Comorbid Alcoholism and Depression: Treatment Issues

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Unless there is decisive professional intervention, people who suffer from both a depressive disorder and alcoholism are at great risk of chronic impairment, both at home and in the workplace; persistent symptomatic misery; and premature death. Untreated alcoholism intensifies depressive states, decreases responsiveness to conventional therapeutics, and increases the likelihood of suicide, suicide attempts, and other self-destructive behavior. During the past decade, evidence has emerged from placebo-controlled studies supporting the utility of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) for treatment of depressed alcoholics. The superior safety and tolerability of SSRIs provide strong justification for their first-line use despite higher drug acquisition costs. Evidence has similarly emerged concerning the use of several novel pharmacotherapies and focused psychotherapies for people with alcoholism. These newer therapeutic options complement more traditional intervention such as chemical dependence counseling, disulfiram, and Alcoholics Anonymous so that it is now possible for a majority of depressed alcoholics to be treated effectively. The availability of effective treatments provides further impetus for health care professionals to improve recognition of comorbid alcoholism and depressive disorders. Improved recognition and treatment will save lives, and the benefits are likely to extend across generations.

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Periods of depression commonly complicate the course of alcoholism, and most people who are withdrawing from alcohol experience insomnia and dysphoria.[1–3] Conversely, a substantial minority of people with mood disorders subsequently develop episodic alcohol abuse or dependence.[4] Without definitive intervention, comorbid alcoholism and depressive disorders are associated with an elevated risk of suicide,[5] and conventional therapeutics may be less effective for patients with this comorbidity than for other patients.[1] Although depressive syndromes associated with alcohol withdrawal states often resolve within days or a few weeks without specific treatment,[6] clinicians may not have the luxury of taking a "wait and see" approach, particularly if the depressed alcoholic's insomnia, subjective despair, or psychomotor agitation necessitate symptomatic intervention. Given the safety of most newer antidepressants, overly restrictive treatment plans that require an arbitrary number of sober weeks before prescription of an antidepressant may run the risk of unnecessarily prolonging the patient's suffering and disability. For most comorbid alcoholism-depression patients, the best intervention includes chemical dependence counseling and involvement in self-help programs (i.e., Alcoholics Anonymous [AA]) in addition to medication management. This article describes such a comprehensive approach to treatment. For simplicity's sake, the term *alcoholism* is used throughout the article to describe alcohol dependence and abuse unless the distinction has specific treatment implications.

RECOGNITION

The comorbidity of depression and alcoholism is frequently overlooked in treatment settings with a general focus, including both primary care and psychiatric clinics. Both conditions are stigmatized, and there is a tendency to

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focus on the presenting symptoms, which more typically fall within the depressive syndrome. Clinicians sometimes unwittingly reinforce patient denial by not asking even the most basic questions about substance usage patterns.

It is a good basic practice to ask all patients seeking treatment about their use of alcohol and prescription and nonprescription (illicit) drugs. A number of simple screening scales, including the Short Michigan Alcoholism Screening Test,[7] the CAGE questionnaire,[8] and the Alcohol Use Disorders Identification Test,[9] are available to facilitate detection. All patients beginning antidepressant therapy should also be counseled to abstain from alcohol use at least until treatment is well established and there are clear-cut symptomatic benefits.

The inability to refrain from drinking during the course of treatment sometimes provides the first unequivocal evidence that a patient's alcohol use has crossed over into the pathologic range. Of course, even in this scenario the patient may not be able to admit that there is a problem. A "don't ask, don't tell" policy may permit such life-threatening and treatment-defeating behavior to continue. Therefore, it is useful to inquire periodically about drug and alcohol use patterns throughout a course of treatment and to always consider unrecognized alcoholism or substance abuse as a potential causal factor if treatment is not working, is tolerated poorly, or fails after an initial period of success.

TREATMENT PHASES

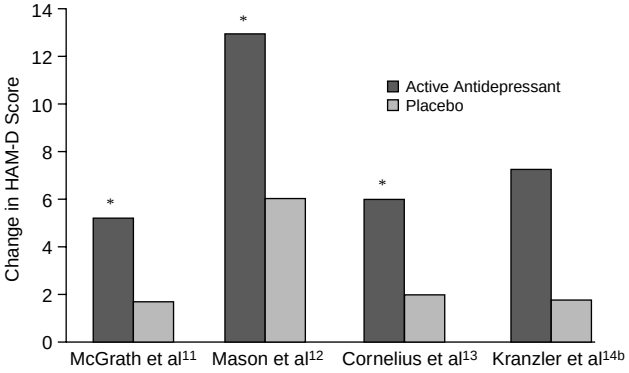
Treatment of comorbid alcoholism and depression can be conceptualized in 3 phases: (1) an acute phase that is focused on engagement, detoxification, and symptom stabilization; (2) a continuation phase that targets sustained sobriety and remission of residual depressive symptoms; and (3) a maintenance phase that is intended to support recovery and prevent relapse or recurrence of both disorders.[10]

ACUTE PHASE TREATMENT

Antidepressant medication and symptom-focused psychotherapy have little chance for success if the depressed patient continues to drink heavily. Managing alcohol withdrawal and establishing sobriety are thus high priorities early in the course of acute phase therapy.

