Dual diagnosis in Depression: treatment recommendations

Patología dual en Depresión: recomendaciones en el tratamiento

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Abstract

Comorbidity between substance use disorders (SUD) and major depression (MD) is the most common dual pathology in the field of addiction to substances and has prevalence rates ranging between 12% and 80%, which complicates the response to treatment and worsens the prognosis of patients.

Differentiating between diagnoses of induced depressive episodes and primary depressive episodes concurrent to substance use is especially relevant for therapeutic management.

This article presents the state of the art of the currently available pharmacologic treatments of comorbid depression in patients with SUD, taking into account the safety and risk of abuse of antidepressant drugs.

Due to the fact that comorbidity of MD and SUD is frequent and presents greater psychopathological and medical severity, as well as worse social functioning, it is crucial to treat MD and SUD simultaneously using the integrated treatment model and not to treat both conditions separately.

Keywords: Depression; Dual pathology; Comorbidity; Treatment; Recommendations.

Resumen

La comorbilidad entre los trastornos por uso de sustancias (SUD) y la depresión mayor (DM) es la patología dual más común en el campo de las adicciones a sustancias, con prevalencias que oscilan entre el 12 y el 80% complicando la respuesta al tratamiento y empeorando el pronóstico de los pacientes. Diferenciar entre el diagnóstico de episodios depresivos inducidos y episodios depresivos primarios concurrentes al uso de sustancias es especialmente relevante para el manejo terapéutico.

En este artículo se presenta el estado actual de los tratamientos farmacológicos disponibles hasta el momento para la depresión comórbida en pacientes con SUD, teniendo en cuenta la seguridad y el potencial de abuso de los fármacos antidepresivos.

Debido a que la comorbilidad de DM y SUD es frecuente y a que estos pacientes presentan mayor gravedad psicopatológica y peor funcionamiento social, es crucial un modelo de tratamiento integrado y no abordar el tratamiento por separado.

Palabras clave: Depresión; Patología dual; Comorbilidad; Tratamiento; Recomendaciones.

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Mood disorders and anxiety disorders are the mental disorders most frequently associated with substance use disorders (SUD) (San, Arranz, & Grupo de Expertos de la Guía de Práctica Clínica de Patología Dual, 2016). In this review we present an update of what is known about the comorbidity of depression and SUD, and resulting treatment recommendations. To indicate the simultaneous presence of an episode of MD and an SUD, the terms dual depression, comorbid depression with SUD, or MD + SUD are used interchangeably in this paper.

The prevalence of this combination varies between 12% and 80% across the different studies. According to Torrens and Rossi (2015), several factors explain this wide range. The factors to consider include: the main substance consumed (tobacco, alcohol, cocaine, opiates, hypnosedatives, etc.); whether the study was conducted among the general population or with a sample of substance users - and in the latter case, whether they were recruited in addiction treatment centers, in mental health care facilities or in other populations (prison, the homeless), or methodological aspects such as diagnostic criteria (DSM or ICD, in their different versions), and the diagnostic tools used (diagnostic interviews such as PRISM, SCID or SCAN, or screening tools such as DDSI).

In a systematic review with meta-analysis of epidemiological studies in the general population carried out between 1990 and 2014, the authors confirm the close link between MD and SUD (Lai, Cleary, Sitharthan, & Hunt, 2015). This association is stronger for the use of illegal drugs than for alcohol, and greater for disorders with dependence criteria than for disorders due to abuse, regardless of the temporal criterion for establishing prevalence (during a lifetime or over the previous 12 months). The main results are shown in Table 1.

The prevalence of MD and SUD comorbidity at the European level among clinical populations in different care facilities and among some special populations (e.g. prisoners or the homeless), is available in various publications such as Insight 19 from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2015) and others (Arias et al., 2013; Torrens & Rossi, 2015).

Furthermore, studies performed both in the general population and in the clinical population show that comorbid MD with SUD is more frequent in women than in men, and is twice as frequent as in women of the general population. Women with SUD thus constitute a particularly vulnerable group (Torrens et al., 2011).

