

# Managing Depression in HIV Disease, Viral Hepatitis, and Substance Abuse

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DR. FERRANDO BEGAN HIS SEPTEMBER 2005 PRN LECTURE BY EXPLAINING that depression is the most common psychiatric disorder for which HIV-infected patients receive treatment. "A number of epidemiological studies have been conducted," he said. "However, the rates of depression vary greatly. This has a lot to do with variations in the studies themselves. The studies have been conducted in different settings and involved different risk groups." Some studies assessed depression using screening instruments in clinic settings. While screenings are efficient, they tend to overestimate prevalence rates. Others involved highly structured psychiatric clinical diagnostic interviews in research cohorts. Regardless of the settings and methods of assessment, Dr. Ferrando explained, rates of depression and other psychiatric disorders are elevated in HIV-positive patients.

Dr. Eric Bing and his colleagues at the Charles R. Drew University of Medicine and Science in Los Angeles analyzed data from the HIV Cost and Services Utilization Study (HCSUS) to examine mental health and substance use in a large, nationally representative probability sample of adults receiving care for HIV in the United States (Bing, 2001). Study participants were administered a brief instrument that screened for mental health disorders and drug use during the previous 12 months.

Nearly half of the sample screened positive for a psychiatric disorder in the past 12 months, including 36% for major depression; 26.5% for dysthymia, a chronic yet less severe form of depression; 15.8% for generalized anxiety disorder; and 10.5% for history of panic attacks. Nearly 40% reported using an illicit drug other than marijuana, and more than 12% screened positive for drug dependence.

The proportion of people screening positive for mental health and substance abuse disorders in the HCSUS sample is considerably higher than that obtained from general population samples. For example, the proportion of people screening positive for major depression in HCSUS is nearly five times greater than the proportion found in the National Household Survey on Drug Abuse (NHSDA).

In another study, conducted at Weill Cornell Medical Center, Dr. Judith Rabkin and her colleagues, including Dr. Ferrando, assessed the prevalence of major psychiatric disorders in HIV-positive gay and bisexual men with AIDS-defining conditions (Rabkin, 1997). Secondary goals were to identify correlates of distress and psychopathology, and to determine whether there is a gradient of distress associated with progressive HIV illness.

The study enrolled 112 men with AIDS-defining conditions; 61 HIV+ men without AIDS, and 84 HIV-negative gay men were assessed. Measures included the Structured Clinical Interview for DSM-IV (SCID), Hamilton Rating Scale for Depression (HAM-D), and other dimensional measures of distress and outlook, as well as laboratory markers of HIV stage, including viral load assays.

Rates of major depression, consistent with other findings using structured diagnostic interviews, were in the 5% to 10% range. Mean scores on dimensional measures of distress and outlook were within the

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"not depressed" range and did not increase despite increasing HIV illness severity. However, rates of dysthymia were elevated among men with CD4+ counts less than 500 cells/mm<sup>3</sup>, and the cumulative rates of any current axis I depressive disorder for three of the four study groups were in the range of 15% to 20%. The strongest correlates of dimensional measures of distress were current HIV symptoms and social support, and to a lesser extent, a lifetime history of major depression and current use of antidepressants and/or anxiolytics.

As for injection drug users receiving methadone maintenance treatment, Dr. Ferrando highlighted data published by Dr. Steven Batki and his colleagues at the State University of New York Upstate Medical University (Batki, 1996). Dr. Batki's group found 80% to be receiving psychiatric intervention, including 42% for depression, 19% for cognitive disorders, 17% for insomnia disorders, 8% for anxiety disorders, 8% for psychotic disorders, and 2% for bipolar disorders. More than 70% of these patients were actively abusing illicit non-opioid drugs while in MMT, including cocaine (60%), alcohol (36%), benzodiazepines (23%), and amphetamines (11%).

As for axis I disorders among medically hospitalized patients with HIV and AIDS, Dr. Ferrando and his colleagues found that 31% had major depression, 19% had delirium and/or dementia, 19% had current substance abuse disorders, 16% had bipolar spectrum disorders, and 13% had anxiety disorders (Ferrando, 1998).

There have also been studies looking at rates of depression over time, whether it's as HIV disease progresses or improves in response to antiretroviral therapy.

