Published in final edited form as:

Psychiatr Ann. 2008 November 1; 38(11): nihpa128505.

Treatment of Co-occurring Depression and Substance Dependence:

Using Meta-analysis to Guide Clinical Recommendations

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Depression is a common phenomenon among patients with alcohol or drug dependence, as is evident to any practitioner working with these patients. Numerous studies have documented high rates of depressive disorders among patients seeking treatment for substance use disorders.¹ Community surveys have consistently found elevated rates of major depression and dysthymia among patients with alcohol or drug dependence.^{2–6} Further, current major depression has been associated with worse clinical outcome among substance-dependent patients.^{1,7,8} The data are less clean on the prognostic implications of a past depression or elevated depressive symptoms without identification of a depressive disorder. These epidemiological data suggest that a co-occurring depressive disorder is important and warrants clinical attention.

Yet the management of this co-occurring depression has been a source of confusion and considerable controversy. The data are also clear that in many cases depressive symptoms resolve within days or weeks after a patient becomes abstinent or enters an effective treatment modality such as methadone maintenance.^{9–13} Thus, one school of thought holds that such depression is mostly a consequence of ongoing addiction — effects of substance intoxication, or withdrawal, or perhaps the stress of the addicted lifestyle. The appropriate treatment is treatment of the addiction to get the patient abstinent and into recovery, after which the depression should resolve. Another school holds that depression should be treated and that such treatment might help patients achieve abstinence, perhaps because the addiction is partly driven by “self-medication” of the symptoms of depression. This leads to the problem of how to determine who to treat among actively using outpatients with substance abuse and co-occurring depression. Should clinicians treat any elevation of depression symptoms? Or should the treat only depressive syndromes, such as major depression, accompanied by a convincing past history of independent depression? If a depression syndrome (eg, major depression) persists after a period of abstinence, then virtually all clinicians would acknowledge that at some point it be declared an independent disorder and treated as such with antidepressant medication or psychotherapy. But what length of abstinence is needed to make this determination? Two decades ago, many experts might have recommended that a depression should persist for 6 months into abstinence. The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, published in 1994, curtailed this period to 1 month.¹⁴

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Dr. Nunes and Dr. Levin have disclosed no relevant financial relationships.

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Seeking evidence to address these questions, numerous placebo-controlled clinical trials have now been conducted testing antidepressant medications among substance-dependent populations meeting various depression criteria. The results, if simply tallied up, are decidedly mixed, with a number of studies suggesting that antidepressant medication is effective among substance-dependent patients with depression and a similar number of studies showing no beneficial effect. This is where a quantitative review of the literature, namely a meta-analysis, can be helpful. In this article, we will review meta-analyses of the literature on antidepressant treatment among substance-dependent patients and show how these analyses help to explain discrepancies between positive and negative studies, thereby informing clinical recommendations.

PRIMER ON META-ANALYSIS

In meta-analysis, a group of studies with similar methodology is combined mathematically into one large study in an effort to obtain a more precise estimate of the treatment effect.^{15–17} Similar to any good research, a good meta-analysis defines a principal question or hypothesis, a comprehensive search strategy to identify appropriate studies, and inclusion/exclusion criteria for selecting studies that can be included. Generally, studies need to be addressing the same basic question, with the same methodology and the same or similar outcome measures. The literature on antidepressant medication among substance-dependent patients contains many studies that are randomized, double-blind, placebo-controlled trials, with trial lengths of 6 to 12 weeks and common outcome measures, usually the Hamilton Depression Rating Scale (HAM-D)³⁴ or some other standard scale for rating symptoms of depression, as well as measures of the frequency or quantity of substance use.

