1:0002a; www:http://journals.apa.org/treatment.

50 Rickels K: Use of placebo in clinical trials. Psychopharmacol Bull 1986;22:19–24.

51 Hollon SD, DeRubeis RJ: Placebo-psychotherapy combinations: Inappropriate representations of psychotherapy in drug-psychotherapy comparative trials. Psychol Bull 1981; 90:467–477.

52 Ambrosini PJ, Bianchi MD, Rabinovich H, Elia J: Antidepressant treatments in children and adolescents. I. Affective disorders. J Am Acad Child Adolesc Psychiatry 1993;32:1–6.

53 Dujovne VF, Barnard MU, Rapoff MA: Pharmacological and cognitive-behavioral approaches in the treatment of childhood depression: A review and critique. Clin Psychol Rev 1995;15:589–611.

54 Fisher RL, Fisher S: Antidepressants for children: Is scientific support necessary? J Nerv Ment Dis 1995;184:99–102.

55 Fisher RL, Fisher S: Are we justified in treating children with psychotropic drugs? in Fisher S, Greenberg RP (eds): From Placebo to Panacea: Putting Psychiatric Drugs to the Test. New York, Wiley & Sons, 1997, pp 307–322.

56 Hazell P, O'Connell D, Heathcote D, Robertson J, Henry D: Efficacy of tricyclic drugs in treating child and adolescent depression: A meta-analysis. BMJ 1995;310:897–901.

57 Goleman D: Use of antidepressants in children at issue. New York Times 1993, December 15, C17.

58 Riddle MA, Geller B, Ryan N: Another sudden death in a child treated with desipramine. J Am Acad Child Adolesc Psychiatry 1993;9:283–289.

59 Simeon JG, Dinicola VF, Ferguson HB, Copping W: Adolescent depression: A placebo-controlled fluoxetine treatment study and follow-up. Prog Neuropsychopharmacol Biol Psychiatry 1990;14:791–795.

60 Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, Rintelmann J: A double-blind randomized placebo-controlled trial of fluoxetine in depressed children and adolescents. Arch Gen Psychiatry 1997;54: 1031–1037.

61 McElroy SL, Keck PE, Friedman LM: Minimizing and managing antidepressant side effects. J Clin Psychiatry 1995;56(suppl 2):49–55.

62 Settle EC: Antidepressant side effects: Issues and Options. J Clin Psychiatry Monogr 1992; 10:48–61.

63 Jefferson JW: Treatment of depressed patients who have become nontolerant to antidepressant medication because of cardiovascular side effects. J Clin Psychiatry Monogr 1992;10:66–71.

64 Moir DC, Crooks J, Cornwell WB, O'Malley K, Dingwall-Fordyce I, Turnbull MJ, Weir RD: Cardiotoxicity of amitriptyline. Lancet 1972; ii:561–564.

65 Seagraves RT: Sexual dysfunction complicating the treatment of depression. J Clin Psychiatry Monogr 1992;10:75–79.

66 Popkin MK, Callies AL, Mackenzie TB: The outcome of antidepressant use in the medically ill. Arch Gen Psychiatry 1985;41:469–477.

67 Halbreich U, Shen J, Panaro V: Are chronic psychiatric patients at increased risk for developing breast cancer? Am J Psychiatry 1996; 153:559–560.

68 Anderson IM, Tomenson BM: Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: A meta-analysis. BMJ 1995;310:1433–1438.

69 Nelson J: Are the SSRIs really better tolerated than the TCAs for treatment of major depression? Psychiatr Ann 1994;24:628–631.

70 Menting JEA, Honig A, Verhey FRJ, Harmans M, Rozendaal N, de Vet HCW, van Praag HM: Selective serotonin reuptake inhibitors (SSRIs) in the treatment of elderly depressed patients: A qualitative analysis of the literature on their efficacy and side-effects. Int Clin Psychopharmacol 1996;11:165–175.

71 Hotopf M, Hardy R, Lewis G: Discontinuation rates of SSRIs and tricyclic antidepressants: A meta-analysis and investigation of heterogeneity. Br J Psychiatry 1997;170:120–127.

72 Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC: Explicit criteria for determining inappropriate medication use in nursing homes. Arch Intern Med 1991;151: 1825–1832.

73 Kapur S, Mieczkowski T, Mann JJ: Antidepressant medication and the relative risk of suicide attempt and suicide. JAMA 1992;268: 3441–3445.