A study conducted by Dr. Constantine Lyketsos and his colleagues at Johns Hopkins University sought to determine whether rates of depressive symptoms change from early- to late-stage HIV infection and to determine the predictors of depressive symptoms as AIDS develops. The data for this study were from 911 HIV-positive men enrolled in the Multicenter AIDS Cohort Study. None of the patients had symptomatic disease upon enrolling in the MACS; all developed AIDS while participating in the study. The outcome measures—overall depressive symptoms, nonsomatic depressive symptoms, syndromal depression, and severe depression—were assessed over the five years before and the two years after AIDS diagnosis from responses on the Center for Epidemiologic Studies Depression Scale (CES-D Scale).

Depressive symptoms were stable over time from month 60 to month 18 before AIDS developed. However, beginning 12 to 18 months before the AIDS diagnosis, there was a significant rise in all measures of depression, which reached a plateau within six months before AIDS developed. At this plateau, there was a 45% increase in mean CES-D Scale scores above baseline. An elevated CES-D Scale score in the earlier stages of infection, a self-report of AIDS-related symptoms (e.g., lymphadenopathy), concurrent unemployment, cigarette smoking, and limited social supports were consistent predictors of higher rates of depression as AIDS developed.

Dr. Ferrando also reviewed data evaluating the impact of depression

**TABLE 1. Diagnosis of Depression in HIV Infection**

Cognitive/Affective	
Depressed mood	
Loss of interest	
Guilt, worthlessness	
Suicidal ideation	
Somatic	
Appetite/weight loss	
Sleep disturbance	
Psychomotor agitation/retardation	
Fatigue	
Loss of concentration	
A diagnosis of depression requires five or more symptoms, including depressed mood and/or loss of interest, for two weeks or more to meet the diagnostic criteria for Major Depressive Disorder.	

Source: Stephen J. Ferrando, MD

on morbidity and mortality in the setting of HIV (Ickoviks, 2001). These data, involving HIV-positive women participating in the HIV Epidemiologic Research Study (HERS), are particularly noteworthy given the fact that women with HIV may have higher rates of depression than their male counterparts.

A total of 765 HIV-positive women aged 16 to 55 years were included in the analysis. The main outcome measures were HIV-related mortality and CD4+ cell count slope decline over a maximum of seven years, compared among women with limited or no depressive symptoms, intermittent depressive symptoms, or chronic depressive symptoms, as measured using the self-report CES-D Scale.

In multivariate analyses controlling for clinical, treatment, and other factors, women with chronic depressive symptoms were two times more likely to die than women with limited or no depressive symptoms. Among women with CD4+ counts of less than 200 cells/mm<sup>3</sup>, HIV-related mortality rates were 54% for those with chronic depressive symptoms and 48% for those with intermittent depressive symptoms, compared with 21% for those with limited or no depressive symptoms. Chronic depressive symptoms were also associated with significantly greater declines in CD4+ cell counts after controlling for other variables in the model, especially among women with baseline CD4+ counts of less than 500 cells/mm<sup>3</sup> and baseline viral loads greater than 10,000 copies/mL.

The relationship between psychiatric problems and the return to physical health using combination antiretroviral therapy has also been explored. One report published in 2000 by Dr. Rabkin and her colleagues was based on five semiannual assessments of medical, psychosocial, and psychiatric parameters in a group of gay and bisexual men with symptomatic HIV/AIDS who enrolled in a Cornell-based longitudinal study in mid-1995 (Rabkin, 2000). "The intention of this cohort at the time was to follow medically symptomatic patients as they approached death to look at end-of-life issues," Dr. Ferrando explained. "Of course, this isn't what ended up happening, given that protease inhibitors and triple-combination therapy became mainstay therapies by the end of 1995. In turn, we ended up looking at psychosocial and psychiatric parameters associated with restoration of health rather than diminution of health over time."

Dr. Rabkin's group observed a statistically significant but clinically modest reduction in measures of depression and hopelessness in the sample as a whole. Overall, the decline in distress was significantly correlated with increasing CD4+ cell count, declining HIV symptoms, and improved social support. As seen in previous studies, physical symptoms were more strongly correlated to psychological distress than were laboratory findings.

## Diagnosis of Depression

GIVEN THE HIGH RATES OF DEPRESSION IN HIV, SCREENING FOR depression and other mental health and substance abuse issues is a vital component of the clinical management of HIV-infected individuals.

There are both affective and somatic symptoms to be aware of. Affective symptoms include depressed mood, loss of interest, feelings of guilt and/or worthlessness, and suicidal ideation. Somatic symptoms include appetite and/or weight loss, sleep disturbances, psychomotor agitation or retardation, and fatigue. "Of course," Dr. Ferrando said, "the diagnosis of depression in HIV-infected patients may be confounded by somatic symptoms common to depression and HIV illness itself."

