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Treatment of Substance Abusing Patients with Comorbid Psychiatric Disorders

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Abstract

Objective—To update clinicians on the latest in evidence-based treatments for substance use disorders (SUD) and non-substance use disorders among adults and suggest how these treatments can be combined into an evidence based process that enhances treatment effectiveness in comorbid patients.

Method—Articles were extracted from Pubmed using the search terms “dual diagnosis,” “comorbidity” and “co-occurring” and were reviewed for evidence of effectiveness for pharmacologic and psychotherapeutic treatments of comorbidity.

Results—Twenty-four research reviews and 43 research trials were reviewed. The preponderance of the evidence suggests that antidepressants prescribed to improve substance-related symptoms among patients with mood and anxiety disorders are either not highly effective or involve risk due to high side-effect profiles or toxicity. Second-generation antipsychotics are more effective for treatment of schizophrenia and comorbid substance abuse and current evidence suggests clozapine, olanzapine and risperidone are among the best. Clozapine appears to be the most effective of the antipsychotics for reducing alcohol, cocaine and cannabis abuse among patients with schizophrenia. Motivational interviewing has robust support as a highly effective psychotherapy for establishing a therapeutic alliance. This finding is critical since retention in treatment is essential for maintaining effectiveness. Highly structured therapy programs that integrate intensive outpatient treatments, case management services and behavioral therapies such as Contingency Management (CM) are most effective for treatment of severe comorbid conditions.

Conclusions—Creative combinations of psychotherapies, behavioral and pharmacological interventions offer the most effective treatment for comorbidity. Intensity of treatment must be increased for severe comorbid conditions such as the schizophrenia/cannabis dependence comorbidity due to the limitations of pharmacological treatments.

Keywords

Substance Use Disorder; Comorbid; Psychiatric Disorder; Treatment

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1. Introduction

The last ten years of research has verified that mental disorders are associated with risk for later substance use conditions (Swendsen et al., 2010). There have been reviews of “comorbid” conditions over that time but most have focused on treatment of a particular non-substance condition and substance abuse, e.g., schizophrenia and substance abuse (Wobrock and Soyka, 2009), Attention Deficit Hyperactivity Disorder (ADHD) and SUD (Upadhyaya, 2007), Post Traumatic Stress Disorder (PTSD) and substance abuse (Schafer and Navajits, 2007).

Few papers have reviewed treatment for multiple non-substance and substance-related conditions. For example, Brady and colleagues (2007) reviewed treatments of substance use disorders that are comorbid with psychotic disorders, mood disorders, PTSD, ADHD and personality disorders. The Brady and colleagues (2007) review focused on pharmacologic treatment but indicated that Cognitive-Behavioral Therapy (CBT) has shown effectiveness for comorbid PTSD and substance use disorders and that CM has shown effectiveness among patients with personality disorders. Kay-Lambkin and colleagues (2004) review of treatment effectiveness focused on findings of psychotherapies, primarily Motivational Interviewing (MI) and CBT but did not discuss Contingency Management or 12-Step treatment.

While the existing reviews are enlightening, there has not been enough synthesis of research to inform clinicians of treatment combinations that are likely to be effective in clinical practice. Orford (2008) and others have recently called for changes in the process of research that recognizes addiction as a multiply determined disorder that cannot be adequately treated by applying the narrow biomedical model of prescribing one medication or one psychosocial treatment. Moos (2007) has called for more emphasis on “empirically supported treatment processes” rather than empirically supported treatments. McClellan (2010) has described this as practicing “evidence *informed* treatment” (Clinical Trial Network Steering Committee, September, 2010, italics added).

The purposes of the current review are to: 1) update clinicians on the latest in evidence-based treatments for substance use and non-substance use disorders among adults and 2) suggest how these treatments might be combined into an evidence based process that enhances treatment effectiveness in comorbid patients.

2. Method

We extracted articles from Pubmed using the search terms “dual diagnosis,” “comorbidity,” and “co-occurring disorders” and reviewed the evidence for both pharmacologic and psychotherapeutic treatments of the comorbidity cited in each article. Tiet and Mausbach (2007) indicate that therapies designed for individual psychiatric and substance use conditions can be effective for treatment of dual diagnosis. Therefore, we also reviewed treatments of individual SUD and Non-SUD psychiatric conditions with putative positive effects in order to consider their effectiveness for particular comorbidities.

The current review focuses on recommendations for combining treatments that are likely to be effective in the treatment of patients with comorbidities of substance use disorders and Axis I non-substance disorders. Our objective is to apply clinical wisdom and logic in hypothesizing how combinations of treatments may be used to bring about more effective treatments for comorbid conditions. This, in fact, is the process that clinicians providing clinical care “in the real world” must apply in developing treatment plans for their patients.

As a result of the above objective we exercised latitude for the possible over-inclusion of studies because we considered it less detrimental to our focus of using a best-estimate process in treatment planning. We limited ourselves to studies of medications and evidence-based psychotherapies and behavioral therapies conducted in Westernized societies, e.g., MI, CBT, and CM. We highlight reviews of comorbid treatment for DSM-IV defined clinical populations and randomized clinical trials (RCT), as well as the results of less stringently controlled studies. We do not include studies of sub-groups of populations such as incarcerated women or HIV-positive patients. Nor do we include case reports or single case studies. We included studies of anti-agonist medications for treatment of substance abuse, e.g., naltrexone. We also included studies of agonist therapies such as methadone when the report focuses on evidence-based treatments for comorbidity. Tables 1 and 2 provide a synopsis of the reviews and studies included, the methods used and outcomes of each study.

3. Results

3.1 Pharmacotherapy of Psychosis and Alcohol and Cannabis Use Disorder

The drugs used most by schizophrenic patients are alcohol, cannabis and cocaine and the schizophrenia/cannabis comorbidity has been characterized as an epidemic (Green et al., 2005; Wilson & Cadet, 2009). Emergency department studies find that cannabis is the drug most often associated with exacerbations of schizophrenia and acute psychotic episodes and cannabis use contributes to poor treatment outcomes for psychotic patients (Latt et al., 2011; Moore et al., 2007). The atypical antipsychotic clozapine has been found to be the most effective medication in reducing alcohol and cannabis use (Green et al., 2003; Lybrand & Caroff, 2009; San et al., 2007), while findings on other medications are equivocal. Baker and colleagues' (2010) review suggests that using antipsychotics may be helpful in reducing cannabis use but studies that have found improvement have used active psychotherapies, thereby obscuring the degree of benefit from pharmacotherapy. Two recent RCTs (Sevy and colleagues (2011); van Nimwegen et al., 2008) found no difference between patients receiving olanzapine or risperidone on cravings or use of cannabis.

3.2. Pharmacotherapy of Psychosis and Cocaine Use Disorder

Two open-label studies found one first generation antipsychotic, flupenthixol decanoate, to be effective against cocaine and alcohol use (Levin et al., 1998, Soyka et al., 2003) and two small studies (Siris et al., 1993; Ziedonis et al, 1992) found that TCA antidepressants were beneficial in reducing use of cocaine and other substances. It is reasonable to assume that SSRIs may also be effective, although there is little evidence for this (Wobrock and Soyka, 2008). Two studies found that schizophrenic patients treated with risperidone and olanzapine had significant reductions in cravings and use of cocaine, compared to patients treated with haloperidol (Smelson et al., 2002; 2006). Conversely, Sayers and colleagues (2005) found a significant difference in cravings for cocaine among patients receiving haloperidol, compared to olanzapine. Sayers and colleagues (2005) measured cravings by self-report while Smelson and colleagues (2006) used a cue response method for measuring cravings, which may be more reliable. Interestingly, the olanzapine group in the Sayers and colleagues (2005) study displayed a trend toward fewer positive drug screens for cocaine over the course of the 6 month study. Smelson and colleagues (2006) followed their original study up with another RCT and found that patients treated with olanzapine had fewer cravings compared to those treated with haloperidol.