Table 1. *SUD-MD prevalence in general population epidemiological surveys (Lai et al., 2015).*

MD with SUD	Alcohol	Abuse OR 1.53, 95% CI 1.20-1.95 Dependence OR 3.09, 95% CI 2.38-4.03
	Other drugs	Abuse OR 3.80, 95% CI 3.02-4.78 Dependence OR 4.83, 95% CI 3.01-7.73

Note. SUD: substance use disorder; MD: major depression; OR: odds ratio; CI: confidence interval.

Etiopathogenesis

Three hypotheses are proposed to explain the frequent concurrence of MD and SUD:

1. SUD and MD share common risk factors, such as stressful life events, psychological trauma, genetic vulnerability and/or previous neurobiological impairments leading to the occurrence of both disorders without a causal relationship between them.
2. Continued use of certain substances of abuse leads to neurobiological changes through neuroadaptive mechanisms that mediate MD.
3. SUD develops to relieve the MD (self-medication hypothesis). In this case, MD increases the risk behaviors linked to consumption.

In both MD and SUDs, genetic and environmental factors play a crucial role in facilitating neurobiological mechanisms related to their psychopathogenesis (Brady & Sinha, 2005; Schuckit, 2006). The major neural and molecular mechanisms involved in the neurobiology of depression include the monoaminergic system, the hypothalamic-pituitary-adrenal axis, the immunological system, neurotrophic factors, the endocannabinoid system, the circadian rhythm, and the system controlling ingestion and metabolism (Belmaker & Agam, 2008; Krishnan & Nestler, 2010; Valverde & Torrens, 2012; Valverde et al., 2009).

Most of these systems are also involved in the development of SUDs (Brady & Sinha, 2005; Gutiérrez-Sacristán et al., 2015; Valverde & Torrens, 2012). Similarly, reward circuits, which are highly relevant to the pathogenesis of addiction (Wise, 1989), are involved in the neurobiology of depressive disorders (Nestler & Carlezon, 2006).

Clinical aspects

The clinical diagnosis of MD in substance users is complex due to different factors. On the one hand, the acute or chronic effects of substance use may mimic depressive symptoms, making it difficult to distinguish between the symptoms of a case of MD independent of symptoms related to consumption or withdrawal. On the other hand, diagnoses of psychiatric disorders such as MD are more syndromic than those of diseases with clear pathophysiology and associated biological markers. This lack of biological markers has forced psychiatrists to develop operative diagnostic criteria, including DSM and ICD, and to design clinical diagnostic interviews to improve the validity and reliability of psychiatric diagnoses. With reference to the diagnosis of other psychiatric disorders among substance users, the criteria used changed over time until they matched those of DSM-IV (American Psychiatric Association, 1994) and were maintained in DSM-IV-TR (American Psy-

chiatric Association, 2002) and DSM-5 (American Psychiatric Association, 2013), with three conditions considered necessary to facilitate a more accurate diagnosis:

- *"Expected effects":* this refers to symptoms considered specific to intoxication or withdrawal from a given substance which should therefore not be taken into account as symptoms for diagnosing depression (e.g. insomnia during acute stimulant poisoning or during a period of opiate withdrawal).
- "*Substance-Induced":* disorders that appear in relation to substance use or withdrawal, but can be considered excessive in relation to the expected effects.
- *"Primary":* mental disorders that are not induced by substances or arising from medical illness, i.e., independent disorders.

Medical professionals tend to bear in mind the concept of primary or independent disorder and that of induced disorder more than the concept of "expected effect", which is, nevertheless, very relevant in order to increase diagnostic validity and reliability.