The Effect Size

The outcome of each study is expressed as an effect size, the most common measure of effect size being Cohen's d , which is defined as the difference in the mean score of the outcome measure at study endpoint (eg, HAM-D) between placebo and active treatment groups, divided by the pooled standard deviation of those groups (the weighted average of the standard deviations of the active treatment and placebo groups, weighted by sample size in each group). It thus represents the standardized difference between the outcome of the two groups (active medication compared with placebo) expressed in standard deviation units. As a general guideline, an effect size of 0.2 (meaning that active treatment and placebo differ by 0.2 standard deviations) is considered "small," 0.5 is considered "medium," and 0.8 is "large." Most psychotherapy or medication treatments in psychiatry and behavioral health have effects sizes in the small-to-medium range. A recent meta-analysis showed that the effect size for antidepressant medication treatment of routine outpatient depression is 0.43, representing an effect in the range between small and medium.¹⁸ An important point to keep in mind is that when one conducts a power analysis, the sample size needed in a clinical trial to detect an effect size of 0.5 between medication and placebo is around 60 per group. As the effect size diminishes into the range between medium and small (0.4 to 0.2 or less), the required sample size grows exponentially. It is difficult to recruit large samples at any one site. Thus, many single site studies with typical sample sizes between 30 and 60 per group end up being underpowered to detect effects of treatment. Combining similar studies with meta-analysis results in a much larger overall sample size than any single study, helping to address the problem of power.

Heterogeneity of Effect and the Analysis of Moderators

In addition to an estimate of overall effect size, meta-analysis also yields an estimate of heterogeneity of effect.¹⁷ The test for heterogeneity estimates whether all the studies come from the same distribution, differing mainly because of random differences in sampling, or whether the differences in magnitude of effect size between studies are large enough to suggest that the studies differ significantly among themselves. If the test for heterogeneity is significant, this invites analyses of moderators, namely methodological features of studies that may explain why some studies show larger effects of the treatment, while others show little or no effect. The analysis of moderators, and the methodological differences they reveal, can be among the most useful products of a meta-analysis, helping to explain why clinical trials yield contradictory outcomes. The methodological features associated with beneficial effects of medication can be used to develop clinical guidelines for how treatment should be conducted.

Cautions in the Interpretation of Meta-analysis

A meta-analysis is only as good as the underlying studies. Systematic biases in those studies as might result, for example, from poor blinding will result in biased estimate of effect size. Then there is the "file drawer problem," namely that negative studies tend not to get published, biasing published studies in the direction of positive. Negative studies tend not to get published in part because journals, in their review process, tend to favor studies that show a positive result, and perhaps also because investigators tend to feel discouraged about negative studies and lose interest. It is important that a meta-analysis makes every effort to search the field for both published and unpublished data sets. This also illustrates why it is important that all clinical trials be published, regardless of the findings. A negative result from a well-designed study is just as important as a positive result and is equally important in helping the field to estimate the efficacy of a treatment from the aggregate of studies published on that treatment to date.

EDUCATIONAL OBJECTIVES

1. To understand how meta-analysis can be used to evaluate antidepressant treatment efficacy for depression in substance abusers seeking treatment.
2. To gain knowledge of what methodologic features of pharmacologic treatment trials targeting depressed substance abusers predict better treatment response.
3. To understand recommendations derived from findings of placebo-controlled antidepressant medication trials for clinical management and treatment of depressed, substance-dependent patients.

FINDINGS: ANTIDEPRESSANT MEDICATION FOR CO-OCCURRING DEPRESSION AND SUBSTANCE DEPENDENCE

The Questions

In 2003, we undertook a meta-analysis to address the question of whether antidepressant medication is effective in the treatment of patients with drug or alcohol dependence and co-occurring diagnosed depressive disorders.¹⁹ Three component questions were addressed: 1) whether medication is effective in treating depressive symptoms; 2) whether medication is effective in treatment the substance use; and 3) what methodological features of studies are associated with stronger medication effects.

Selection of Studies

A search of the literature and the field was undertaken. Studies were included in the analysis if the study was a placebo-controlled trial and patients selected into the trial had both a substance use disorder (abuse or dependence) and a current DSM-III, DSM-III-Revised, or DSM-IV depressive disorder. Fourteen such studies were located^{20–33} and were included in the analysis. Placebo-controlled trials of antidepressant medications in patients with elevated depressive symptoms (but no diagnosis reported), or simply substance dependence without any selection for depression, were not included. This was because of the substantial evidence on the transient nature of depressive symptoms in the substance-dependent population and the clinical consensus of the field already that a DSM diagnosis of a depressive disorder was a minimal requirement. The literature contained many such studies, most with negative findings.