Petrakis and colleagues (2006) found no significant difference on Addiction Severity Index (ASI) scores among schizophrenic patients treated with second generation antipsychotics

(SGAs), compared to those treated with first-generation antipsychotics when demographic and clinical variables were accounted for in multivariate analyses.

Overall, one inference to be drawn from these studies is that all antipsychotics improve the positive symptoms of schizophrenia but second generation antipsychotics appear to be most effective in reducing cravings for cocaine. Smelson and colleagues (2008) suggest that lower side effect profiles also make newer antipsychotics a better choice compared to first-generation antipsychotic medications.

3.3. Behavioral and Psychotherapeutic Interventions for Psychotic and Substance Use Disorders

Unlike pharmacotherapy of comorbid psychotic and substance use disorders, behavioral and psychotherapeutic treatments are not specific to a particular substance. Drake and colleagues (2008) indicate that treatment should be integrated with an emphasis on engaging patients and motivational counseling based on the Transtheoretical Model (Prochaska & DiClemente, 1992) of relapse prevention strategies and maintaining an active therapy in order to retain patients in treatment. One recent, large scale RCT suggests that combined MI, CBT and family therapy can be an effective approach for reducing substance use among schizophrenic patients for at least one year (Barrowclough et al., 2010). Another study found a once weekly, 90 minute group therapy was effective against psychosis and substance use among a group of highly motivated patients who were consistently encouraged to participate (James et al., 2004). This approach holds promise if it is effective with a more representative sample of the clinical population.

The preponderance of the evidence suggests that CM is effective against cannabis use and mood disorders but that patient drug use returns to baseline when it is stopped (Moore et al. 2007) Hjorthøj and colleagues (2009) report that MI and CBT appear to be effective when cannabis outcomes are grouped with other drug outcomes but, in fact, are ineffective against cannabis use as an outcome separate from other drugs. The authors suggest that studies of outcomes for several different types of drugs together may be overlooking differential effects of interventions. Psychotherapies such as CBT and MI are often used as stand-alone therapies in non-intensive, one-on-one treatments. However, taken together, these findings suggest that treatment of moderate to severe cannabis use disorder requires more intensive approaches that should include CM and intensive outpatient therapy or partial hospitalization.

Bellack and colleagues (1998) developed a combined MI/CM approach that includes relapse prevention strategies and short-term goal setting which has been found effective in a RCT (Behavioral Treatment for Substance Abuse in Severe and Persistent Mental Illness (BTSAS)). Fifty-nine percent of the BTSAS group vs. 25% of the control sample stayed in treatment and provided clean urine samples. Patient self-determination in goal setting has been emphasized as a critical part of this approach (Tenhula et al., 2009). Lubman and colleagues (2010) describe BTSAS as a complex, multifaceted approach which is difficult to implement but that refinement of the approach currently includes a case management component that may improve its effectiveness (Bellack et al., 2006).

Leweke and colleagues (2004) discuss the possibility that schizophrenic patients are more vulnerable to the deleterious effect of cannabis because of sensitivities in the endogenous cannabinoid system and because of their particular reactions to exogenous cannabinoids. They conclude that it is critical for psychotic patients to receive intensive case management services and specialized psychotherapeutic programs and that they be strongly encouraged to stop their use of cannabis.

3.4. Combined Treatment for Alcohol Abuse and Depression

SSRI antidepressants have been found to be effective against mood disorders but contradictory evidence exists for the effect of SSRI antidepressants on drinking outcomes (Mariani and Levin, 2004; Torrens and colleagues, 2005). Improvement in drinking outcomes appear to be related to improvement in depression and the best outcomes have been found in studies combining antidepressants with psychotherapy. One of these studies used fluoxetine and CBT (Cornelius et al., 1997) and was effective in improving drinking outcomes. Another 24 week long study showed efficacy of desipramine compared to most other studies that were 12 weeks or less (Mason et al., 1996). Moak and colleagues (2003), used CBT specifically targeted the alcohol use and depression and patients treated with sertraline and the CBT had fewer drinks compared to those on placebo. The individual therapy used in the Moak and colleagues (2003) study appears to have been a more structured approach compared to group formats, or less structured psychotherapies such as supportive psychotherapy. Pettinatti (2004) points out that both the Cornelius and colleagues' and Mason and colleagues' trials did not start treatment until after their patients had been treated on an inpatient unit for one or two weeks, suggesting that antidepressant treatment may be more effective against drinking outcomes when patients have two weeks of abstinence or inpatient care.

3.5. Pharmacotherapy of Cannabis Use Disorder and Depression

Moore and colleagues (2007) review of the psychosis comorbidity suggests a causal relationship between cannabis abuse and psychotic disorders since patients with substance induced psychoses often report an acute onset of symptoms associated with taking the drug. However, a causal interpretation of the relationship between cannabis use disorders and depression is not as clear due to smaller effect sizes in underpowered studies of affective disorders. Clinical experience also suggests the reverse relationship, i.e., depression contributing to cannabis use, because affective syndromes associated with cannabis abuse often present with a much more insidious onset prior to addiction. Only one study (Cornelius et al., 1999) found a significant time by treatment effect in favor of fluoxetine against use of cannabis among depressed older adolescents.

3.6. Combined Treatments for Cocaine Use Disorder and Depression

Torrens and colleagues (2005) reviewed five studies of the effectiveness of antidepressants among patients with comorbid cocaine dependence and depression and report that antidepressants are somewhat effective for reducing depressive symptoms but not effective for reducing cocaine use. This is consistent with Schmitz and colleagues (2001) who found no differences on cocaine use between a group taking fluoxetine and one taking placebo. However, Schmitz et al., found CBT and relapse prevention psychotherapy improved depressive symptoms and cocaine outcomes in their sample. Furthermore, regarding behavioral therapies, CM has been found effective for patients providing drug free urines among depressed cocaine users (Torrens et al., 2005).

Cornelius and colleagues (1998) found that cocaine use exacerbates depression and this could account for the reduced effect of antidepressants on depression. Similarly, two studies in Torrens' and colleagues (2005) review found limited effectiveness of antidepressants on cocaine use and that any effectiveness was likely to be related to improvement in depression. Therefore, it should be noted that the positive effect of decreased mood symptoms on substance use argues for not taking the time to determine the etiology of the mood disorder and for treating the mood disorder early and aggressively (Davis et al., 2008).

3.7. Combined Treatments for Opioid Abuse and Depression

Treatment for comorbid opioid dependence and depression has focused on studies that included patients on methadone maintenance. Seven reviewed studies found that treatment with antidepressants was not effective for treatment of depression among depressed patients with opioid dependence (Torrens et al., 2005). Therefore, while primary treatments such as methadone, buprenorphine and residential treatment have been associated with improvements in depression, studies do not consistently support the effectiveness of antidepressants for reducing depression or opioid use.

One exception is Nunes and colleagues (1998) study of imipramine. In another placebo controlled study, doxepine was found to be effective for reducing depression among opioid dependent patients (Titievsky et al., 1982). Nunes and colleagues (1998) found a trend for methadone patients treated with imipramine for providing more consecutive cocaine free urines compared to those on placebo. A meta-analysis of the Nunes and colleagues (1998) and another study (Woody et al., 1975) found a statistically significant difference for doxepine and imipramine to be superior to placebo for reducing illicit opioid use. Here again, Nunes and Levin (2004) report that antidepressants appear to have an indirect effect in reducing substance use through their effects on depression.

3.8. Pharmacotherapy of Bipolar Disorder and Alcohol Use Disorder

Pharmacotherapy of comorbid SUD and bipolar disorder typically involves use of mood stabilizers or atypical antipsychotics and antidepressants for the mood disorder and concomitant use of a medication specifically for the SUD, e.g., naltrexone for alcohol use disorder. It is important to treat patients prophylactically against antidepressant-induced mania. Azorin & Kaldjian (2009) suggest that a best practice strategy is to begin with the mood stabilizer/antipsychotic and add antidepressants or other approved drugs, as needed by trial and error. Levin and Hennessy (2004) reviewed treatments for bipolar disorder and SUD and noted that use of add-on medications such as anticonvulsants to lithium have primarily shown some effectiveness in reducing cravings but not actual substance use. In contrast to the Levin and Hennessy (2004) review, lithium has been found to be effective against relapse among patients with bipolar disorder and alcohol dependence (Maremmani et al., 2010) and lithium+valproate has been found to reduce drinking among bipolar patients (Salloum et al., 2005).

