REVIEW ARTICLE

Updated review on the integrated treatment of co-occurring disorders

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Objectives: The aim of this paper is to review current treatment guidelines regarding the treatment of common co-occurring disorders including evidence for the use of psychotherapeutic techniques and concurrently administered integrated treatment, and to highlight areas for future study.

Methods: A PubMed search was conducted between 6/2017 to 2/2018 to identify published articles examining the treatment of co-occurring substance use and primary psychiatric disorders. Search terms included 'co-occurring', 'dual diagnosis', 'amphetamines, 'methamphetamines', 'alcohol', 'cocaine', 'cannabis', 'post-traumatic stress disorder/PTSD', 'Major Depressive Disorder/MDD', 'Bipolar Disorder', 'Borderline Personality Disorder', 'Schizophrenia', 'psychosis,' 'treatment', 'therapy', 'pharmacotherapy', 'psychotherapy', 'medications'. As the focus is specifically on treatment, articles that did not address treatment were excluded as were any articles that did not address integrated treatment.

Results: Review of available literature base is consistent with the notion that patients with co-occurring substance use and psychiatric disorders represent unique subpopulations requiring targeted care, supports a concurrent, combined approach to treatment as opposed to treating one disorder first, and emphasizes the importance of psychotherapeutic techniques.

Conclusion: Although many gaps exist in the current literature and considerable additional research is necessary, available evidence supports concurrent integrated treatment, questions traditional treatment practices that treat each disorder in isolation and emphasizes the importance of psychotherapeutic techniques in addition to Medication-Assisted Treatment. Clinical practice should take these results into consideration and modify treatment protocols accordingly.

Key Words: *Dual diagnosis; Co-occurring disorders; Integrated treatment; Substance use; Addiction; Therapy*

INTRODUCTION

Despite the high prevalence of substance use disorders in patients with mood disorders (1-4), PTSD (5), Borderline Personality Disorder (6), and Schizophrenia (2,3), there is a distinct paucity of literature regarding treatment of patients with these co-occurring disorders. Studies of primary mood or psychotic disorders typically exclude individuals with co-occurring substance use disorders (SUDs) (7-9). Even when included, co-occurring diagnosis patients may not be considered a distinct clinical group (10).

Guided by DSM's criteria, many physicians attempt to differentiate 'primary' from 'substance induced' disorders. When a disorder is determined to be 'substance induced', clinicians often attempt to treat the substance use first and then wait to see if the associated "induced" disorder clears without further treatment, and vice versa (i.e. treating presumed 'primary' disorders first to see if the SUD then resolves) (11). However, delay in treating either a mood disorder or a substance use disorder while treating the other might lead to poor outcomes, such as suicidality, mania, increased duration of untreated psychosis, or loss of hope for recovery and abandonment of treatment (11-13). Findings from the National Epidemiologic Survey on Alcohol and Related Conditions suggest that treatment for mood disorders that co-occur with substance use disorders should continue to be administered even if mood symptoms go into remission (3,14), which is in line with the latest research supporting concurrent treatment for concurrent disorders (15).

LITERATURE REVIEW

The current literature examining treatment options for co-occurring disorders is sparse and scattered, usually focusing on only one primary psychiatric disorder. Additionally, most review papers only discuss psychopharmacologic treatments (5,16-19). This paper consolidates treatment research for five common psychiatric disorders and five common substance use disorders, including psychotherapeutic techniques, and gives clear recommendations based on current evidence as well as points out important avenues for continued research.

This paper follows the usual convention of organizing studies of dual diagnosis conditions according to the primary psychiatric diagnosis, i.e. Post Traumatic Stress Disorder (PTSD), Major Depressive Disorder, Bipolar Disorder, Borderline Personality Disorder, and Schizophrenia. Within each of these primary psychiatric diagnoses, specific research regarding alcohol, cocaine, cannabis, cocaine, and amphetamine use disorders will be discussed along with studies that do not specify type or number of substances used (heretofore referred to as nonspecific studies.

Post-Traumatic Stress Disorder (PTSD)

Co-occurring PTSD and substance use have been studied extensively by the Department of Veteran Affairs (VA). Although PTSD is not generally conceptualized as 'substance induced', there are complex synergies between addiction and PTSD (20-22). Individuals with a substance use disorder and PTSD tend to have poorer addictions treatment responses, faster relapse after substance use treatment (23), and more severe psychiatric and medical complications (24).

Co-occurring alcohol use disorder

Research supports the use of medications and therapy. In particular, sertraline has been found to be efficacious in decreasing both PTSD symptoms and alcohol use (25). It stands to reason that other antidepressants with a similar mechanism of action will likely be similarly effective. Specific alcohol use disorder medication adjuncts have also been tested. Both naltrexone and disulfiram remain effective for decreasing alcohol use in co-occurring patients (26), although disulfiram may be more efficacious than naltrexone at concurrently decreasing PTSD symptoms on the Clinician Administered PTSD Scale (CAPS) (21). Nearly all studies include psychotherapy (most commonly cognitive behavioral therapy (CBT)) even within their placebo groups, which makes it difficult to identify the exact treatment effects of CBT. However, Coffey and colleagues did find that 60-minute prolonged exposure therapy, which included psychoeducation about the relationship between PTSD and SUD symptoms and weekly check-ins about substance use, was effective for treating PTSD symptoms in these co-occurring patients (27). It would be beneficial to have more studies on specific therapy approaches and an examination of the impact of co-occurring SUD on treatment outcomes.

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Co-occurring opioid use disorder

No specific studies on selective serotonin reuptake inhibitors (SSRIs) or other antidepressant medications in this population could be found, indicating an important concentration for future research. From a therapy standpoint, Saunders and colleagues have found that Integrated CBT (an 8-12-week manual-guided individual therapy designed to address PTSD and co-occurring substance use concurrently) reduces both PTSD symptoms and opioid use (28). Interestingly, the effects of Integrated CBT on PTSD symptoms were attenuated when used in combination with the initiation of buprenorphine or methadone, which Saunders felt may be due to opioid agonist activity impairing the ability to alter and create neural pathways in the acute setting. They did not study these effects in the setting of long-term pharmacological maintenance. However, this study may indicate that physicians should not be discouraged if the clinical effects of therapy are not apparent during the initiation phases of these medications.

Co-occurring cannabis use disorder

Cannabis has not been associated with alterations in effects of primary treatments for PTSD (29), suggesting that SSRIs and psychotherapy should continue to serve as the mainstay of treatment for PTSD in these co-occurring patients. Mindfulness based cognitive therapy for co-occurring patients led to significant improvement in PTSD symptoms as well as a decrease in cannabis use in a small study of teenagers (30). Although in lay media cannabis has been lauded as helpful with anxiety and sleep, research findings in this area are mixed. Some studies have shown short term decreases in anxiety and depressive symptoms as well as enhanced sleep in those with PTSD (31,32). A synthetic cannabinoid, nabilone, has been reported to aid in the reduction of nightmares although no head to head trials exist comparing nabilone with other medications for nightmares (33,34). Furthermore, a review of preclinical research by Papini and colleagues indicated that chronic nabilone use might be associated with impaired fear extinction (35), which could ultimately lead to worsening of PTSD. Available research supports treatment of both PTSD and cannabis use without altering standard treatment of either and does not support using cannabis as a medication to treat PTSD in the long term.

