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# Psychopharmacological interventions for co-occurring substance use and mental health disorders: a comprehensive review

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## ABSTRACT

The co-occurrence of mental disorders and a substance use disorder, referred to as dual diagnosis, is perhaps the most clinically demanding condition because both disorders mutually exacerbate each other. This systematic review encompasses psychopharmacologic therapy in this patient population. We utilized major electronic databases and recent 10-year publications, as well as research published in English, Spanish, Polish, German, and Italian. Second-generation antipsychotics are the first-line treatment for comorbid psychosis with improved tolerability despite metabolic side effects. SSRIs and SNRIs are first-line therapy for depression, but the optimal timing of their initiation is controversial. Mood stabilizers like anticonvulsants are very important in bipolar disorder but require careful monitoring due to unique adherence and drug level concerns. We are also cautious with anti-anxiety medication because they are high-risk for abuse. The review shows that medication is not enough on its own. We combine it with social support and EBM therapies. There are still significant areas for future research, including the need for more long-term studies and the development of new medications that target standard neurobiological processes.

**Keywords:** addiction, psychotropic medications, dual diagnosis, comorbidity, pharmacological therapy

## 1. INTRODUCTION

When a person is struggling with both a disorder of mental illness and a disorder of drug abuse simultaneously—a condition we usually refer to as a dual diagnosis—it is one of the oldest and most challenging conditions of modern medicine (Hyman et al., 2001). It is not a situation of two independent illnesses that coincidentally co-occur; it is an enmeshed relationship in which each disease is active, exacerbating the other. This entwinement leads to much worse consequences, a much more laborious recovery process, and a poor quality of life. Simply put, it should not be surprising in the least that people who have a dual diagnosis experience more relapses and comment on traditional treatments, which commonly address one

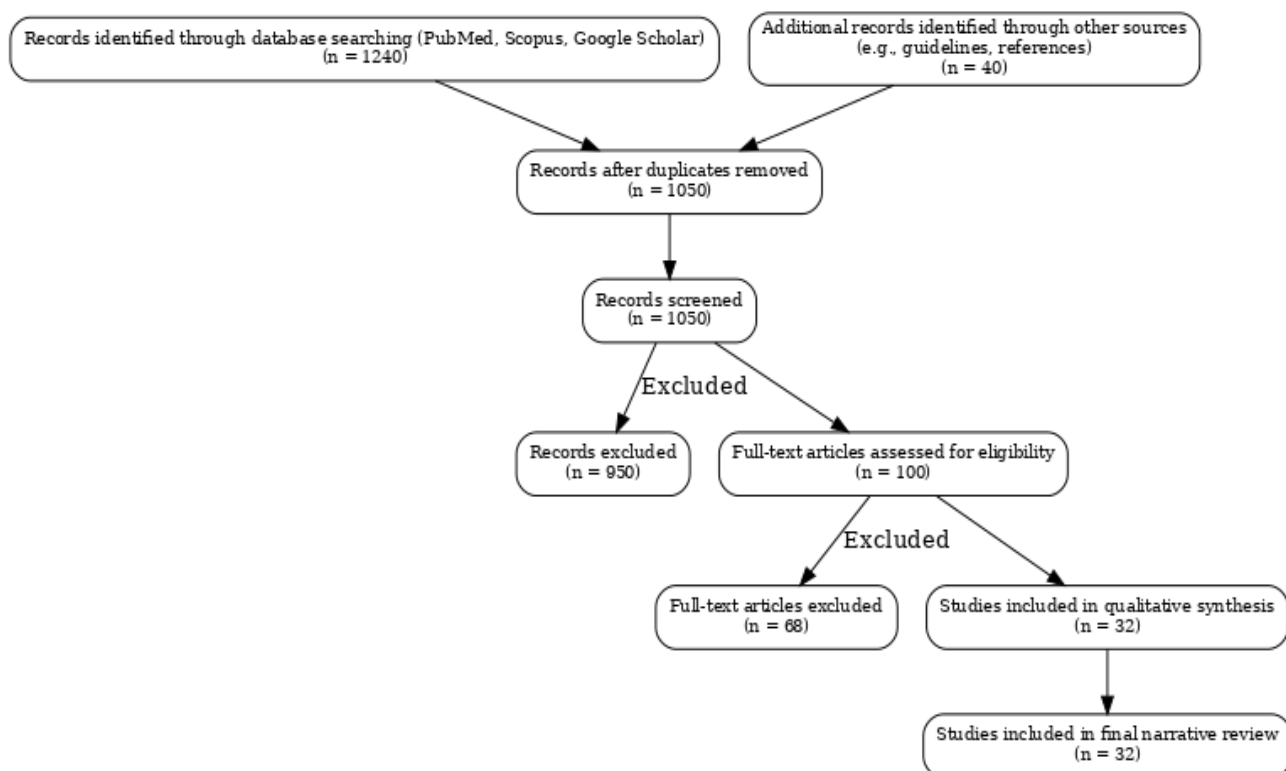
problem only, as inadequate. This intricate process, in which a person might use chemicals to hide psychiatric symptomatology, and the substances subsequently trigger and amplify those very same symptoms, necessitates an entirely different, merged approach (Drake et al., 1998).