3.9. Pharmacotherapy of Cocaine, Cannabis Use Disorders and Bipolar Disorder

Nordstrom and Levin (2007) report on several trials that investigated cannabis and other drug use among comorbid patients. One study found decreased cannabis use among patients in a small sample of adolescents treated with lithium but there are no other data to support the conclusion that lithium is effective in decreasing cannabis use (Geller et al., 1998). One RCT of lithium and divalproex vs. lithium alone found some evidence of effectiveness for reducing use of cannabis and cocaine among comorbid bipolar patients (Kemp et al. 2009). However, the sample in this study was quite small because only 20% of patients were able to be randomized to trial following a stabilization period. With this exception, RCTs of cannabis dependent patients using divalproex, bupropion, lamotrigine, gabapentin, and nefazadone found that none of these medications were effective for reducing cannabis or cocaine use among comorbid patients (Levin et al., 2004; Elkashef et al., 2008; Maremmani et al., 2010).

3.10. Psychotherapy for Bipolar Disorder and Substance Use Disorders

Patients with bipolar disorder are difficult to treat because of the wide range of emotions they experience. This often affects their relationship with their therapists and Quello and

colleagues (2005) point out the importance of developing a close working relationship with bipolar patients. Integrative Group Therapy (IGT) is a CBT-based intervention developed by Weiss and colleagues (1999) for comorbid SUD and bipolar disorder. The treatment targets both mood and substance use symptoms and has shown efficacy for reducing substance use and mood symptoms in an open label study (Weiss et al., 2000).

One other behavioral treatment has been developed specifically for bipolar disorder, Interpersonal and Social Rhythm Therapy (IPSRT) (Frank et al., 2000). IPSRT focuses on helping bipolar patients gain insight in the relationship between mood changes and interpersonal events. A major objective of therapy is to stabilize circadian rhythm by structuring daily routines, including sleep cycles and by addressing interpersonal problems. The therapist provides psychoeducation about the disorder and the patient and therapist work together on symptom control by the patient incorporating strategies for managing their daily activities. Outcome studies indicate that IPSRT is more effective for preventing relapse, improving functioning in relationships, and increasing life satisfaction than medication management alone (Chambless & Hollon, 1998; Miklowitz et al., 2007; Miklowitz et al., 2007).

3.11. Pharmacotherapy of Anxiety Disorders and Comorbid SUD

Brady and Verduin (2005) reviewed the literature and stress that many symptoms of withdrawal from substances can be mistaken for anxiety and that detoxification from substances, often result in the clearing of what appear to be anxiety-related symptoms. Tricyclic antidepressants have received the most empirical support for treatment of anxiety disorders, but their high side effect profiles and toxicity precludes their use as a first-line treatment (Brady & Verduin, 2005). The SSRIs or SNRIs (e.g., venlafaxine) are generally considered first-line treatments with tricyclics and, due to the high risk for addiction, the use of benzodiazepines is not recommended for use in substance-abusing populations (Fatseas et al., 2010). Related to this is the important consideration of using medications that are not likely to contribute to potentially toxic interactions with drugs and alcohol (Brady & Verduin, 2005). Cornelius and colleagues (2003) reviewed the literature and report that buspirone has been found to be effective for alcohol dependent patients with comorbid anxiety.

3.12. Behavioral and Psychotherapy of Anxiety Disorders

CBT has been found to be highly effective against anxiety associated with all DSM-defined anxiety disorders, as long as therapists are well-trained and supervised and use manual-based therapies (Hofmann & Smits, 2008; Stewart & Chambless, 2009). Hesse (2009) reviewed the available studies on integrated psychological treatment for comorbid anxiety and SUD and indicates that psychological intervention increased days abstinent, decreased symptoms, and improved retention, albeit these last two at a non-significant level. He concluded that psychological intervention alone is not sufficient for treatment of anxiety and SUD and that there is a need for other integrated treatments for this comorbidity. Combining CBT with antidepressants has the most evidence-based support for treatment of comorbid opioid and anxiety disorder (Fatseas et al., 2010). One trend that is emerging is that provocative therapies such as imaginal exposure and the homework for CBT can be beneficial but should not be emphasized prior to control of substance use because the anxiety associated with the therapy may exacerbate substance abuse.

3.13. Pharmacotherapy of PTSD, Alcohol Abuse and Opioid Abuse

Comorbid PTSD and substance use disorders are prevalent in clinical populations with current comorbidities at 14-41% (Shafer and Najavits, 2007) and symptoms tend to be more severe in comorbid patients compared to patients who have only one or the other disorder

(Jacobsen et al., 2001). Women are more likely to need treatment for PTSD (Bromet et al., 1998) and it appears that the substance-related comorbidities of PTSD patients may be with harder drugs such as amphetamines and opioids, rather than with alcohol and cannabis (Mills et al., 2006; Najavits et al., 1997). One caveat to this is that alcohol use disorders are quite high among combat veterans with PTSD (Jacobsen et al., 2001). SSRI antidepressant medications and topiramate may be effective pharmacologic treatments for the PTSD but there is little evidence that SSRIs are effective against alcohol dependence (Labbate et al., 2004; Brady et al., 2005). In favor of SSRI treatment, Brady et al. (2005) found patients with less severe alcohol dependence and early onset PTSD who were treated with sertraline drank less than the placebo-treated group. Conversely, patients in the placebo group with later onset PTSD and severe alcohol dependence drank less alcohol. Clearly, subgroups associated with the PTSD and alcohol abuse comorbidity must be considered in treatment planning.

Among alcohol dependent male veterans with PTSD, naltrexone and disulfiram were found to be effective in reducing drinking days per week and consecutive non-drinking days, compared to a placebo treated group (Petrakis et al., 2006). Interestingly, patients in the disulfiram only group also reported decreased PTSD symptoms. This finding represents a potential confounding factor because abstinence could be responsible for the improvement of PTSD symptoms and suggests that patients who choose to pursue abstinence as a treatment objective may be more likely to experience reduced PTSD symptoms. Furthermore, research suggests that the severity of its effects for those who drink on it, it should be used only in highly structured treatment programs, or with people who have high levels of support for remaining abstinent. In fact, disulfiram is most effective among older males who have high motivation to abstain from alcohol (Mariani and Levin, 2004).

Trafton and colleagues (2006) found that opioid substitution therapy was as effective for reducing other substance use among opioid dependent patients who had PTSD as for those who did not. As above, it is possible that a confounding effect was operating in this study because PTSD patients received higher doses of medication and attended more counseling sessions, suggesting that higher doses of medication and more frequent counseling sessions moderates the effect of PTSD among patients with opioid dependence.

3.14. Psychotherapy and Behavior Therapy of PTSD

The current evidence suggests that PTSD often causes or exacerbates substance use compared to the reverse temporal order (Back et al., 2006). Cravings for substances increase among PTSD patients in response to trauma-related cues and one treatment study found that patients who received a course of imaginal exposure therapy reported less distress and decreased alcohol cravings compared to a control group (Coffey et al., 2005; Coffey et al., 2006; Saladin et al., 2003). A review of treatment studies for comorbid PTSD and SUD (Tiet & Mausbach, 2007) indicates that, although cue-exposure therapies are considered first-line psychotherapies for PTSD, they should only be used for patients with comorbid PTSD/SUD after substance abuse is under control. This makes clinical sense as the exacerbation of PTSD symptoms often stimulate drug cravings and increase the risk for substance abuse. A very good strategy for controlling substance use prior to uncovering therapies is to use contingency management. One recent study found that CM resulted in reduced cocaine drug use among opioid dependent patients with PTSD compared to a control condition (Mancino et al., 2010).