Co-occurring cocaine use disorder

Few studies have been published regarding this sub-population. Behavioral contingency management (rewarding patients for negative urine drug screens) used in combination with case management aid (focusing on housing and vocational training) has been found to lead to a decrease in PTSD symptoms, such as avoidance and distraction, and to an increase in 'approach coping', or the ability to plan and ask others for help as measured by the Coping Orientations to Problems Experienced questionnaire (36). This might indicate that contingency management leads to increased abstinence, which might in turn correlate with increased ability to treat PTSD symptoms. This hopeful evidence supports the usefulness of integrated treatment. Additionally, patients have been found to prefer integrated treatment of PTSD symptoms and cocaine use disorder over sequential treatment (first cocaine use treatment then PTSD treatment or vice versa) (37), although simultaneous *vs.* sequential treatments were not compared with regard to clinical outcomes.

Co-occurring amphetamine use disorder

No specific studies could be found regarding the treatment of this population.

Co-occurring use disorder (unspecified)

In studies that did not differentiate between substance use disorders, current research supports concurrent treatment with therapy and medications. Research has suggested that N-Acetyl Cysteine (NAC) restores glutamate transporters and antiporters in the nucleus accumbens (38), which may indicate treatment potential since PTSD and substance use disorders both impair glutamate synapse regulation in the nucleus accumbens (39-42). In a double blind, randomized, placebo-controlled study of NAC for individuals with PTSD and a substance use disorder (43), NAC was found to decrease both PTSD symptoms and substance cravings when used in conjunction with CBT. No differences in substance use were seen; however, since the patients were all in intensive outpatient addiction treatment this may have represented a floor effect. Hien and colleagues found that prolonged exposure therapy and relapse prevention therapy improved outcomes in regard to both substance use (including alcohol, crack cocaine, cocaine, heroin, and cannabis) and PTSD compared to standard community care (44).

Summary

Specific evidence-based therapies (i.e. prolonged exposure, CBT, and mindfulness-based therapies), mainstay medical treatment of substance use disorders (i.e. disulfiram/naltrexone for alcohol use, buprenorphine/methadone for opioid use), and SSRI treatment of PTSD should all be implemented in an integrated fashion for the treatment of these dual diagnosis patients. Cannabis may acutely decrease anxiety and depressive symptoms. However, research is mixed, and there is some evidence that cannabis may worsen PTSD in the long term and should not be used as a treatment for PTSD.

Major depression

Patients with a primary mood disorder are twice as likely to develop a substance use disorder and vice versa (4). Episodes of Major Depressive Disorder (MDD) increase in frequency independent of consumption rate of comorbid substance use (45), indicating complex relationships and not merely linear correlations. Physicians understandably attempt to differentiate between 'primary' and 'substance induced' major depression because substance use and/or withdrawal can generate difficulties with sleep, low mood, and poor appetite, mimicking depressive symptoms. However, in a study following 95 treatment-seeking alcoholics for 12 months, at least 25 percent of patients first diagnosed with substance induced depression at baseline were reclassified as having MDD over the following year (46).

Lack of or delay in treating major depression, regardless of whether it is primary or secondary, has been associated with increased frequency of subsequent major depressive episodes (45) and increased risk of suicide (47). Additionally, treatment of major depressive symptoms in patients being treated for alcohol dependence is associated with decreased time to first drink and to full relapse compared to those without depressive features on admission (48). If discharged without antidepressants, these patients were likelier to return to substance use. Thus, risks of not treating these patients is severe, and potential treatment benefits may be robust.

Co-occurring alcohol use disorder

Although SSRIs are the most commonly used antidepressants in studies of dual diagnosis patients, results regarding SSRIs in this subpopulation have been inconsistent (49). Many studies have found no significant SSRI efficacy for depressive symptoms (50-53). Two systematic reviews of randomized control trials suggest that non-SSRIs (ex: nefazodone, imipramine, desipramine) may lead to better results, but these are based on only a few small studies with limited enrollments of 10 to 71 patients (16,54,55). Psychotherapies such as CBT remain effective for depressive symptoms and may aid with decreases in alcohol use as well, as evidenced by a moderately sized randomized and controlled study of 332 patients in Thailand (56).

Contradictory findings can indicate subtle but impactful variations within populations, producing different responses to the same treatment. Studies of genetic polymorphisms offer one promising approach to identify such intra-group variations. Reportedly, individuals with a specific functional polymorphism (Asn40Asp) in the gene encoding for the M-opioid receptor OPRM1 obtain greater subjective effects from alcohol such as euphoria and intoxication (57). Patients with these Asp40 alleles were 3.5 times more responsive to naltrexone in terms of likelihood to relapse (58). These findings might indicate an identifiable subgroup within this population that would be better served with naltrexone treatment; pooled data may obscure naltrexone's efficacy for this particular subgroup.

Overall, concurrent integrated care of alcohol use and depression has shown better results for both disorders than parallel or sequential treatment. Samokhvalov and colleagues found that 81 patients undergoing integrated care of major depressive disorder and alcohol use disorder showed significant reduction in alcohol use and depressive symptoms, with a remarkably lower dropout rate than 81 age, sex, and disorder severity matched controls (18.5% dropout *vs.* 69.1% dropout, $p<0.001$ at 16 weeks treatment respectively) (59). This was a clinical chart review so further randomized controlled trials should be done to confirm these results.

Co-occurring opioid use disorder

Antidepressant monotherapy may not be effective for these patients. According to a meta-analysis of 4 studies including a total of 317 patients, monotherapy with imipramine, fluoxetine, or sertraline is no better than placebo for dual diagnosis patients on methadone maintenance (60). Methadone and buprenorphine remain effective in the treatment of opioid use disorder, and high dose buprenorphine (32 mg) may even decrease depressive symptoms (61), though this study only included 40 patients in the acute setting. Therapy continues to remain important and effective. Since depression and opioid use cause cognitive deficits, problem solving therapy (PST) has been considered as a less cognitively taxing alternative to

CBT (62). PST seems to be a reasonable alternative as it has been found to have equivalent efficacy to other psychological treatments of depression in a metanalysis of 30 randomized controlled trials with 3530 total patients (63).

Co-occurring cannabis use disorder

There is very little specific research in this area. Venlafaxine has been found to be no better than placebo in a 12-week randomized, double blind, placebo-controlled trial of 103 outpatient participants (64). It is unclear if other depressants would be more effective. Motivational interviewing and CBT combined may aid in decreasing both depressive symptoms and cannabis use (65), emphasizing the importance of integrated therapy treatment.

There are five case reports about individuals who reported antidepressant effect of cannabis past acute intoxication (66). Of course, the results must be viewed in the context of being retrospective self-reports. In two double blind placebo-controlled trials of less than 10 patients, the main cannabinoid in cannabis, delta-9-tetrahydrocannabinol (THC) was not found to have an antidepressant effect, and in fact actually led to dysphoria (67,68). However, there are a couple case reports showing the synthetic cannabinoid dronabinol either alone or as an adjunct may improve mood stability and quality of life (69). More controlled research is needed, but the current evidence points toward the possibility that synthetic cannabinoids may be a useful treatment option whereas THC, which is present in recreational cannabis, may worsen symptoms of depression.

Co-occurring cocaine use disorder

There is very little specific research in this area. One study found that venlafaxine with CBT has no significant effect on cocaine use and no difference in efficacy than placebo with CBT, though it did lead to a quicker decline in depressive symptoms (70).

Co-occurring amphetamine use disorder

There are no specific studies on standard antidepressant treatment in this sub-population. Second line antidepressants (mirtazapine, imipramine, and bupropion) have not proved to be effective for treatment of depressive symptoms or methamphetamine use (55,71-75). Modafinil (400 mg/d) as an adjunct to an antidepressant may decrease depressive symptoms when used with weekly CBT and contingency management treatment (76). Therapy remains paramount and with remarkable results in this patient population. Baker and colleagues found an increase in abstinence from methamphetamines after only 2 CBT sessions and a decrease in depressive symptoms after only 4 CBT sessions in a randomized control trial of 214 methamphetamine. These results were maintained 6 months out from the therapy sessions (77,78).