The entire process becomes immensely complicated owing to several cross-occurring issues. There is, in the first instance, the problem of diagnosis: the problem is astronomical; the clinician finds himself attempting to sort out symptoms of an actual psychiatric illness from those which follow from drug use alone, no simple task (Woody, 1996). To this is added continual concern about possible life-threatening drug interactions between psychotropic medications and drugs of abuse. Although medication is an essential method for controlling most symptoms, doctors must closely monitor its application in this particular group of patients. It cannot be guaranteed to be safe or effective over the long term for many. Ignoring all these difficulties, the purpose of this article is to provide a very detailed overview of the latest research on pharmacological treatment for patients suffering from both substance abuse and other psychiatric problems (Brunette et al., 2008). Our goal is not only to summarize the available evidence but also to evaluate the safety and effectiveness of specific medications and address common challenges faced by clinicians in the field, so that we can later identify the most critical research gaps that still need to be filled.

We will review the use of antipsychotics, antidepressants, and mood stabilizers before talking about real, everyday clinical issues such as patients' compliance and the enormous danger of medication misuse. We hope this paper can ultimately be a helpful resource for you, doctors, and scientists. We aim to provide you with a deeper understanding and more effective, integrated approaches to treatment for these specific patients.

## 2. REVIEW METHODS

We conducted a systematic literature search to identify relevant studies (Figure 1). We conducted our search in major academic databases, primarily PubMed (on a smaller scale, also Scopus and others). We concentrated on publications from the last 10 years (utilizing some research from the previous 25 years as needed). We did not limit our search to our language only. We also looked at papers in Polish, English, Spanish, German, and Italian. Our primary focus for inclusion was original research and systematic reviews. We ignored case reports and opinion articles. Our goal was to provide reliable and evidence-based information for our analysis.



**Figure 1.** Study selection process according to PRISMA guidelines

3. RESULTS AND DISCUSSION

Major Classes of Drugs and Their Uses

This chapter focuses on the details of how we use the different classes of psychotropic medications in patients with both substance use and psychiatric disorders. The selection is not a one-size-fits-all situation; each drug class presents its own set of benefits, risks, and unique challenges that the clinician must consider. It's the heart of what's so complex and often, frankly, difficult about treating this population. We'll review the key pharmacological tools available to us, exploring both their potential and their limitations.

Antipsychotics

When a person with a serious mental illness like schizophrenia is also using substances, it's a huge problem. Substance use can severely worsen psychotic symptoms, interfere with how well medications work, and generally lead to more relapses and hospitalizations. The neurobiological basis for this is a complex interplay of dopamine system dysregulation, which plays a key role in both psychosis and the reward circuits of addiction. In the past, doctors used first-generation, or "typical," antipsychotics like haloperidol (Skryabin et al., 2021). These medications can be effective in treating acute psychosis through potent dopamine D2 receptor antagonism, but they have a list of horrible side effects (Table 1). Involuntary muscle movements (extrapyramidal symptoms) and tardive dyskinesia—a potentially irreversible neurological syndrome—are significant issues that can discourage patients from sticking with treatment.

Nowadays, the go-to option for dual diagnosis is nearly always second-generation, or "atypical," antipsychotics. These medications—consider clozapine, olanzapine, or risperidone—are usually better tolerated and have a different side-effect profile. They still have their own issues, but they're less likely to cause the debilitating movement disorders of their predecessors because they also impact other neurotransmitter systems, such as serotonin. What's interesting is that certain of these atypical antipsychotics might even have a direct or indirect influence on cravings or an individual's urge to use a particular substance (Kishi et al., 2013). For instance, some research has suggested that they might decrease the rewarding effects of stimulants, although the research is still ongoing.