Whereas inpatient and residential programs were once widely considered to be the settings of first choice to initiate treatment of the comorbid patient, ambulatory programs are increasingly utilized for detoxification and initiation of acute phase antidepressant therapy.[1] Such an emphasis on ambulatory services reduces the cost of care, although the treating physician must assume extra responsibility to ensure that the potential medical and psychiatric risks of unsupported alcohol withdrawal are not overlooked.[1,10] When outpatient treatment is feasible, we recommend a treatment team approach involving an addiction recovery counselor, a physician (preferably a psychiatrist), and an informed self-help program that addresses comorbid alcoholism (a "double trouble" program) and will support professional treatment of a psychiatric illness. This approach to treatment requires close coordination of care, as well as the availability of after-hours crisis services to provide an emergency "safety net."

Figure 1. Side-By-Side Comparison of Outcomes of Placebo-Controlled Studies of Antidepressant Treatment of Alcoholics With Major Depressive Disorder[a]



[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
[b]Only 14% of the sample met the criteria for major depression.
*$p < .05$.

Efficacy of Antidepressants in Comorbid Alcoholism and Major Depression

Depressed patients with alcoholism are almost always excluded from studies of new antidepressants. The onus for funding relevant treatment research in the United States thus falls squarely on the National Institutes of Health, and there can be only a limited number of these highly competitive grants. As a result, there is a dearth of evidence concerning treatment of comorbid disorders. Four well-controlled studies published in the 1990s provide the best evidence that antidepressants can have meaningful benefits for depressed alcoholics.[11–15] In the study by McGrath et al.,[11] 69 outpatients with primary depression (i.e., the mood disorder diagnosis clearly preceded the onset of alcoholism or followed at least 6 months of sobriety) were randomly assigned to 12 weeks of double-blind therapy with the standard tricyclic antidepressant (TCA) imipramine (mean ± SD dose = 262 ± 43 mg/day; range, 150–300 mg/day) or placebo. All patients received chemical dependence counseling. Results indicated a significant effect on depressive symptoms (Figure 1), but the drug-placebo differences were not statistically significant on measures of alcohol intake in the overall sample. However, among those who responded to imipramine, there were large reductions in alcohol intake.

In the second controlled study, Mason et al.[12] studied 71 outpatients with primary alcohol dependence and a range of depressive symptoms. Patients were randomly assigned

to up to 6 months of double-blind therapy with desipramine (mean dose for completers = 200 mg/day) or placebo. Patients received chemical dependence counseling in addition to pharmacotherapy. The sample was stratified on the basis of the presence (N = 28) or absence (N = 43) of comorbid major depressive disorder. All depressed patients had remained symptomatic for at least 1 week after detoxification.

Mason et al.[12] found significant effects for desipramine therapy on measures of both depressive symptoms (see Figure 1) and alcohol use. However, desipramine therapy had little effect on both minor depressive symptoms and alcohol consumption for the patients who did not meet criteria for syndromal depression. Among the subgroup of depressed patients who completed the study (N = 22), 4 (40%) of the 10 patients randomly assigned to placebo had an alcohol relapse, as compared with only 1 (8.3%) of the 12 patients treated with desipramine.

In the third report, Cornelius et al.[13] examined the selective serotonin reuptake inhibitor (SSRI) fluoxetine (20–40 mg/day) in a placebo-controlled study of 51 depressed alcoholics. All patients were initially hospitalized; 90% had suicidal ideation and 35% were admitted following a suicide attempt. The patients had remained depressed following detoxification and a 1-week medication-free washout. The first 2 weeks of double-blind treatment were provided in the hospital before discharge to ambulatory care. While in the hospital, all patients participated in daily group therapy sessions. Following discharge, patients received 10 weekly chemical dependence counseling sessions. Both patients with "primary" and "secondary" depressive syndromes were enrolled, although the vast majority of this severely symptomatic study group had chronic substance abuse problems that antedated the onset of the major depressive disorder. Cornelius et al.[13] reported a significant effect favoring active fluoxetine over placebo on the Hamilton Rating Scale for Depression (HAM-D) (see Figure 1) and Global Assessment Scale. The effect was not statistically significant on the self-reported Beck Depression Inventory (BDI), despite a comparable difference in mean scores, because of larger intersubject variabilities. Fluoxetine therapy also was associated with significantly greater reductions on most measures of alcohol intake. Despite these significant benefits, however, only 25% of the fluoxetine group remained totally abstinent during the 12-week trial, which was not statistically significantly greater than the 15% abstinence rate in the placebo control group.