In a recent treatment study from the Clinical Trials Network (NIDA), Hien and colleagues (2010) conducted a RCT among women with PTSD and a substance use disorder. Participants received treatment as usual and 12 sessions of a specific psychotherapy entitled Seeking Safety (SS), or 12 sessions that focused on women's health education. These

investigators (2009; 2010) hypothesized that reducing PTSD symptoms would result in reduced substance use but not the reverse. They found no overall differences between the groups but found that participants with the most severe substance abuse in SS decreased their substance use more than those in the control condition.

One other model associated with physical or sexual abuse is Trauma Recovery and Empowerment Model (TREM). TREM is a 33 session group treatment that focuses on support for the impact of abuse while enhancing empowerment through developing coping skills (Fallot and Harris, 2002). A recent review of treatment for PTSD and alcohol dependence emphasizes the importance of using a multi-faceted approach to treatment, including structured psychotherapeutic approaches like Seeking Safety and TREM in conjunction with SSRI antidepressants or topiramate (McCarthy and Petrakis, 2010). This strategy is similar to that advocated for treatment of comorbid PTSD and opioid dependence (Trafton et al., 2006). Several other manualized treatments for PTSD and various drug disorders have been developed that combine MI, CBT, psychodynamic, case management and 12-Step treatments (Back et al., 2001; Brady et al., 2001; Donovan et al., 2001; Triffleman et al., 1999; Zatzick et al., 2004). Although these models have much less empirical support such integration of evidence-based practices warrants further investigation.

3.15. Pharmacotherapy and Psychotherapy of SUD and Generalized Anxiety Disorder(GAD)

Research on pharmacotherapy of GAD is scant and there is even less of it for comorbid GAD and substance use disorders. Brady & Verduin (2005) noted that GAD cannot be accurately evaluated during active withdrawal but antidepressants should be considered if GAD symptoms persist following detoxification. Davidson (2009) reviewed the literature on pharmacotherapy of GAD and indicates that TCAs, SSRIs and SNRIs are effective in treating it. Furthermore, imipramine has been found to be superior to diazepam in reducing anxiety (Rickels et al., 2003) and in another paroxetine was more effective than chlordesmethyldiazepam (Rocca et al., 1997).

Simon (2009) suggests that patients with GAD are often not treated aggressively enough despite the evidence that untreated GAD often leads to major depression. In addition to antidepressants, Kranzler and colleagues (1994) found use of buspirone, a non-addictive benzodiazepine resulted in reduced anxiety and some alcohol-related improvements. Buspirone was not effective for reducing anxiety among methadone treated opioid users in another placebo-controlled trial but showed some positive effects against depression and substance abuse (McCrae et al., 2004).

A psychotherapy that has been adapted from chronic pain management, Affect Focused Body Psychotherapy (ABP) (Thornquist and Bunkan, 1990) has been used with GAD patients. ABP is based on exploring affect related to anxiety and integrates bodily techniques into a psychodynamic treatment. One randomized study found patients in the ABP group were improved over the TAU condition. However, the TAU condition consisted of directive counseling using a problem solving approach, while the approach ABP was more supportive, exploratory and less-directive. A cluster analysis confirmed that the supportive, exploratory aspects of the treatment were more important than the content of the ABP (Berg et al., 2008).

3.16. Pharmacotherapy of Social Anxiety Disorder (SoAD) and AUD

Comorbid SoAD and AUD affects 2.4% of the general population (Schneier et al., 2010). Alcohol is more likely to be abused than other drug by patients with SoAD because of its

tranquilizing effects (Zvolensky & Schmidt, 2004). One possible exception to this may be adolescents who often have easier access to cannabis and the support of its use by their social network. Brady and Verduin (2005) point out that social anxiety can be aggressively treated with pharmacotherapy because, unlike GAD, its anxiety-related symptoms are specific to the social situations which define it. Therefore, the anxiety in these patients should be diagnosed and treated early in order to facilitate their continuing in treatment. MAOI and SSRI antidepressants have been found to be effective for treatment of social anxiety and that paroxetine has specifically been identified as a first-line treatment for social anxiety. In fact, Randall and colleagues (2001) compared 6 alcohol dependent patients with social anxiety patients who received paroxetine to 9 who received placebo over 8 weeks and found the paroxetine group improved significantly on a measure of social anxiety (effect size=.81). In addition to the SSRIs, venlafaxine, bupropion, ondansetron and buspirone are likely to be effective, although we are unaware of any RCTs for using these agents for social anxiety.

3.17. Psychotherapy of Social Anxiety Disorder and AUD

Randall and colleagues (2001) conducted one of the first RCT of comorbid social anxiety disorder and alcohol dependence using individual CBT with comorbid patients based on the manualized treatment used in Project Match (Kadden et al., 1992). One group received CBT for alcohol dependence and the other received CBT that focused on both alcohol dependence and social anxiety disorder. Randall and colleagues (2001) hypothesized that patients in the group that focused on treatment of both disorders would improve more because improvement in social anxiety would decrease the need for self medication.

These investigators found that both groups improved (no significant differences) on percent days abstinent from alcohol and heavy drinking days. Furthermore, both groups improved on social phobia and social anxiety over 12 weeks of treatment and maintained their gains during 3 month follow-up. They noted that one reason why the experimental group did not improve more was due to their possibly drinking more as a result of homework they had to perform that necessarily exposed them to anxiety-provoking situations. Interestingly, the investigators did not encourage attendance at AA meetings but collected data on attendance at AA meetings during the treatment. They found that AA attendance increased in both groups during active treatment and decreased again following the active phase of the study. These findings suggests that patients responded to their improvement by voluntarily attending more AA meetings and suggests further that a group-based intervention, whether it be CBT or, possibly, 12-Step facilitation (Donovan and Floyd, 2008) can be helpful to alcohol dependent patients with social anxiety.

Schade and colleagues (2005) conducted a RCT of CBT for anxiety plus TAU versus TAU among alcohol dependent patients in an intensive outpatient program. Patients in the CBT arm also received fluvoxamine, if they wanted it. While the CBT treatment group had a significantly greater reduction of anxiety, no difference was found between the groups on alcohol relapse rates.

3.18. Pharmacotherapy and Psychotherapy for Panic Disorder and SUD

Reviews of pharmacotherapy for comorbid SUD and panic disorder are quite limited in the literature. Brady and Verduin (2005) indicate that TCA, SSRI and MAOI antidepressants are effective for treatment of panic disorder but emphasize that potentially activating medications such as SSRIs must be monitored closely because they could exacerbate symptoms early on in treatment and increase the risk for drug or alcohol use.

One study of psychotherapy for panic disorder found that 12 hours of CBT for panic added to TAU for alcohol treatment was no more effective against drinking behavior than the alcohol program alone (Bowen et al., 2000). However, more recent studies have found that exposure therapy, consisting of exposure to avoided emotions is beneficial to developing and practicing distress tolerance skills for panic, as well as the negative mood states associated with drug craving (Otto et al., 2004). Furthermore, a study of Panic-Focused Psychodynamic Psychotherapy (PFPP), which focuses on anger recognition and ambivalence related to autonomy and feelings about loss or abandonment, found that 73% of patients assigned to PFPP experienced a significant decrease in panic severity compared to 39% of patients who received a similar amount of relaxation treatment (Milrod et al., 2007).

3.19. Pharmacotherapy and Psychotherapy for Obsessive Compulsive Disorder (OCD) and SUD

CBT is effective against OCD (Hofmann & Smits, 2008) and should be used routinely in the treatment of OCD. However, there has been only one study of comorbid OCD/SUD. Fals-Stewart and Schafer (1992) point out that, symptoms of OCD are often confusing or even nonsensical to the patient and, therefore, patients may be unwilling to even report them. Patients with OCD are, therefore, vulnerable to use of drugs or alcohol and often do not receive treatment. Furthermore, because these symptoms are often not reported the prevalence of OCD among substance abusers is likely to be higher than what is otherwise indicated. Fals-Stewart and Schafer (1992) conducted a RCT using a three-arm design with patients diagnosed with OCD and SUD in a residential setting. The treatment condition was behavior therapy and TAU. One control condition consisted of TAU and another being TAU and relaxation training. They found the combined treatment condition was more effective than the two control conditions for reducing substance use during follow-up.