Co-occurring use disorder (unspecified)

Psychotherapeutic techniques with an integrated approach stand out as important and effective. Treating substance use and depression at the same time has been found to be superior to parallel or sequential treatment (15). The BRIGHT project (Building Recovery by Improving Goals, Habits, and Thoughts) found better clinical results with greater treatment adherence and greater improvement in depressive symptoms for individuals treated with residential substance use treatment coupled with cognitive behavioral therapy as opposed to residential substance use treatment alone (79).

Summary

An integrated treatment approach should be used to treat substance use disorders and depression. Traditional antidepressant treatment for MDD may be less effective in this patient population. Specific substance use medications, such as naltrexone/disulfiram for alcohol use disorder or methadone/buprenorphine for opioid use disorder, remain effective. More research is needed, but current limited research indicates that synthetic cannabinoids may aid depressive symptoms and THC may worsen symptoms. As our knowledge base grows, more targeted treatments may be possible as genetic studies differentiate between subclinical populations. Therapy (particularly CBT) remains key in the treatment of these individuals and should not fall by the wayside while pursuing various pharmacological treatments.

Bipolar disorder

Community based studies have shown 60-70 percent of people with bipolar disease meet criteria for a substance use disorder at some point in their lives compared to 10% in the general population (2). These two diseases seem to be intrinsically linked such that the presence of either leads to an increased likelihood of the presence of the other (80).

In a secondary analysis of information gathered in the STEP-BD trial, Fossey and colleagues found that the distinction between primary and secondary substance use is not validated when the age at onset of the bipolar disorder is controlled for, indicating we may not be able to rely on temporal sequence as the sole indication of primary versus secondary disease (81). Fleck and colleagues similarly found that alcohol use disorder onset is around 17 years old regardless of onset of bipolar disorder, though early onset bipolar disorder is more linked with alcohol use (82). They found that patients within the early onset group displayed more severe bipolar symptoms as rated on the Young Mania Rating Scale and Hamilton Depression Rating Scale as well as more correlation between bipolar symptoms and increased alcohol use. Therefore, the age of onset of bipolar disorder may be the most salient factor when determining subgroups to investigate further rather than the primary versus secondary distinction upon which most clinicians focus.

When substance use is present, accurate diagnosis of bipolar disorder is often delayed (83,84). In fact, Lagerberg and Colleagues found a median treatment delay of 2.0 years for bipolar disorder when co-occurring substance use was present (85). The co-occurrence of bipolar disorder has been found to lower treatment adherence (86,87), quadruple the risk of suicide (88), and increase the lethality level of suicide attempts (89). Timely diagnosis and appropriate treatment may decrease deaths. Furthermore, co-occurring diagnosis patients may have the potential for greater improvement as patients with isolated alcoholism were more likely to continue to have symptoms of alcohol use disorder at a 5 year follow up than those with alcoholism and depression when concurrent treatment was given (90,91). Despite the ingrained desire to pinpoint a definitive diagnosis, analysis of data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) suggests treatment for a co-occurring mood disorder should not be withheld from substance dependent individuals when mood symptoms are in remission on the assumption, they were attributable to intoxication or withdrawal (1,14).

Co-occurring alcohol use disorder

There is mixed research on the efficacy of atypical antipsychotics such as quetiapine and risperidone as adjuncts to mood stabilizers and therapy to decrease alcohol use and depressive symptoms (92-95), but it may be reasonable to reach for these when other medications and therapies are falling short of desired effects. Therapy, again, remains important. One study found that Early Recovery Adherence Therapy (ERAT), an integrated individual therapy for co-occurring disorders which uses motivational enhancement therapy, relapse prevention, and education and disease management, leads to a significant improvement in alcohol use and depressive symptoms (96).

Co-occurring opioid use disorder

No specific studies were found regarding treatment of this sub-population.

Co-occurring cannabis use disorder

Though some researchers have implied that cannabis may have mood stabilizing properties (97,98), the systemic studies published thus far suggest that cannabis use leads to poor treatment adherence (99,100) and increased duration and/or severity of mania (101,102). Strakowski and colleagues found rapid rates of relapse into cannabis use over the course of 5 years for hospitalized individuals with co-occurring bipolar disorder and cannabis use (103). They propose that aggressive substance use treatment immediately after first psychiatric hospitalization may decrease rates of cannabis use disorder in bipolar disorder. Unfortunately, no specific studies looking at integrated treatment of this population were found.

Co-occurring cocaine use disorder

No specific studies looking at pharmacological or psychotherapeutic effects on mood stabilization were found. Pramipexole, a dopamine agonist, and citicoline, a cholinergic nutritional supplement, may decrease cravings for and use of cocaine (104-106).

Co-occurring amphetamine use disorder

There is little specific research about patients with co-occurring bipolar disorder and amphetamine use disorder. Citicoline (2000 mg/week) as an adjunct to a mood stabilizer and relapse prevention therapy may lead to decreased depressive symptoms, though it has no effect on methamphetamine use (107). In one case study of a 38-year-old female on Seroquel 800 mg/day and Depakote 1000 mg/day, a modafinil adjunct of 600 mg/day was found to decrease fatigue, depressive symptoms, and cravings for methamphetamines, leading to a 6-month period of abstinence from methamphetamines (108). Unfortunately, there are no large, double blinded, and/or controlled studies.

Co-occurring use disorder (unspecified)

Those with co-occurring diagnoses may warrant specific considerations for optimal treatment. In a retrospective review of 204 Bipolar I patients with or without substance use histories, Goldberg and colleagues found anticonvulsant medications such as divalproex and carbamazepine to be more effective than lithium for resolution of acute mania in the co-occurring subgroup (109). Weiss and colleagues, in a survey of 44 patients with co-occurring bipolar disorder and substance use, also discovered that these patients report higher adherence with anticonvulsants compared to lithium (110). In fact, those with co-occurring substance use disorders generally have a poorer response to lithium monotherapy (109,111,112), though lithium can still be effective as an adjunct to Depakote (113).

There is a growing interest in antipsychotics with mood stabilization properties. A small open label study on Risperdal augmentation found clinical improvement in affective symptoms and abstinence from alcohol and drugs (94). Quetiapine has been tested in larger randomized, placebo-controlled studies, one of which was a multisite trial, and was found to have no effect on alcohol use (93,114), though Brown and colleagues did find that dosing up to 600 mg per day helpful in decreasing depressive symptoms of bipolar disorder in dual diagnosis patients (95).

At least half of patients diagnosed with bipolar disorder, and an even greater portion of those with comorbid substance use disorders, demonstrate poor adherence to treatment over the course of their illness (109,115,116). Poor adherence to treatment may account for at least 20% of hospital readmissions for acute mania (117).

Psychosocial treatments and psychotherapy can play a positive role. Weiss and colleagues found that, for 45 patients with bipolar disorder and unspecified substance dependence, those who underwent an open trial of Integrated Group Therapy (IGT) showed a greater degree of abstinence, a lower composite addiction severity rating, and decreased mood episodes after 6 months when compared to monthly assessments without IGT (118). IGT had similar effects even when shortened to 12 sessions led by substance use counselors without special training (119).

Further studies are required for more definitive treatment recommendations as the number of multisite randomized studies is low, and many include 'alcohol and substance use disorders' as a cohesive group instead of separating by specific use disorder.