In clinical practice, the differentiation between primary depressive episodes and those induced by substance use is one of the difficulties in the diagnosis of depressive symptoms when there is co-occurrence of substance use. To help with this issue, different diagnostic interviews are available to establish the diagnosis. Among them, the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) (Hasin et al., 1996) enables the diagnosis of primary or substance induced depression in a valid and reliable way. This difference may be especially relevant for treatment management. Table 2 shows the main clinical indicators that facilitate the differential diagnosis of induced depressive episodes and primary depressive episodes concurrent with substance use.

Table 2. *Clinical indicators for the diagnosis of a depressive episode concurrent to the use of substances.*

Primary depression	Induced depression
Depressive symptomatology appears during a phase of stable consumption	Appearance of depressive symptomatology during an increase in consumption
Depressive symptomatology persists after a period of abstinence	Appearance of depressive symptomatology during a significant decrease in consumption
History of depressive episodes in the absence of substance use	
History of good response to antidepressant treatments	
Family history of depression	

Table 3. *Principal clinical characteristics of dual depression.*

Clinical characteristics of dual depression
Dual MD is more frequent when SUD severity is moderate-severe than if SUD is mild (DSM-IV criteria show dual MD to be more frequent in dependence disorders than in abuse disorders)
Dual MD is more frequently independent rather than induced (except in the case of alcohol SUD)
The presence of MD (primary or induced) is associated with unfavorable SUD progress
The presence of SUD is associated with unfavorable MD progress
Patients with dual depression have a higher prevalence of attempted/completed suicides
Patients with dual depression have more medical and psychiatric comorbidities (including more SUDs)
Patients with dual depression present greater social problems and increased use of health resources, including more psychiatric admissions

It has been observed in the case of SUDs involving cocaine, opiates or among polydrug users that episodes of MD usually occur more frequently independently of consumption (Torrens, Gilchrist, & Domingo-Salvany, 2011), whereas in the case of alcohol a higher prevalence of association with induced MD has been reported (Schuckit, Smith, & Kalmijn, 2013). However, both types of depression (primary and induced) can be found in the same patient (Langås, Malt, & Opjordsmoen, 2013; Torrens, Gilchrist, & Domingo-Salvany, 2011). It has also been observed that patients with MD are twice as likely to develop a SUD and that patients with SUD are twice as likely to have MD during their lifetimes (Boden & Fergusson, 2011). In addition, the coexistence of both disorders has been linked to an unfavorable course for both pathologies, with worse response to treatment and worse prognosis (Agosti & Levin, 2006; Davis, Uezato, Newell, & Frazier, 2008). Thus, in follow-up studies among samples of substance-dependent patients it has been observed that the presence of major depressive episodes, both primary and induced, has facilitated relapse to substance use (Landheim, Bakken, & Vaglum, 2006; Samet et al. 2013). Indeed, several studies have found that SUD comorbidity in patients with MD increases the clinical severity of these patients, and there is a greater risk of suicidal behavior (Marmorstein, 2011; Szerman et al., 2011). In addition, these patients are more likely to develop other medical comorbidities, making treatment even more difficult. Thereby, and as expected due to their high clinical severity, these dual patients also present considerable psychosocial severity and make greater use of health resources, including emergency services and psychiatric admissions (Martin-Santos et al., 2006; Mueller et al., 1994; Pettinati, O'Brien, & Dundon, 2013; Samet et al., 2013).

Given the available knowledge it can thus be affirmed that induced depressive episodes can be as or more serious than primary or independent ones, both in terms of relapse to substance use and in the severity of depressive symptomatology, including risk of suicide.

Table 3 summarizes the main clinical features of dual depression.

Treatment of dual depression

Since the frequency and clinical and social severity of these dual patients is high, their treatment is important. However, we hardly have any studies on the treatment of dual depression, and most have been carried out on patients with alcohol dependence. The current state of clinical management of patients with MD and SUD is presented below.

General recommendations

1. A depressive episode should be treated even though the patient is actively using substances. The treatment of dual depression should take both disorders into account; depression treatment cannot replace addiction treatment.
2. The addiction should be treated even if the patient is in a depressive episode. Treatment with antidepressants has a limited impact on substance use; specific concomitant treatment should be considered for SUD.
3. Substance use is not a limitation for the treatment of depression.
4. The effects of antidepressants are greater when patients have primary MD.
5. Treatment should consider pharmacological and psychotherapeutic approaches.