A diagnosis of Major Depressive Disorder (MDD) requires the presence of five or more symptoms, including depressed mood and/or loss of interest, for two weeks or more (see Table 1).

As evident in the epidemiological studies discussed above, there are several validated instruments for screening to identify depressive symptoms (see Table 2). The Beck Depression Inventory (BDI) and clinician-administered Hamilton Rating Scale for Depression (HAM-D) are frequently used in studies. "The BDI is a self-report," Dr. Ferrando said. "It has been used for many years. The HAM-D is really the gold standard in psychopharmacological research, but does require admin-

**TABLE 2. Screening Instruments for Patients with Depression**

Screening Instrument	Administration	Notes
Beck Depression Inventory (BDI)	Self-report	Cognitive and somatic subscales; widely used clinically.
Hamilton Rating Scale for Depression (HAM-D)	Clinician	Affective and vegetative symptom subscales; primarily used in depression treatment research.
Center for Epidemiological Studies—Depression (HAM-D)	Self-report	Cognitive and somatic subscales; cut-scores for clinically relevant symptoms; primarily used in epidemiological research.
Patient Health Questionnaire-9 (PHQ-9) Depression Module	Self-report	Extensively validated in primary-care settings; keyed to depression diagnostic criteria; other modules screen for somatic symptoms, anxiety disorders, and substance abuse.
Hospital Anxiety and Depression Scale (HADS)	Self-report	Screens depression and anxiety; designed for use in medical settings; excludes somatic symptoms.

Source: Stephen J. Ferrando, MD

istration by a trained clinician." There is also CES-D, used mostly in epidemiological studies, which measures generalized distress rather than being specific for depressive symptoms.

For primary care clinicians, Dr. Ferrando recommends the Patient Health Questionnaire-9 (PHQ-9) Depression Module, which can provide a provisional psychiatric diagnosis. "This screening instrument was designed for use in primary care settings," he explained. "The idea was to take the DSM and make it user friendly. The advantage of this questionnaire is that it has all of the nine symptom criteria for major depression and has a scoring algorithm. It has been extensively validated in primary-care settings. Basically, a score of ten or more is considered to be clinically significant. And, of course, you always want to query your patients about suicide. Suicidal ideation is highly correlated with depression. The questionnaire takes two to three minutes to look over and it takes very little time for patients to fill out."

When it comes to depression, the differential diagnosis is very broad in HIV. HIV infection of the central nervous system—manifested as minor cognitive motor disorder (MCMRD) or HIV-associated dementia (HAD)—is an important consideration, along with CNS opportunistic illnesses and cancers. "Substance intoxication and withdrawal can also mimic symptoms of depression," Dr. Ferrando said. Neuropsychiatric side effects of other medications—including efavirenz, interferon, and steroids—should also be considered. "We also have endocrine abnormalities," Dr. Ferrando said. "The association between testosterone deficiency—hypogonadism—and depression is well established, especially in HIV-positive men."

One important issue in diagnosing depression is to screen for bipolar disorder. The reason is that antidepressant medications, when given as monotherapy to such patients, can cause mood cycling or precipitate mania (antidepressants should usually be accompanied by lithium or an anticonvulsant in such patients). A simple clinical screen is to ask patients: Have they ever been told they had bipolar illness? Do they have a family history of bipolar illness?

## Treatment of Depression

OVER THE YEARS, THERE HAVE BEEN SEVERAL OPEN-LABEL AND DOUBLE-BLIND CLINICAL TRIALS OF ANTIDEPRESSANT TREATMENTS FOR DEPRESSION IN HIV. "More than 1,000 patients have been treated in clinical trials involving antidepressants," Dr. Ferrando said. While data have generally yielded favorable results, there are a number of issues that need to be considered when reviewing completed studies. For starters, women and intravenous drug users have been underrepresented in clinical trials, whereas gay and bisexual men have been overrepresented. Depression diagnoses (i.e., inclusion criteria) and outcome criteria have varied considerably. HIV illness stages have also varied, with some clinical trials enrolling patients with more advanced HIV disease than others. There has also been variability in the duration of studies, with some involving four weeks of follow-up and others involving up to a year of follow-up. Finally, attrition rates have also been high.