In the fourth placebo-controlled study, Kranzler et al.[14] evaluated fluoxetine (20–60 mg/day) treatment of alcoholism in 101 outpatients with minimal-to-moderate depressive symptoms. Only 14% of the sample met criteria for a current diagnosis of major depression, so the primary analyses of efficacy focused on the HAM-D and BDI as continuous outcome measures. Patients received concomitant chemical dependence counseling sessions. The investigators found a significant 3-way interaction (i.e., time by medication by current major depression) on the HAM-D, which reflected that fluoxetine had a significantly greater effect than placebo on depressive symptoms among the patients with current major depression (see Figure 1), but not among the large majority of nondepressed patients. This difference did not reach significance on the BDI, although with only about 5 depressed patients per treatment group, statistical power was minuscule. Unlike the findings of Cornelius et al.,[13] the effect of fluoxetine treatment on alcohol intake was not statistically significant. The lack of effect of fluoxetine on alcohol intake was probably found because so few depressed alcoholics participated in the Kranzler et al.[14] trial.

In summary, the results of 4 placebo-controlled studies confirm that antidepressant treatment has significant effects on comorbid depressive symptoms regardless of whether alcoholism was the primary or secondary disorder. Both noradrenergic and serotonergic antidepressants showed therapeutic effects. The effects of antidepressant treatment on alcohol use were less consistent, however, and appeared to be contingent on an antidepressant effect. Moreover, even when alcohol intake was suppressed by pharmacotherapy, the average patient did not achieve sustained abstinence.

Selecting an antidepressant. The data from controlled studies indicate that an initial antidepressant trial with a TCA or SSRI will help between 40% and 50% of depressed alcoholics. The probability of response is maximized by sobriety, adherence, careful monitoring, and cautious titration of medication to maximally tolerated therapeutic doses across 6, 8, or even 12 weeks of acute phase treatment. The SSRIs have become the antidepressants of first choice for depressed alcoholics for a number of very good reasons. When compared with their commonly prescribed predecessors, the TCAs, the SSRIs are more readily prescribed at therapeutic doses, better tolerated by the average patient, and profoundly safer in overdose.[15] The high lifetime suicide risk of depressed alcoholics makes the latter characteristic a compelling strength. The SSRIs may have an additional pharmacologic advantage over the more noradrenergic TCAs, namely, a potentially broader spectrum of effects on disturbances linked to impulsivity, compulsivity, anxiety, and irritability or aggressivity.[10,16]

The SSRIs are grouped together because of presumed mechanism of action, not structural similarity. Within the SSRI class there are several important pharmacokinetic and clinical differences that can influence drug selection. However, no one agent is preferred uniformly over the others. Differences are found in elimination half-lives, the therapeutic activity of metabolites, linearity or nonlinearity of dose–blood level relationships, selectivity (i.e., secondary effects on dopamine or norepinephrine reuptake in addition to serotonin reuptake), and effects on various cytochrome P450 isoenzymes[15] (Table 1). Among the 5 SSRIs, fluvoxamine is approved by the United States Food and Drug Administration (FDA) only for treatment of obsessive-compulsive disorder, not for depression. Three of the

Table 1. Comparative Pharmacokinetic Properties of Selective Serotonin Reuptake Inhibitors[a]

Value	Fluoxetine	Paroxetine	Sertraline	Fluvoxamine	Citalopram
Typical dose, mg/d	10–60	20–50	50–200	50–300	20–60
Active metabolites	Norfluoxetine	None	*N*-desmethylsertraline[b]	None	None
Elimination half-life					
Parent drug	2–3 d	21 h	26 h	15 h	35 h
Active metabolite	7–9 d	…	2–4 d	…	…
Steady state	30–60 d	4–5 d	4–5 d	3 d	7–8 d
Linearity	Nonlinear	Nonlinear	Linear	Nonlinear	Linear
Protein binding, %	> 95	> 95	> 95	≈ 77	≈ 80
Age effect[c]	Yes	Yes	Yes	No	No
Hepatic disease[d]	× 3	× 1.8	× 2	× 1.6	× 2
Renal disease[d]	No	No	× 1.5	No	No
Cytochrome P450 inhibitory effect	Yes	Yes	No	Yes	No

[a]Adapted from Sachs and Thase.[17]
[b]Activity of metabolite is markedly lower than that of parent compound.
[c]Increased levels in the elderly.
[d]Increases levels (× 2 = 2-fold elevation).

SSRIs, fluoxetine, sertraline, and paroxetine, have received FDA approval for additional indications that overlap with mood disorders, such as bulimia, premenstrual dysphoric disorder, social phobia, and panic disorder. Recent studies[18,19] suggest that citalopram may also have efficacy for these conditions. None of the SSRIs have received approval for treatment of alcoholism.