Ravindran and Stein (2010) and Pittenger and colleagues (2005) have conducted thorough reviews and report that clomipramine was first found to be effective against OCD but that its high side-effect profile has limited its use in clinical practice. Among the newer generation of antidepressants, SSRIs are beneficial but two SNRI antidepressants, venlafaxine and duloxetine, have recently been found to be among the best antidepressants for treatment of OCD. Two atypical antipsychotics, risperidone and olanzapine have been found to be effective against OCD symptoms. A third generation neuroleptic, aripiprazole also shows promise in this area. Pittenger and colleagues (2005) suggest that treatment should consist of antidepressants as initial monotherapies with use of atypical antipsychotics as augmentation for refractory OCD symptoms.

3.20. Pharmacotherapy of AUD

Consistent with some findings cited above, disulfiram is a highly effective adjunct for treatment of alcohol dependence. Krampe and Ehrenreich (2010) reviewed the literature and conclude that disulfiram is the most effective pharmacologic treatment of alcohol dependence, and it should be integrated with psychotherapy. The last 10 years has seen research of several medications other than disulfiram for SUD. Naltrexone, an opioid antagonist, blocks the intoxicating effects of alcohol and is most effective for reducing cravings, while acamprosate reduces withdrawal symptoms (Garbutt, 2009). However, Mark and colleagues (2003) have documented barriers to use of naltrexone, including lack of awareness of it, unwillingness to prescribe medications and patient reluctance to take it. Addiction physicians are treating only 13% of their alcohol dependent patients with it. The most recent research suggests that treatment effects may be enhanced by testing for individualized biological markers that could reveal how specific patients are likely to respond, thereby allowing for the creation of more homogeneous treatment groups (Mann & Hermann, 2010). One other medication, odansetron, is approved for post-operative nausea

and blocks 5-HT at 5-HT₃ receptors in the mid-brain. Preliminary evidence shows that ondansetron is effective in reducing drinking among alcohol dependent patients but it is not clear that it is more effective compared to sertraline (Kenna, 2010). Topiramate has been found to be superior to placebo among alcoholic patients for reducing drinking and cravings but not consistently superior to naltrexone. Topiramate shows promise for treatment of alcoholism, although one study found disulfiram superior to topiramate on drinking outcomes (Johnson et al., 2010; DeSousa et al., 2008). We are unaware of any studies of topiramate in comorbid populations.

The COMBINE study, which tested the effects of medications and psychotherapy in an alcohol dependent sample found that combining the two medications may be more effective than use of naltrexone alone (Soyka and Rosner, 2008). However, treatment with both medications affected treatment adherence, due to increased side effects (Zweben et al., 2008). This is critical since treatment adherence in these studies was associated with improved outcomes (Gueorguieva et al., 2009). Studies have found Combined Behavioral Intervention (CBI), which is an integration of CBT, MI and 12-Step Facilitation, has effects on drinking outcomes which complement the effects of naltrexone alone (Gueorguieva et al., 2009).

The primary limitation in determining clinical findings for treatment planning for comorbid patients from the alcohol literature is that the samples were selected to exclude comorbidity (Donovan et al., 2008). Notwithstanding this issue, Longabaugh and colleagues (2009) conducted one study of a psychotherapy, Broad Spectrum Treatment (BST) that was developed to include elements of CBT, MET and 12-Step Facilitation. They found that BST was superior to MET for increasing abstinence and reducing alcohol use. The authors note that they operationalized MET to include only four sessions (the number of sessions found to be effective in Project Match, Project Match Research Group, 1997), while eight to twelve BST sessions were allowed in the BST arm. This may have affected outcomes in favor of BST but the design of BST is a step forward, as it combines effective elements of the same technology, i.e., psychotherapy, for treatment of addicted patients. It is becoming increasingly clear that integrating the best elements of different evidence-based psychotherapies is necessary to produce larger effect sizes and more effective outcomes.

3.21. Pharmacotherapy for Opioid and Cocaine Use Disorder

Karila and colleagues (2008) reviewed the literature on pharmacologic treatments for cocaine dependence and found that available medications that may improve cocaine-related outcomes include bupropione, disulfiram, topiramate, modafinil, baclofen, and methyphenidate. One effective treatment for cocaine use among opiate dependent patients is bupropione in conjunction with contingency management. Nunes and colleagues (1995) found a treatment by time interaction in a study of imipramine suggesting that it improved depressive symptoms and decreased cocaine cravings over time, compared to placebo.

Baclofen has shown efficacy for reducing cocaine use among non-opioid dependent addicts in a laboratory study but it is not clear that baclofen can be effective outside of the laboratory. Interestingly, however, some aspects of the major study of baclofen suggests that it could be effective in combination with contingency management (Haney et al. 2006).

Disulfiram has been shown to reduce cocaine use by blocking the metabolism of cocaine. This actually increases the availability of the cocaine, which makes the “high” very unpleasant due to the anxiety associated with high levels of cocaine (Kampman, 2010). However, this feature also increases the risk of possible cardiovascular toxicity and limits the use of disulfiram because of the risk of it potentiating with cocaine (Karila et al., 2008).

A study by Brady and colleagues (2002) found that carbamazepine reduced drug cravings among cocaine addicts but did not find that the medication reduced actual drug use.

Topiramate too has shown effectiveness for reducing cocaine use in conjunction with CBT and clinical trials of other anticonvulsants are now underway. Methylphenidate appears to be most effective for reducing cocaine use in patients with ADHD symptoms and its action may be due to its mediating effect on ADHD symptoms. Studies have not reported risk for increased cardiovascular events in conjunction with it, although the potential exists. Studies have also shown low abuse potential with sustained release methylphenidate. Modafinil has mild stimulant-like effects and has been shown to reduce cocaine use, primarily through its potential to reduce withdrawal symptoms and cravings (Karila et al., 2008).

A Cochrane Database review found some evidence that psycho-stimulant drugs, or those with psycho-stimulant effects, have increased cocaine abstinence among addicted patients. Interestingly, the antidepressant bupropion was found to be among two others, dextroamphetamine and modafinil, in showing a trend for increasing cocaine abstinence. It should be noted that none of the medications investigated had an effect on decreasing cocaine use but there was a statistical trend showing that more patients receiving medication achieved cocaine abstinence compared to those receiving placebo (Castells et al., 2010). Castells and colleagues (2009) also reviewed the findings on cocaine use among patients on opioid replacement therapies and found that higher doses of methadone were more effective for retaining patients in treatment and for their achieving abstinence from heroin. Furthermore, methadone was somewhat superior to buprenorphine for maintaining abstinence from cocaine. Finally, adjunctive therapies such as dopamine agonists (e.g., bupropione) and CM are effective in treating patients on opioid replacement for dual-addictions such as opioid and cocaine use disorders.

3.22. Other Important Findings

Despite the now well-known finding that the tested psychotherapies in Project Match were generally equivalent in reducing alcohol use, some findings should be noted. First, CBT and TSF (Twelve-Step Facilitation) were found to bring about larger decreases in frequency and amount of drinking in the first month of treatment, compared to MET, possibly indicating CBT or TSF may be better choices of psychotherapy in order to reduce drinking as quickly as possible (Project Match Research Group, 1998a). Related more to comorbidity, however, Karno and Longabaugh (2003) report that therapist focus on low levels of emotionality during the 12 weeks of treatment in Project Match was associated with greater improvements in depression. This finding is critical since Connors and colleagues (2005) found that depression level is predictive of drinking severity and that even modest changes in depressive states during the 12 weeks of treatment in Project Match were associated with dramatic reductions in alcohol use.