Table 1: Overview of antipsychotic medications

Feature	First-generation (typical) antipsychotics	Second-generation (atypical) antipsychotics
Examples	Haloperidol	Risperidone, olanzapine, clozapine
Mechanism of action	Strong dopamine D2 receptor antagonism	Dopamine D2 receptor antagonism with effects on other neurotransmitters (e.g., serotonin)
Typical side effects	Extrapyramidal symptoms, tardive dyskinesia	Metabolic effects (weight gain, elevated blood sugar), sedation
Primary use in dual diagnosis	Acute psychotic states (less common)	Treatment of psychosis/schizophrenia
Advantages	High effectiveness in treating psychosis	Lower risk of extrapyramidal symptoms, better tolerability, and potential influence on cravings
Disadvantages	Severe and often irreversible side effects that lower adherence	Significant metabolic risk, potential for sedation, adherence/compliance issues

The most significant challenge with atypical antipsychotics, however, is metabolic effects (Biagi et al., 2017). Significant weight gain, elevated blood sugar, and diabetes risk (metabolic syndrome is the name of this condition) are a considerable concern, especially because many individuals with a dual diagnosis already practice poor health habits. Sedation is also a frequent effect, a double-edged sword that may ameliorate agitation in the short run but make the individual feel groggy and unmotivated to the point of discontinuing meds entirely. Risk-benefit analysis is key here, and a continual balancing act for the physician. The biggest problem is mostly adherence. Long-acting injectable formulations, such as injections (so-called depots), are a good option for such patients. That way, the doctor can learn about the actual administered doses. It also enhances the treatment's effectiveness (Tiihonen et al., 2019).

Antidepressants

It's a near certainty that an individual with a substance use disorder is also suffering from depression—the two conditions often go hand in hand, frequently reinforcing one another. Someone may feel down and use a substance to escape, and the substance use then exacerbates the depressive condition (Table 2). It's a classic vicious cycle. Because of this, antidepressants are a mainstay of treatment. First-line treatment nowadays is usually Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) (Fadus et al., 2019; Nunes et al., 2004). Medications such as sertraline, escitalopram, and venlafaxine are commonly employed since they're practical, safe, and low risk for abuse. They function by altering the chemical messengers of the brain, primarily serotonin, and eventually can help improve a person's mood as well as decrease self-medication with drugs.

One of the big, unanswered questions, however, is one of timing. When is the best time to introduce an antidepressant? Should a doctor bring it on board during the very first detox phase, when a person's brain chemistry is still in flux? Or do they wait until they've been clean for a while and depression symptoms aren't just a withdrawal symptom? Starting early can smooth out a person's mood and might even keep them in treatment longer, but it can also be hard to tell if symptoms are a real psychiatric problem or just part of the withdrawal syndrome. Waiting offers a cleaner diagnostic picture, but there is also the risk that the patient will suffer due to their depressive symptoms for weeks or even months, which could very easily end in relapse (Chan et al., 2019).

There is no straightforward answer - it's the decision made with the patient, based on their own clinical history. For example, in patients with opioid use disorder, some research has suggested certain SSRIs may have a modest effect on relapse rates. Even if SSRIs and SNRIs are the basic first-line treatment, the doctors can occasionally prescribe other antidepressants. For example, bupropion can be a good choice because it not only treats depression but also helps in smoking cessation - a prevalent comorbid condition (Richmond et al., 2003). It is worth mentioning that other antidepressants, such as Tricyclic Antidepressants (TCAs), are very infrequently used now as their side effects and risk of dangerous interactions between drugs make them inappropriate choices for these patients. TCAs can be fatal in overdose, a very real concern in a population with suicidal thoughts (Vitali et al., 2018). Also, their anticholinergic side effects can be harsh to tolerate. Always, the pairing of medication with therapy (like CBT or motivational interviewing) is the best strategy for a successful recovery.

Mood Stabilizers

Bipolar disorder is closely related to the use of alcohol and drugs; one tends to go with the other. The individual may use alcohol or drugs during the manic phase in an attempt to heighten the high, or he may use them during the depressive phase in an effort to gain some relief. This sort of substance use can exacerbate manic and depressive episodes significantly and even induce new ones. For this reason, mood stabilizers are an absolute necessity for controlling the condition.