The long elimination half-life of norfluoxetine, the principal active metabolite of fluoxetine, can be both a limitation and a strength.[15] When therapy is not effective, norfluoxetine levels may persist for weeks or even several months after the medication is withdrawn. This long elimination half-life could complicate the transition to another medication and flatly contraindicates use of a monoamine oxidase inhibitor (MAOI) for at least a month. When fluoxetine therapy is effective, however, the long elimination half-life of norfluoxetine provides a protective "cushion" against intermittent or occasional noncompliance. This can be an asset for treatment of a noncompliance-prone population, such as those with alcoholism. Moreover, fluoxetine is the least likely medication within the SSRI class to be associated with a discontinuation syndrome after abrupt cessation.[20]

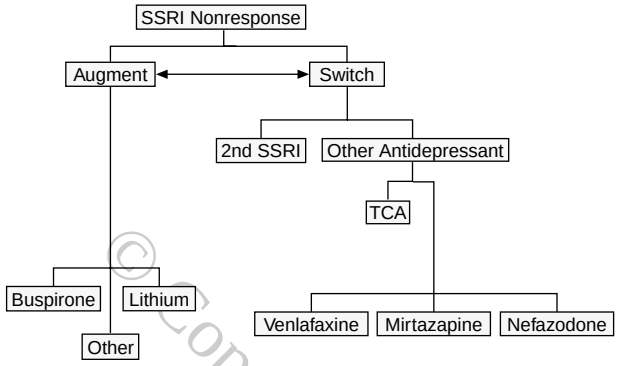
All things considered, sertraline and citalopram have less complicated pharmacokinetic and metabolic profiles than the remainder of the SSRI class.[15,21] Such metabolic simplicity is an advantage for treatment of patients with frank or incipient liver disease. Citalopram may also have a slight advantage over the other SSRIs with respect to incidence of side effects,[21] but this issue has not been resolved definitively, and there are too few comparative trials to ensure that issues such as dose titration have been fairly balanced. Further, small differences in grouped data should not obscure the fact that individual patients respond better to one SSRI over another.

The major drawbacks of SSRI therapy are cost (in the United States, all 5 SSRIs are still patent-protected) and serotonergically mediated side effects. Cost will become less of an issue in a few years as some of the SSRIs become available in generic form. In the short run, headache, tremor, nausea or other gastrointestinal side effects, sexual dysfunction, and anxiety/insomnia are the most prevalent side effects.[15] In our experience, recently detoxified alcoholics tend to be less tolerant of SSRI side effects than other groups of depressed patients, even though hepatic enzyme induction may result in lower blood antidepressant levels. Tremor, "jitters," and insomnia can be particularly problematic. We suspect that prolonged alcohol intake alters postsynaptic serotonin receptors, perhaps resulting in a state of increased receptor sensitivity. Management of such sensitivity begins with psychoeducation (forewarned is forearmed) and can include prescription of lower initial doses, slower subsequent dose titration, and, if necessary, cotreatment of side effects.

Concerns surfaced a number of years ago that the SSRIs, and fluoxetine in particular, might provoke a paradoxical increase in suicidal ideation and behavior.[22] Published case reports and provocative news stories provided the material for various antipsychiatry groups to promulgate the apparent dangers of SSRI treatment. There is no doubt that a small percentage of people who begin antidepressant therapy subsequently complete suicide or behave violently. As noted previously, depressed people with comorbid alcohol or drug use problems are at particularly high risk for violent or self-destructive behavior. However, after more than a decade of study, there is no evidence of a direct link between initiation of SSRI treatment and provocation of suicidal or violent behavior.[15] In fact, there is evidence that following the introduction of fluoxetine, a disproportionate percentage of depressed patients with a prior history of violent or suicidal behavior were treated with this medication (relative to TCAs) because of its more favorable safety profile.[23]

Nevertheless, there is little doubt that our patients' ambivalence about taking psychotropic medications can be heightened by negative publicity. The potential risks of

Figure 2. Management of SSRI-Resistant Major Depression in Alcoholics: Alternate Antidepressant Strategies[a]



[a]Abbreviations: SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

treatment must always be balanced against the compounded hazards of untreated depression and alcoholism. Initiation of antidepressant therapy should include an open discussion about what the patient may have heard about the danger of treatment. Written materials may help to enhance knowledge about the disorders and treatment, but should not replace doctor-patient communication. Whenever possible, it is a good idea to involve significant others in these discussions.