Summary

Bipolar disorder and substance use are intrinsically linked. Co-occurring patients appear to respond better to Depakote rather than lithium monotherapy, though lithium can still be used effectively as an adjunct. Research on antipsychotics has been mixed, but they may be a good adjunctive medicine. Risperidone may decrease mood symptoms and alcohol use, quetiapine may decrease depressive symptoms, and pramipexole may decrease craving for cocaine. Particularly in the context of poor medication adherence and mixed research results, therapy maintains a key role in treatment. Integrated group therapy and early recovery adherence therapy have both been shown to aid with substance use and mood symptoms for co-occurring patients. A combination of medications and integrated therapy is currently the ideal treatment, though the need for more research and larger studies is paramount.

Borderline personality disorder

Patients with co-occurring borderline personality disorder and substance use disorders have been found to have more serious psychopathology, including parasuicidal behavior, depression, and dissociation, as well as higher rates of relapse to substance use (17,120). Unfortunately, there are very few research studies for this extremely common co-occurring diagnosis, and the majority of those that exist are underpowered. Regarding co-occurring alcohol use disorder, there are no specific studies about antidepressants. A couple of small open label studies showed that naltrexone and opioid antagonists (Nalmefene) may decrease alcohol use and borderline symptomatology such as self-injury and binge eating (121,122), but there are no large, double blinded, and/or controlled studies. Lana and colleagues did a study of 51 individuals diagnosed with borderline personality disorder and a substance use disorder (alcohol, cannabis, opioid, and/or stimulant use disorders) which showed that integrated specialized psychotherapy such as dialectical behavioral therapy (DBT) and mentalization based treatment (MBT) led to a decrease in substance use, hospitalizations, and ER visits (123). These effects were maintained at a 36 month follow up. More research needs to be done regarding treatment of patients this common personality disorder and co-occurring substance use disorders.

Summary

There is a striking dearth in the literature regarding this extremely common clinical population. As it stands standard treatment of substance use disorder along with integrated specialized therapy (particularly DBT and MBT) should be the mainstay. Substance use should not be a rule out for these effective, focused therapies, and utilizing the modified versions that take an integrated approach appears to be significantly effective.

Schizophrenia

There are remarkably few studies about co-occurring patients with psychotic spectrum disorders despite the fact that the Epidemiologic Catchment Area study found that nearly half of patients with schizophrenia have a substance use or dependence disorder (3), and these patients are three times more likely to use alcohol and six times more likely to use other substances than those without schizophrenia (2). Those with co-occurring substance use and schizophrenia have been shown to have decreased motivation, increased drop-out rates, slower progress (18,124,125), increased symptoms (126), increased illness relapse (127), and increased risk of violent behavior (128,129) compared to those without substance use disorders.

Across the board, Clozaril stands out as a superior medication in increasing abstinence from substances and reducing psychosis (130-135). In fact, in both a naturalistic, longitudinal study (136) and a retrospective survey (132), patients with schizophrenia and substance use disorders treated with Clozaril were found to have 63-85% remission rates and achievement of abstinence during treatment. Additionally, integrated therapies addressing both substance use and psychosis, including motivational interviewing, CBT, and Acceptance Commitment Therapy (ACT) have been shown to lead to decreased substance use and improved stated quality of life (124,136,137).

Co-occurring alcohol use disorder

Clozaril has been found to be four times more efficacious for abstinence than other atypical antipsychotics (19). Naltrexone and disulfiram remain effective for decreasing alcohol craving and amount of daily drinking (138-140), though disulfiram has the potential to worsen psychotic symptoms (141). Especially considering the limited pharmacotherapeutic options, psychosocial treatments will likely remain key moving forward. Few specific interventions have been studied, though it has been posed that traditional interventions such as Alcoholics Anonymous (AA), may require too much social wherewithal for those with significant psychosis (136). Less socially taxing alternatives to AA could help fill a treatment gap for this patient population.

Co-occurring opioid use disorder

Some studies have suggested combining antipsychotic and opioid agonist medication with intensive psychosocial support (142). A small study of 5 patients found treatment with methadone and clozapine led to improvement in substance use and psychotic symptoms (143). More research is needed in this area for more definitive evidence-based treatments.

Co-occurring cannabis use disorder

Clozaril has been found to be four times more efficacious for abstinence than other atypical antipsychotics (137,144). THC has been shown to induce psychotic symptoms in health volunteers and patients with schizophrenia (145-149). However, recent studies have shown that cannabidiol, a non-psychoactive metabolite of cannabis, demonstrates an ability to attenuate the psychoactive properties of THC in healthy volunteers and patients with schizophrenia and may even improve disease trajectory (149-155). McGuire and colleagues performed a double-blind parallel group trial and found that cannabidiol decreased positive symptoms of schizophrenia on the PANNS and improved scores on the clinical global impressions scale (CGI) (154). There is no research yet on long-term effects.

Co-occurring cocaine use disorder

There is little research about this population. One study indicates Clozaril has an association with decreased craving for cocaine (156). Smelson and colleagues review specifically examining typical versus atypical antipsychotics found no compelling evidence for a difference in efficacy between typical and atypical antipsychotics for treatment of psychosis and cocaine use (157). However, in the case that a typical antipsychotic is tried first, and it fails, a small study run by Brown and colleagues found that switching to the atypical antipsychotic quetiapine may lead to reduced psychotic symptoms and cocaine use (158). Large, controlled trials are needed to clarify ultimate treatment goals.

Co-occurring amphetamine use disorder

Very little research exists regarding this sub-population. This is striking as in clinical experience methamphetamine use is often linked both acutely and chronically with development and worsening of psychotic symptoms. In fact, studies in Japan and California have found a link between methamphetamine use and chronic psychotic symptoms (159,160). Similar to cocaine use, Brown and colleague's small study showed that switching from a failed typical antipsychotic treatment to quetiapine may lead to reduced psychotic symptoms and amphetamine use (158). Breen and colleagues performed a small preliminary integrative RNA sequencing study in 2016 profiling peripheral blood gene expression in 10 patients with methamphetamine-associated psychosis, 10 patients with methamphetamine dependence without psychosis, and 10 healthy controls which suggested similar molecular and neurocognitive underlying pathophysiology between schizophrenia and methamphetamine-associated psychosis (161). Specifically, both were associated with lower bilateral hippocampal volumes as well as upregulation of biomarkers for RNA degradation (CLN3, TB1D2, and ZNF821CLN3, FBP1, TBC1D2 and ZNF821), associated with circadian rhythm (ELK3 and SINA3), and ubiquitin-mediated proteolysis (PIGF and UHMK1). Breen was able to differentiate between the individuals with methamphetamine dependence without psychosis and methamphetamine-associated psychosis with 95% accuracy. Though this preliminary data is a promising indication that with similar biomarkers, methamphetamine-associated psychosis and schizophrenia may respond to similar treatments, there are not yet any larger or confirmatory studies and no treatment specific comparison studies. More research needs to be done in this area to examine possible pharmacotherapeutic and psychosocial interventions to aid this sub-population.

Summary

Clozaril stands out above and beyond other antipsychotics in terms of efficacy for treatment substance use and psychosis. There is no compelling evidence for a difference in efficacy between typical or atypical antipsychotics, though if a typical antipsychotic fail, quetiapine may be considered. Naltrexone may be helpful as an adjunct for those with an alcohol use disorder to decrease craving rather than disulfiram as there is some evidence that disulfiram may exacerbate psychotic symptoms. Though THC worsens psychotic symptoms, cannabidiol may ameliorate symptoms. More research needs to be done on the long-term effects of cannabidiol. Psychosocial treatments are key. MI and CBT or MI and ACT can be particularly helpful.

DISCUSSION

Despite the large clinical population of co-occurring patients, research studies often preclude this subset of patients from participating. For example, up to 90% of community based bipolar patients screened for clinical trials of acute mania were turned away (9). This inhibits our ability to have an accurate evidence base for optimal treatment of dual diagnosis patients. This artificial separation of psychiatric disorders and substance use disorders in research likely contributes to the common refusal of patients with significant substance use disorders at psychiatric treatment facilities and vice versa.