74 Kathol RG, Henn FA: Tricyclics: The most common agent used in potentially lethal overdoses. J Nerv Ment Dis 1982;171:250–252.
75 Nemeroff CB, DeVane CL, Pollock BG: Newer antidepressants and the cytochrome P450 system. Am J Psychiatry 1996;153:311–320.
76 Taylor D: Selective serotonin reuptake inhibitors and tricyclic antidepressants in combination: Interactions and therapeutic uses. Br J Psychiatry 1995;167:575–580.
77 US Department of Health and Human Services: Annual Medical Examiner Data 1994: Data from the drug abuse warning network. DHHS Publication No. (SMA) 96–3078, 1996.
78 Rascati K: Drug utilization review of concomitant use of specific serotonin reuptake inhibitors or clomipramine with antianxiety/sleep medications. Clin Ther 1995;17:786–790.
79 Sturm R, Wells KB: How can care for depression become more cost-effective? JAMA 1995; 273:51–58.
80 Mills KC: Serotonin syndrome. Clin Pharm 1995;52:1475–1482.
81 Linden RD, Wilcox CS, Heiser JF, Cavanaugh E, Wisselink PG: Are selective serotonin reuptake inhibitors well tolerated in somaticizing depressives? Psychopharmacol Bull 1994;30: 151–156.
82 Gitlin MJ: Psychotropic medications and their effects on sexual dysfunction: Diagnosis, biology, and treatment approaches. J Clin Psychiatry 1994;55:406–413.
83 Modell JG, Katholi CR, Modell JD, DePalma RL: Comparative sexual side effects of bupropion, fluoxetine, paroxetine, and sertraline. Clin Pharmacol Ther 1997;61:476–487.
84 Pastuszak A, Schick-Boschetto B, Zuber C, Feldcamp M, Pinelli M, Sihn S, Donnenfeld A, McCormack M, Leen-Mitchell M, Woodland C, Gardner A, Horn M, Koren G: Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). JAMA 1993;269:2246–2248.
85 Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL: Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996; 335:1010–1015.
86 Lenhoff M: Potential complications of fluoxetine. VA Practitioner 1994;11:33–41.
87 Leo RJ: Movement disorders associated with the serotonin selective reuptake inhibitors. J Clin Psychiatry 1996;57:449–454.
88 Teicher MH, Glod C, Cole J: Emergence of intense suicidal preoccupation during fluoxetine treatment. Am J Psychiatry 1990;147: 207–210.
89 Beasley CM, Dornseif BE, Bosomworth JC, Sayler ME, Rampey AH, Heiligenstein JH, Thompson VL, Murphy DJ, Masica DN: Fluoxetine and suicide: A meta-analysis of controlled trials of treatment for depression. BMJ 1991;303:685–692.
90 Heiligenstein JH, Beasley CM, Potvin JH: Fluoxetine not associated with increased aggression in controlled clinical trials. Int Clin Psychopharmacol 1993;8:277–280.
91 Tollefson GD, Rampey AH, Beasley CM, Enas GG, Potvin JH: Absence of a relationship between adverse events and suicidality during pharmacotherapy for depression. J Clin Psychopharmacol 1994;14:163–169.
92 Lemonick MD: The mood molecule. Time 1997, September 29, pp 75–82.
93 Dilsaver SC, Greden JF: Antidepressant withdrawal phenomena. Biol Psychiatry 1984;19:237–256.
94 Coupland NJ, Bell CJ, Potokar JP: Serotonin reuptake inhibitor withdrawal. J Clin Psychopharmacol 1996;16:356–362.
95 Koranyi ED: Morbidity and rate of undiagnosed physical illnesses in a psychiatric clinic population. Arch Gen Psychiatry 1979;36: 414–419.
96 Hall RC, Popkin MK, Devaul RA, Fallaice LA, Stickney SK: Physical illness presenting as psychiatric disease. Arch Gen Psychiatry 1978;35:1315–1320.
97 Gatz M, Pedersen NS, Plomin R, Nesselroade JR, McClearn GE: Importance of shared genes and shared environments for symptoms of depression in older adults. J Abnorm Psychol 1992;101:701–708.
98 Kendler KS, Kessler RC, Walter EE, MacLean C, Neale MC, Heath AC, Eaves LJ: Stressful life events, genetic liability, and onset of an episode of major depression in women. Am J Psychiatry 1995;152:833–842.