For patients with comorbid alcoholism and depression who do not respond to the first SSRI, we often recommend at least one within-class switch before considering other options (Figure 2). In depressed patients, such a strategy has been shown to be effective in approximately one half of patients who either do not respond to or tolerate the first SSRI prescribed.[24,25] This conservative strategy is based on the lack of data pertaining to other options aside from the TCAs. If a second SSRI is not effective or if there is only partial symptom remission, an attempt to augment the antidepressant can be considered. For example, ensuring optimal thyroid function (i.e., a below-median thyrotropin value and an above-median free thyroxine [T_4] value) by prescription of adjunctive levothyroxine or liothyronine occasionally will convert a nonresponse into a remission. Many other augmentation strategies are sometimes helpful.[26] Lithium augmentation has a well-established empirical track record for TCA nonresponders,[27] although this strategy has not been studied extensively with the SSRIs. In our experience, increased sensitivity to lithium-induced side effects (such as tremor and sedation) can be problematic, and we recommend use of low doses initially (e.g., 300 or 450 mg/day) and slow upward titration.

Buspirone augmentation therapy may have particular promise because of its direct anxiolytic effects. In addition, buspirone is not habit forming and does not potentiate the effects of alcohol.[28,29] Some research suggests that buspirone may have a weak suppressant effect on the alcohol intake of anxious patients.[28] Buspirone cotherapy also may counteract selected SSRI sexual side effects.[29] In our experience, the dose-response relationships of buspirone are unpredictable, and clinical responses can be seen at doses that range from quite low (i.e., 5 mg b.i.d.) to remarkably high (i.e., 20 mg t.i.d.).

Anxiety and insomnia that persist despite SSRI therapy sometimes justify coprescription of benzodiazepines such as clonazepam or lorazepam. Although acute symptom-reducing effects are indisputable, concomitant benzodiazepine therapy runs the obvious risks of abuse, cross-dependence, and potentiation of alcohol intoxication. Benzodiazepines and SSRIs, while generally safe in overdose when taken alone, also have much greater lethality when ingested with alcohol. Benzodiazepines therefore must be prescribed judiciously and monitored carefully, and the rationale for therapy must be well documented.

Antidepressants that are not habit forming, such as low doses of sedating TCAs, trazodone, and mirtazapine, are often preferred to the benzodiazepines for adjunctive treatment of insomnia. γ-Aminobutyric acid (GABA) agonists such as divalproex sodium or gabapentin are also sometimes prescribed empirically and may help to improve control of subtle "mixed" symptoms.[10,30] These anticonvulsant agents may, of course, have additional benefits during the acute postdetoxification period.

The switch to monotherapy with other newer antidepressants (e.g., venlafaxine, nefazodone, or mirtazapine) may be considered instead of augmentation. Mirtazapine and nefazodone should be considered for SSRI-intolerant patients because these agents are less likely to elicit similar side effects.[15] Among all of the newer antidepressants, mirtazapine and nefazodone also have the most beneficial effects for insomnia.[15]

Physicians are less likely to prescribe bupropion to depressed alcoholic patients because of the risk of lowering seizure threshold. In fact, the manufacturers of bupropion list a history of seizures or head injury to be contraindications to therapy. Bupropion also may have less coverage for co-occurring panic-anxiety symptoms,[31] although this point remains controversial. Nevertheless, the effectiveness of bupropion for nicotine addiction, as well as its utility for bipolar spectrum depressions, justifies its consideration for some patients.

TCAs, MAOIs, and electroconvulsive therapy are typically held in reserve for more severely ill, treatment-resistant patients. MAOIs must be used quite judiciously with alcoholics because of the potentially lethal interaction with tyramine-rich alcohol beverages, including red wine, beer, and other "colored" spirits (e.g., whiskey, rum, and most liqueurs).

Pharmacotherapy of Alcoholism

Failure to respond to appropriate antidepressant therapy may indicate the need for more intensive pharma-

cologic management of the alcoholism or associated addictions. For example, in our group's placebo-controlled study of fluoxetine treatment of comorbid alcoholism-depression, patients who abused cocaine were essentially refractory to study treatments.[32] Adjunctive strategies, including disulfiram[33] and naltrexone,[34] are probably underutilized and can make a world of difference for particular patients.

Disulfiram (125 to 500 mg/day) alters alcohol metabolism by inhibition of the enzyme aldehyde dehydrogenate. The rapid accumulation of acetaldehyde after ingestion of alcohol can deter relapses by causing dysphoria, severe nausea, and vomiting. The oldest pharmacologic strategy for alcoholism still in use, disulfiram therapy essentially establishes a response-cost paradigm that does not lessen craving but, rather, imposes an explicit, harsh, and nearly immediate consequence for drinking. The main problem with this type of contingency is that the plan can be readily subverted by not taking disulfiram for 1 to 2 days before a planned lapse.