Patients with co-occurring psychiatric and substance use disorders have been found to have worsened disease trajectories, poorer treatment responses, and increased mortality (17,18,23,24,45,47,82,86-89,120,124,125,127-129,162). Therefore, this gap in the knowledge base significantly impedes the ability to provide the best care.

Additionally, in the few reviews looking at integrated treatment, usually for a specific primary psychiatric disorder, psychotherapeutic techniques are often not included (5,16-19).

CONCLUSION

The limited number of studies that have been performed and detailed in this paper support integrated treatment of substance use disorders along with primary psychiatric disorders as opposed to parallel or sequential treatment and emphasizes the importance of psychotherapeutic techniques. Clinical practice should begin to take these results into consideration and further research studies should specifically target this important population.

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REFERENCES

1. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2004;61:807-16.
2. Reiger DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: Results from the Epidemiologic Catchment Area (ECA) Study. JAMA. 1990;264:2511-8.
3. Kessler RC, Crum R, Warner L, et al. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry. 1997;54:313-21.
4. Boden JM, Fergusson DM. Alcohol and depression. Addiction. 2011;106:906-14.
5. Jacobsen LK, Southwick SM, Kosten TR. Substance use disorders in patients with posttraumatic stress disorder: A review of the literature. Am J Psychiatry. 2001;158(8):1184-90.
6. Grant BF, Chou SP, Goldstein RB, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: Results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2008;69:533-45.
7. Kranzler HR, Del-Boca FK, Rounsaville BJ. Comorbid psychiatric diagnosis predicts three-year outcomes in alcoholics: A post-treatment natural history study. J Stud Alcohol. 1996;57:619-26.
8. Davis LL, Wisniewski SR, Howland RH, et al. Does comorbid substance use disorder impair recovery from major depression with SSRI treatment? An analysis of the STAR*D level one treatment outcomes. Drug Alcohol Depend. 2010;107:161-70.
9. Bowden CL, Calabrese JR, Wallin BA, et al. Illness characteristics of patients in clinical drug studies of mania. Psychopharmacology Bulletin. 1995;31:103-9.
10. Simon NM, Otto MW, Weiss RD, et al. Pharmacotherapy for bipolar disorder and comorbid conditions. Baseline data from STEP-BD. J Clin Psychopharmacol. 2004;24:512-20.
11. Nunes EV, Hennessy G, Slezer J. Depression in patients with substance use disorders, in substance dependence and co-occurring psychiatric disorders. Civic Research Institute. 2010.
12. Winokur G, Turvey C, Akiskal H, et al. Alcoholism and drug abuse in three groups: Bipolar I, unipolars and their acquaintances. J Affect Disord. 1998;50(2-3):81-9.
13. Carlson GA, Bromet EJ, Sievers S. Phenomenology and outcome of subjects with early- and adult-onset psychotic mania. Am J Psychiatry. 2000;157:213-9.
14. Hasin DS, Goodwin RD, Stinson FS, et al. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2005;62:1097-1106.
15. Torrens M, Rossi PC, Martinez-Riera R, et al. Psychiatric co-morbidity and substance use disorders: Treatment in parallel systems or in one integrated system. Subst Use Misuse. 2012;47:1005-14.
16. Torrens M, Fonseca, F, Mateu G, et al. Efficacy of antidepressants in substance use disorders with and without comorbid depression: A systemic review and meta-analysis. Drug Alcohol Depend. 2005;78(1):1-22.
17. Pennay A, Cameron J, Reichert T, et al. A systemic review of interventions for co-occurring substance use disorder and borderline personality disorder. J Subst Abuse Treat. 2011;41(4):363-73.
18. Drake RE, Mueser KT, Brunette MF, et al. A review of treatments for people with severe mental illnesses and co-occurring substance use disorders. Psychiatr Rehabil J. 2004;27:360-74.
19. Tiet QQ, Mausbach B. Treatments for patients with dual diagnosis: A review. Alcohol Clin Exp Res. 2007;31:513-36.
20. Back SE, Waldrop AE, Brady KT. Treatment challenges associated with comorbid substance use and posttraumatic stress disorder: Clinicians' perspectives. Am J Addict. 2009;18(1):15-20.

21. Van DD, Ehring T, Vedel E, et al. Trauma-focused treatment for posttraumatic stress disorder combined with CBT for severe substance use disorder: A randomized controlled trial. BMC Psychiatry. 2013;13:172.

22. Read JP, Brown PJ, Kahler CW. Substance use and posttraumatic stress disorders: Symptom interplay and effects on outcome. Addict Behav. 2004;29:1665-72.

23. Norman SB, Myers US, Wilkins KC, et al. Review of biological mechanisms and pharmacological treatments of comorbid TPSD and substance use disorder. Neuropharmacology. 2012;62(2):542-51.

24. Coker KL, Stefanovics E, Rosenheck R. Correlates of improvements in substance abuse among dually diagnosed veterans with post-traumatic stress disorder in specialized intensive VA treatment. Psychol Trauma. 2016;8(1):41-8.

25. Back SE, Brady KT, Sonne SC, et al. Symptom improvement in co-occurring PTSD and alcohol dependence. J Nerv Ment Dis. 2006;194(9):690-6.

26. Petrakis IL, Poling J, Levinson C, et al. Naltrexone and disulfiram in patients with alcohol dependence and comorbid posttraumatic stress disorder. Biol Psych. 2006;60:777-83.

27. Coffey SF, Schumacher JA, Nosen E, et al. Trauma-focused exposure therapy for chronic posttraumatic stress disorder in alcohol and drug dependent patients: A randomized control trial. Psychol Addict Behav. 2016;30(7):778-90.

28. Saunders EC, McGovern MP, Lambert-Harris C, et al. The impact of addiction medications on treatment outcomes for persons with co-occurring PTSD and opioid use disorder. Am J Addict. 2015;24(8):722-31.

29. Ruglass LM, Shevorykin A, Radoncic V, et al. Impact of cannabis use on treatment outcomes among adults receiving cognitive-behavioral treatment for PTSD and substance use disorders. J Clin Med. 2017;6(2):14.

30. Fortuna LR, Porche MV, Padilla A. A treatment of development study of a cognitive and mindfulness-based therapy for adolescents with co-occurring post-traumatic stress and substance use disorder. Psychol Psychother. 2017;91(1):42-62.

31. Elliott L, Golub A, Bennett A, et al. PTSD and Cannabis related coping among recent veterans in New York City. Contemp Drug Probl. 2015;42:60-76.

32. Berardi A, Schelling G, Campolongo P. The endocannabinoid system and post-traumatic stress disorder (PTSD): From preclinical findings to innovative therapeutic approaches in clinical settings. Pharmacol Res. 2016;111:668-78.

33. Fraser GA. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). CNS Neurosci Ther. 2009;15:84-8.

34. Jetly R, Heber A, Fraser G, et al. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. Psych neuroendocrinology. 2015;5:585-8.

35. Papini S, Sullivan GM, Hien DA, et al. Toward a translational approach to targeting the endocannabinoid system in posttraumatic stress disorder: A critical review of preclinical research. Biol Psychol. 2015;104:8-18.

36. Lester K, Milby JB, Schumacher JE, et al. Impact of behavioral contingency management intervention on coping behaviors and PTSD symptom reduction in cocaine-addicted homeless. J Trauma Stress. 2007;20(4);565-75.

37. Back SE, Brady KT, Jaanimagi U, et al. Cocaine dependence and PTSD: A pilot study of symptom interplay and treatment preferences. Addict Behav. 2006;31:351-4.