Pharmacotherapy

The pharmacological treatment approach for MD with SUD should consider not only the efficacy of different drugs, but also aspects relating to the safety of using antidepressants, their possible interactions with the consumption of different substances and the abuse potential of the different drugs administered for the treatment of dual depression.

The following outlines the most important aspects to be taken into account when prescribing antidepressants.

Efficacy of antidepressant drugs in dual depression

Two systematic reviews of controlled clinical trials analyzed with meta-analysis are currently available (Nunes & Levin, 2004; Torrens, Fonseca, Mateu, & Farré, 2005). The main results were that selective serotonin reuptake inhibitors (SSRIs) yielded worse results than non-SSRI antidepressants in the treatment of dual MD and that antidepressants did not directly affect the improvement in substance use. Other studies were subsequently published on the treatment of dual depression. The following summarizes the seven ensuing studies on the efficacy of antidepressants in the treatment of comorbid MD with alcohol consumption disorder (Table 4), and the six subsequent studies on the efficacy of antidepressants in the treatment of comorbid MD with cocaine use disorder (Table 5).

With regard to the efficacy of antidepressant treatment in comorbid depression with opioid use disorder, it should be noted that following the systematic review with meta-analysist of Torrens (Torrens et al., 2005), only one review of the Cochrane (Pani, Vacca, Trogu, Amato, & Davoli, 2010) was published, which included the same studies. Subsequently and to date, no other study has been published.

As for the treatment of MD and cannabis dependence disorder, only a single randomized, placebo-controlled trial in 103 patients with cannabis and MD or dysthymia disorder is available, which compared the effect of delayed release venlafaxine with placebo for 12 weeks. In addition, all patients received concomitant treatment with weekly sessions of individual cognitive-behavioral therapy. No significant differences were found in terms of clinical depression and an increase in cannabis use was observed in patients in the delayed-release venlafaxine group (Levin et al., 2013).

The review of the available literature on the pharmacological treatment of dual depression thus allows us to assert that:

1. SSRIs are the most commonly used antidepressants in the studies and have in no case demonstrated efficacy in the treatment of depression comorbid with alcohol, cocaine or opiate use disorders.
2. There are few studies with other non-SSRI antidepressant drugs, and in this case evidence indicates that: a) imipramine and desipramine are effective in improving depression in patients with MD and alcohol use disorder, and desipramine in MD and cocaine use disorder; b) other antidepressants studied, such as venlafaxine, mirtazapine and nefazodone, have not proved efficacious in improving dual depression.
3. No antidepressant has been shown to be effective in reducing substance use.

The safety of antidepressant drugs in dual depression

An especially relevant aspect in the pharmacological treatment of dual depression is the possibility of pharmacological interactions between antidepressants and the substances of abuse themselves, the drugs used for the treatment of SUD, or the drugs used for the treatment of other medical comorbidities that the patient may suffer (e.g. human immunodeficiency virus infection or hepatitis C virus). It is notable that methadone is the second most frequent cause of drug arrhythmia after dofetilide (Kao et al., 2013), according to the adverse event reporting system of the Food and Drug Administration (FDA). Because methadone is one of the most widely used drugs in the treatment of opioid use disorder, a review of Chou's (2014) methadone interactions is recommended. Table 6 summarizes the most relevant interactions that should be taken into account in the clinical management of dual depression. Special caution should be exercised with monoamine oxidase inhibitors (MAOIs) due to their interaction with fatal results with tyramine in some foods or alcoholic beverages, with the consumption of stimulants (cocaine, amphetamines, methamphetamine, MDMA) also totally contraindicated.