The effects of disulfiram also can be unpredictable, and some people are so sensitive that the minute amounts of alcohol absorbed from a mouthwash, perfume, or aftershave can induce a reaction. Disulfiram has a number of interactions with medications that can complicate therapy, and it is contraindicated for patients with liver disease. There are also case reports suggesting that disulfiram therapy can induce psychosis and exacerbate depression. Together, these problems further limit its potential utility. There are, nevertheless, some patients who are able to safely adhere to disulfiram therapy, and, for those patients, the benefits of disulfiram greatly outweigh the hazards.

Naltrexone (50–100 mg/day)[34] is a selective opiate receptor antagonist that probably reduces alcohol consumption by altering central reinforcement mechanisms. Naltrexone is usually well tolerated, and more than 90% of patients are able to complete a 6- to 8-week trial of therapy. The principal side effects of naltrexone therapy are nausea, anxiety, and headaches. For the patient with concomitant opiate addiction, naltrexone will precipitate opiate withdrawal. Moreover, naltrexone therapy will antagonize the therapeutic effects of narcotic analgesics. Naltrexone does not appear to have significant interactions with commonly prescribed antidepressants,[35] nor does it interact with alcohol.

In a pilot study by our group,[36] 14 depressed alcoholics who continued to drink heavily despite antidepressant therapy (fluoxetine, N = 10; paroxetine, N = 2; sertraline and nefazodone, N = 1 each) were treated for up to 12 weeks with naltrexone, 50 mg/day. Patients also received individual chemical dependence counseling. Although the addition of naltrexone had minimal antidepressant effects, alcohol intake decreased markedly. Eight patients (58%) were judged to be responders. Continued heavy drinking was associated with a failure of naltrexone therapy to curb alcohol-related cravings or urges. This finding might indicate that higher than usual naltrexone doses could help some nonresponders. A confirmatory double-blind study is now underway at the University of Pittsburgh.

A third option, the GABA analogue acamprosate (2000 mg/day),[37] is available in Europe and should be approved for use in the United States within the next few years. The principal side effects of acamprosate therapy are itching and loose stools. We have prescribed acamprosate only to patients in double-blind clinical trials, which excluded patients with comorbid depression. However, acamprosate is not known to affect hepatic metabolism and would not be expected to interact negatively with antidepressants. Acamprosate also does not have appreciable central nervous system toxicity, which should be an asset for treatment of comorbid mood disorders.

Psychosocial Therapies

Psychotherapy and counseling options for the depressed alcoholic include chemical dependence counseling, more traditional dynamically oriented therapies, cognitive-behavioral therapies, and brief interventions designed to enhance motivation for sobriety. These treatment options vary with respect to cost, complexity, and the requisite clinical experience and psychotherapeutic sophistication of the provider. Both group and individual formats are utilized. Although group interventions are likely to be less costly, the treatment provider should keep in mind that many recently detoxified alcoholics are struggling with issues of shame or uncovered social anxiety that may render group therapy more aversive or less acceptable than anticipated.

There are no studies of comparative effects of different psychotherapies for depressed alcoholics. In the largest study of psychosocial treatment of alcoholism, a brief motivation-enhancing intervention was as helpful as more intensive cognitive-behavioral or 12-step models of intervention.[38] A parallel finding emerged in the largest study of psychosocial treatments of cocaine addiction: the combination of individual and group addiction recovery counseling was significantly more effective than group counseling in combination with individual cognitive-behavioral or dynamically oriented therapies.[39]

It is not clear that these rather pessimistic data will generalize to patients with comorbid depressive disorders. In an early study of methadone-maintained opiate addicts, for example, patients with significant affective symptomatology did show extra symptomatic benefits when cognitive-behavioral or dynamic therapies were added to standard care.[40] The key difference between the studies of cocaine and heroin addiction may be the use of methadone to quell the cravings and physiologic withdrawal symptoms of the heroin addicts. Specifically, if the neurobiological intensity of the addiction can be controlled pharmacologically, the patient may be better able to allocate his or her cognitive-

affective-interpersonal resources to counseling or psychotherapy. Concomitant treatment with naltrexone or acamprosate may thus facilitate the depressed alcoholic's participation in psychotherapy.[34]

In the absence of definitive data, we recommend that all depressed alcoholics be offered psychosocial intervention that includes group or individual addiction recovery counseling. Further, all treatment interventions should incorporate the motivation enhancement strategies[38] early in the course of treatment. Psychosocial interventions also should not be viewed as an alternative to participation in AA or a comparable self-help program.

Combining Psychotherapy and Antidepressants

Although many psychiatrists consider combined psychotherapy and pharmacotherapy to be the best treatment plan for most depressed patients, evidence from controlled studies of (nonalcoholic) depressed outpatients generally do not reveal large, additive effects that would offset the greater cost of the combination.[41] In the absence of stronger data, we typically recommend that comorbid patients receive antidepressants in combination with chemical dependence counseling rather than individual psychotherapy. The best evidence of additive psycotherapy effects in studies of major depressive disorder comes from studies of more impaired patient groups, including those in severe, recurrent,[42] or chronic[43] depressive episodes. These data suggest that patients who have not responded to standard treatment plans may be the most likely to benefit from addition of psychotherapy.