38. Baker DA, McFarland K, Lake RW, et al. Neuroadaptations in cysteine-glutamate exchange underlie cocaine relapse. Nature Neurosci. 2003;6:743-9.

39. Aupperle RL, Melrose AJ, Stein MB, et al. Executive function and PTSD: Disengaging from trauma. Neuropharmacology. 2012;62:686-94.

40. Bremner JD, Elzinga B, Schmahl C, et al. Structural and functional plasticity of the human brain in posttraumatic stress disorder. Prog Brain Res. 2008;167:171-86.

41. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. Nat Rev Neurosci. 2011;12:652-69.

42. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010;35:217-38.

43. Back SE, McCauley JL, Korte KJ, et al. A double-blind randomized controlled pilot trial of N-Acetylcysteine in veterans with PTSD and substance use disorders. J Clin Psychiatry. 2016;77(11):1439-46.

44. Hien D, Lopez-Castro T, Papini S, et al. Emotion dysregulation moderates the effect of cognitive behavior therapy with prolonged exposure for co-occurring PTSD and substance us disorders. J Anxiety Disord. 2017;52;53-61.

45. Torrens M, Gilchrist G, Domingo-Salvany A. Psychiatric comorbidity in illicit drug users: Substance-induced *vs.* independent disorders. Drug Alcohol Depend. 2011;113:147-56.

46. Ramsey SE, Kahler CW, Read JP, et al. Discriminating between substance-induced and independent depressive episodes in alcohol-dependent patients. J Stud Alcohol. 2004;65:672-6.

47. Aharonovich E, Liu X, Nunes E, et al. Suicide attempts in substance abusers: Effects of major depression in relation to substance use disorders. Am J Psychiatry. 2002;159(9):1600-2.

48. Greenfield SF, Weiss RD, Muenz LR, et al. The effect of depression on return to drinking: A prospective study. Arch Gen Psychiatry. 1998;55(3):259-65.

49. Tirado-Munoz J, Farre A, Mestre-Pinto J, et al. Dual diagnosis in depression: Treatment recommendations. Addiciones. 2018;30(1):66-76.

50. Kranzler HR, Armeli S, Tennen H, et al. A double-blind, randomized trial of sertraline for alcohol dependence: moderation by age of onset and 5-hydroxytryptamine transporter-linked promoter region genotype. J Clin Psychopharmacol. 2011;31:22-30.

51. Pettinati HM, Volpicelli JR, Luck G, et al. Double-blind clinical trial of sertraline treatment for alcohol dependence. J Clin Psychopharmacol. 2001;21(2):143-52.

52. Gual A, Balcells M, Torres M, et al. Sertraline for the prevention of relapse in detoxicated alcohol dependent patients with a comorbid depressive disorder: A randomized controlled trial. Alcohol Alcohol. 2003;38(6):619-25.

53. Moak DH, Anton RF, Latham PK, et al. Sertraline and cognitive behavioral therapy for depressed alcoholics: results of a placebo-controlled trial. J Clin Psychopharmacol. 2003;23(6):553-62.

54. Mason BJ, Kocsis JH, Ritvo EC, et al. A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. JAMA. 1996;275:761-7.

55. Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: A meta-analysis. JAMA. 2004;291:1887-96.

56. Thapinta D, Skulphan S, KitsumbanV, et al. Cognitive behavior therapy self-help booklet to decrease depression and alcohol use among people with alcohol dependence in Thailand. Issues Ment Health Nurs. 2017;38(11):964-70.

57. Ray LA, Barr CS, Blendy JA, et al. The role of the Asn40Asp polymorphism of the mu opioid receptor gene (OPRM1) on alcoholism etiology and treatment: A critical review. Alcohol Clin Exp Res. 2012;36:385-94.

58. Oslin DW, Berrettini W, Kranzler HR, et al. A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. Neuropsychopharmacology. 2003;28:1546-52.

59. Samokhalov AV, Awan S, George TP, et al. Integrated care pathway for co-occurring major depressive disorder and alcohol use disorders: Outcomes for the first two years. Am J Addict. 2017;26(6):602-9.

60. Pedrelli P, Lovieno N, Vitali M, et al. Treatment of major depressive disorder and dysthymic disorder with antidepressants in patients with comorbid opiate use disorders enrolled in methadone maintenance therapy. J Clin Psychopharmacol. 2011;31(5):582-6.