Depression Outcome

All the selected studies used the HAM-D as a depression outcome measure. Studies ranged between 6 and 12 weeks in length. The effect size (Cohen's *d*) was calculated for each study, namely the difference between the mean Hamilton score at the end of study in the placebo group minus the mean Hamilton score at end of study in the medication group, divided by the pooled standard deviation of the groups. Effects sizes ranged between 1.07 (95% confidence interval: 0.23 to 1.92), representing a large effect in favor of medication, to −0.21 (95% confidence interval: −0.99 to 0.56) representing a small effect in favor of placebo. However, the latter is not considered a statistically significant effect because the 95% confidence interval encompasses zero (no effect). The 95% confidence interval is the range within which the true effect size likely resides (with 95% probability), based on the statistical uncertainty in the sample. The pooled effect size was 0.38 (95% confidence interval: 0.18 to 0.58). Because all of the values in the confidence interval are positive, this indicates that in all likelihood the true effect is positive and in the small-to-medium range. Note that this estimate of effect size is very close to the effect size of 0.43 calculated from studies of the treatment of routine outpatient depression.¹⁸ Also note how the 95% confidence interval of the pooled estimate is more narrow than the 95% confidence intervals for the individual studies, reflecting the greater precision of estimate of effect size resulting from combining many studies together. The test for

heterogeneity was significant, suggesting that the studies differ significantly from each other, inviting the analysis of moderators described below.

Substance Use Outcome

Most of the studies included one or more continuous or count measures reflecting quantity of substance use (usually days of use, quantity used or some combination), usually by self-report. These measures differed across studies, but were similar enough to be analyzed together. One of the strengths of the effect size is that it is expressed in standard deviation units, so that measures that are not identical, but are still conceptually similar, can be combined. The pooled effect size was smaller at 0.25 (95% confidence interval: 0.08 to 0.42). However, there was a strong positive association between the size of the effect of medication on depression (ie, HAM-D) and the effect on substance use outcome. For studies where the effect size of medication on depression symptoms was medium (0.50) or greater (ie, where the medication was shown to have a strong effect of improving depression outcome), the effect size of medication on substance use outcome was larger, in the medium range at 0.56 (95% confidence interval: 0.33 to 0.79). This finding is consistent with correlations found within some individual studies between mood improvement and substance use improvement at the patient level.^{23,27} This finding also suggests that when medication has a strong effect on improving depressed mood, beneficial effects in improving substance use can also be expected. At the same time, some studies also included dichotomous measures reflecting abstinence, remission, or absence of relapse. Remission rates were generally modest, the effect size for medication on these measures, although positive, was smaller. This suggests that medication treatment of depression may be of benefit in reducing substance use but cannot be expected to produce high rates of remission. Therefore, ongoing direct treatment of the substance use would be needed to increase the likelihood of full remission of substance use.

Moderators of Medication Effect

Arguably the most valuable part of the meta-analysis was the analysis of moderators, which addresses the question of why some studies demonstrated substantial beneficial effects of antidepressant medication treatment, while others showed no effect at all. Placebo response rate was the strongest moderator, explaining more than 70% of the variation in effect sizes on depression outcome across studies. Studies with low placebo response^{20–25,27} were much more likely to show beneficial effects of medication, while the remainder of the studies with higher placebo response were likely to show no effect of medication. Placebo response rates of 30% to 60% were observed in about half of the studies.^{26,28–33} Other moderators included the following: 1) if patients were required to have been abstinent for at least a week before being diagnosed with depression and entered in the trial, this was associated with beneficial effects of medication; 2) if a manual-guided psychosocial intervention for substance dependence was offered to all patients as a platform treatment for the trial, this was associated with absence of benefit from medication; and 3) studies of drug-dependent samples (opioid or cocaine dependence) and studies of selective serotonin reuptake inhibitors (SSRIs) yielded inconsistent effects of medication. Beneficial effects of medication were more clearly evident among studies of alcohol-dependent patients and studies of non-SSRI medications (mainly tricyclic antidepressants).

Several moderators were notable for their lack of effect, particularly for type of depression (major depression only compared with samples with mixtures of major depression or dysthymia) and severity of depression (measured as the mean HAM-D score at baseline in the study sample). This means that effect sizes appeared equivalent between studies that required major depression (versus allowing dysthymia, a milder but chronic form of depression) and between studies with samples that showed more or less severe depression at baseline. Caution is warranted because the meta-analysis could not examine patient level data.