Table 4. *Double blind and controlled clinical trials on MD and alcohol consumption disorder included and not included in previous meta-analyzes.*

Authors	Study type	Medication	N	Duration	Concomitant treatment	Efficacy on depression	Efficacy on substance use
Altamura 1990*	PC-RCT	Viloxazine	27	12 wks	4 weeks hospital followed by outpatient treatment	Yes. Decreased depressive symptomatology with significant differences between both groups	Both groups improved alcohol consumption without significant differences between groups
Mc Grath 1996*	PC-RCT	Imipramine	56	12 wks	Individual BCT and relapse prevention	Yes. Decreased depressive symptomatology with significant differences between both groups	No effect
Mason 1996*	PC-RCT	Desipramine	22	24 wks	Alcoholics Anonymous	Yes. Decreased depressive symptomatology with significant differences between both groups	Decreased consumption with significant differences between both groups
Cornelius 1997*	PC-RCT	Fluoxetine	51	12 wks	Support psychotherapy	Yes. Decreased depressive symptomatology with significant differences between both groups	Decreased consumption with significant differences between both groups
Roy 1998*	PC-RCT	Sertraline	15	6 wks	Inpatient treatment followed by intensive day hospital	Yes. Decreased depressive symptomatology with significant differences between both groups	Not assessed
Roy-Byrne 2000*	PC-RCT	Nefazodone	31	12 wks	Group CBT	Yes. Decreased depressive symptomatology with significant differences between both groups	Decreased consumption with no differences between both groups
Pettinati 2001*	PC-RCT	Sertraline	29	14 wks	12-Step Therapy	No. No differences between both groups	No differences between both groups
Gual 2003*	PC-RCT	Sertraline	46	24 wks	2 weeks of abstinence after detoxification	No. Decreased depressive symptomatology without significant differences between both groups	Decreased consumption with no differences between both groups
Moak 2003*	PC-RCT	Sertraline	82	12 wks	Individual CBT for alcohol and depression	No. Decreased depressive symptomatology without significant differences between both groups	Decreased consumption with no differences between both groups
Hernández-Àvila 2004*	PC-RCT	Nefazodone	41	10 wks	Support psychotherapy	No. Decreased depressive symptomatology without significant differences between both groups	Decreased consumption with no differences between both groups
Kranzler 2006	PC-RCT	Sertraline	328	10 wks	No	No. Decreased depressive symptomatology without significant differences between both groups	No
Altintoprak 2008	RCT	Amitriptiline vs Mirtazapine	44	8 wks	No	No. Decreased depressive symptoms without differences between the two drugs. Better mirtazapine tolerance	No Both reduced alcohol craving
Muhonene 2008	RCT	Memantine vs Escitalopram	80	2 años	No	No. Both drugs decreased depressive symptoms without differences	Not assessed
Cornelius 2009	PC-RCT	Fluoxetine	40	12 wks	Standard CBT motivational therapy	No. Both drugs decreased depressive symptoms without differences	No Both decreased consumption
Petinatti 2010	PC-RCT	Setraline vs Naltrexone vs Sertraline + Naltrexone vs placebo	170	14 wks	Placebo group standard CBT relapse prevention	No. Sertraline + naltrexone improved depression at the end of the study compared to other groups, with no significance	Sertraline + naltrexone improve abstinence and lengthen time to relapse
Adamson 2015	PC-RCT	Natrexone + Citalopram vs Natrexone + Placebo	138	12 wks	No	No. Decreased depressive symptomatology without significant differences between both groups	Decreased consumption with no differences between both groups
Foulds 2015	PC-RCT	Natrexone + Citalopram Vs Natrexone + Placebo	138	12 wks	No	No. Improvement on the induced depression scales, although without being able to determine a significant effect of the treatment in relation to decrease in consumption	Greater decrease of consumption in induced than independent depression

Note. PC-RCT: Placebo-controlled, Randomized Clinical Trial. RCT: Randomized Clinical Trial. No: no efficacy. SSRI: Selective serotonin reuptake inhibitors. CBT: Cognitive Behavioral Therapy. AD: Antidepressant. * Studies included in previous metaanalysis.