61. Ahmadi J, Sefidfard JM. Ultra-rapid influence of buprenorphine on major depression in opioid-dependent patients: a double blind, randomized clinical trial. Subst Use Misuse. 2017;17:1-4.
62. Rosen D, Morse J, Reynolds CF. Adapting problem-solving therapy for depressed older adults in methadone maintenance treatment. J Subst Abuse Treat. 2010;40:132-41.
63. Cuijpers, P, Van-Straten A, Warmerdam L. Problem solving therapies for depression: A meta-analysis. Eur Psychiatry. 2007;22:9-15.
64. Levin FR, Marlani J, Brooks DJ, et al. A randomized double-blind placebo-controlled trial of venlafaxine-extended release for cooccurring cannabis dependence and depressive disorders. Addiction. 2013;108(6):1084-94.
65. Kay-Lambkin FJ, Baker AL, Lewin TJ, et al. Computer-based psychological treatment for comorbid depression and problematic alcohol and/or cannabis use: A randomized controlled trial of clinical efficacy. Addiction. 2009;104:378-88.
66. Gruber AJ, Pope HG, Brown ME. Do patients use marijuana as an antidepressant?. Depression. 1996;4(2):77-80.
67. Kotin J, Post RM, Goodwin FK. Δ9-Tetrahydrocannabinol in depressed patients. Arch Gen Psychiatry. 1973;28(3):345-8.
68. Ablon SL, Goodwin FK. High frequency of dysphoric reactions to tetrahydrocannabinol among depressed patients. Am J Psychiatry. 1974;131(4):448-53.
69. Blass K. Treating depression with cannabinoids (Cannabinoids 3). Washington, DC: US Government Printing Office. 2008.
70. Raby WN, Rubin E, Garawi F, et al. A randomized, double-blind, placebo-controlled trial of venlafaxine for the treatment of depressed cocaine-dependent patients. Am J Addict. 2014;23:68-75.
71. Cruickshank CC, Motebello ME, Dyer KR, et al. A placebo-controlled trial of mirtazapine for the management of methamphetamine withdrawal. Drug and Alcohol Review. 2008;27(3):326-33.
72. Elkashef AM, Rawson RA, Anderson AL, et al. Bupropion for the treatment of methamphetamine dependence. Neuropsychology. 2008;33:1162-70.
73. Galloway GP, Newmeyer J, Knapp T, et al. Imipramine for the treatment of cocaine and methamphetamine dependence. J Addict Dis. 1994;13(4):201-16.
74. Galloway GP, Newmeyer J, Knapp T, et al. A controlled trial of imipramine for the treatment of methamphetamine dependence. J Subst Abuse Treat. 1996;13(6):493-7.
75. Shoptaw S, Heinzerling KG, Rotheram-Fuller E, et al. Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. Drug Alcohol Depend. 2008;96(3):222-32.
76. McGaugh J, Mancino MJ, Feldman Z, et al. Open-label pilot study of modafinil for methamphetamine dependence. J Clin Psychopharmacol. 2009;29(5):488-91.
77. Baker A, Lee NK, Claire M, et al. Brief cognitive behavioral interventions for regular amphetamine users: A step in the right direction. Addiction. 2005;100:367-78.
78. Baker A, Lee NK, Claire M, et al. Drug use patterns and mental health of regular amphetamine users during a reported 'heroin drought'. Addiction. 2004;99:875-84.
79. Watkins KE, Hunter SB, Hepner KA, et al. An effectiveness trial of group cognitive behavioral therapy for patients with persistent depressive symptoms in substance abuse treatment. Arch Gen Psychiatry. 2012;68:577-84.
80. Salloum IM, Thase ME. Impact of substance abuse on the course and treatment of bipolar disorder. Bipolar Disord. 2000;2:269-80.
81. Fossey MD, Otto MW, Yates WR, et al. STEP-BD Investigators: Validity of the distinction between primary and secondary substance use disorder in patients with bipolar disorder: data from the first 1000 STEP-BD participants. Am J Addict. 2006;15:138-43.
82. Fleck DE, Arndt S, Delbellow MP, et al. Concurrent tracking of alcohol use and bipolar disorder symptoms. Bipolar Disord. 2006;8(4):338-44.
83. Ananth J, Vandewater S, Kamal M, et al. Missed diagnosis of substance abuse in psychiatric patients. Hosp Community Psychiatry. 1989;40:297-9.
84. Lehman AF, Myers CP, Corty E. Assessment and classification of patients with psychiatric and substance abuse syndromes. Hosp Community Psychiatry. 1989;40:1019-25.
85. Lagerberg TV, Larsson S, Sundet K, et al. Treatment delay and excessive substance use in bipolar disorder. J Nerv Ment Dis. 2010;198(9):628-33.
86. González-Pinto A, Mosquera F, Alonso M, et al. Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. Bipolar Disord. 2006;8:618-24.
87. González-Pinto A, Reed C, Novick D, et al. Assessment of medication adhe-rence in a cohort of patients with bipolar disorder. Pharmacopsychiatry. 2010;43:263-70.
88. Goldberg JF, Garno JL, Portera L, et al. Correlates of suicidal ideation in dysphoric mania. J Affect Disord. 1999;56:75-81.
89. Elliott AJ, Pages KP, Russo J, et al. A profile of medically serious suicide attempts. J Clin Psychiatry. 1996;57:567-71.
90. Goldberg JF. Bipolar disorder with comorbid substance abuse: diagnosis, prognosis, and treatment. J Psychiatr Pract. 2001;7(2):109-22.
91. Winokur G, Coryell W, Keller M, et al. A prospective follow-up of patients with bipolar and primary unipolar affective disorder. Arch Gen Psychiatry. 1993;50(6):457-65.
92. Stedman M, Pettinati HM, Brown ES, et al. A double-blind, placebo-controlled study with quetiapine as adjunct therapy with lithium or divalproex in bipolar I patients with coexisting alcohol dependence. Alcohol Clin Exp Res. 2010;34:1822-31.
93. Brown ES, Davila D, Nakamura A, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in patients with bipolar disorder, mixed or depressed phase, and alcohol dependence. Alcohol Clin Exp Res. 2014;38:2113-8.
94. Albanese MJ. Risperidone in substance abusers with bipolar disorder. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico. 2000;pp:9-14.
95. Brown ES, Garza M, Carmody TJ. A randomized, double-blind, placebo-controlled add-on trial of quetiapine in outpatients with bipolar disorder and alcohol use disorders. J Clin Psychiatry. 2008;69(5):701-5.
96. Salloum IM, Douaihy AB, Kelly TM, et al. Integrating pharmacotherapy and a novel individual counseling for alcoholism with bipolar disorder. Alcohol: Clin Exp Res. 2008;32:260.
97. Grinspoon L, Bakalar JB. The use of cannabis as a mood stabilizer in bipolar disorder: Anecdotal evidence and the need for clinical research. J Psychoactive Drugs. 1998;30:171-7.
98. Ashton CH, Moore PB, Gallagher P, et al. Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential. J Psychopharmacol. 2005;19:293-300.
99. Strakowski SM, Keck PE Jr, McElroy SL, et al. Twelve-month outcome after a first hospitalization for affective psychosis. Arch Gen Psychiatry. 1998;55:49-55.
100. Calabrese JR, Shelton MD, Bowden CL, et al. Bipolar rapid cycling: Focus on depression as its hallmark. J Clin Psychiatry. 2001;62:34-41.
101. Strakowski SM, DelBello MP, Fleck DE, et al. The impact of substance abuse on the course of bipolar disorder. Biol Psychiatry. 2000;48:477-85.
102. Baethge C, Baldessarini RJ, Khalsa HMK, et al. Substance abuse in first-episode bipolar I disorder: Indications for early intervention. Am J Psychiatry. 2005;162:1008-10.
103. Strakowski SM, Del-Bello MP, Fleck DE, et al. Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization for mania. Arch Gen Psychiatry. 2007;64:57-64.
104. Rosenbaum JF, Fredman SJ. Pramipexole treatment for cocaine cravings (letter). Am J Psychiatry. 1999;156:1834.
105. Renshaw PF, Daniels S, Lundahl LH, et al. Short-term treatment with citicoline (CDP-choline) attenuates some measures of craving in cocaine-dependent subjects: a preliminary report. Psychopharmacology (berl). 1999;142:132-8.

106. Brown ES, Gorman AR, Hynan LS. A randomized, placebo-controlled cocaine dependence. J Clin Psychiatry. 2007:27;498-502.

107. Brown ES, Gabrielson B. A randomized, double blind, placebo-controlled trial of citicoline for bipolar and unipolar depression and methamphetamine dependence. J Affect Disord. 2012;143:257-60.

108. Camacho A, Ng B, Frye M. Modafinil for bipolar depression with comorbid methamphetamine abuse. The Am J Addict. 2012:19;190-1.

109. Goldberg JF, Garno JL, Leon AC, et al. A history of substance abuse complicates remission from acute mania in bipolar disorder. J Clin Psychiatry. 1999;60:733-40.

110. Weiss RD, Greenfield SF, Najavits LM, et al. Medication compliance among patients with bipolar disorder and substance use disorder. J Clin Psychiatry. 1998;59(4):172-4.

111. Himmelhoch JM, Garfinkel ME. Sources of lithium resistance in mixed mania. Psychopharmacology Bulletin. 1986;22:613-20.

112. Passmore MJ, Garnham J, Duffy A, et al. Phenotypic spectra of bipolar disorder in responders to lithium *vs.* lamotrigine. Bipolar Disord. 2003;5:1130-3.

113. Salloum IM, Cornelius JR, Daley DC, et al. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: A double-blind placebo-controlled study. Arch Gen Psychiatry. 2005;62:37-45.

114. Stedman M, Pettinati HM, Brown ES, et al. A double-blind, placebo-controlled study with quetiapine as adjunct therapy with lithium or divalproex in bipolar I patients with coexisting alcohol dependence. Alcohol Clin Exp Res. 2010;34:1822-1.

115. Goodwin FK, Jamison KR. Manic-depressive illness. New York: Oxford University Press. 1990.

116. Strakowski SM, Keck PE, McElroy SL, et al. Twelve-month outcome after a first hospitalization for affective psychosis. Arch Gen Psychiatry. 1998;55:49-55.

117. Kocsis JH, Stokes PW. Lithium maintenance: Factors affecting outcome. Am J Psychiatry. 1979;136:563-6.

118. Weiss RD, Najavita LM, Greefield SF. A relapse prevention group for patients with bipolar and substance use disorders. J Substance abuse Treatment. 1999;16:46-54.

119. Weiss RD, Griffin ML, Greenfield SF, et al. Group therapy for patients with bipolar disorder and substance dependence: Results of a pilot study. J Clin Psychiatry. 2000;61:361-7.

120. Lee JH, Bagge CL, Schumacher JA, et al. Does comorbid substance use disorder exacerbate borderline personality features?: A comparison of borderline personality disorder individuals with *vs.* without current substance dependence. Personal Disord. 2010;1(4):239-49.