The classical mood stabilizer (lithium) is still the first-line treatment (Alda, 2015). It modulates intracellular signals and neurotransmitter release. It is vastly effective at preventing manic and/or depressive episodes. However, it is a medication that requires very detailed and attentive monitoring of blood levels as it has a very narrow therapeutic window. That is the main problem in dual diagnosis situations. Active substance use (especially with alcohol) can affect those levels, making the medication ineffective or even toxic. Symptoms of lithium toxicity include ataxia, slurred speech, and confusion, and can be easily mistaken for intoxication, which makes it even more challenging to manage the patient properly. If a patient is not attending their appointments regularly or is actively using alcohol (or other substances), it can be challenging to manage the patient's safety.

Table 2: Antidepressants and mood stabilizers selection in dual diagnosis

Drug class	Examples	Use in dual diagnosis	Main considerations
Antidepressants	SSRIs, SNRIs	Treatment of depression in patients with addiction	Question of optimal timing (detox vs. abstinence), low risk of abuse
Anticonvulsants	Valproate (Depakote), Lamotrigine (Lamictal)	Mood stabilization in bipolar disorder	Need for drug level monitoring (valproate), risk of rash (lamotrigine)
Lithium	Lithium	Mood stabilization in bipolar disorder	Narrow therapeutic window, need for blood level monitoring, high risk of toxicity with alcohol use
Other drugs	Bupropion	smoking cessation, affective disorders treatment (depression)	Low abuse potential, distinct pharmacological mechanism

Other drugs Bupropion smoking cessation, affective disorders treatment (depression) Low abuse potential, distinct pharmacological mechanism for these reasons, many clinicians use anticonvulsants, which also have mood-stabilizing effects. Drugs like valproate (Depakote) and lamotrigine (Lamictal) are common choices (McElroy et al., 1992). Valproate acts by blocking voltage-sensitive sodium channels and increasing its levels; therefore, it is a reasonable choice, especially in patients with multiple mixed episodes or rapid cycling. Lamotrigine is often preferred in bipolar depression, as it is safer during that particular phase. These medications are not without their problems, however. Valproate can be brutal on the liver and requires its own blood level monitoring. Lamotrigine is, in some rare cases, associated with a potentially severe skin rash (Stevens-Johnson syndrome), a risk that we must carefully weigh against the benefits for the patient (Crapanzano et al., 2022). Compliance is, again, a huge factor here, as missed doses can lead to unsteady mood and a heightened risk of a relapse into substance abuse. With all of these medications, close monitoring—not just for drug levels, but also for liver function and blood counts—cannot be stressed enough.

Anti-anxiety medications

Anxiety and addiction go hand in hand. For some, a substance is a means of self-medication—a fast method of shutting up the voice in the head or blunting a panic attack. Such a strategy is where the issue of anti-anxiety medication gets extremely sensitive. The most potent ones, such as benzodiazepines (Xanax, Klonopin), are also terribly addictive and possess a high potential for abuse (Kaplan et al., 2005). Taking them long-term can make one dependent, and mixing them with other central nervous system depressants, such as alcohol or opioids, can be lethal because of the risk of respiratory depression. Due to these very legitimate risks, the majority of clinicians are extremely hesitant, if not downright opposed, to prescribing them to an individual with a history of substance use disorder. So what are the alternatives? The good news is that many of the same antidepressants —namely, SSRIs and SNRIs—are also first-line treatments for a slew of anxiety disorders (Baldwin et al., 2010). They work more slowly but do not share the same risks of patients getting addicted. Also, offer other non-addictive alternatives as well. Buspirone is an appropriate option for generalized anxiety as it works on serotonin receptors and has very low abuse potential. Another alternative is hydroxyzine, a potent antihistamine with sedating properties that can be used for short-term periods (with little to no risk of abuse). In such a population, anxiety medication is a supportive strategy with the proper long-term treatment by therapy. Cognitive Behavioral Therapy (CBT) or Dialectical Behavior Therapy (DBT) are the main strategies that help people learn to control their anxiety without using medication.

Clinical Dilemmas and Practical Issues

Clinicians see dual diagnosis patients as having many more problems than just selecting the correct drug. Throughout this chapter, the specific, everyday issues clinicians encounter when working with this population will be addressed. What to treat isn't so much the concern as how to function within a treatment plan that is typically dangerous and complex (Table 3).