Table 5. *Double-blind and controlled clinical trials on MD and cocaine use disorder included and not included in previous meta-analyzes.*

Authors	Study type	Medication studied	N	Duration	Concomitant treatment	Efficacy on depression	Efficacy on substance use
Ziedonis 1991*	RCT	Desipramine or Amantadine	14	12	PMM	Decreased depressive symptomatology	Yes. Decreased consumption with differences between both groups
Nunes 1995*	RCT	Imipramine	69	12	Individual counseling	No. No effect	No. Decreased consumption without differences between both groups
Cornelius 1998*	RCT	Fluoxetine	17	12	Support therapy	No. Decreased depressive symptomatology without differences between both groups	No
Schmitz 2001*	RCT	Fluoxetine	68	12	CBT and relapse prevention	No. Decreased depressive symptomatology without differences between both groups	No
Gonzalez 2003*	RCT	Desipramine	56	12	Contingency management	No. No significant differences	No
MacDowell 2005	RCT	Desipramine	111	12 wks	Standard CBT and relapse prevention	Yes. Clinical improvement in patients in the desimipramine group	No
Ciraulo 2005	RCT	Nefazodone	69	8 wks	1 hour counseling sessions	No. Both groups improve without differences	No
Afshar 2012	RCT	Mirtazapine	24	12 wks	Manual-guided relapse prevention therapy	No. Decreased clinical depression in both groups	No
Oliveto 2012	RCT	Sertraline	86	12 wks	Standard CBT and relapse prevention	No. No significant differences	No
Mancino 2014	RCT	Sertraline vs Sertraline + Gabapentine	99	12 wks	Standard CBT and relapse prevention	No. Improvement in all groups	Group with sertraline increased time to relapse
Raby 2014	RCT	Venlafaxine	130	8 wks	Manual-guided relapse prevention therapy	No	No

Note. PC-RCT: placebo-controlled randomized clinical trial. CBT: cognitive behavioral treatment. *Studies included in previous meta-analyses.

Abuse liability of antidepressant drugs

Since the 1970s, case series have been described which suggest that some antidepressants may have potential for abuse, with those with stimulant or sedative properties being the most risky. The antidepressants with the highest risk and with which special care should be taken in patients with SUDs (Evans & Sullivan, 2014; Haddad, 1999; Jasinski, Faries, Moore, Schuh & Allen, 2008; Reeves, Ladner, Perry, Burke, & Laizer, 2015; Volkow et al., 2005) are outlined below.

- MAOIs: Tranylcypromine and phenelzine have been involved in oral abuse due to their amphetamine-like structure; series of cases have been reported in particular with tranylcypromine.
- Tricyclics: Especially those with sedative and anticholinergic properties have been reported in oral abuse. Cases have been described where amitriptyline and dothiepin (the analogue of amitriptyline used in Europe) have been used to get a feeling of euphoria.
- Bupropion: Intranasal abuse with cocaine-like effects has been described. Isolated cases of intravenous abuse have also been reported.
- SSRIs: There are studies indicating that fluoxetine has been used orally to give amphetamine-like effects in combination with alcohol or MDMA.
- SNRIs: A case of venlafaxine abuse has been reported with withdrawal symptoms and requiring admission for detoxification.

- Tianeptine: This is an antidepressant approved in France and recently in Spain. Cases of oral abuse have been reported to provide a psychostimulant effect.
- Amineptine: Oral abuse has stimulant-like effects.

Psychological treatments

Treatment of dual depression with cognitive-behavioral therapy (CBT) is well recognized. However, it is still not routinely applied in clinical practice despite available data on its efficacy.