Other Meta-analyses

Torrens and colleagues³⁵ conducted a meta-analysis that cast a wider net, including all placebo-controlled studies of antidepressant medications (both of which selected depressed patients and those that included patients without depression) and examining as moderators whether the study involved drug compared with alcohol-dependent patients and whether depression was required for inclusion in trial. Similar to the meta-analysis described in some detail above¹⁹ this meta-analysis concluded, cautiously, that there was evidence of effectiveness of antidepressant medication among alcoholics with depression. Among studies of patients with drug dependence, there was less clear effect, with the conclusion that more research in such patients is needed. Interestingly, this meta-analysis also raises questions about the efficacy of SSRI antidepressants in substance-dependent populations. Antidepressant medications were shown to be effective among nicotine-dependent patients without current depression, consistent with the well-known efficacy of bupropion as well as nortriptyline³⁶ for smoking cessation.

The story of antidepressants and nicotine dependence is an interesting one in showing that antidepressant medications may have effects other than treatment of depressive disorders per se. The evidence suggests nortriptyline was helpful by reducing the dysphoria that patients experience immediately after quitting cigarettes, independent of a past history of depression.³⁶ Note that patients with current major depression were excluded from this trial³⁶ and virtually all other smoking cessation trials. Thus, here, nortriptyline appeared to treat withdrawal symptoms.

Another meta-analysis was conducted among studies of patients with opioid dependence and depression, including both studies that required a DSM diagnosis of depression and studies that merely required depressive symptoms as indicated by an elevated score on a depression scale at treatment entry.³⁷ More than half of the studies reviewed were negative or inconclusive, but there was, again similar to the previous finding, a strong relationship between demonstrated beneficial effect of medication and low placebo response.³⁷ Studies that select patients based simply on an elevated score on a scale measuring depressive symptoms probably select a more heterogeneous sample that contains a mixture of transient, substance-induced effects (intoxication, withdrawal, effects of chronic substance use) as well as depressive disorders that would meet DSM criteria had a diagnostic history been conducted. The heterogeneity of outcome and the preponderance of negative studies here support our recommendation regarding the importance of a clinical diagnostic history and diagnosis of a current DSM depressive disorder when evaluating depression for treatment among substance-dependent patients.

SUMMARY OF CLINICAL RECOMMENDATIONS

A summary of the analysis of the moderators, and the clinical implications that we infer from them, is shown in Table 1 (see page 735). From the association of high placebo response, absence of diagnosis during abstinence, and presence of a manual-guided psychosocial intervention for substance dependence, with lack of medication effect we infer that entry into treatment for a substance use problem, particularly if an evidence-based psychosocial intervention is offered, often results in substantial improvement in depression, such that specific antidepressant treatment is not needed. This could result from reducing substance use, which in turn reduces depression symptoms caused by substances (ie, dysphoria related to intoxication, withdrawal, chronic use, or the stress of the lifestyle of an addicted patient). It could also result from direct beneficial effects of treatment for substance dependence on depression. Manual-guided interventions such as relapse prevention feature modules on how to handle bad moods, which resemble approaches to treatment of depression used in effective psychotherapeutic methods for depression such as cognitive behavioral therapy. This is also

not surprising, given well-known observational studies showing that entry into treatment is associated with improved depression.^{9–13}

Thus, the obvious clinical recommendation is to always initiate treatment for the substance use disorder, and allow at least a week or two to observe whether mood will improve with this alone. Treatment options for the substance use disorder would include hospitalization, outpatient behavioral or psychosocial treatments, or medications. Among behavioral treatments, consideration should be given to those that are manual guided and evidence-based, as suggested by the moderator analysis¹⁹ as well as outcome of depression symptoms in other trials of approaches such as the community reinforcement approach for treatment of substance abuse.³⁸ Medications would include methadone¹² or buprenorphine for opioid dependence and naltrexone or disulfiram for alcohol dependence.^{39,40} How long to wait for after abstinence, or substantial reduction in substance use, to be achieved (1 week, 2 weeks, 1 month) depends upon clinical judgment and how long the dysphoric effects of the substances that a given patient has been taking might be expected to last.