Improving Adherence

The optimal treatment plan for a depressed alcoholic thus may include (1) pharmacotherapy with antidepressants, (2) pharmacologic adjuncts to lessen cravings and/or inhibit alcohol intake, (3) self-help programs, (4) group and individual counseling, (5) psychotherapy, or (6) all of the above. All of these approaches are useless, however, without the patient's participation. Recognition of the patient's readiness for change is a key starting point. This is particularly important because treatment may have been imposed or coerced by a family member, employer, or legal agency. If treatment is mandated before the patient is ready to consider change (sometimes called the "precontemplative stage"[44]), it is useful to help the patient to recognize explicitly his or her reasons for continued drinking in addition to exploring the potential reasons for stopping. Often, a lack of confidence in one's ability to stop drinking (i.e., low self-efficacy) underpins what appears to be defiance or disregard of negative interpersonal, medical, financial, or legal consequences.[45] The perceived "benefits" of continued drinking typically go unexplored and include the transient relief of symptoms (e.g., alcohol's rapid, albeit typically brief, effects on insomnia, anxiety, or dysphoria), not disputing one's lifestyle and social network, and maintaining the illusion of mastery or invincibility ("I can always quit if I want to"). The acronym FRAMES (***F***eedback, ***R***esponsibility, ***A***dvice, ***M***enu of treatment options, ***E***mpathy, and ***S***elf-efficacy) has been used to describe an overall approach to enhance treatment readiness and subsequent adherence. Our group has found that a single session of adherence-focused counseling following the FRAMES model increased the likelihood of subsequent treatment participation by more than 20%.[46]

Another useful approach to enhance adherence is based on the recognition that people are often noncompliant with a wide range of medical regimens. The high incidence of nonadherence during treatment of less stigmatized chronic illnesses, such as diabetes or hypertension, is illustrative. From this perspective, noncompliance is anticipated and adherence must be addressed proactively.[47] In this way, the complex chains of cognitions, affects, and behaviors that comprise noncompliant acts can be viewed as understandable events rather than the result of some trait ("lack of willpower") or an unconscious process ("denial").

Pharmacotherapy adherence tends to be facilitated by use of relatively simple medication schedules (e.g., q.d. or b.i.d.) and by pairing medication times with high probability events (e.g., brushing teeth or morning coffee). When necessary, prompts such as a note on the refrigerator or a wristwatch alarm may be helpful. The prescribing psychiatrist also needs to make it clear that unpleasant side effects will be addressed promptly and that longer term use of a particular medication will be considered only if there are both unequivocal benefits and tolerability is acceptable. Although the fact that antidepressants are not habit forming is a strength of this type of drug, this does not mean that they can be felicitously discontinued. Beyond recognizing that there is an increased risk of relapse that follows medication withdrawal, patients need to be informed that some antidepressants, particularly paroxetine and venlafaxine, can elicit uncomfortable discontinuation syndromes when stopped abruptly.

CONTINUATION PHASE TREATMENT

This phase of treatment begins when there is a definite antidepressant response to pharmacotherapy or psychotherapy.[48] Continuation pharmacotherapy is routinely recommended because the risk of relapse is unacceptably high without complete remission and normalization of social function is unlikely if even minor depressive symptoms persist. The goals of continued pharmacotherapy typically shift toward consolidation of the response into a remission, which implies complete resolution of the depressive syndrome. Both antidepressants and various adjuncts should be continued at the full doses used during the acute phase. For the dually diagnosed patient, the continuation phase of pharmacotherapy usually coincides with the second or third month of sustained sobriety.

The frequency of pharmacotherapy visits generally diminishes during the continuation phase, with monthly or every-6-weeks doctor's visits commonplace. The frequency of counseling or psychotherapy visits must be titrated on a case-by-case basis. Resolution of depressive symptoms does not spare the patient from stress or from return to work, resumption of usual responsibilities at home, the tempting offers of old friends, and other demands of daily life, which may provoke renewed, classically conditioned urges to drink. The value of concomitant psychosocial therapies and participation in self-help programs thus may prove to be greater during the continuation phase than during acute treatment.

We do not recommend tapering pharmacologic adjuncts for alcoholism until at least 6 to 9 months of sustained sobriety have been achieved. Given the paucity of research on treatment of comorbid depression-alcoholism, it should not be too surprising to learn that the intensity, type, and duration of adjunct therapies used to prevent relapse during continuation antidepressant therapy have not been established empirically.