There are currently several combined treatments for MD and SUD, including psychotherapeutic treatments as adjuvants or alternatives to pharmacological treatment. A recent systematic review with meta-analysis has assessed the efficacy of CBT and motivational intervention on MD in patients with alcohol-induced SUD vs usual treatment (Riper et al., 2014). The authors observed that in both cases the interventions yielded a slight clinically significant effect both in the reduction of depressive symptoms and in the decrease in alcohol consumption, although the effect size was lower compared to that obtained with the pharmacological treatments. Furthermore, the BRIGHT project (Building Recovery by Improving Goals, Habits, and Thoughts), which compared residential SUD treatment with residential SUD treatment and CBT together, yielded better clinical results with greater treatment adherence and greater improvement of depressive symptoms in patients who also received CBT (Watkins et al., 2011).

Table 6. *Main interactions in the clinical management of dual depression.*

Substance/medication	Antidepressant	Effect
Benzodiazepines	Tricyclics	↑ plasma concentrations of *desipramine* and *imipramine*
	SSRI	*Fluoxetine and fluvoxamine* ↑ plasma concentrations of *alprazolam* and *diazepam*
Disulfiram	Tricyclics	↑ plasma concentrations of *desipramine* and *amitriptiline* via metabolism ⚓ and increased neurotoxicity of the combination
	MAOI	*Tranylcypromine,* Confusional psychosis in combination
Opioids	Tricyclics	*Methadone:* ↑ risk of QTc interval prolongation ↑ risk of death with overdose ↑ plasma concentrations of methadone if co-administered with *desipramine*: *Morphine:* ↑ bioavailability and analgesic effect *Doxepine* may induce delirium during OWS
	SSRI	*Methadone and buprenorphine* ↑ risk of serotonin syndrome ↑ plasma concentrations of methadone through ⚓ elimination with *Fluvoxamine*
	MAOI/RIMA	*Moclobemide:* ↑ effects of morphine, fentanyl and methadone
	Other antidepressants	*Mirtazapine* ↑ Risk of prolonging the QTc interval with *methadone*
Alcohol	Tricyclics	↑ alcohol toxicity ↓ cognitive function risk of convulsions (*maprotiline*)
	SSRI	↑ sedation (*fluvoxamine*)
	MAOI	↑ effects of alcohol Hypertensive crisis through ↑ release of catecholamines
	Other antidepressants	↑ sedation (*trazodone and mirtazapine*)
Stimulants (Cocaine/amphetamine)	Tricyclics & SSRIs	↓ craving, and convulsive threshold ↑ of heart rate and diastolic pressure by 20-30%, increased risk of arrhythmia
	MAOIs	Absolute contraindication

Note. OWS: opiate withdrawal syndrome; MAOIs: monoamine oxidase inhibitors; SSRIs : selective serotonin reuptake inhibitors; RIMA: reversible MAO-A inhibitor.

Intervention protocol

Diagnostic assessment

Since antidepressant drugs have been shown to be more effective in independent than in induced disorders, one of the key points for treatment is a good diagnostic approach, as discussed previously. The medical literature indicates that structured interviews are the best tool to establish these diagnoses and that the PRISM (Psychiatric Research Interview for Substance and Mental Disorders) is the most appropriate for this. In addition to this, it is also important to assess the intensity of the episode in order to consider the possibility of starting treatment with antidepressants.

Scope of treatment

In an outpatient setting it is not always possible to keep patients abstinent nor to guide them to a significant reduction in consumption. To stabilize the patient, hospital admission, whether urgent or scheduled, should be considered even in patients with moderate depressive symptomatology, regardless of whether it is induced or primary.

SUD treatment

Despite the presence a depressive symptomatology, the treatment of SUD should not be neglected and psychosocial and pharmacological interventions must be initiated to reduce substance use (e.g. naltrexone or nalmefene for alcohol dependence, methadone or buprenorphine-naloxone for the treatment of opioid dependence). To reduce the risk of long-term relapse for those dependent on alcohol and other drugs it is important to assess and treat major depression.

Pharmacological treatment of depression

Treatment with non-SSRI antidepressants should be considered for patients. Adding a more dopaminergic and noradrenergic profile or mixed mechanisms of action appears to be more effective. Figure 1 shows a therapeutic algorithm for the treatment of MD-SUD dual pathology.