The exception to this guidance would be if the depression is severe and/or obviously independent (eg, a patient who is currently drinking, but has a past history of major depressive episodes while abstinent and currently has substantial suicidal ideation). Reliable semi-structured clinical interviews have been developed for diagnosing independent depressive disorders (in the DSM-IV sense), even in the presence of current substance use, the best developed being the Psychiatric Research Interview for Substance and Mental Disorders (PRISM).^{8,41} Work with the PRISM to date has focused on alcohol, opioids, or cocaine and may need to be updated to address the relationship between depression and cannabis dependence, a common comorbidity particularly among adolescents and young adults.^{42,43}

It is important to note that a recent large study, which used the PRISM to select outpatient alcoholics with major depression, and also required depression to persist during at least a week of abstinence, yielded a high placebo response rate and no clear beneficial effect of medication.

⁴⁴ Perhaps one week is too short of a wait among alcohol-dependent patients. In any case, more

research is needed on diagnostic criteria that would select good candidates for antidepressant medication. In the meantime, there remains an important role for clinical judgment. Factors that might also be taken into account could include past history of independent major depression, family history of depression, or past history of good response to antidepressant medication. Another approach that has been suggested is that a depression that develops during a stable period of substance use may be more likely an independent depression, compared with a depression that emerges during a period of either escalating use or cessation of use.^{45,46}

That the findings were inconsistent for SSRI antidepressants^{35,37} is intriguing, given that SSRIs have been associated with no benefit, or even worse drinking outcome, in several studies among alcoholics not selected for depression, but with the early onset alcohol dependence^{47,48} and a similar pattern among patients with PTSD and depression treated with sertraline.⁴⁹ On the other hand, several of the largest beneficial effects of medication were demonstrated among alcoholics with major depression, diagnosed on inpatient units after at least a week of abstinence.^{21,25} A recently published study among adolescent patients with substance use disorders, conduct disorder, and major depression found fluoxetine beneficial for depression outcome, but not substance use outcome.⁵⁰ We continue to favor SSRIs as the first line of treatment because of their good safety and tolerability, and low levels of sedation, suggesting less risk of adverse interactions with substances of abuse. However, if an SSRI trial fails, or there is a history of failed SSRI trials, a non-SSRI, with dopaminergic, noradrenergic, or mixed mechanisms of action should be tried (eg, bupropion, venlafaxine, duloxetine, mirtazapine, or even a tricyclic antidepressant). There is little direct evidence on the efficacy of any of these among depressed substance abusers, other than for tricyclics where the evidence is substantial. Tricyclics, however, are associated with more side effects and toxicity than the other new generation medications.

That the beneficial effects of antidepressant medication are clearer among alcohol-dependent patients, than among drug-dependent patients^{19,35} suggests to us that more research is needed in the latter group. There were fewer studies among opioid- or cocaine-dependent patients, and no published controlled trials to date among cannabis-dependent patients. In the meantime, more caution is needed in approaching those patients, and more clinical judgment in regard to which depression disorders should be treated. Again, a history of past independent episodes of depression, family history of depression, or past successful trials of antidepressant medication would all weigh in favor of initiating medication treatment.

It is perhaps counterintuitive, although noteworthy, that studies including dysthymia, and studies with more or less severely depressed samples, showed equivalent effect sizes.¹⁹ This finding suggests that chronic depression, even if more mild, should be taken seriously among substance-dependent patients. A chronic course of depression offers more opportunities to examine whether the depression persisted during ups and downs of substance use, and has been associated with greater effect sizes, compared with placebo, in studies of treatment of routine outpatient depression.

CONCLUSIONS

One could argue that we have come a long way to conclude what we already knew: namely, that it is important to treat the substance use disorder, to try to get the patient abstinent (or at least to cut down on substance use), and to initiate antidepressant medication when we have good evidence that the depression is independent of substance use and/or severe and convincing enough to warrant immediate attention. However, what we have as a result of the accumulated evidence of dozens of studies, not to mention the considerable investment of funds and of time and effort on the part of all the investigators involved, is a more detailed and nuanced evidence-base upon which to craft guidelines, as well as areas to focus on in future research.

Meta-analysis is a valuable tool for summarizing treatment research and formulating treatment guidelines. Studies should be designed using similar designs and common outcome measures, so that future meta-analytic work is facilitated. The fact that the antidepressant medication trials had a similar design of a placebo controlled trial, 6 to 12 weeks in length, and used the HAM-D and some measure of quantity/frequency of substance use as outcome measures greatly facilitated the meta-analysis. Meta-analysis also depends upon the published reports analyzing the outcome data and presenting it in a way that is similar to past papers, so that comparison of outcome between papers is facilitated.