The earliest clinical trials involving HIV-infected patients with depression utilized tricyclic antidepressants (TCAs). Data from trials of imipramine and desipramine demonstrated efficacy. Other TCAs used in clinical practice include amitriptyline and nortriptyline. Of concern, however, are the side effects associated with TCA use, including constipation, dry mouth, drowsiness (which may be beneficial to patients bothered by insomnia), headache, cognitive problems, dizziness, and sexual dysfunction. TCAs can rarely produce cardiotoxicity (prolonged QRS and/or QT), seizures, and are quite lethal in overdose. Careful history for seizures and cardiac problems, and a baseline ECG, are advisable, and

overdose risk should be considered. "Because of the rates and severity of side effects in clinical trials and during the early years of clinical use, TCAs are not used all that much anymore," Dr. Ferrando said. "There is much greater interest in the selective serotonin reuptake inhibitors."

Early open-label and more recent placebo-controlled trials utilizing standard doses of the SSRIs fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil) for major depression across HIV illness stages produced encouraging response rates, ranging from 70% to 90%, with relatively few adverse effects, and improvements in both affective and somatic depressive symptoms. Another popular SSRI option is escitalopram (Lexapro).

Generally speaking, SSRIs have relatively low toxicity, even in overdose, and are thus rather safe, easily tolerated medications. Common mild to moderate side effects of SSRIs can include weight gain; memory impairment; and sexual dysfunction, including anorgasmia and sometimes loss of libido. One issue to beware of is that patients started on SSRIs or related medicines will occasionally develop severe jitteriness in the first few weeks of treatment; this can be very distressing and calls for dose reduction, or change to another medication if dose reduction does not result in improvement. Once jitteriness ceases, the dose can usually be increased again.

Rarely, patients started on an SSRI or other antidepressant may develop increased suicidal ideation. The U.S. Food and Drug Administration is in the process of issuing warnings about this in regard to SSRIs and various other classes of psychotropic medication; this may be part of the jitteriness syndrome just described, or it may indicate underlying bipolar illness, wherein antidepressant treatment without a concomitant mood stabilizer can induce mood cycling or dysphoric mixed-mood states. While this is rare, it is important for clinicians to ask their patients about suicidal ideation prior to initiating antidepressant treatment, in order to have a baseline to compare to. Many depressed patients have suicidal thoughts. If these thoughts worsen upon starting SSRI treatment—or at any point—psychiatric consultation is advisable.

Other conventional antidepressants include venlafaxine (Effexor), mirtazapine (Remeron), nefazodone (Serzone), and bupropion (Wellbutrin, Zyban). The first three listed agents have been studied in small open-label trials in patients with major depression and HIV infection. All were associated with favorable response rates and few adverse effects. While bupropion is less likely to cause sexual side effects, it can increase the risk of seizures in patients with risk factors for seizures. Nefazodone has been associated with extremely rare cases of irreversible hepatotoxicity, which has discouraged its use, although it can be a good second-line medication in patients who fail to respond to a trial of an SSRI. Nefazodone, mirtazapine, and trazodone are all sedating, which can be very helpful for patients bothered by insomnia, but may not be useful for patients with fatigue.

Psychostimulant and wakefulness agents have also been studied for the treatment of depressed mood, fatigue, and cognitive impairment in the context of HIV infection, usually in advanced illness and where rapid onset of action is desirable. Open-label studies of dextroamphetamine (Dexedrine), methylphenidate (Ritalin), and modafinil (Provigil) found them to be efficacious in treating depressive symptoms, with relatively few side effects. Modafinil is currently being studied in two placebo-controlled trials at Columbia University Medical Center: one for HIV-infected patients with fatigue and another for HIV-infected patients using crystal methamphetamine (call Judith Rabkin at 212/543-5762 for more information).

A review of the conventional antidepressants studied in HIV-infected patients and reviewed in Table 3 on page 22.

**TABLE 3. Conventional Antidepressants Studied in HIV-Infected Patients**

Tricyclic Antidepressants
Imipramine (Tofranil)*
Desipramine (Norpramin)
Nortriptyline (Pamelor)
Amitriptyline (Elavil)
SSRIs
Fluoxetine (Prozac)*
Sertraline (Zoloft)*
Paroxetine (Paxil)*
Citalopram (Celexa)
Escitalopram (Lexapro)
Fluvoxamine (Luvox)
Psychostimulants
Dextroamphetamine (Dexedrine)*
Methylphenidate (Ritalin)
Pemoline (Cylert)
Modafinil (Provigil)
Others
Venlafaxine (Effexor)
Nefazodone (Serzone)
Trazodone (Desyrel)
Bupropion (Wellbutrin)
Mirtazapine (Remeron)

\* Medications for which there is double-blind trial evidence in HIV-infected patients.