Finally, it is necessary to emphasize that despite the high prevalence of MD in patients with SUD, the available evidence regarding the best treatment is scarce. Future research should propose controlled trials to analyze the efficacy, safety and interactions profile of the new antidepressants available.

Parallel, sequential or integrated treatment

It is important to note that in most countries there are two separate networks for the treatment of mental illness and for the treatment of SUD. This implies that patients with dual pathology are very frequently treated in two facilities (parallel treatment model): a mental health care center and a center for addiction. In addition, substance abstinence is a fundamental prerequisite in many cases for the treatment of depression (sequential treatment model). Currently, it is recommended that these models of treatment are replaced by the so-called integrated model, which involves a simultaneous and coordinated approach to both addictive and affective disorders in order to improve the adherence and effectiveness of treatment (Torrens, Rossi, Martinez-Riera, Martinez-Sanvisens, & Bulbena, 2012).

Conclusions

The comorbidity of MD and SUD is frequent and all patients affected by a dual disorder present greater psychopathological and medical severity, as well as worse social functioning. It is very important that MD and SUD are treated simultaneously on the basis of the integrated model and not approached via the treatment of both pathologies separately or sequentially. It is also of the highest priority to

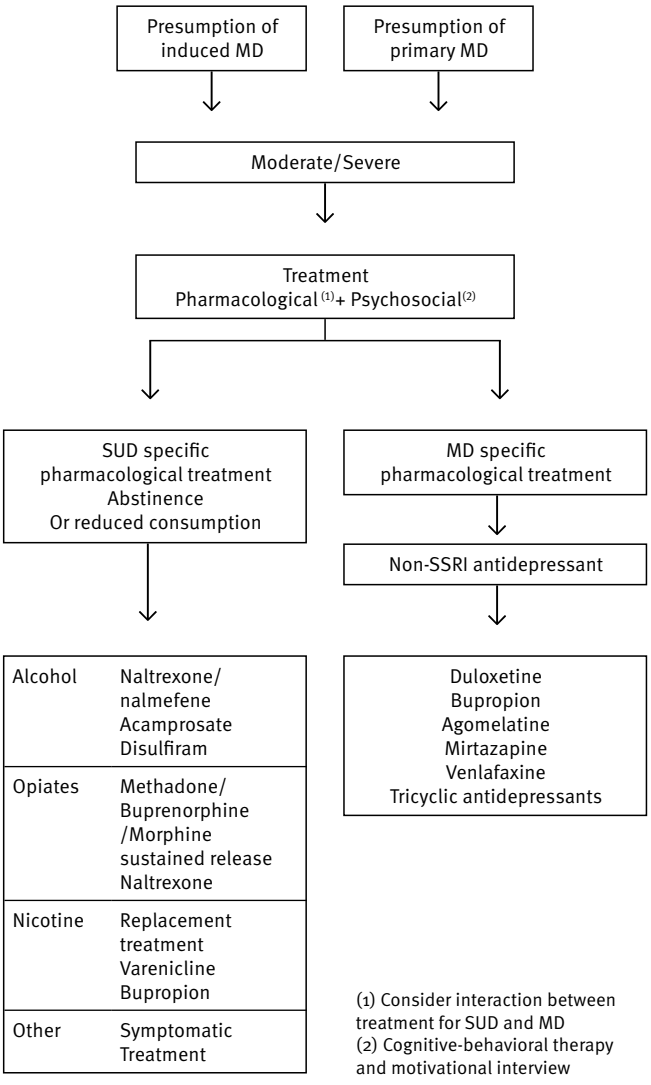

Figure 1. Therapeutic algorithm for the treatment of major depression and substance use disorder.

further investigate the neurobiology of the mechanisms of action involved in dual disorders in order to develop more effective prevention strategies and treatments.

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Conflicts of Interest

All authors declare that they have no conflict of interest.

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