99 Kendler KS, Walters EE, Kessler RC: The prediction of length of major depressive episodes: Results from an epidemiological sample of female twins. Psychol Med 1997;27: 107–117.
100 Blehar MC, Weissman MM, Gershon ES, Hirschfeld RMA: Family and genetic studies of affective disorders. Arch Gen Psychiatry 1988;45:289–292.
101 Richelson E: Biological basis of depression and therapeutic relevance. J Clin Psychiatry 1991;52(suppl):4–10.
102 Higley JD, Suomi SJ, Linnoila M: A nonhuman primate model of type II alcoholism? 2. Diminished social competence and excessive aggression correlates with low cerebrospinal fluid 5-hydroxyindoleacetic acid concentrations. Alcohol Clin Exp Res 1996;20:643–650.
103 Hallman J, Oreland L: Serotonergic mechanisms and psychiatric disorders. Nord Psykiatr Tidsskr 1989;43:53–59.
104 Cooper JR, Bloom FE, Roth RH: The Biochemical Basis of Neuropharmacology. New York, Oxford University Press, 1996.
105 Tollefson GD: Selective serotonin reuptake inhibitors; in Schatzberg AF, Nemeroff CB (eds): The American Psychiatric Press Textbook of Psychopharmacology. Washington, American Psychiatric Press Inc., 1995, pp 161–182.
106 Fava GA: Holding on: Depression, sensitization by antidepressant drugs, and the prodigal experts. Psychother Psychosom 1995;64:57–61.
107 Fava GA: Do antidepressant and antianxiety drugs increase chronicity in affective disorders? Psychother Psychosom 1994;61:125–131.
108 Baldessarini RJ: Risks and implications of interrupting maintenance psychotropic drug therapy. Psychother Psychosom 1995;63: 137–141.
109 Meterissian GB, Bradwejn J: Comparative studies on the efficacy of psychotherapy, pharmacotherapy, and their combination in depression: Was adequate pharmacotherapy provided? J Clin Psychopharmacol 1989;9: 324–339.
110 Brugha TS, Bebbington PE, MacCarthy B, Sturt E, Wykes T: Antidepressants may not assist recovery in practice: A naturalistic prospective survey. Acta Psychiatr Scand 1992; 86:5–11.
111 Kocsis JH, Hanin I, Bowden C, Brunswick D: Imipramine and amitriptyline plasma concentrations and clinical response in major depression. Br J Psychiatry 1986;148:52–57.
112 Simpson BM, White KL, Boyd JL, Cooper TB, Halaris A, Wilson IC, Raman EJ, Ruther E: Relationship between plasma antidepressant levels and clinical outcome for inpatients receiving imipramine. Am J Psychiatry 1982; 139:358–360.
113 Amsterdam JD, Fawcett J, Quitkin FM, Reimherr FW, Rosenbaum JF, Michelson D, Hornig-Rohan M, Beasley CM: Fluoxetine and norfluoxetine plasma concentrations in major depression: A multicenter study. Am J Psychiatry 1997;154:963–969.
114 Fava GA: The concept of recovery in affective disorders. Psychother Psychosom 1996; 65:2–13.
115 Ribeiro SCM, Tandon R, Grunhaus L, Greden JF: The DST as a predictor of outcome in depression: A meta-analysis. Am J Psychiatry 1993;150:1618–1629.
116 McKnight DL, Nelson-Gray RO, Barnhill J: Dexamethasone suppression test and response to cognitive therapy and antidepressant medication. Behav Ther 1992;23:99–111.
117 Thase ME, Buysee DJ, Frank E, Cherry CR, Cornes CL, Mallinger AG, Kupfer DJ: Which depressed patients will respond to interpersonal psychotherapy? The role of abnormal EEG sleep profiles. Am J Psychiatry 1997; 154:502–509.
118 Simons AD, Thase M: Biological markers, treatment outcome, and 1-year follow-up in endogenous depression: Electroencephalographic sleep studies and response to cognitive therapy. J Consult Clin Psychol 1992;60: 392–401.
119 Baxter LR, Schwartz JM, Bergman KS, Szuba MP, Guze BH, Mazziotta JC, Alazraki A, Selin CE, Ferng H, Munford P, Phelps ME: Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Arch Gen Psychiatry 1992;49:681–689.