Since Brady and colleagues (2005) reported on it, more robust support has been found for the use of CM as an adjunctive treatment for SUD. Studies have shown that adding CM treatment to usual care of cannabis and stimulant users, as well as for patients on methadone maintenance, results in longer retention in treatment, submission of more drug-free urines and maintaining complete abstinence from drugs compared to participants in usual care (Alessi et al., 2011; Petry et al., 2005; Pierce et al., 2006). Twelve-step participation has been found to be very effective for dual-diagnosed patients. Aase and colleagues (2008) reviewed the literature and found that 12-Step participation was effective for reducing substance use and mental illness through the meditational role of social support and improvement in self-efficacy. Easton and colleagues (2007) compared 12-Step participation to integrated treatment for substance abuse and domestic violence and found similar effects, although there was indication that the integrated treatment was somewhat superior. These

findings suggest that the best approach may be to encourage 12-Step participation to assist with sobriety while providing other needed services. Floyd and Donovan (2008) have discussed methods for improving 12-Step participation and indicate that Twelve-Step Facilitation (TSF) should be routinely integrated into treatment of addiction. The CTN has just completed data analysis of a Twelve-Step Facilitation therapy, which is designed to promote 12-Step participation and publications of this study are forthcoming.

4. Discussion

Several important conclusions can be inferred from this review. First, more effective treatment planning can be achieved by recognizing that the most effective treatment for comorbid patients is a multi-faceted endeavor. Effective treatment for comorbid conditions often combines using different therapeutic “technologies,” i.e., psychotherapy, pharmacotherapy and behavioral treatments and these different technologies exert a synergistic effect on treatment. Often, non-substance related disorders precede comorbid substance use disorders (Jane-Llopis & Matysina, 2006) and comorbidity adds to severity (Merikangas & Kaladjian, 2007) and severe conditions must be matched to higher intensity treatments to maximize psychiatric and substance-related outcomes (Baker et al. 2010; Chen et al., 2006). The number and types of treatments must be determined by number of available effective treatments, for the substances being abused and the severity of the comorbidity. For example, it may be possible to treat alcohol dependence and depression with less intensive psychotherapeutic approaches because effective pharmacotherapy treatments for both depression and alcohol abuse are available. However, treatment of depression or anxiety with severe cannabis dependence may require intensive outpatient psychotherapy, or residential treatment, since no pharmacological treatment for cannabis dependence exists.

It is critical to bring the substance dependence to remission in order to be able to properly assess depressive or anxiety-related symptoms. Patients being treated in Partial Hospitalization with an emphasis on getting active in 12-Step programs are much more likely to remain drug free than those being treated with medication and once or twice a week in individual or group therapy. Similarly, CM can be a critical adjunct to treatment planning for severe substance disorders because the outcomes result from a stimulus-response process that does not rely on “insight,” which takes time to develop in psychotherapy.

For the most severe cases it is likely that inpatient treatment will be necessary prior to initiating outpatient care. Stability in recovery is contingent on achieving abstinence from substances as soon as possible and the preponderance of the evidence suggests that patients maintain improvements longer in outpatient treatment when abstinence is achieved early on (Fals-Stewart & Schafer, 1992; Cornelius et al, 1997; Mason et al., 1996; Weinstock et al., 2010). Although reducing drug use is imperative for overall improvement during treatment, non-substance related pathology must not be neglected early in treatment. Treatment research indicates that improvement of non-substance related disorders such as depression and PTSD precedes improvement of substance use symptoms and elements of the treatment plan should address substance and non-substance-related symptoms concomitantly (Hein et al., 2010, Stulz et al., 2010).

Treatment planning must begin at the level of the interaction between the patient and the therapist because a treatment plan will only be effective if patients trust their therapist and are willing to cooperate with him/her. Motivational interviewing emphasizes keeping resistance to a minimum by using an egalitarian, non-judgmental, non-threatening approach where self-determination is a mainstay of treatment. Treatment research has continuously supported this approach (Barrowclough et al., 2010, Daley et al., 1998, Herbeck et al., 2005,

Hides et al., 2010, Sysko & Hildebrandt, 2009, Horsfall et al., 2009; Ziedonis et al., 2005) and it is consistent with recommendations of psychodynamically oriented practitioners who have listed principles of therapist activity and therapeutic engagement that are associated with improvement of depression (Beutler et al., 2000). Indeed, outcomes for addiction treatment have been found to be directly related to the quality of the therapeutic alliance (Dundon et al, 2008; Horvath & Symonds, 1991; Martin et al., 2000) and studies have found that aspects of the MI approach and an adequate dose of MI are critical to the functioning of effective psychotherapy (e.g., Berg et al., 2008; Polcin et al. 2004).

Shaffer and Robbins (1995) emphasize the importance of using MI in tandem with the Transtheoretical Model or Stage of Change (Diclemente & Velasquez, 2002), as Miller and Rollnick (1991, 2002) have developed it. Martin and colleagues (2000) found support for the hypothesis that the therapeutic relationship alone, notwithstanding the content of the psychotherapy, is associated with improved treatment outcomes. This finding is reflected in MI because it is a style of relating in how therapists interact with patients over material introduced by the patient, as compared to psychotherapies that specify content that must be covered to ensure that the treatment is being properly conducted. In this regard, at least one paper has noted the probability that CBT failed to be as effective as it might have been in Project Match because some of the important treatment content was to take place after session 7 and few patients in the CBT arm completed the 12 session program (Project Match Research Group, 1998b).

Despite the effectiveness of any model of therapy as a stand-alone treatment, the most recent evidence suggests that combining evidence-based treatments results in the most effective psychotherapies for comorbidity to date. The BST approach which combines MI, CM and 12-Step Therapy (Longabaugh et al., 2009) and BTSAS (Bellack et al., 2006) which combines MI, CM, CBT and case management for patients with psychotic and substance use comorbidities hold the most promise for treatment of addiction and comorbid psychiatric disorders. One study that is currently being conducted by the NIDA Clinical Trial Network is Smoking Cessation and Stimulant Treatment (S-CAST). This study combines counseling with CM, bupropione and nicotine replacement for the treatment of cigarette smoking among patients addicted to amphetamine and cocaine. The Addiction Severity Index (McClellan et al., 1992) used in the S-CAST study will assess the effect of substance use on psychiatric outcomes in follow-up. One expectation is that the use of multiple evidence-based therapies in S-CAST will increase effect sizes on comorbidity over those typically found in studies that do not provide such integration of treatments.

Treatment of comorbidity must also consider the need to maintain patients in treatment for as long as possible. Time spent in treatment moderates improvement (Conner et al., 2008; van Zanne et al., 2010) and research has found that this applies to virtually all drugs of abuse, including alcohol, cocaine, cannabis, methamphetamine, and heroin (Baker et al, 2010; Hser et al., 2006; Magura et al., 2009; Marsden et al., 2009; Teeson et al., 2008; van Zanne et al., 2010; Zhang et al., 2003). In their review of treatment for opioid dependence Veilleux and colleagues (2010) indicate that the quality of psychosocial treatments vary so greatly that it is difficult to determine what, or how much is needed and they suggest further research. Despite this lack of clarity, the current state of the art suggests that establishing a strong therapeutic alliance and enhancing support for patients results in their staying involved in intensive treatment. This is critical since both partial hospitalization and 12-Step programs have been shown to increase abstinence rates (Aase et al., 2008; Magura et al., 2009).

Importantly, longitudinal research consistently finds that treatment effects for chronic, relapsing diseases such as addiction degrade over time. Donovan and colleagues (2008)

address this issue by suggesting that patients remain in treatment, possibly in a low intensity treatment during periods of remission. In this way, if stress increases or patients report cravings and lapses that threaten recovery, treatment can be adjusted early in the process to help the patient maintain stability.

Extrapyramidal effects of medications impacts patient medication compliance and continuation in treatment. Although tricyclic antidepressants appear to be superior to SSRIs for treatment of depression and comorbid alcohol abuse, their benefits must be weighed against their decidedly higher side-effect profiles. Similarly, some first generation anti-psychotics may be effective for reducing psychiatric symptoms but their unintended effects may preclude their use among comorbid patients who are more likely to stop treatment due to finding them intolerable.