Non-conventional agents include depot testosterone, dehydroepiandrosterone (DHEA), and s-adenosyl methionine (SAM-e).

Testosterone deficiency, with clinical symptoms of hypogonadism (e.g., depressed mood, fatigue, diminished libido, decreased appetite, and loss of lean body mass) is present in up to 50% of men with symptomatic HIV or AIDS.

In an initial study of testosterone replacement therapy for libido, mood, energy, and body composition, Dr. Rabkin and her colleagues treated 34 HIV-infected men (79% with AIDS) with low serum testosterone and major depression in an eight-week open-treatment phase (400 mg IM every two weeks), followed by a placebo-controlled double-blind discontinuation phase (Rabkin, 1999). In the open-treatment phase, mood response was 79%. In the placebo-controlled phase, response was maintained in the testosterone group but dropped to 13% in the placebo group. In a follow-up double-blind, placebo-controlled study of testosterone (400 mg IM biweekly) in 26 HIV-infected men with low serum testosterone and subclinical depressive disorders, 58% responded to testosterone compared to 18% placebo (Rabkin, 2000a). Among reported side effects were irritability, tension, bossiness, hair loss, and acne; however, fewer than 5% dropped out due to adverse effects.

DHEA, which has mild androgenic/anabolic effects and is a precursor to testosterone, has also been studied in an eight-week, double-blind, placebo-controlled trial in which 145 men and women with HIV and minor depression or dysthymia were enrolled (Rabkin, in press). The

doses ranged from 100 mg/day to 400 mg/day. Clinician-rated response rates for patients randomized to DHEA were 56% for the DHEA group, compared to 31% for the placebo group. Few adverse events were reported and no significant changes in CD4+ cell counts or HIV-RNA levels were observed in either group. Patient acceptance was high, as reflected in the low (5%) drop-out rate and multiple requests for extended treatment after completion of the formal trial.

S-adenosylmethionine has undergone a small open-label eight-week trial in 15 HIV-infected patients with major depression, with encouraging results (Jones, 2002).

In concluding his review of psychotropic medications, Dr. Ferrando briefly discussed the issue of drug-drug interactions—a common concern in today's polypharmaceutical management of HIV and other comorbidities. Because psychotropic drugs are metabolized by and may inhibit or induce the same hepatic enzymes as the protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) and are highly protein bound, clinically relevant drug interactions may result when these medications are combined. Fortunately, Dr. Ferrando explained, relatively few serious interactions have been reported in the literature, and this is reflected in general clinical experience.

Fear over the potential for drug interactions may dissuade some clinicians from initiating needed psychotropic treatment for an HIV-infected patient. "We're probably much more at risk for underdiagnosing and undertreating depression than we are for having a drug interaction," Dr. Ferrando said. However, he did stress that care should always be maintained when prescribing psychotropics with PIs and NNRTIs, and potential interactions should be investigated prior to initiating therapy.

## Depression in HIV/HCV Coinfection

VARIOUS STUDIES HAVE DEMONSTRATED HIGH RATES OF DEPRESSION IN patients chronically infected with the hepatitis C virus (HCV). According to one paper, 44% of HCV-monoinfected patients meet criteria for Major Depressive Disorder, before treatment is even started. Similar, if not higher, rates of depression are believed to exist in the HIV/HCV-coinfected population of patients.

The reason for the high rate of depression in HCV patients is unknown. "It may be that chronic HCV infection has an effect on central monoamine metabolism, which may lead to depression," Dr. Ferrando said. "Concomitant illicit drug use may also be a factor and there is clearly an additive risk of cognitive impairment related to the severity of liver disease. There is also increased depression and suicidal ideation that comes with pegylated interferon and ribavirin treatment."

A study published earlier this year by investigators at Emory University School of Medicine evaluated the prevalence and prediction of depression in HCV-monoinfected patients receiving pegylated interferon and ribavirin (Raison, 2005). At baseline, approximately 7% of 162 patients had moderate-to-severe depression. Four weeks after commencing therapy, approximately 19% had depression. At eight weeks and 12 weeks, moderate-to-severe depression was documented in approximately 18% and 16% respectively. And after 24 weeks of treatment, approximately 26% of patients had moderate-to-severe depression.