During continuation therapy, sexual dysfunction and, more idiosyncratically, weight gain can compromise an otherwise effective treatment. Sexual dysfunction, most typically low libido and/or decreased ability to achieve orgasm, may resolve spontaneously or can sometimes be managed by dose reduction or, for the SSRIs with short half-lives, drug "holidays."[49] Occasionally, switching within the SSRI class (e.g., from fluoxetine or paroxetine to citalopram) is beneficial. For other patients, various "antidotes" are used to try to reverse sexual dysfunction, including the herb *Ginkgo biloba*, sildenafil, bupropion, buspirone, cyproheptadine, and psychostimulants.[49] Psychostimulants must be considered with caution for patients with a history of addiction and should probably be a treatment of last resort. If these strategies are not helpful, switching to a dissimilar compound (i.e., bupropion, nefazodone, mirtazapine, or, outside of the United States, moclobemide or reboxetine) may be necessary. However, it cannot be assumed that switching to an antidepressant with a different presumed mechanism of action will provide the same spectrum of symptom coverage as an SSRI.

MAINTENANCE PHASE TREATMENT

An indefinite course of preventive therapy is now routinely recommended for virtually everyone who has had multiple, recurrent depressive episodes.[48] The more numerous the prior episodes, the greater the likelihood that recovery will be short-lived without preventive pharmacotherapy. For example, more than 50% of those who have suffered at least 3 prior episodes will have a recurrence within 6 months of stopping antidepressant medication.[48] By contrast, fewer than 10% of those high-risk individuals who remain on treatment with antidepressants (and take them reliably) will experience "breakthrough" depressive episodes during a comparable time period. It is not known if the risk of recurrence after medication withdrawal diminishes after a number of years of sustained recovery. The results of a small study conducted by the Pittsburgh group suggest that a high risk of recurrence after medication withdrawal may persist even after 3½ years of recovery.[50]

It appears that reduction of the dosage of maintenance antidepressant therapy is associated with decreased prophylactic efficacy.[48] The results of several studies suggest, for example, that the drug-placebo difference (i.e., the relative benefit of maintenance phase therapy) is cut in half by a 50% reduction in antidepressant dosage.[51,52]

Studies of (nonalcoholic) patients with recurrent depression indicate that models of ongoing "maintenance" psychotherapy (e.g., monthly visits) also have protective effects against recurrent episodes.[53,54] However, the magnitude of the benefit with psychotherapy may be smaller than that observed with pharmacotherapy.[53] In the study of Frank et al.,[55] the value of monthly sessions of interpersonal therapy was entirely dependent upon the ability of the therapist and patient "dyad" to maintain a high interpersonal focus. Sequential, time-limited models of cognitive-behavioral therapy targeting residual symptoms and other vulnerabilities have also been shown to reduce the risk of recurrent illness after medication discontinuation.[56,57]

Less is known about long-term prophylaxis of alcoholism with newer agents such as naltrexone and acamprosate or, for that matter, psychosocial treatments and self-help activities. One large, Veterans Affairs (VA)–cooperative study of disulfiram was, in fact, entirely negative.[58] Until sound data from well-controlled trials are available, we recommend that a parallel course of maintenance pharmacotherapy for alcoholism be considered when there is a history of multiple relapses of problem drinking despite maintenance antidepressant medication and appropriate psychosocial therapy.

CONCLUSIONS

Unless there is decisive professional intervention, people who suffer from both a depressive disorder and alcoholism are at great risk of chronic impairment, both at home and in the workplace; persistent symptomatic misery; and premature death. Untreated alcoholism intensifies depressive states, decreases responsiveness to conventional therapeutics, and increases the likelihood of suicide, suicide attempts, and other self-destructive behavior.

During the past decade, evidence has emerged from placebo-controlled studies supporting the utility of TCAs and SSRIs for treatment of depressed alcoholics. The superior safety and tolerability of SSRIs provide strong justification for their first-line use despite higher drug acquisition costs. Evidence has similarly emerged concerning the use of several novel pharmacotherapies and focused psy-

chotherapies for people with alcoholism. These newer therapeutic options complement more traditional interventions, such as chemical dependence counseling, disulfiram, and AA, so that it is now possible for a majority of depressed alcoholics to be treated effectively. The availability of effective treatments provides further impetus for health care professionals to improve recognition of comorbid alcoholism and depressive disorders. Improved recognition and treatment will save lives, and the benefits are likely to extend across generations.

Drug names: bupropion (Wellbutrin, Zyban), citalopram (Celexa), clonazepam (Klonopin and others), cyproheptadine (Periactin), desipramine (Norpramin and others), disulfiram (Antabuse), divalproex sodium (Depakote), fluoxetine (Prozac, Sarafem), fluvoxamine (Luvox), gabapentin (Neurontin), levothyroxine (Synthroid, Levoxyl, and others), liothyronine (Cytomel, Triostat, and others), lorazepam (Ativan and others), mirtazapine (Remeron), naltrexone (ReVia), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), sildenafil (Viagra), venlafaxine (Effexor).

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