As regards future directions for research, there is little research on the comorbidity of some Axis I non-substance disorders and substance use disorders. For example, this review found scant research that can be applied to comorbidities of substance use disorders with OCD and Panic Disorder. The reasons for this may be much more or less important. For example the DSM-IV TR Revised (2000) indicates that Panic Disorder is highly comorbid with other mood and anxiety disorders. This suggests that Panic may be a symptom of more pervasive disorders and will remit with proper treatment of the dominant disorder. This is consistent with the clinical logic of diagnosing the most “pervasive disorder” (DSM-IV-TR, 2000) when symptoms of other conditions are less severe and it makes clinical sense to make one categorical diagnosis. Conversely however, Kessler and colleagues (2011) recently reported on the development of psychiatric comorbidities and, while they found OCD to have one of the lowest prevalence rates of any psychiatric disorder, it is among the most predictive of other disorders. Therefore, while OCD is quite impairing it is being overlooked in designing treatment studies for mood and anxiety disorders, thereby reducing the volume of treatment studies on its comorbidity with substance use disorders. When OCD is detected it is important that its symptoms be targeted first with pharmacotherapy since clinical logic dictates that other, less severe symptoms will improve as it remits. Of course, the psychotherapy must first focus on behavioral strategies to get substance use under control. Only then can insight develop in order to further the recovery process.

Limitations of this review include the likely possibility that some important studies were excluded. However, a significant effort was expended to review the relevant areas of the SUD and Non-SUD treatment literature. Furthermore, the conclusions drawn about how combinations of treatments may operate to improve both SUD and Non-SUD symptoms could be in error. Due to a paucity of comorbidity studies, discussions about how some combinations of treatments are likely to work are admittedly inferred from studies of individual treatments and not from studies of the combined treatments in comorbid SUD/ Non SUD samples. Of course, one objective of the review is to develop informed hypotheses of how combined treatments may work in clinical practice because this is the best that can be done given the current state of the art.

Notwithstanding the limitations, this review suggests that many treatments with potential benefits for comorbid patients are available. Treatment plans that combine, for example, MI with CBT and pharmacotherapy, CM with pharmacotherapy, MI with 12-Step Enhancement Therapy and pharmacotherapy represents creatively combining treatments that represent different evidence-based “technologies.” Such multi-faceted treatment plans are necessary in order to bring greater effectiveness for the treatment of comorbid psychiatric and addictive disorders.

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Highlights

- Research finds limited evidence that antidepressants should be used for reducing substance use
- Pharmacotherapy of comorbid patients should focus on non-substance related symptoms
- Medications for substance abuse symptoms should be used as needed
- Psychotherapy and behavioral therapies should initially target behaviors related to substance abuse.
- Treatment of comorbid patients should include combinations of psychotherapy, pharmacotherapy and behavioral therapies such as Contingency Management

Table 1

Reviews of Treatment for Comorbid Disorders

Author(s)/Year	Comorbidities	Psychotherapies/Pharmacotherapies	Major Findings
Asse et al./2008	Unspecified Dual Diagnoses	Yes / No	12-Step participation was associated with abstinence in 80% of reports w/abstinence as an outcome; 43% of studies found 12-Step improved psychological functioning
Baker, et al./2010	Can/Psychotic/Depressive	Yes / Yes	Longer, more intensive treatments may be necessary for can users with chronic mental disorders, compared to brief interventions (<10 sessions)
Brady & Verduin/2005	Sub Use Dis/Mood, Anx	No / Yes	Meds for mood, anx disorders may also help sub use; meds for patients with comorbidity should be chosen on safety, toxicity, abuse potential
Cornelius et al./2003	Alc/Dep/Anx	No / Yes	SSRIs and tricyclic antidepressants may be effective for both disorders; buspirone may be helpful for alc/anx
Drake et al./2008	Sub Use/Severe Mental Dis	Yes / No	CM, group, residential treatments are beneficial for sub use; case management, legal intervention are positive for stability in community and treatment retention
Fatseas et al./2010	Opioids/Anx	Yes / Yes	Most effective meds are tricyclics; SSRIs may work (try SSRIs first for reduced side effects); avoid benzos; best treatment is integrated pharmacotherapy and psychotherapy
Green et al./2002	Alc.Others/Schizophrenia	No / Yes	Clozapine superior to other meds, abstinence is critical
Hesse/2009	Sub Use/Anx, Dep	Yes / No	Integrated psychotherapy alone is not effective in comorbid sub use and dep/anx; new approaches needed
Hjorthoj et al./2009	Can/Schizophrenia	Yes / No	CM effective against can use; MI and CBT effective against drug use in combined analyses but not against can alone; should use separate analyses for different drugs
Levin & Hennessy/2004	Sub Abuse/Bip	Yes / Yes	Integrated treatments of group therapy should be used w/med specific for sub abuse, if available; disulfiram is promising for bip/alc patients
Lubman et al./2010	Substances/Schizophrenia	Yes / Yes	Clozapine and naltrexone are effective; integrated treatment is best psychosocial approach
Lybrand et al./2009	Alc., Can, Coc/Schizophrenia	No / Yes	Atypical antipsychotics are effective; clozapine is superior
Marenmami et al./2010	Drugs of Abuse/Mood Disorders	No / Yes	Mood stabilizers may be better choices than antidepressants for drug/mood comorbidity; valproate is best
McCarthy & Petrakis/2010	Alc/PTSD	Yes / Yes	Effective treatment includes integrated evidence-based psychotherapies (e.g., Seeking Safety) and medication (SSRI, topiramate)
Negrete/2003	Can, Opioids/Psychosis	Yes / Yes	Need for intense, integrated treatment; atypical antipsychotics superior to 1 st generation antipsychotics
Nunes & Levin/2004	Alc, Other Drugs/Dep	No / Yes	Antidepressants have a modest effect on comorbid dep-sub use disorders; sub use should be treated with substance specific pharmacotherapies, if available
Pettinati/2004	Alc/Dep	No / Yes	Antidepressants have little impact on alc use; treat alc abuse with specific medication
Quello et al./2005	Sub Use D/O/Dep, Bipolar	Yes / Yes	Lithium + valproate may be most effective med treatment; critical elements of manual guided psychotherapy should be used
San et al./2007	Alc.Coc,Can/Schiz	No / Yes	Clozapine effective against alc and can; olanzapine and risperidone appear effective against coc; more research needed

Author(s)/Year	Comorbidities	Psychotherapies/Pharmacotherapies	Major Findings
Schafer & Nejavits/2007	Sub Abuse/PTSD	Yes / Yes	Five structured psychotherapies reviewed. Seeking Safety has most support; both naltrexone and disulfiram should be considered for alc abuse
Smelson et al./2008	Alc, Opioids/Schizophrenia	Yes / Yes	Atypical antipsychotics superior; enhance retention in treatment; clinicians should be familiar with evidence-based approaches and be flexible in treatment planning
Tiet & Mausbach/2007	Sub Use Disorders/Mental Illness	Yes / Yes	Efficacious treatments for both mental and sub use disorders are effective when combined for dual diagnosis; the efficacy of integrated treatment is unclear
Torrens et al./2005	Alc, Coc, Nic, Opioids/Dep	No / Yes	Antidepressants (buprop/nortrip) effective for nicotine; not clear for others; more research needed
Upadhyaya/2007	Sub Use Dis/ADHD	No / Yes	Stimulants may be abused; include family in treatment planning; use long-acting meds; try non-stimulants first with sub-abusing patients; higher doses of stimulant meds for ADHD may reduce coc use

Notes: alc=alcohol; can=cannabis; anx=anxiety; buprop=buproprione; dep=depression; dis=disorder; meds=medications; nortrip=nortriptyline; coc=cocaine; SSRI=Selective Serotonin Reuptake Inhibitor; CM=contingency management