Incidence rates of depression and fatigue in HIV/HCV-coinfected patients receiving pegylated interferon and ribavirin have also been reported (Jones, 2004). After 48 weeks of treatment, 64% of 92 patients had fatigue, 36% had depression, and 25% had both fatigue and depression. Fatigue developed very early in the study, at week 1 for the majority of patients. However, fatigue was not a predictor for early treatment discontinuation. Depression was slower to develop, but in the majority of

cases occurred by week 12. Of the 33 patients that became depressed, six had a history of depression, whereas 26 did not, suggesting that 28% became depressed during pegylated interferon/ribavirin therapy. There was one episode of suicidal ideation. However, there were no reports of suicide attempts, mania, or psychosis.

Of interest to many clinicians with patients undergoing or about to begin treatment for hepatitis C are data evaluating SSRI therapy as a prophylaxis against depression (Schaeffer, 2005). The study, conducted in Berlin, enrolled 14 HCV-monoinfected patients (group A) with psychiatric disorders and provided them with citalopram (20 mg/day) before and during therapy with interferon-alfa. The incidence of major depression was compared to rates among 11 HCV-monoinfected patients with psychiatric disorders (group B) and 11 HCV-monoinfected patients without psychiatric risk factors (group C) who underwent Interferon-alfa treatment without a preemptive antidepressant therapy.

According to the study results published earlier this year, pre-treatment of psychiatric patients with citalopram significantly reduced the incidence of major depression during the first six months of anti-HCV treatment as compared to the two control groups (14% in group A vs. 64% and 55% in groups B and C). While larger double-blind placebo-controlled studies are required to confirm these results, these data suggest that anti-HCV treatment-induced depression in psychiatric risk patients can be ameliorated with the prophylactic use of antidepressants. "These results are similar to those seen in another patient population, including patients undergoing interferon therapy for melanoma," Dr. Ferrando commented. "These are very encouraging results."

## Conclusion

IN CONCLUDING HIS LECTURE, DR. FERRANDO REITERATED THAT depression is common in the context of HIV, hepatitis C, and substance abuse. "Substantial evidence exists for the efficacious treatment of depression in these populations," he said. And while clinicians must remain weary of potential drug-drug interactions, "the risk of clinically significant interactions is outweighed by the risk of underdiagnosed and undertreated depression in HIV." 

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# DEPRESSION AND SUBSTANCE ABUSE

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SUBSTANCE ABUSE CAN CAUSE DEPRESSIVE SYMPTOMS, WHICH CAN result from intoxication, withdrawal, or chronic use. All of the common substances, including alcohol, opioids, cocaine and stimulants (methamphetamine), or cannabis, can do this. Thus, it is useful to advise a depressed patient who is also using substances to get treatment for his or her substance abuse. Abstinence might help them feel better. While the treatment of substance abuse is beyond the scope of this article, brief advice from a physician is often an effective intervention by itself.

One issue is how to ask about substance abuse. Patients are often defensive about this, and a directive approach on the part of the clinician ("You know it's bad for you, and you should stop") will often backfire. Motivational Interviewing (Miller, 2002), and various brief motivational interventions, suggest that it is often better to take a collaborative stance with patients abusing substances. A simple formula is to: 1) Ask about substance use; 2) Elicit the patient's point of view (Does the patient see it as a problem? If so why? If not, why not?); then 3) Suggest a course of action, which might be a treatment referral if the patient seems open to it, or just "maybe we can keep an eye on this, and talk about it some more next time we meet" if the patient does not seem open to changing his or her use at this moment. Obviously, if the level of substance use seems dangerous or life threatening (e.g. the patient is driving drunk, or seems at risk of overdosing on opioids), the clinician needs to step in more forcefully.

Depression may persist even after a patient cuts down on substance use or becomes abstinent. Alternatively, a patient may remain depressed, and be unable to cut down on substance use. A recent meta-analysis of placebo-controlled trials suggests antidepressant medications are effective in improving depression for patients with substance use disorders (Nuñes, 2004). Also, those trials that showed the largest medication effects on depression also showed significant medication effects in improving substance use. The largest effects of medication were observed in trials where patients were abstinent, at least briefly, before the diagnosis of depression was confirmed and treatment started. However, medication was also beneficial in some trials where patients were actively using substances at baseline. The management of depression in the setting of substance abuse is a matter for clinical judgment, but a simple rule of thumb would be to try to get the patient to cut down or abstain. If that fails, or the patient has already tried to cut down, go ahead and treat with an antidepressant. The trials suggest this is generally safe, although patients should be warned that mixing the medication with alcohol or other drugs could result in increased sedation or intoxication. If the substance abuse is severe, an inpatient detoxification would be advisable before proceeding. 

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