Table 3. Clinical challenges in dual diagnosis pharmacotherapy

Challenge	Problem Description	Recommended Management Strategies
Drug interactions	Risk of dangerous interactions between psychotropic agents and psychoactive substances (e.g., serotonin syndrome, respiratory depression)	Clinical vigilance, patient education, and a thorough history of drug use
Treatment compliance	Trouble with adherence to medication due to addiction, skepticism about treatment, and forgetfulness	Implementation of long-acting injectable forms, intensive psychoeducation
Abuse risk	Addictive potential of some psychotropic drugs, especially benzodiazepines	Substitution of drugs with high abuse liability for alternative medications
Incorporation of treatment	There is a greater risk of viewing the drug as a "cure-all." This perspective reduces the need for changing behaviors.	Augmenting pharmacotherapy with psychotherapy (CBT, MI) and support

Amongst clinician issues in clinical practice is the constant issue of heightened risk of drug-drug interaction amongst prescribed psychotropic drugs and drugs taken by the patients. For example, a combination of an antidepressant (SSRI) and medications like



stimulant ecstasy entails the risk of serotonin syndrome, which is fatal. Mixtures of central nervous system depressants, such as alcohol or opioids, with sedative antipsychotics or specific mood stabilizers can be deadly in terms of sedation and/or respiratory collapse (McGovern et al., 2014). We have to watch drug-drug interactions very closely, and complete knowledge about the patient's history of drug use, not necessarily revealed by the patient, is necessary.

An additional concern is the potential for abuse (Manwani et al., 2007). For the most part, antidepressants and mood stabilizers have no abuse potential, although there is some potential for misuse if they cause sedation. The most likely and most common drug likely to be diverted or abused is benzodiazepines, which are of high addiction potential. There can be some potential risk for individuals abusing an atypical antipsychotic as a sedative, but not to such an extent (Kaplan et al., 2005). This risk needs to be weighed against the prescribing process and the prescribed medications, along with alternatives and non-addictive medications, as required.

Finally, introducing these drugs into the whole process of addiction can be marvelous and atrociously misplaced. Psychotropic drugs, when used skillfully and cautiously, can stabilize the mood of a patient, dampen cravings characteristic of their addiction, and render the patient open to the acceptance of long-term therapy and behavior change. Concurrently, we can divert their attention away from their treatment and assign to the assignment of a shift in behavior, no longer being something mandatory or obligatory, because they are on medication that is a "cure." The notion is that medication should be added regularly, along with a plan of intervention that involves counseling, peer support, and social integration for the patient, thereby incorporating biopharmacology into the manner in which they construct their recovery course of action (Herman et al., 2000; Acosta et al., 2012).

#### 4. CONCLUSION

This review has ascertained that, though psychotropic medication is of immense value in the treatment of dual diagnosis, its application is far from simple. We now know that, for co-morbid psychosis, it is second-generation antipsychotics that, in most cases, emerge as the preferred agents because of superior tolerability, despite enough metabolic risk. The role of SSRIs and SNRIs in depression is now well established, even if there is a public debate on when, precisely, to commence with them. Mood stabilizers, particularly anticonvulsants, are necessary for the treatment of comorbid bipolar disorder but pose unique adherence and therapeutic drug monitoring complications in a population with active substance use. Most critically, perhaps, we've highlighted the necessity for extreme caution with anti-anxiety agents given their high potential for abuse and dependency.

Ultimately, it is essential to recognize that professionals should include medication for dual diagnosis in a complete treatment plan. Medical professionals need to take a holistic (whole-person) approach, using medicines alongside a thorough therapeutic plan. We emphasize proven psychotherapies, such as Cognitive Behavioral Therapy and Motivational Interviewing, as well as social networks. Medications help patients gain stability, allowing them to engage in therapy, but they are not a quick solution.

Looking ahead, there are still significant gaps in our understanding. Much of the research data derives from short-term studies, and we need more long-term prospective studies to establish the longer-term safety and effectiveness of these interventions. We need to try the new pharmacological agents that would specifically address the neurobiological pathways common to addiction and mental illness—continued research in these areas is necessary to optimize clinical outcomes.

#### List of abbreviations

CBT - Cognitive Behavioral Therapy

DBT - Dialectical Behavior Therapy

MAOIs - Monoamine oxidase inhibitors

SNRIs - Serotonin-Norepinephrine Reuptake Inhibitors

SSRIs - Selective Serotonin Reuptake Inhibitors

TCAs - Tricyclic Antidepressants

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### Conflict of interest

The authors declare that there is no conflict of interest.

### Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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