Table 2

Research Trials for Comorbid Disorders

Authors/Year	Comorbidities	Design	Sample Size	Major Findings
Barrowclough et al./2010	Sub Misuse/Psychosis	RCT/104 Wks	327	No effect of intervention vs TAU on non-sub related symptoms or frequency of sub use but did increase readiness to change; intervention decreased drug use and total drugs used over 2 yrs
Bellack et al./2006	Can,Coc,Heroin/Serious MI	RCT/26 Wks	110	Higher retention; lower % of positive tests; higher quality of life; reduced spending
Bowen et al./2000	Alc/Panic D/O	RCT/52 Wks	231	Reduced anxiety symptoms in all groups; CBT had no effect on drinking behavior
Brady et al./2002	Coc/Affective	RCT/12 Wks	139	Coc/affective group given carbamazepine had more negative UDS, less time to relapse than non-affective group
Brady et al./2005	Alc/PTSD	RCT/12 Wks	94	No difference between groups but some difference in subgroups based on severity; SSRIs may affect patients differently based on clinical characteristics
Cornelius et al./1998	Coc/Dep	RCT/12 Wks	17	No difference on drug use among fluoxetine vs. plc group; increased depression among coc using depressed alcoholics
Cornelius et al./1997	Alc/Dep	RCT/12 Wks	51	Fluoxetine effective against dep and alc use vs. plc
Cornelius et al./1999	Can/Dep	RCT/12 Wks	22	Dep/Can users treated with fluoxetine report smoking 20 times fewer marijuana cigarettes vs. plc group
Daley et al./1998	Coc/Dep	Assigned/52 Wks	23	Inpts given an MI session prior to discharge followed through with outpt. more often, had a higher rate of completed treatment and a lower rate of rehospitalization at 52 wks, compared to the non-MI group
Fals-Stewart & Schafer/1992	Sub Use Dis/OCD	RCT/ 52 Wks	60	Group treated with TAU and for OCD had more alcohol free pts.; pts. in this group who relapsed had longer abstinence at 12-Mo follow-up
Geller et al/1998	Can, Alc/Bipolar	RCT/6 wks	46	Patients responded with decreased psychopathology and more negative UDS to treatment with lithium
Green at al./2003	Can, Alc/Schizophrenia	Retro/52 wks	41	Significantly more (54%) of pts. treated with clozapine stopped use of can and alc compared to those treated with risperidone (8%)
Hien et al./2010	Sub Use D/O/PTSD	RCT/52 Wks	353	Improvement in PTSD symptoms resulted in decreased sub use; greater effect among heavy sub users
James et al./2004	Illicit Drugs, Alc/Psychosis	RCT/6 Wks	63	Reduced psychopathology, sub use, severity of addiction, less anti-psychotic needed with group therapy intervention
Kemp et al./2009	Alc,Coc, Can/Bipolar	RPG/26 Wks	31	Neither lithium/divalproex vs. lithium alone effective against relapse into mood episodes (primarily mania); both groups reduced sub use
Kranzler et al./1994	Alc/Anx	RCT/26 Wks	61	Patients treated with buspirone stayed in treatment longer, had reduced anxiety, more time to return to heavy drinking and fewer drinking days during follow-up
Labbate et al./2004	Alc/PTSD	RCT/12 Wks	93	Sertraline effective for PTSD, dep, and alc use despite severity of condition
Levin et al./1998	Coc/Schizophrenia	Open Label/10 Wks	8	Decreased psychiatric symptoms; decreased cocaine-positive urines using flupenthixol
Magura et al./2009	Drug Use/Mood/Bip/Sch	iz Consecutive/26 Wks	229	More patients who attend day treatment stop using drugs than patients who initiate using; no difference between drug users and non-users on psychiatric benefit from treatment
Mason et al./1996	Alc/Dep	RCT/26 Wks	71	Decreased dep and trend toward increased abstinence with desipramine in dep group

Authors/Year	Comorbidities	Design	Sample Size	Major Findings
McRae et al./2004	Opioids/Anx	RCT/12	36	Bupropion did not reduce anx symptoms but showed a trend toward reducing dep and return to sub use
Moak et al./2003	Alc/Dep	RCT/12 Wks	82	Decreased dep and alc use in group treated with sertraline & CBT vs. plc & CBT
Nunes et al./1995	Coc/Dep	RCT/12 Wks	113	Decreased coc cravings & dep in imipramine treated vs. plc group, no difference in coc use, not as effective for IV or freebase coc users
Nunes et al./1998	Opioids, Coc/Dep	RCT/12 Wks	84	Decreased dep and self-reported use of opioids (trend in decreased coc use) in imipramine group vs. plc; no difference between groups on UDS
Petrakis et al./2007	Alc/Dep	RCT/12 Wks	254	Naltrexone and disulfiram do not adversely affect dep; outcomes for dep vs. non-dep groups improved and not different; disulfiram more effective against cravings in depressed group
Petrakis et al./2006	Alc/PTSD	RCT/12 Wks	93	PTSD patients had better outcomes when treated with an active medicine vs. plc; PTSD improved in all groups; disulfiram somewhat better than naltrexone
Petrakis et al./2006	Alc/Schizophrenia	Rec. Review/	249	No difference between typical and atypical antipsychotics on ASI use in multivariate analysis
Randall et al./2001	Alc/SoAnx	RCT/8 Wks	15	Paroxetine effective against SoAnx for patients with alcohol; no effect on alc use
Randall et al./2001	Alc/SoAnx	RCT/24 Wks	93	No difference between groups treated with CBT for Alc/SoAnx and group treated for Alc problems; group treated with Alc/SoAnx CBT worse on 3 of 4 outcomes; may need to stage treatment
Rubio et al./2006	Sub Abuse/Schizophrenia	RCT/26 Wks	115	Injectible risperidone superior to depot zuclopenthixol in decreasing psychiatric symptoms and positive UDS
Salloun et al./2005	Alc/Bipolar	RCT/24 Wks	59	Valproate decreases heavy drinking for bipolar alcoholics taking lithium
Sayers et al./2005	Coc/Schizophrenia	RCT/26 Wks	24	No differences on outcomes except coc cravings lower in haloperidol treated patients
Schade et al./2005	Alc/Phobia	RCT/32 Wks	96	No difference between groups on drinking outcomes; significant effect on anxiety in group treated with CBT for anxiety
Schmitz et al./2001	Coc/Dep	RCT/12 Wks	68	Fluoxetine no better than plc for dep or coc when treated with CBT
Sevy et al./2011	Alc, Cam/Schizophrenia	RCT/16 Wks	49	Olanzapine and risperidone; no difference on symptoms
Smelson, et al./2002	Coc/Schizophrenia	Open Label/6 Wks	18	Risperidone reduces craving for cocaine more than typical neuroleptics
Smelson, et al./2006	Coc/Schizophrenia	RCT/6 Wks	31	Reduced cue exposure to coc cravings in olanzapine vs. haloperidol
Soyka et al./2003	Alc/Schizophrenia	Open Label/26 Wks	27	Slight psychiatric improvement, marked decrease in drinking on flupenthixol
Trafton et al./2006	Opioids/PTSD	Naturalistic/52 Wks	255	Opioid therapy was as effective in treating sub use among patients with and w/o PTSD; PTSD patients used more treatment but their psychiatric symptoms were not responsive to treatment
Van Nimwegen et al./2008	Cam/Schizophrenia	RCT/6 wks	128	Olanzapine and risperidone, both improved subjective well-being; no difference on cravings
Weiss et al./2000	Sub Depend/Bipolar	Open Label/26 Wks	45	IGT group lower ASI scores; more months of no alc/drug use vs. non-IGT; IGT group reduced mania; no difference on dep
Woody et al./1975	Opioids/Dep,Anx	RCT/16 Wks	35	Methadone patients treated with doxepine less depressed, anxious; less cravings; less use of amphetamines
Ziedonis et al./1992	Coc/Schizophrenia	Open Label/12 Wks	27	Patients treated with desipramine and antipsychotics had fewer positive urines compared to patients on antipsychotics alone

Notes: TAU=Treatment As Usual; MI=Mental Illness; Sub=Substance; Can=Cannabis; Coc=Cocaine; Alc=Alcohol; RCT=Randomized Clinical Trial; Dep=Depression; Anx=Anxiety; pl=placebo; SoAnx=Social Anxiety; CBT=Cognitive Behavioral Therapy; UDS=Urine Drug Screen; IGT=Integrative Group Therapy; Retro=retrospective