121. Martín-Blanco A, Patrizi B, Soler J, et al. Use of nalmefene in patients with comorbid borderline personality disorder and alcohol use disorder: A preliminary report. Int Clin Psychopharmacol. 2017;32(4):231-4.

122. Roth AS, Ostroff RB, Hoffman RE. Naltrexone as a treatment for repetitive self-injurious behavior: An open label trial. J Clin Psychiatry. 1996;57(6):233-7.

123. Lana F, Sanchez-Gil C, Adroher ND, et al. Comparison of treatment outcomes in severe personality disorder patients with or without substance use disorders: A 36-month prospective pragmatic follow up study. Neuropsychiatr Dis Treat. 2016;12:1477-87.

124. Barrowclough C, Haddock G, Fitzsimmons M, et al. Treatment development for psychosis and co-occurring substance misuse: A descriptive review. J of Mental Health. 2006;15:619-32.

125. Gregg L, Barrowclough C, Haddock G. Reasons for increased substance use in psychosis. Clin Psycho Rev. 2007;27:494-510.

126. Swartz MS, Wagner HR, Swanson JW, et al. Substance use in persons with schizophrenia: baseline prevalence and correlates from the NIMH CATIE study. J Nerv Ment Dis. 2006;194(3):164-72.

127. Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry. 1994;51(4):273-9.

128. Abram KM, Teplin LA. Co-occurring disorders among mentally ill jail detainees. Implications for public policy. Am Psychol. 1991;46(10):1036-45.

129. Swanson JW, Holzer CE, Ganju VK, et al. Violence and psychiatric disorder in the community: Evidence from the epidemiologic catchment area surveys. Hosp Community Psychiatry. 1990;41(7):761-70.

130. Albanese MJ, Khantzian EJ, Murphy SL, et al. Decreased substance use in chronically psychotic patients treated with clozapine. Am J Psychiatry. 1994;151:780-1.

131. Marcus P, Snyder R. Reduction of comorbid substance abuse with clozapine (letter). Am J Psychiatry. 1995;152:959.

132. Zimmet SV, Strous RD, Burgess ES, et al. Effects of clozapine on substance use in patients with schizophrenia and schizoaffective disorder: A retrospective survey. J Clin Psychopharmacol. 2000;20(1):94-8.

133. McEvoy JP, Liebeman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry. 2002;159:1018-27.

134. Buckley P, Thompson P, Way L, et al. Substance abuse among patients with treatment-resistant schizophrenia: Characteristics and implications for clozapine therapy. Am J Psychiatry. 1994;151(3):385-9.

135. Drake RE, Xie H, McHugo GJ, et al. The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. Schizophrenia Bulletin. 2000;26(2):441-9.

136. Tsuang J, Fong TW, Lesser I. Psychosocial treatment of patients with schizophrenia and substance use disorders. Addiction Disorder Treatment. 2006;5:53-66.

137. Green AI, Burgess ES, Dawson R, et al. Alcohol and cannabis use in schizophrenia: effects of clozapine *vs.* risperidone. Schizophr Res. 2003;60(1):81-5.

138. Petrakis IL, O'Malley S, Rounsaville B, et al. Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia. Psychopharmacology (Berl). 2004;172:291-7.

139. Green AI, Salomon MS, Brenner MJ, et al. Treatment of schizophrenia and comorbid substance use disorder. Curr Drug Targets CNS Neurol Disord. 2002;1(2):129-39.

140. Mueser KT, Noordsy DL, Fox L, et al. Disulfiram treatment for alcoholism in severe mental illness. Am J Addict. 2003:12:242-52.

141. Kingsbury SJ, Salzman C. Disulfiram in the treatment of alcoholic patients with schizophrenia. Hosp Community Psychiatry. 1990;41:133-45.

142. Drake RE, O'Neal EL, Wallach MA. A systemic review of psychosocial research on psychosocial interventions for people with co-occurring severe mental and substance use disorders. J Subst Abuse Treat. 2008;34(1):123-38.

143. Unglaub W, Kandel M, Zenner D, et al. Neuroleptic therapy of comorbid narcotic dependent patients in ambulatory methadone maintenance. Psychiatrische Praxis. 2003;30(2):121-4.

144. Brunette MF, Dawson R, O'Keefe CD, et al. A randomized trial of clozapine *vs.* other antipsychotics for cannabis use disorder in patients with schizophrenia. J Dual Diagn. 2011;7(1-2):50-63.

145. D'Souza D, Perry E, MacDougall L, et al. The psychomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharm. 2000;29:1558-72.

146. D'Souza D, Abi-Saab WM, Madonick S, et al. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biol Psychiatry. 2005;57(6):594-608.

147. Morrison PD, Nottage J, Stone JM, et al. Disruption of frontal theta coherence by delta-9-tetrahyrdocannabinol is associated with positive psychotic symptoms. Neuropsychopharm. 2011;36:827-36.

148. Henquet C, Van-Os J, Kuepper R, et al. Psychosis reactivity to cannabis use in daily life: an experience sampling study. Br J Psychiatry. 2010;196:447-53.

149. Iseger TA, Bossong MG. A systemic review of the antipsychotic properties of cannabidiol in humans. Schizophr Res. 2015;162(1-2):153-61.

150. Bhattacharyya S, Morrison PD, Fusar-Poli P, et al. Opposite effects of

delta-9-tetrahydrocannabinol and cannabidiol of human brain function and psychopathology. Neuropsychopharmacology. 2010;35:764-74.

151. Zuardia AW, Crippa JA, Hallak JE, et al. Cannabidiol, a cannabis sativa constituent, as an antipsychotic drug. Braz J Med Biol Res. 2006;39:421-9.

152. Leweke FM, Schneider U, Radwan M, et al. Different effects of nabilone and cannabidiol on binocular depth inversion in man. Pharmacol Biochem Behav. 2000;66:175-81.

153. Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry. 2012;2:94.

154. McGuire P, Robson P, Cubala WJ, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial. Am J Psychiatry. 2018;175(3):225-31.

155. Hahn B. The potential of cannabidiol treatment for cannabis users with recent-onset psychosis. Schizophr Bull. 2018;44(1):46-53.

156. Yovell Y, Opler LA. Clozapine reverses cocaine craving in a treatment-resistant mentally ill chemical abuser: A case report and a hypothesis. J Nerv Ment Dis. 1994;182:591-2.

157. Smelson DA, Dixon L, Craig T, et al. Pharmacological treatment of schizophrenia and co-occurring substance use disorders. CNS Drugs. 2008;22:903-16.

158. Brown ES, Nejtek VA, Perantec DC, et al. Cocaine and amphetamine use in patients with psychiatric illness: A randomized trial of typical antipsychotic continuation or discontinuation. J Clin Psychopharmacol. 2003;23:284-8.

159. Akiyama K, Saito A, Shimoda K. Chronic methamphetamine exposure produces a delayed, long-lasting memory deficit. The American Journal on Addictions. 2011;20:240-9.

160. Callaghan RC, Cunningham JK, Allebeck P, et al. Methamphetamine use and schizophrenia: A population-based cohort study in California. Am J Psychiatry. 2012;169(4):389-96.

161. Breen MS, Uhlmann A, Nday CM, et al. Candidate gene networks and blood biomarkers of methamphetamine-associated psychosis: An integrative RNA-sequencing report. Transl Psychiatry. 2016;6:802.

162. Mueser K, Drake R, Sigmon S, et al. Psychosocial interventions for adults with severe mental illnesses and co-occurring substance use disorders: A review of specific interventions. J of Dual Diagnoses. 2005;1:57-82.