Thus, despite today's ascendancy of powerful new statistical models, all outcome papers should include simple summary measures, such as means and standard deviations on outcome measures, proportions of responders in each treatment groups, and ideally calculations of effect size, so that studies can be readily compared. Finally, for a meta-analysis to arrive at accurate, unbiased estimates of treatment effects, negative studies need to be published, as well as positive ones. Investigators need to appreciate the value of negative studies and stay motivated to publish them, and journal editors and reviewers likewise need to value negative studies.

Acknowledgments

Research in this article has been supported by Grants P50 DA09236 and K24 DA022412 (Dr. Nunes) and K02 000465 (Dr Levin).

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TABLE

A Summary of the Meta-analysis of Placebo-controlled Trials of Antidepressant Medication among Substance Dependent Patients with Depressive Disorders¹⁸

Methodological Feature Functioning as Moderator and Direction of the Effect	Implied Recommendations for Evaluation and Treatment of Patients with Co-occurring Mood and Substance Use Disorders
<p>Placebo response: Low placebo response associated with greater effect of medication; high placebo response associated with lack of effect of medication</p> <p>Diagnosis of depression after at least a week of abstinence: Diagnosis during abstinence associated with greater effect of medication; studies that diagnosed depression in actively using outpatients had more inconsistent results</p> <p>Manual-guided psychosocial intervention offered to all patients in trial: Trials where a manual-guided intervention was offered to all patients had high placebo response and less evidence of efficacy of medication compared with placebo</p>	<p>Initiate treatment for the substance use disorder: Could be hospitalization for detoxification, outpatient psychosocial treatment, or the latter plus an effective medication such as naltrexone (alcohol dependence) or buprenorphine (opioid dependence)</p> <p>Try to get the patient abstinent or at least to substantially reduce substance use: Depression may resolve with abstinence; this may be discussed with the patient to promote motivation</p> <p>Depression that persists for at least a week after abstinence is achieved should be considered for specific antidepressant treatment: A depressive disorder (major depression or dysthymia) that persists after a week or more of abstinence is likely independent of substance abuse and should be treated; exactly how long to wait after abstinence is achieved is up to clinical judgment; if patient cannot achieve abstinence, then clinical judgment may dictate treating the depression depending upon its history (evidence of past episodes of independent depression) and severity</p> <p>Consider a psychosocial/behavioral treatment for depression: Cognitive behavioral and other psychotherapeutic techniques are effective treatments for depression and do not carry concerns about side effects and interactions of medications with substances of abuse; more research on such treatments is needed</p>
<p>Class of antidepressant medication: Most positive studies involved tricyclic antidepressants or other medications with noradrenergic or mixed mechanisms; most SSRI studies were negative; two SSRI studies were positive in samples of severely depressed inpatient alcoholics who were abstinent when depression was diagnosed</p>	<p>Give more consideration to non-SSRI antidepressant in patients with co-occurring depression and substance use disorders: SSRIs still a good first choice due to safety, tolerability, low sedation, and fewer concerns about interactions with drugs or alcohol; if SSRI trial fails, or past history of failed SSRI trial, move to medication with noradrenergic or mixed mechanism of action; more research needed with such medications among patients with comorbidity</p>
<p>Alcohol dependent patients versus drug dependent patients: More consistent evidence of medication benefit among depressed alcoholics; among cocaine or opioid dependent patients, studies more inconsistent; fewer studies among drug than among alcohol dependent patients</p>	<p>Proceed with more deliberation among drug dependent patients with depression: Make efforts to get patient abstinent and initiate psychosocial and pharmacological interventions for the drug problem; use clinical judgment to determine if depression is independent of substance abuse or severe enough to warrant specific antidepressant treatment; more research needed on drug dependent populations</p>
<p>Type of depression (major depression compared with dysthymia) and severity of depression did not predict effect size: Caution required since this is a null finding and based on study level rather than patient level data</p>	<p>Chronic depression, even if more mild in severity, should be taken seriously among substance dependent patients: Initiate treatment for substance use disorder, try to get the patient abstinent, and consider antidepressant medication if depression persists in abstinence or clinical judgment suggests it is independent</p>